Australian Government
Department of Health
Therapeutic Goods Administration

# Australian Public Assessment Report for Armodafinil

## Proprietary Product Name: Nuvigil

## Sponsor: Teva Pharmaceuticals Australia Pty Ltd

**May 2016**

TGA Health Safety Regulation

# About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

# About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

# Contents

# Common abbreviations

| Abbreviation | Meaning |
|---|---|
| ACPM | Advisory Committee on Prescription Medicines |
| ACSOM | Advisory Committee on the Safety of Medicines |
| AE | adverse event |
| AO | asymmetric oxidation |
| ARTG | Australian Register of Therapeutic Goods |
| AUC | area under the plasma drug concentration-time curve |
| BFI | Brief Fatigue Inventory |
| $C_{max}$ | maximum concentration of drug in serum |
| CDR | Cognitive Drug Research |
| CGI | Clinical Global Impression |
| CGI-C | Clinical Global Impression of Change |
| CGI-S | Clinical Global Impression of Severity |
| CHMP | Committee for Medicinal Products for Human Use |
| CL/F | apparent clearance |
| CPAP | continuous positive airways pressure |
| DAT | dopamine transporter |
| DDI | drug-drug interaction |
| EMA | European Medicines Agency |
| ESS | Epworth Sleepiness Scale |
| FAS | full analysis set |
| IC50 | half maximal inhibitory concentration |
| ICH | International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| ICSD | International Classification of Sleep Disorders |
| IP | intraperitoneal |

| Abbreviation | Meaning |
|---|---|
| IV | intravenous |
| Ki | inhibitory constant |
| KSS | Karolinska Sleepiness Scale |
| MRHD | Maximum Recommended Human Dose |
| MSLT | Multiple Sleep Latency Test |
| MWT | Maintenance of Wakefulness Test |
| NOAEL | no observed adverse effect level |
| NOEL | no observed effect level |
| OSA | Obstructive Sleep Apnoea |
| OSAHS | Obstructive Sleep Apnoea/Hypopnoea Syndrome |
| PADER | Periodic Adverse Drug Experience Report |
| PD | pharmacodynamic |
| PI | Product Information |
| PK | pharmacokinetic |
| PO | per os (oral) |
| PPK | population pharmacokinetic |
| PSG | polysomnography |
| PVT | Psychomotor Vigilance Task |
| QD | quaque die (once daily) |
| RMP | Risk Management Plan |
| SAE | serious adverse event |
| SE | sleep efficiency |
| SJS | Steven-Johnson Syndrome |
| SWSD | Shift Work Sleep Disorder |
| $T_{max}$ | amount of time a drug is present at the maximum concentration in serum |

| Abbreviation | Meaning |
|---|---|
| V/F | volume of distribution |
| WASO | wake after sleep onset |

# I. Introduction to product submission

## Submission details

| | |
|---|---|
| *Type of submission:* | New chemical entity |
| *Decision*: | Approved |
| *Date of decision:* | 24 November 2015 |
| *Date of entry onto ARTG* | 26 November 2015 |
| *Active ingredient:* | Armodafinil |
| *Product name:* | Nuvigil |
| *Sponsor's name and address:* | Teva Pharmaceuticals Australia Pty Ltd<br>Level 2, 37 Epping Road<br>Macquarie Park NSW 2113 |
| *Dose form:* | Immediate release uncoated tablets |
| *Strengths:* | 50 mg, 150 mg, 250 mg |
| *Container:* | HDPE bottles with polypropylene child resistant closures<br>PVC/Aluminium foil blisters (physician's packs; 150 mg and 250 mg tablets only) |
| *Pack sizes:* | 7 (blisters), and 30 tablets (bottles) |
| *Approved therapeutic use:* | Nuvigil is indicated:<br>• To improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy;<br>• To treat excessive sleepiness associated with moderate to severe chronic shift work sleep disorder where nonpharmacological interventions are unsuccessful or inappropriate;<br>• As an adjunct to continuous positive airways pressure (CPAP) in obstructive sleep apnoea/hypopnoea syndrome in order to improve wakefulness. |
| *Route of administration:* | Oral |
| *Dosage:* | The maximum recommended daily dose for Nuvigil is 250 mg for narcolepsy or Obstructive Sleep Apnoea/Hypopnoea Syndrome (OSAHS) and 150 mg for Shift Work Sleep Disorder (SWSD), taken with or without food |
| *ARTG numbers:* | 226557, 226558, 226559, 226560, 226561 |

## Product background

This AusPAR describes the application by Teva Pharmaceuticals Australia Pty Ltd to register armodafinil (trade name, Nuvigil) as a new chemical entity. Armodafinil is a wakefulness promoting agent for oral administration. Armodafinil is the R-enantiomer of the racemate modafinil, which is currently registered in Australia with the trade name Modavigil.

The proposed indications for Nuvigil are:

- to improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy;
- to treat excessive sleepiness associated with moderate to severe chronic shift work sleep disorder where nonpharmacological interventions are unsuccessful or inappropriate; and
- use as an adjunct to continuous positive airways pressure (CPAP) in obstructive sleep apnoea/hypopnoea syndrome in order to improve wakefulness.

The proposed indications for Nuvigil are identical to the currently approved indications for Modavigil.

## Regulatory status

The international regulatory status of armodafinil at the time of submission to TGA is listed in Table 1.

**Table 1: International regulatory status of armodafinil at the time of submission.**

| Country | Date of submission or approval | Status | Comment |
|---|---|---|---|
| US | 15 June 2007 | Approved | See below for indication |
| Colombia | 4 September 2012 | Approved | See below for indication |
| Puerto Rico | 4 April 2012 | Approved | See below for indication |
| Brazil | 19 August 2011 | Rejected | Rejection was due to incomplete information as per local country requirements |
| Mexico | 17 November 2011 | Under evaluation | n/a |
| South Korea | 24 October 2012 | Under evaluation | n/a |
| Ukraine | 13 December 2012 | File withdrawn | Submission was withdrawn for commercial reasons |
| Turkey | 15 February 2009 | Under evaluation | n/a |
| Venezuela | 11 July 2012<br>Resubmitted 18 July 2013 | Rejected<br>Resubmission under evaluation | Rejection was due to incomplete information as per local country requirements |
| South Africa | 8 November 2013 | Under evaluation | n/a |

The approved indication for the US, Columbia and Puerto Rico is as follows:

> *Nuvigil is indicated to improve wakefulness in patients with excessive sleepiness associated with obstructive sleep apnea, narcolepsy and shift work disorder.*

In OSA, Nuvigil is indicated as an adjunct to standard treatment(s) for the underlying obstruction. If CPAP is the treatment of choice for a patient, a maximal effort to treat with CPAP for an adequate period of time should be made prior to initiating Nuvigil. If Nuvigil is used adjunctively with CPAP, the encouragement of and periodic assessment of CPAP compliance is necessary.

This is the first application to register armodafinil in Australia. Modafinil, the racemate, is approved in Australia for the same indications as being sought for armodafinil. Modafinil (Modavigil) has been on the Australian Register of Therapeutic Goods (ARTG) since 2 July 2002.

### Product Information

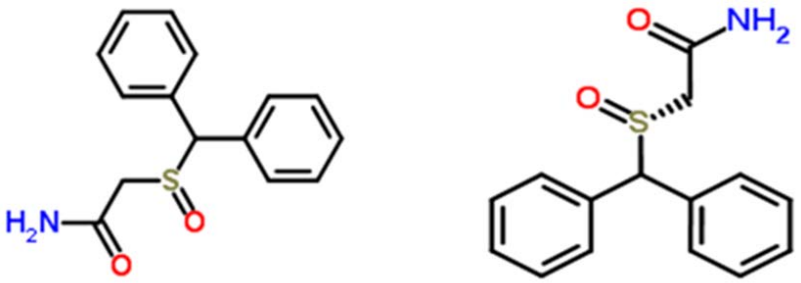
The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

# II. Quality findings

### Introduction

The centrally acting sympathomimetic drug substance armodafinil [the (R)-enantiomer of the racemate modafinil (Figure 1)] is a new chemical entity developed as a wakefulness promoting agent for oral administration. While both enantiomers are pharmacologically active, the (S)-enantiomer is eliminated from the body 3 times faster than the (R)-enantiomer.[1] The dossier states that the mechanism of action is unknown, but that armodafinil has similar pharmacological properties to modafinil in animal and in vitro studies. Both are indirect dopamine receptor agonists, binding in vitro to the dopamine transporter (DAT) and inhibiting dopamine reuptake. For modafinil, this activity has been associated in vivo with increased extracellular dopamine levels in some brain regions of animals. In genetically engineered mice lacking the DAT, modafinil lacked wake promoting activity, suggesting that this activity was DAT dependent. However, the wake promoting effects of modafinil, unlike those of amphetamine, were not antagonised by the dopamine receptor antagonist haloperidol in rats. In addition, α-methyl-p-tyrosine, a dopamine synthesis inhibitor, blocks the action of amphetamine, but does not block locomotor activity induced by modafinil.

**Figure 1: Chemical structures of modafinil (left) and armodafinil (right).**




### Drug substance (active ingredient)

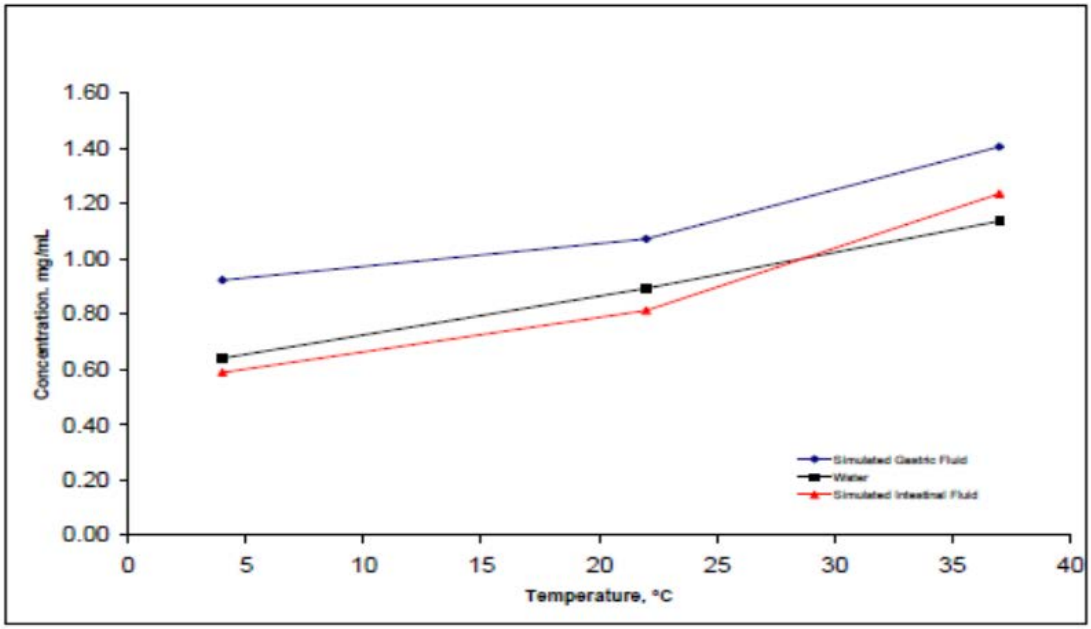
Armodafinil (designated CEP-10953 by the sponsor) has one chiral centre associated with the sulfinyl group, for which the absolute configuration is (R). The drug substance is manufactured by asymmetric oxidation (AO) of the corresponding sulfide amide synthon 2-(diphenylmethyl)thio]acetamide (designated CEP-9419 by Teva).

Three non solvated polymorphic forms are described in the dossier (Forms A, B and C), of which the most stable (Form A) is consistently produced by the manufacturing process. The literature[2] reports 5 polymorphic forms (Forms A, B, C, D and E), as well as dimethyl carbonate, methyl acetate, THF and acetic acid solvates and a hemihydrate.

[1] Prisinzano V, et al. Synthesis and determination of the absolute configuration of the enantiomers of modafinil *Tetrahedron: Asymmetry* 5: 1053-1058 (2004).
[2] Braude V, et al. United States Patent Application 11/709906 (Publication Date 12/20/2007).

The dossier reports the respective solubilities of armodafinil in water at 4°C, 22°C and 37°C to be 0.64 mg/mL, 0.89 mg/mL and 1.14 mg/mL, whilst in simulated gastric fluid these are 0.92 mg/mL, 1.07 mg/mL and 1.41 mg/mL and in simulated intestinal fluid are 0.59 mg/mL, 0.81 mg/mL and 1.24 mg/mL. A plot of the solubility at various temperatures in these 3 aqueous media (Figure 2) is reproduced below.

**Figure 2: Armodafinil saturated solubility in three aqueous media (simulated gastric fluid, water, and simulated intestinal fluid).**




The dossier states that the pKa = 10.4, and that LogP =1.1 in octanol/water [Lit. 1.53; Lit 1.17 (predicted)].

Compelling evidence was provided that the limits applied to the particle size distribution of the drug substance gave tablets with acceptable in vitro behaviour. The absence of a limit for D10 was accepted for this reason.

The content of the (S)-enantiomer (CEP-10952) in the drug substance is controlled by a test for Chirality (limit: ≥ 96% (R)-isomer). Four other potential impurities are controlled in the drug substance: the sulfide amide starting material (CEP-9419), a sulfone (CEP-6239) which can arise from over oxidation during the AO process, the sulfinyl acid (CEP-1641) which can arise by acid or base catalysed hydrolysis in aqueous solution, and the corresponding methyl ester of the sulfinyl acid (CEP-6240) which can be generated by acid or base catalysed hydrolysis in methanolic solution. Of these, CEP-6239 and CEP-1641 are human metabolites and limited in the API specification. CEP-6240 [the (R)-isomer of Impurity C in the European Pharmacopoeia (Ph. Eur.) monograph for modafinil] cannot be formed by the AO synthesis, and although the sponsor was advised to remove the test and limit (≤ 0.50%) from the drug substance specification, to date has neglected to do so. The amended limit applied to CEP-9419 (≤ 0.30%) has been accepted on the advice of the toxicology evaluator.

A number of issues relating to the quality control of the armodafinil drug substance that were raised with Teva remain unresolved at this time.

## Drug product

The proposed tablets are round (50 mg) or oval (150 mg and 250 mg) white to off-white immediate release uncoated tablets, debossed with "  "[3] on one side and "205" (50 mg), "215" (150 mg) and "225" (250 mg) on the other side. The tablets will be marketed in High Density Polyethylene (HDPE) bottles with polypropylene child resistant closures (packs of 30). The 150 mg and 250 mg tablets will also be available in polyvinyl chloride (PVC)/aluminium blisters (physician's packs of 7 tablets).

No overage is employed.

Although a 50 mg armodafinil capsule formulation (reproduced below) was initially developed for Phase I clinical studies, a 50 mg white, round film coated tablet formulation with a slight modification of the ratio of excipients (reproduced below) was subsequently developed for the pivotal clinical studies. These tablets and the placebo tablets were film coated to ensure blinding and to mask any minor lot-to-lot drug substance colour variations.

Two additional commercial presentations were subsequently developed: oval shaped uncoated tablets containing armodafinil 150 mg and 250 mg, with a common master blend used for all 3 tablet strengths. The coating process was not retained for the commercial tablet presentation since there was no further need for blinding, and no inter batch colour variability was observed in the drug substance.

The dissolution profiles of the 50 mg capsule and the 50 mg film coated tablet were similar, and five of the 50 mg film coated tablets were also shown to be bioequivalent to the uncoated 250 mg tablet (commercial formulation).

The dissolution test method conditions [Ph. Eur./United States Pharmacopeia (USP) Apparatus 2 (paddles); 900 mL of 0.1 N HCl at 37°C; 50 rpm] are consistent with those recommended by the US Food and Drug Administration (FDA) Office of Generic Drugs[4] for armodafinil tablets and stipulated in the USP monograph for the racemic analogue (modafinil tablets), and have been shown to be discriminatory. As the quantity of the drug substance reported dissolved after 30 minutes corresponded to the total quantity of drug substance present as determined by the Assay using the chosen method, the company was requested to apply a more discriminatory sampling time (20 minutes), but declined. The proposed acceptance criterion "Q = 80% of Label Claim dissolved after 30 minutes" was accepted on the grounds that it is more stringent than the corresponding acceptance criterion in the USP monograph for modafinil tablets.

The revised expiry limit proposed for the CEP-9419 impurity (≤ 0.3%) in the finished products is tighter than the ICH guideline qualification limit (0.2%),[5] based on a maximum recommended daily dose of 250 mg, but has been accepted based on advice from the toxicology evaluator.

The stability data support a shelf life of 48 months stored below25°C protected from light and moisture for the tablets packaged in the HDPE bottles with polypropylene child resistant closures and the PVC/aluminium blisters proposed for Australia.

An issue raised with the sponsor regarding the organic impurities by High Performance Liquid Chromatography (HPLC) test procedure remains unresolved.

[3] Described as a "Cephalon C"; "Cephalon®" is the US pharmaceutical company that manufactures the finished products in the USA (acquired by TEVA in May 2011).
[4] US FDA Office of Generic Drugs; Dissolution Methods Database.
[5] European Medicines Agency, "ICH Topic Q 3 B (R2) Impurities in New Drug Product, Step 5: Note for guidance on impurities in new drug products (CPMP/ICH/2738/99)", June 2006.

## Biopharmaceutics

Two bioavailability/bioequivalence studies were included in the submission: Studies C10953/1023/BE/US and C10953/1036/BE/US.

Although an absolute bioavailability study was not provided, as stipulated for a new chemical entity by the Australian Regulatory Guidelines for Prescription Medicines (ARGPM),[6] this was accepted on the grounds that the statement in the PI for the racemate ("Modavigil" tablets) that

> *The absolute oral bioavailability could not be determined due to the aqueous insolubility (< 1mg/mL) of modafinil, which precluded intravenous administration*

is inferred to also apply to the individual enantiomers. A justification was subsequently provided for the omission which was accepted by the clinical evaluator.

A relative bioavailability study was also not provided, as stipulated for a new chemical entity by the ARGPM.[7] Although the sponsor's justification was considered to be of limited merit from a regulatory perspective, it was accepted based on advice from the clinical evaluator.

A pivotal food effect study was also not provided, as stipulated for a new chemical entity by the ARGPM,[8] and no justification was provided for the omission. This was accepted based on the inference that the statement in the PI for "Modavigil" tablets is that

> *Food has no effect on the overall bioavailability of modafinil, however, its absorption ($T_{max}$) may be delayed by approximately one hour if taken with food*

would also apply to the individual enantiomers, plus a subsequent explanation from the company for the difference reported between $T_{max}$ of the racemate and (R)-enantiomer.

A justification for not conducting bioequivalence studies using a chiral method of analysis was accepted on the basis of the statement in the PI for "Modavigil" tablets that

> *The enantiomers do not interconvert.*

Details of Studies C10953/1023/BE/US and C10953/1036/BE/US are presented below.

### *Relative bioequivalence study (C10953/1036/BE/US)*

This was a single dose, open label, randomised, 3 way crossover study for which the primary objective was to assess whether a reference 250 mg tablet and each of two test 250 mg tablets of armodafinil manufactured at 2 different facilities in scale up batches were bioequivalent, as measured by $C_{max}$ and $AUC_{0-\infty}$. The secondary objective of the study was to characterise the pharmacokinetic (PK) profile of armodafinil from reference and test tablets over a 72 h period immediately following study drug administration. The test and reference tablets were identical to the formulation intended for marketing in Australia. The results confirmed the bioequivalence of the reference 250 mg tablet to each of the two test tablets.

### *Relative bioequivalence study (C10953/1023/BE/US)*

This was an open label, randomised, single dose, 2 period crossover study for which the primary objective was to assess the bioequivalence of one 250 mg armodafinil tablet and 5 x 50 mg armodafinil tablets following administration of a single dose to healthy adult male and female subjects. The 50 mg tablets were film coated, and contained hypromellose, glycerol triacetate and titanium dioxide and additional lactose as components of the

[6] Therapeutic Goods Administration, "Guidance 15: Biopharmaceutic studies", Version 1.1, April 2015.
[7] Therapeutic Goods Administration, "Guidance 15: Biopharmaceutic studies", Version 1.1, April 2015.
[8] Therapeutic Goods Administration, "Guidance 15: Biopharmaceutic studies", Version 1.1, April 2015.

Opadry II White Y-30-18037 proprietary film coating ingredient (ARPING 3667). These are unlikely to impact on the study outcome.

Of the 30 subjects who entered the study, one withdrew consent on Day 4 of Period 1 due to an unrelated adverse event (AE) requiring hospitalisation, and two withdrew consent on day 6 of period 1 for personal reasons. Results from 27 subjects were available for use in the PK analysis. However, pre-treatment drug levels (> 5% of $C_{max}$) were observed in 2 of the 27 subjects, who were excluded from the statistical analysis. The PK parameters obtained from 25 of 30 subjects were therefore used for bioequivalence assessment, and the company's results for armodafinil, (R)-modafinil acid and modafinil sulfone are reproduced below.

**Table 2: Mean ± SD PK parameters for (R)-modafinil, (R)-modafinil acid and modafinil sulfone in male and female volunteers (n = 27) administered as a single oral dose of Treatment A (5 x 50 mg CEP-10953 tablets) or Treatment B (1 x 250 mg CEP-10953 tablet).**

| | (R)-Modafinil | | (R)-Modafinil Acid | | Modafinil Sulfone | |
|---|---|---|---|---|---|---|
| | Treatment A | Treatment B | Treatment A | Treatment B | Treatment A | Treatment B |
| $C_{max}$ (µg/mL) | 8.53 ± 1.26 | 8.45 ± 1.65 | 0.77 ± 0.20 | 0.75 ± 0.20 | 0.60 ± 0.16 | 0.59 ± 0.19 |
| $t_{max}$ (hr)[a] | 1.5 [0.5-4.0] | 2.0 [1.0-6.0] | 1.5 [0.5-4.0] | 2.0 [1.0-6.0] | 24.0 [10.0-48.0] | 24.0 [13.0-48.0] |
| $t_{1/2}$ (hr)[b] | 12.9 | 12.5 | 12.9 | 12.6 | 30.7 | 31.4 |
| $AUC_{0-t}$ (µg•hr/mL) | 146.1 ± 26.9 | 140.4 ± 25.3 | 10.5 ± 3.4 | 9.9 ± 3.0 | 28.7 ± 8.3 | 28.1 ± 9.6 |
| $AUC_{0-\infty}$ (µg•hr/mL) | 155.0 ± 33.5 | 147.7 ± 28.0 | 15.8 ± 4.1 | 15.4 ± 5.4 | 41.8 ± 9.3 | 42.6 ± 15.0 |
| CL/F (mL/min) | 28.0 ± 5.6 | 29.3 ± 5.8 | NA | NA | NA | NA |
| $V_z$/F (L) | 32.5 ± 6.3 | 32.5 ± 5.7 | NA | NA | NA | NA |

NA: Not Applicable.
[a] Median [range]
[b] Harmonic mean

| | Plasma CEP-10953 | | | |
|---|---|---|---|---|
| Pharmacokinetic parameters | Treatment B (N=25) | Treatment A (N=25) | 90% CI[a] | % Mean Ratio[a] |
| $C_{max}$ (µg/mL) | 8.45±1.72 | 8.54±1.30 | 93.43, 103.9 | 98.5 |
| $AUC_{0-t}$ (µg•hr/mL) | 138.3±24.73 | 141.9±22.73 | 94.27, 99.03 | 96.6 |
| $AUC_{0-\infty}$ (µg•hr/mL) | 144.7±26.31 | 148.6±24.25 | 94.25, 99.02 | 96.6 |
| $t_{max}$ (hr) | 2.3±1.5 | 1.8±1.0 | NA | NA |
| %Extrapolation | 4.4120±1.8797 | 4.4757±1.8234 | NA | NA |
| $t_{1/2}$ (hr) | 12.8±2.84 | 13.0±3.07 | NA | NA |
| $\lambda_z$ (1/hr) | 0.0566±0.0132 | 0.0558±0.0121 | NA | NA |
| CL/F (mL/min) | 29.8±5.71 | 28.8±4.97 | NA | NA |
| $V_z$/F (L) | 32.2±5.67 | 31.8±5.98 | NA | NA |

**Table 3: Nonparametric statistical comparison of plasma CEP-10953 tmax and t1/2: Treatment B (one 250 mg tablet of CEP-10953) versus Treatment A (five 50 mg tablets of CEP-10953).**

| Pharmacokinetic Parameter | Median | | Difference B–A | | |
|---|---|---|---|---|---|
| | Treatment B | Treatment A | Median[a] | 95% CI | p-value |
| $t_{1/2}$ | 12.5 | 12.9 | –0.25 | –0.70, 0.30 | 0.3066 |
| $t_{max}$ | 2.0 | 1.5 | 0.25 | –0.25, 1.00 | 0.3797 |

SOURCE: Summary 15.2.10.
The confidence interval is constructed using Walsh Averages and appropriate quantile of the Wilcoxon Signed Ranks Test statistic.
P-value is from the Wilcoxon Signed Ranks Test.
[a]Median of the Walsh averages (Hodges-Lehmann estimator).
$t_{1/2}$=terminal half-life calculated as $\ln(2)/\lambda_z$; $t_{max}$=time of the maximum drug concentration obtained without interpolation; CI=confidence interval.
Treatment A=single oral dose of five 50-mg CEP-10953 tablets.
Treatment B=single oral dose of one 250-mg CEP-10953 tablet.

| Pharmacokinetic parameters | Plasma R-modafinil acid | |
|---|---|---|
| | Treatment B (N=25) | Treatment A (N=25) |
| $C_{max}$ (µg/mL) | 0.77±0.20 | 0.78±0.20 |
| $t_{max}$ (hr) | 2.2±1.2 | 2.0±0.99 |
| $AUC_{0-t}$ (µg•hr/mL) | 10.1±3.06 | 10.7±3.37 |
| $AUC_{0-\infty}$ (µg•hr/mL) | 15.5±5.42 | 15.6±3.85 |
| %Extrapolation | 34.3091±10.3588 | 32.4909±8.55852 |
| $t_{1/2}$ (hr) | 13.8±5.85 | 13.4±3.26 |
| $\lambda_z$ (1/hr) | 0.0557±0.0146 | 0.0550±0.0139 |

The results confirmed the bioequivalence of the 250 mg armodafinil tablet proposed for Australia to the five x 50 mg film coated armodafinil tablets in terms of $C_{max}$ and $AUC_{0-\infty}$, and in relation to administration of a single dose in the fasted state.

### Quality summary and conclusions

There are no objections in respect of Biopharmaceutics to registration of these products.

However, a number of matters relating to the quality control of the drug substance and the finished products require resolution before approval can be recommended from a Quality perspective.

### Supplementary matters and final conclusion

The company has provided a response to the Quality/Biopharmaceutics evaluation report that has satisfactorily addressed all matters relating to the quality control of the drug substance and the finished products.

There are now no objections in respect of Quality or Biopharmaceutics to registration of these products.

# III. Nonclinical findings

### Introduction

The nonclinical dossier was comprised of bridging studies comparing armodafinil to racemic modafinil, studies of armodafinil alone and additional studies of racemic modafinil. The safety pharmacology, pivotal repeat dose toxicity, genotoxicity, carcinogenicity and reproductive toxicity studies were conducted under Good Laboratory

Practice (GLP) conditions. The major limitation in all in vivo studies were the small exposure ratios achieved.

## Pharmacology

### Primary pharmacology

The pharmacological profile of armodafinil was shown to be similar to that of racemic modafinil. In studies that directly compared armodafinil to racemic modafinil there was no significant difference in the effects on wakefulness or spontaneous locomotor activity in rodents. Doses of ≥30 mg/kg intraperitoneal (IP) armodafinil increased wakefulness in mice and rats. Compared to racemic modafinil, armodafinil had a greater effect on stereotypy in rats pre-treated with a hepatic microsome inhibitor.

In comparison to methamphetamine, armodafinil induced wakefulness was not associated with rebound hypersomnolesence, hyperthermia or with increased intensity of locomotor activity in rats. Hypothermia was observed with high doses of armodafinil (300 mg/kg IP).

Intraperitoneal administration of armodafinil to rats was associated with increased Fos activity in brain regions involved in arousal, sleep, circadian rhythm, motivation, body movement, emotion and memory. In rats, ≥10 mg/kg IP armodafinil decreased immobility time in a forced swim test, suggesting anti-depressant type activity. Reduced immobility was also observed in mice, with no difference between armodafinil, racemic modafinil and S-modafinil. Armodafinil did not affect performance in the elevated plus maze test, suggesting it does not alter anxiety levels in rats. Armodafinil administration decreased food intake immediately after dosing, with total food intake decreased over 3 h in mice that received ≥64 mg/kg IP.

In SN 99-2026-1 it was shown that the metabolites modafinil acid and modafinil sulfone had some weak pharmacological effects on locomotor activity, barbitone induced sleep and reactivity in rodents. No further information was provided on the pharmacological activity of these metabolites. Given the relatively modest effects and lower clinical exposure to metabolites compared to armodafinil, it is unlikely that these metabolites make a major contribution to the pharmacological effects of armodafinil. Therefore, exposures to metabolites were not included in exposure ratios.

### Secondary pharmacodynamics and safety pharmacology

Secondary pharmacology of armodafinil was assessed in in vitro studies on neurotransmitter receptors, transporters and selected enzymes potentially involved in sleep-wake regulation. Armodafinil inhibited the dopamine transporter with an IC50 ~4 μM, which was also observed for racemic modafinil. The $C_{max}$ for armodafinil at the Maximum Recommended Human Dose (MRHD) was 10.5 μg/mL (38 μM). Plasma protein binding of armodafinil in humans was not described, but was 60-65% for racemic modafinil. Therefore, it is possible that armodafinil may inhibit dopamine transport at clinically relevant doses (ratio of IC50 to (presumed) unbound clinical $C_{max}$ is 0.3). No other significant binding or inhibition was observed, including at the histamine, melanocortin, muscarinic, serotonin, orexin-1 and galanin receptors.

In vivo secondary pharmacology studies further investigated the CNS effects of armodafinil. Some evidence was provided to support improved cognitive performance in aged rats, including reduced reaction times at doses ≥30 mg/kg IP. However, increased accuracy was observed only in a narrow dose range (30-60 mg/kg), and not consistently over the two week testing period. Social memory improved in rats treated with ≥3 mg/kg IP armodafinil, with less time spent investigating a familiar compared to a novel rat. In a progressive ratio schedule of lever pressing for food reward, rats treated with ≥32 mg/kg

IP armodafinil had a higher number of lever presses and an increased "break point" suggesting enhanced motivation. At higher doses (≥178 mg/kg IP) armodafinil enhanced pre-pulse inhibition. Lower doses (≥30 mg/kg) increased no-stimulus and or startle amplitude, which may be associated with enhanced wakefulness. Together, these data provide some evidence for armodafinil improving cognitive performance, memory and motivation. However, it was unclear the extent to which enhanced wakefulness contributes to these observations.

Safety pharmacology studies covered the central nervous, cardiovascular and respiratory systems. The studies were conducted according to GLP, and were consistent with ICH guidelines.[9]

Toxicokinetic analysis of the safety pharmacology studies demonstrated a dose proportional increase in $C_{max}$ in dogs, but less than dose proportional increases in $C_{max}$ in rats. The exposures achieved following a single oral dose in rats that received 100–1000 mg/kg were 2.6, 7.0 and 14x, and in dogs that received 7.5-50 mg/kg were 0.6, 1.7 and 3.8× based on $C_{max}$. Based on AUC, relative exposures in rats and dogs were <0.5, ~1 and ~3× (human exposure from clinical study 102, Day 14 of repeat dosing at 250 mg/day). In rats, the increase in $AUC_{0-4h}$ was approximately dose proportional (mean values: 57, 185 and 452 µg·h/mL for 100, 300 and 1000 mg/kg PO armodafinil). Lower levels of the metabolites modafinil sulfone and R-modafinil acid were observed (metabolite AUC <25% of unchanged drug AUC). In dogs, there was a greater than dose-proportional increase in armodafinil $AUC_{0-24h}$ (33, 152, 397 µg·h/mL for 7.5, 20 and 50 mg/kg PO armodafinil). Similar increases were observed for modafinil sulfone (11, 52 and 183 µg·h/mL) but much lower levels of R-modafinil acid were observed (<2% unchanged drug).

Armodafinil induced behavioural changes consistent with CNS stimulation, including increased locomotor activity, increased startle response and stereotyped behaviour at higher doses (100 mg/kg PO). In rats that received the highest dose (1000 mg/kg PO), some signs of CNS suppression were observed in some rats at later timepoints, including decreased alertness, grip strength and body tone.

In isolated Purkinje fibres, armodafinil (50-300 µM) decreased action potential duration at 50 and 90%, indicating minimal risk of QT prolongation. Armodafinil dose-dependently (7.5–50 mg/kg PO) increased heart rate in conscious telemetered dogs by up to 108 bpm, with significant changes in dogs administered ≥20 mg/kg (relative exposure ca 1). Tachycardia was associated with reductions in PR, RR and QT interval, but the corrected QTcF was generally not different to vehicle treated dogs. In contrast, racemic modafinil did not increase heart rate in anaesthetised dogs, but a modest (20 bpm) increase in heart rate was observed in conscious rhesus monkeys (SN 99-2026-1). Respiration rate was not significantly altered by armodafinil (≤1000 mg/kg PO) in rats, but tidal volume increased by up to 60%. This effect may be associated with bronchodilation.

## Pharmacokinetics

**Absorption:** Absorption studies were conducted only in male mice, rats and dogs, and only following single dose oral administration. This deficiency is not overcome by comparison to the data used to support registration of racemic modafinil, as minimal PK data were provided in that submission. In male animals, armodafinil is rapidly absorbed; $T_{max}$ ≤0.5h in rodents and ≤2.5h in dogs, which is comparable to the $T_{max}$ observed in healthy humans (~1-3h). In repeat dose studies in dogs, exposure to armodafinil was greater than dose-proportional on Day 1, and then approximately dose proportional after

[9] European Medicines Agency, "ICH Topic S7A, Safety Pharmacology Studies for Human Pharmaceuticals, Step 5: Note for guidance on safety pharmacology studies for human pharmaceuticals (CPMP/ICH/539/00)", June 2001.

that in the range of 7.5-50 mg/kg/day PO. In rats, exposure was greater than dose proportional in females (60-600 mg/kg/day) and males (≥200 mg/kg/day), but repeated dosing in males led to dose proportional exposures. In human, plasma exposure to armodafinil was dose proportional following repeated dosing over 50-300 mg/day. Plasma half-life was substantially shorter in rats (0.2-1.3h) compared to mice and dogs (1.4-5.2h) and humans (11-20h).

**Distribution:** No studies were submitted for armodafinil. Distribution studies following a single dose of 14C-modafinil (racemate) in rats and dogs found radioactivity in all tissues including CNS. Levels of radioactivity were much higher at 2 compared to 24 h. In mice, the brain: plasma ratio ranged from 0.3-0.7, indicating distribution to the brain. In the evaluation of racemic modafinil, moderate plasma protein binding (~60-65%) was observed in humans, with no plasma binding data for any of the animal species tested in the nonclinical studies.

**Metabolism:** Fourteen metabolites of racemic modafinil were identified in the Modavigil submission, with high levels of M1 (side chain fragment) observed in rat urine (60-65%). Very limited data were provided for the metabolism of armodafinil, with reported data only on plasma levels of R-modafinil acid and modafinil sulfone in rats and dogs.[10]

Deamidation of armodafinil is enzyme catalysed with species-specific enantioselectivity observed. The metabolite profile differs in rats compared to dogs and humans. Plasma deamidation contributes significantly to the metabolite profile in rats, while armodafinil is relatively stable in dog and human plasma. In addition, circulating levels of modafinil sulfone are higher than R-modafinil acid in dogs and humans (sulfone/armodafinil ratios: 0.5 in humans, 0.3-0.4 in dogs; acid/armodafinil ratios: 0.1 in human and <0.1 in dogs based on AUC). In contrast, rats have similar levels of R-modafinil acid and modafinil sulfone (sulfone/armodafinil ratio: 0.01-0.2; acid/armodafinil ratio: 0.1-0.3 based on AUC). Compared to dogs, the half-life of the metabolite modafinil sulfone is >10-times longer in humans (~3h in dogs and 38h in humans).

Racemic modafinil was identified as a CYP2C19 inhibitor. Comparatively, armodafinil is a weak CYP2C19 inhibitor with an inhibitory constant (Ki) of 233 μM and IC50 of 76-90 μM. However, modafinil sulfone was a stronger inhibitor, with an IC50 of 5 μM against recombinant human CYP2C19 and 49 μM in human liver microsomes. The Cmax for modafinil sulfone in humans was 3.8 μg/mL (~13 μM) after two weeks administration at the MRHD (250 mg/day). It is therefore possible that levels of modafinil sulfone at clinically relevant doses may inhibit CYP2C19 and thereby increase exposure to drugs metabolised by CYP2C19. Short term exposure to armodafinil did not increase liver weight in mice, whereas racemic modafinil, S-modafinil, modafinil sulfone and modafinil acid did (4.5 days, 64 mg/kg PO bid). However, chronic administration of armodafinil was associated with increased liver weight in repeat dose toxicity studies. In dogs, increased liver weight was associated with induction of CYP2B6, increased antipyrine metabolism, and inhibition of CYP2D6. In vitro studies indicated CYP2D6 was unlikely to be inhibited in humans. In vitro, modafinil sulfone induced CYP1A2 at ≥30 μM (8.7 μg/mL), whereas armodafinil only modestly induced CYP1A2 in two of three hepatocyte preparations at the highest concentration tested (300 μM). No dose dependent or consistent effect was observed for CYP3A4/5 or CYP2C9. Autoinduction was evident in dogs as armodafinil exposure (measured as AUC) decreased with repeat dosing.

**Excretion:** No data were provided on the excretion of armodafinil. In studies of racemic modafinil, the majority of modafinil and its metabolites were excreted in urine, with humans excreting relatively more unchanged drug (~5%) compared to rats (0.2-0.4%). In

[10] In humans the identified metabolites of racemic modafinil were modafinil acid, modafinil sulfone, modafinil acid sulfone, ring-hydroxylated modafinil acid and two glucuronide conjugates of ring-hydroxylated modafinil.

humans, modafinil acid was the major urinary metabolite (~39%), with modafinil sulfone not detected in urine.

**Conclusion:** Key deficiencies in the PK data include the absence of data on elimination of armodafinil, and the lack of studies in female animals. In addition, data for the metabolism and distribution of armodafinil are incomplete. Based on the relevant EMA guideline,[11] comparative PK data should be provided and therefore reliance on data from the racemate is not sufficient. Compared to humans, armodafinil has a markedly shorter half-life in animals. Of the species examined, dogs are a more suitable model than rats, as the metabolite profile is more similar to humans and the half-life longer.

### PK drug interactions

Armodafinil was a P-glycoprotein substrate, but not inhibitor. Armodafinil, and more potently, its metabolite, modafinil sulfone, inhibited CYP2C19. Induction of CYP3A4/5 was not consistently observed, but is possible. Similarly, there was weak evidence for armodafinil inducing CYP1A2, with stronger induction occurring with modafinil sulfone. CYP2B6 was induced in dogs. Therefore, armodafinil may increase exposure to drugs metabolised by CYP2C19 and decrease exposure to drugs metabolised by CYP1A2, CYP2B6 and CYP3A4/5.

## Toxicology

### Acute toxicity

Single dose oral toxicity studies were conducted in mice and rats. The mouse study had a number of deficiencies including use of only one sex, no necroscopy evaluation or body weight data, limited reporting of study protocol and the absence of raw data for clinical observations. In addition, both studies only used the oral route of administration, but given the high bioavailability and intended oral use in humans this is not considered a deficiency. The maximum non-lethal dose was 845 mg/kg in mice and 700 mg/kg in rats, with erosion of the glandular stomach, kidney defects, hind limb swelling and digit loss observed in rats. In addition, mortality was observed in one of three mice that received 512 mg/kg IP armodafinil in a primary pharmacology study. The exposure ratio at the maximum non-lethal dose in rats was 5 in females and 9 in males based on AUC, indicating a moderate order of acute toxicity by the clinical route.

### Repeat dose toxicity

Repeat dose toxicity studies of daily, oral administration of armodafinil were conducted in mice, rats and dogs. The mouse studies did not comply with the European Medicines Agency (EMA) guideline on repeated dose toxicity[12] as histopathology examinations and toxicokinetic data were incomplete. A deficiency in the rat study was the lack of urinalysis and microscopic analysis of the gallbladder. The design and duration of the 13 week rat and dog studies were consistent with EU guideline 3CC29A Investigation of Chiral Active Substances.[13] In both studies racemic modafinil was administered to a reference control group which enabled comparison of the toxicological profile.

[11] European Medicines Agency, "EU Guideline 3CC29A: Investigation of Chiral Active Substances", October 1993.
[12] European Medicines Agency, "Guideline on repeated dose toxicity (CPMP/SWP/1042/99 Rev 1)", 18 March 2010.
[13] European Medicines Agency, "EU Guideline 3CC29A: Investigation of Chiral Active Substances", October 1993.

### *Relative exposure*

Exposure ratios have been calculated based on animal: human plasma $AUC_{0-\tau}$ (Table 4). The human reference value was taken from the group receiving 250 mg/day armodafinil after 14 days dosing in Clinical Study 102. This was the only study in which toxicokinetic data were obtained using repeated dosing at the MRHD. While it was conducted only in a small number of male subjects, the values obtained were broadly consistent with those derived from similar dosages in larger groups of mixed sex subjects. Due to the marked differences in half-life of armodafinil between species, the relative exposures achieved in animals were generally less than that observed in humans. At the highest exposure in rats and dogs, the relative exposure was approximately equal to that in humans.

**Table 4: Relative exposure to armodafinil in repeat dose toxicity and carcinogenicity studies.**

| Species | Study duration | Dose (mg/kg/day) | $AUC_{0-\tau}$* (µg·h/mL) | | Exposure ratio# | |
|---|---|---|---|---|---|---|
| | | | ♂ | ♀ | ♂ | ♀ |
| **Mouse** (CD-1) | 2 years; values at week 52 (DS-2008-020) [carcinogenicity] | 10 | – | 0.8 | – | <0.1 |
| | | 30 | – | 5 | – | <0.1 |
| | | 100 | – | 67 | – | 0.5 |
| | | 75 | 53 | – | 0.4 | – |
| | | 150 | 109 | – | 0.8 | – |
| | | 300 | 177 | – | 1.3 | – |
| **Rat** (SD) | 4 week (DS-03-027) [day 1 toxicokinetics] | *60* | 7.1 | 28 | 0.1 | 0.2 |
| | | 200 | 29 | 50 | 0.2 | 0.4 |
| | | 600 | 189 | 74 | 1.4 | 0.5 |
| | 13 weeks (DS-02-030) | 60 | 11 | 9 | 0.1 | 0.1 |
| | | 200 | 48 | 67 | 0.4 | 0.5 |
| | | 600 | 127 | 187 | 0.9 | 1.4 |
| **Dog** (beagle) | 13 weeks (DS-02-031) | 7.5 | 14 | 12 | 0.1 | 0.1 |
| | | 20 | 30 | 34 | 0.2 | 0.3 |
| | | 50 | 94 | 98 | 0.7 | 0.7 |
| **Human** (male volunteers) | steady state | 250 mg | 136 | | – | |

*$AUC_{0-t}$ reported in mouse and rat study with plasma armodafinil measured over 24 h in mice and 8h in rats, $AUC_{0-\tau}$ in dog and human studies with a 24 h dosing period. # = animal:human plasma $AUC_{0-\tau}$

Relative exposure to the major metabolites modafinil sulfone and R-modafinil acid are summarised in Table 5. As for armodafinil, the human reference value was taken from the group receiving 250 mg/day armodafinil after 14 days dosing in Clinical Study 102. In dogs and male mice, exposure ratios for modafinil sulfone (≤2.8) were higher than the exposure ratios for R-modafinil acid (≤1.4). In rats and female mice, exposure ratios for modafinil sulfone (≤0.5) were lower than exposure ratios for R-modafinil acid (≤3). Similar to armodafinil, only relatively low exposures to these metabolites was achieved in animal studies. The contribution of armodafinil metabolites to the overall observed pharmacological and/or toxicological activity has not been clearly defined, with weak pharmacological activity observed.

**Table 5: Relative exposure to armodafinil metabolites in repeat dose toxicity and carcinogenicity studies.**

| Species | Study duration | Dose (mg/kg/day) | Modafinil sulfone | | | | R-modafinil acid | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | $AUC_{0-\tau}$* (µg·h/mL) | | Exposure ratio# | | $AUC_{0-\tau}$* (µg·h/mL) | | Exposure ratio# | |
| | | | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ |
| **Mouse** (CD-1) | 2 years (DS-2008-020) [carcinogenicity] | 10 | – | 0 | – | <0.1 | – | 0 | – | <0.1 |
| | | 30 | – | 0.6 | – | <0.1 | – | 0.4 | – | <0.1 |
| | | 100 | – | 10 | – | 0.2 | – | 4.4 | – | 0.4 |
| | | 75 | 17 | – | 0.3 | – | 0.7 | – | <0.1 | – |
| | | 150 | 63 | – | 0.9 | – | 3.6 | – | 0.4 | – |
| | | 300 | 185 | – | 2.8 | – | 9.3 | – | 0.9 | – |
| **Rat** (SD) | 4 week (DS-03-027) [day 1 toxicokinetics] | 60 | 5.9 | 10 | 0.1 | 0.2 | 1.5 | 1.2 | 0.2 | 0.1 |
| | | 200 | 14 | 10 | 0.2 | 0.2 | 4.3 | 7.2 | 0.4 | 0.7 |
| | | 600 | 33 | 11 | 0.5 | 0.2 | 30 | 9.1 | 3.0 | 0.9 |
| | 13 weeks (DS-02-030) | 60 | – | – | – | – | 0.5 | 0.2 | 0.1 | <0.1 |
| | | 200 | 2.8 | 0.8 | <0.1 | <0.1 | 4.1 | 3.4 | 0.4 | 0.3 |
| | | 600 | 26 | – | 0.4 | | 12 | 18 | 1.2 | 1.8 |
| **Dog** (beagle) | 13 weeks (DS-02-031) | 7.5 | 13 | 8.6 | 0.2 | 0.1 | – | – | – | – |
| | | 20 | 24 | 26 | 0.4 | 0.4 | 1.5 | 2.0 | 0.2 | 0.2 |
| | | 50 | 77 | 79 | 1.1 | 1.2 | 5.5 | 6.3 | 0.6 | 0.6 |
| **Human** (male) | steady state | 250 mg | 67 | | – | | 10 | | – | |

*$AUC_{0-t}$ reported in mouse and rat study with plasma armodafinil measured over 24h in mice and 8h in rats, $AUC_{0-\tau}$ in dog and human studies with a 24 hour dosing period. # = animal:human plasma $AUC_{0-\tau}$

### *Major toxicities*

In the pivotal rat and dog studies the toxicological profile and target organs of armodafinil when administered at the high oral dose was similar to racemic modafinil. The major target organs were liver, bone marrow, thymus and kidney, with the urinary bladder also affected in rats.

Dose dependent increases in liver weight associated with hepatocellular hypertrophy were observed in all species. Relative liver weight in high dose armodafinil treated animals was similar to or less than that in racemic modafinil treated animals at similar doses[14]. In mice, hepatic inflammation and necrosis was evident in approximately half of the animals that received the high dose (600 mg/kg/day). Increased liver size was not associated with injury in rats, and was reversed during the recovery period. In dogs there was evidence of cholestasis with treatment at doses of 50 mg/kg/day (relative exposure 0.7). In addition, severe cholestasis was observed following unscheduled sacrifice of a female dog that received 75 mg/kg/day racemic modafinil. Bile stasis was generally of minimal severity, but was associated with serum alkaline phosphatase (ALP) increases of approximately 3x in male and 6x in female dogs treated with 50 mg/kg/day armodafinil for 13 weeks.

[14] In rats, armodafinil has been administered at higher doses (up to 600 mg/kg/day/13 weeks) than modafinil (400 mg/kg/day/4 weeks, 200 mg/kg/day/12 weeks); in dogs, administered maximal dose levels were similar.

However, serum bilirubin remained normal indicating minimal cholestatic liver injury. Instead, the increases in liver size and serum ALP levels are likely indicative of liver enzyme induction, consistent with reduced systemic exposure to armodafinil with repeated dosing and the thyroid hypertrophic response in rats.

Erythroid parameters were decreased in all species, with significant reductions at doses ≥200 mg/kg/day in rats and ≥20 mg/kg/day in dogs. In rats but not dogs, bone marrow hypercellularity and increased extramedullary haematopoiesis were observed after 4 weeks treatment, indicating a regenerative response to red cell loss. Increased reticulocytes (>2x) were observed in a 4 week rat study, also indicating a regenerative response, but this haematology parameter was not reported in the 13 week repeat dose studies. These effects were reversible following cessation of armodafinil administration.

Increased incidence of kidney tubular mineralisation and interstitial lymphohistiocytic infiltrate was observed in rats, and did not fully resolve during recovery. Mineralisation of the kidney tubules was associated with increased serum calcium and inorganic phosphorous. The kidney also showed malformations in embryofoetal development studies in rats, with increased frequency of pelvis dilation in foetuses from dams that received 600 mg/kg/day armodafinil (relative maternal exposure 1.9). In dogs, mineralisation of kidney tubules also occurred, but at a similar incidence in treated and control groups. There were no other treatment related adverse renal effects observed in dogs. Renal abnormalities were also observed with racemic modafinil. Hydronephropathy was observed in male rats that received 60 mg/kg/day racemic modafinil in a 104 week carcinogenicity study. In addition, hydronephrosis was observed in offspring of rats that received 200 mg/kg/day in an embryofoetal development study.

Urinary bladder urothelium hyperplasia and apoptosis was observed in rats, with hyperplasia persisting in females after a 4 week recovery period. Urinary volume was dose-dependently increased in male and female rats following 4 weeks administration of 60-600 mg/kg/day armodafinil (relative exposure ≤1.4). The concentration of urinary electrolytes tended to be decreased, but total urinary potassium and chloride excretion was increased in females that received 600 mg/kg/day. Urinalysis was not performed in rats in the 13 week study, so electrolyte concentrations and the presence or absence of urinary crystals is unknown. In addition, there was an apparent increase in urinary bladder urothelium hyperplasia in male mice that received 300 mg/kg/day armodafinil for 94 weeks (relative exposure 1.3). There were no microscopic abnormalities in urinary bladder in dogs that received armodafinil.

Absolute and relative thymus weight was generally reduced in mice, rats and dogs treated with armodafinil for 4 to 13 weeks, albeit differences were usually not significant. In dogs, reduced weight correlated with thymic involution and lymphocytic depletion. These effects were reversible, with thymus weight tending to be higher following cessation of armodafinil administration.

In summary, the target organs and toxicity profile of armodafinil, characterised by mild anaemia, hepatomegaly, kidney tubule mineralisation and inflammation was similar to that of racemic modafinil. The significance of the urinary bladder changes observed in rodents is unclear, and should be included in the Risk Management Plan (RMP).

### Genotoxicity

The genotoxic potential of armodafinil was assessed in a bacterial reverse mutation assay and in vitro chromosomal aberration assay, both of which were negative. While this does

not meet the ICH guidelines for the standard battery of genotoxicity testing,[15] studies of racemic modafinil were also provided. Racemic modafinil was assessed in the standard battery of tests, as well as an unscheduled DNA synthesis assay in rat hepatocytes and a morphological transformation assay of mouse embryo cells. In general, assays were conducted according to the ICH guidelines, although the maximum concentration exceeded recommendations in the mouse lymphoma assay. Assays were appropriately validated by the use of adequate exposure and positive controls, and all assays gave negative results. Together these data indicate minimal genotoxic potential for armodafinil.

**Carcinogenicity**

Four carcinogenicity studies were submitted, three of which tested the effects of racemic modafinil and one which assessed armodafinil. Two of the racemic modafinil studies were previously submitted as part of the Modavigil application and were not re-evaluated. These studies included a 78 week study in mice and a 104 week study in rats which administered racemic modafinil in the diet. The designs of these studies were inconsistent with EU guideline for carcinogenic potential (3BS7a)[16] and ICH guideline on dose selection (S1C(R2)),[17] as they lacked toxicokinetic monitoring and the high dose groups were not given a maximum tolerated dose. The third study used dermal application of racemic modafinil for 6 months to transgenic mice.[18] In the FDA evaluation report of armodafinil, the validity of this approach was discussed and it was determined that this was no longer considered an appropriate model for assessing the carcinogenicity of an orally administered drug.[19] Therefore, this study was not formally evaluated here.

The carcinogenic potential of armodafinil was assessed in a 104 week study in mice, with study duration reduced to 94-101 weeks due to mortality in female control group. Armodafinil was administered by oral gavage, with dose selection based on a 13 week repeat-dose study. The high dose initially selected for males was reduced following excessive mortality (from 600 to 300 mg/kg/day). In males, the high dose was not associated with reduced body weight or survival, or adverse clinical observations, and led to only minimal reductions in erythrocytes and lymphocytes. In the same study, females received 10, 30 or 100 mg/kg/day armodafinil. Body weight modestly reduced in all dose groups, but survival was increased in the high dose group. No adverse clinical, macroscopic or microscopic observations were made, and no tumours or neoplastic changes were identified in either sex. Toxicokinetics data were collated from samples taken at 1, 3, 5, 8 and 24 h post dose. An earlier study had shown that in mice the Tmax for armodafinil is ~1 h, suggesting the sampling times used may not accurately reflect armodafinil exposure. The estimated exposure ratio was 1.3 for high dose males, and ≤0.8 for other groups. Overall, these data indicate that the high dose used is likely to have been inadequate with respect to ICH guideline S1C(R2) on dose selection for carcinogenicity studies of pharmaceuticals.[20]

No treatment related tumours or neoplastic changes were observed in the studies of orally administered armodafinil or racemic modafinil. While carcinogenicity studies have been

[15] International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, "ICH S2(R1): Guidance on genotoxicity testing and data interpretation for pharmaceuticals intended for human use", 9 November 2011.
[16] European Medicines Agency, "Note for guidance on carcinogenic potential (CPMP/SWP/2877/00)", 25 July 2002.
[17] International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, "ICH S1C(R2): Dose selection for carcinogenicity studies of pharmaceuticals", 11 March 2008.
[18] Conducted to fulfil a Phase IV requirement for modafinil due to inadequacy of the 78 week dietary study (FDA).
[19] Because the carcinogenic assessment of metabolites, or in a full battery of tissues, is inadequate.
[20] International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, "ICH S1C(R2): Dose selection for carcinogenicity studies of pharmaceuticals", 11 March 2008.

conducted in two rodent species, as recommended in ICH guideline S1B,[21] the studies achieved only low relative exposure, and lacked toxic effects in the high dose groups. Because of these deficiencies, the current data are inadequate to fully evaluate the carcinogenic potential of armodafinil.

### Reproductive toxicity

Armodafinil was not studied in the full suite of reproductive toxicity assays recommended by the ICH guidelines.[22] The EU guideline for investigating chiral substances[23] indicates that a bridging pre/postnatal study should be conducted with drug administration starting from conception, including administration of the racemate included as a positive control, which was not done for armodafinil. Regardless, this approach assumes that the reproductive toxicity of the racemate had been adequately defined; which is not the case for racemic modafinil. In the original assessment of racemic modafinil deficiencies were identified in the reproductive toxicity studies as the high dose did not induce maternal toxicity, and estimated exposure (based on body surface area) was similar to expected clinical exposure. These deficiencies have not been fully addressed by the submitted studies.

The submitted studies included three racemic modafinil studies (rat fertility and pre/postnatal development, and rabbit embryofoetal development) and two rat embryofoetal development studies of armodafinil (dose finding and main study). In the armodafinil studies maternal toxicity was observed in the high dose groups and toxicokinetic data were included in the analyses. Based on the ICH guidelines,[24] drug administration occurred at the recommended stages and duration in both the fertility and embryofoetal development studies and group sizes were adequate.

[21] International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, "Testing for carcinogenicity of pharmaceuticals", 16 July 1997.
[22] European Medicines Agency, "ICH Topic S 5 (R2) Detection of toxicity to reproduction for medicinal products & toxicity to male fertility, Step 5: Note for guidance on the detection of toxicity to reproduction for medicinal products including toxicity to male fertility (CPMP/ICH/386/95)", March 1994.
[23] European Medicines Agency, "EU Guideline 3CC29A: Investigation of Chiral Active Substances", October 1993.
[24] European Medicines Agency, "ICH Topic S 5 (R2) Detection of toxicity to reproduction for medicinal products & toxicity to male fertility, Step 5: Note for guidance on the detection of toxicity to reproduction for medicinal products including toxicity to male fertility (CPMP/ICH/386/95)", March 1994.

**Table 5: Relative exposure to armodafinil metabolites in repeat dose toxicity and carcinogenicity studies.**

| Species | Study | Dose (mg/kg per day PO) | Armodafinil / racemic modafinil | | Modafinil sulfone | | R-modafinil acid / modafinil acid | |
|---|---|---|---|---|---|---|---|---|
| | | | AUC0–24h* (µg·h/mL) | ER# | AUC0–24h* (µg·h/mL) | ER# | AUC0–24h* (µg·h/mL) | ER# |
| **Rat** (SD) | Fertility<br>Note: racemic modafinil<br>(DS-99-002) | *100* | *37* | *0.3^* | *4* | *0.1^* | *13* | *NC* |
| | | *240* | *125* | *0.9^* | *21* | *0.3^* | *43* | *NC* |
| | | *480* | *292* | *2.2^* | *178* | *2.7^* | *74* | *NC* |
| | Embryofoetal development – pilot<br>(DS-03-010) | 200 | 26 | **0.2** | – | – | 3 | 0.3 |
| | | 400 | 97 | **0.7** | 0 | 0.0 | 7 | 0.7 |
| | | 800 | 277 | **2.0** | 18 | 0.3 | 25 | 2.5 |
| | Embryofoetal development – main<br>(DS-03-011) | 60 | 7 | **0.05** | – | – | 0.3 | 0.03 |
| | | 200 | 61 | **0.4** | – | – | 6 | 0.6 |
| | | 600 | 265 | **1.9** | 9 | 0.1 | 24 | 2.4 |
| **Rabbit** (NZW) | Embryofoetal development<br>Note: racemic modafinil<br>(DS-01-018) | *45* | *41* | *0.3^* | *9* | *0.1^* | *14* | *NC* |
| | | *90* | *95* | *0.7^* | *17* | *0.3^* | *30* | *NC* |
| | | *180* | *302* | *2.2^* | *56* | *0.8^* | *61* | *NC* |
| **Human** (male volunteers) | steady state | 250 mg per day | 136<br>*135^* | – | 67 | – | 10 | – |

*$AUC_{0-24h}$ calculated by nonclinical evaluator with the assumption that concentrations <LLoQ were 0. # = animal:human plasma $AUC_{0-24h}$. ^$AUC_{0-48h}$ taken from Study DP-95-013 evaluated in modafinil evaluation. Six healthy males were administered 200-800 mg/day racemic modafinil for 7 days. The AUC value is from day 7 of the 400 mg/day group, which corresponds to the maximum recommended human dose of racemic modafinil. NC = not calculated as data for R-modafinil acid were not available (only R/S modafinil acid). - = not detected.

Exposure was similar between pregnant and non-pregnant female rats. Only low relative exposure was achieved in the embryofoetal studies of armodafinil (≤2). Furthermore, this exposure estimate should be treated with caution as the human exposure was calculated in healthy male subjects. Clinical PK data were not available for females alone, with the only chronic exposure data in a mixed sex population being derived from a cohort that included 17% females. In animal studies there was no clear effect of gender on exposure to armodafinil. The exposure ratios for racemic modafinil in the reproductive studies are approximately 2x in the high dose groups.

Placental transfer and excretion into milk of armodafinil were not studied. Studies of racemic modafinil demonstrated placental transfer and excretion into milk of modafinil and/or its metabolites in pregnant and lactating rats. In rats, racemic modafinil did not affect female fertility at doses ≤480 mg/kg/day (relative exposure ~2). Male fertility was also unaffected at doses ≤480 mg/kg, but mortality and adverse clinical signs were present at doses ≥240 mg/kg/day. In both males and females there was a statistically significant increase in time to mating, however this appeared to be due to a shorter than normal time to mate in the control group based on historical data. As the time to mate in the high dose groups was similar to the mean time of historical controls this was not considered an adverse effect.[25]

In rabbits, racemic modafinil dose dependently reduced maternal body weight gain and decreased food intake in the high dose does. Abortions also occurred in the mid (2/19) and high dose (1/19) groups. Apparent reductions in litter size were associated with increased resorptions, and foetal body weight also appeared reduced with high dose racemic modafinil (180 mg/kg/day, relative exposure ~2). Increased foetal variations occurred in the high dose group, which the sponsor attributed to one litter which exhibited high levels of malformations which were suggested to be congenital. However, exclusion of this litter did not remove the trend for increased skeletal malformations such as hemivertebra and fused and split ribs in the high dose group. In rats, maternal weight gain and food intake was also reduced in dams that received the highest dose during the period from implantation to the closure of the hard plate (600 mg/kg/day armodafinil, relative exposure 1.9). Foetal body weight was reduced and early resorptions were increased at this dose. A dose dependent increase in foetal alterations was observed, which was statistically significant in dams that received ≥200 mg/kg/day (relative exposure 0.4). Foetal abnormalities included misplaced umbilical artery, dilation of the kidney pelvis, incomplete sternum ossification and cervical rib on the seventh cervical vertebrae. The sponsor and an independent review (Clark 2014)[26] concluded that the effects at the high dose were secondary to maternal toxicity. However, the foetal body weight was similar to or greater than that of sex matched controls in 45% of pups with renal pelvis dilation or incomplete ossification of the sternum. In addition, the sponsor stated that the effects at 200 mg/kg/day were not treatment related as the individual variations did not show a dose response. Nevertheless, the combined pattern of foetal variations and reduced foetal body weight in rats and rabbits suggest armodafinil and racemic modafinil may be developmental toxicants, which is consistent with the conclusions of the FDA. The NOAEL for embryofoetal toxicity in rats was considered to be 60 mg/kg/day armodafinil (a conclusion consistent with the FDA pharmacology review) which was associated with low relative exposure (0.05).

Pre/postnatal studies were not performed with armodafinil, and those with modafinil were deficient in terms of duration of observations and lack of toxicokinetic data. In the study of racemic modafinil submitted to support registration of Modavigil the NOEL for F1 offspring was 20 mg/kg/day based on increased still births (study dosed pregnant rats from gestational day (GD) 15 to end of lactation with 20, 50 and 100 mg/kg/day racemic modafinil). An independent review of the reproductive toxicity data for modafinil indicated that in this study the methods for determining still birth were inadequate (Clark 2014).[27] However, the Clark review showed that the number of litters with ≥5 post implantation losses showed a dose response, supporting the NOEL (1/23, 2/24, 3/21 and 5/24 in the control, 20, 50 and 100 mg/kg/day groups, respectively). This value was used

[25] The FDA set the NOAEL for fertility at 240 mg/kg/day based on the increased time to mate.
[26] Clark RL (2014) Evaluation of Developmental and Reproductive Toxicity Studies of Modafinil and R-Modafinil.
[27] Clark RL (2014) Evaluation of Developmental and Reproductive Toxicity Studies of Modafinil and R-Modafinil.

in lieu of still births and was calculated by subtracting the number of live pups from the number of implants.

In a separate pre/postnatal study of racemic modafinil, pregnant rats received 50, 100 or 200 mg/kg/day PO from the beginning of organogenesis until the end of lactation. There was no adverse effect of racemic modafinil on pregnancy, parturition or pup development. In this study, the NOAEL for pup toxicity was 200 mg/kg/day. Toxicokinetic data were not provided for either study, but based on the fertility study of racemic modafinil it is estimated that the relative maternal exposure was <1 at the high dose level.

### *Pregnancy classification*

The sponsor has proposed pregnancy Category B3.[28] This is appropriate based on the adverse animal findings in reproductive toxicity studies and is consistent with that for Modavigil. However, the PI indicates reports of adverse pregnancy outcomes in humans, and therefore the pregnancy category should be reviewed by the clinical evaluator.

## Impurities

One impurity was adequately qualified by the nonclinical studies.

## Paediatric use

Armodafinil is not proposed for paediatric use and no specific studies in juvenile animals were submitted.

## Comments on the safety specification of the RMP

The RMP concluded that there are no "important identified risks" or "important potential risks" regarding clinical armodafinil use based on the nonclinical data. This is inaccurate as the nonclinical data identified toxicity in bone marrow, kidney and urinary bladder which may have clinical relevance. These should be discussed in the RMP and included as "important potential risks". The sponsor has objected to this recommendation and provided data from clinical experience, which requires consideration by the RMP and/or clinical evaluators (Non Section 31 Response). Based on the low relative exposures at which the adverse bone marrow, kidney and urinary bladder changes were observed in animal studies, the nonclinical evaluator considers these findings should be listed in the RMP.

The carcinogenic potential has not been adequately assessed it is recommended that carcinogenicity be identified as "missing information". In the "Non Section 31 Response" the sponsor argued that the total of 4 carcinogenicity studies compensates for the deficiencies of these studies. It is acknowledged that the sponsor has made extensive efforts to assess the carcinogenic potential of armodafinil and racemic modafinil. However, the exposures achieved in the studies remain insufficient to conclude that the carcinogenic potential has been adequately assessed. Therefore, the nonclinical evaluator recommends that carcinogenicity be identified as "missing information". The clinical data on carcinogenicity should be considered by the RMP and/or clinical evaluators.

Exposure during pregnancy is currently identified as "missing information". However, the conclusions regarding reproductive toxicity in the RMP do not accurately reflect the nonclinical findings. The RMP states that neither "modafinil or R-modafinil is a reproductive toxin, a selective developmental toxin, a developmental toxicant or a

[28] Pregnancy Category B3: "Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans."

teratogenic agent." These statements were based on an independent expert review, which was considered by the TGA. As discussed above, the nonclinical data indicate that armodafinil is a selective developmental toxicant, which is consistent with the conclusions in the FDA evaluation of armodafinil. The proposed PI information on use in pregnancy also discusses the developmental toxicity observed in the reproductive toxicity tests. Therefore, the "relevance to human usage" in module SII of the RMP should be amended to be an "important potential risk" in order to accurately reflect the nonclinical findings. The clinical data located in the "Non Section 31 Response" should be considered by the RMP and/or clinical evaluators.

## Nonclinical summary and conclusions

### Summary

- The nonclinical dossier contained bridging studies between racemic modafinil and armodafinil, as well as studies of armodafinil or racemic modafinil alone. The critical pharmacology and toxicology studies were conducted according to GLP. However, the systemic exposures achieved in the majority of in vivo studies were similar to or lower than armodafinil clinical exposure at the MRHD, based on plasma AUC.
- The primary pharmacology studies showed similar effects of armodafinil to racemic modafinil and S-modafinil on wakefulness and spontaneous locomotor activity in rodents. Armodafinil increased activity in brain regions involved in arousal, sleep, circadian rhythm, motivation, body movement, emotion and memory.
- Secondary PD studies demonstrated armodafinil and racemic modafinil are inhibitors of dopamine transport (IC50 ~4 µM; 0.3x clinical $C_{max}$ at MRHD). No other agonist or antagonist actions have been identified. Safety pharmacology studies covered the CNS, respiratory and cardiovascular systems. CNS effects were consistent with exaggerated pharmacological effects. Increased heart rate was observed in dogs at exposures 1-4x expected clinical exposures based on Cmax.
- PK studies indicated rapid absorption in mice, rats, dogs and humans. Armodafinil has a long plasma half-life in humans (11-20 h). In contrast, plasma half-life is very rapid in rats (~0.5 h) and also short in mice and dogs (~1-4 h). Plasma AUC was generally dose proportional, but decreased with repeat exposure indicating auto induction of metabolism. Only limited distribution, metabolism and excretion data were provided. The predominant metabolites of racemic modafinil are modafinil sulfone and modafinil acid, with the acid being the major urinary metabolite in humans.
- In acute toxicity studies the maximum non-lethal dose was 845 mg/kg in mice and 700 mg/kg in rats, with armodafinil exposure in rats 9x (female) and 7x (male) anticipated human exposures based on $C_{max}$. Mortality was associated with kidney defects, erosion of glandular stomach, limb swelling and digit loss.
- Bridging, 13 week repeat dose toxicity studies were conducted in rats and dogs to compare the toxicity profile of armodafinil to racemic modafinil. Similar toxicity was observed, which included reduced weight gain in rats and dogs, and a transient decrease in food intake in dogs. Reversible reductions in erythroid parameters and thymus size, and dose dependent increases in liver weight, were observed in both species. In rodents, adverse effects on kidney and urinary bladder occurred, but these observations were generally not replicated in dogs. Thymic involution was observed in dogs at all doses, preventing an NOAEL being identified. In rats, the NOAEL was 60 mg/kg/day excluding effects on urinary bladder, which was associated with a relative exposure ratio of 0.1.

- Armodafinil and racemic modafinil were examined for potential genotoxicity in assays for bacterial mutagenesis, mammalian mutagenesis and in vitro and in vivo clastogenicity, with negative results obtained in all assays. Two year rodent studies revealed no carcinogenic effect in mice and rats, but a major deficiency in the carcinogenicity studies was the low relative exposure achieved (≤1.3x based on AUC).
- An oral fertility study of racemic modafinil in rats found no effects on male or female fertility at doses up to 480 mg/kg/day, but parental toxicity was observed at doses ≥240 mg/kg/day. In rabbits that received oral racemic modafinil during organogenesis there was a trend for increased abortions and number of resorptions, decreased litter size and foetal body weight, and increased skeletal malformations. In rats that received oral armodafinil during organogenesis, foetal body weight was reduced in the high dose group, and there was a trend for increased early resorptions. In addition, the total number of foetal variations was significantly increased in offspring of dams receiving ≥200 mg/kg/day, which included increased visceral and skeletal variations. In rats, the NOAEL was 60 mg/kg/day (relative exposure <0.1). Previous studies of racemic modafinil have shown placental transfer and excretion into milk of modafinil and/or its metabolites in rats.

**Conclusions**

- The studies included met most of the requirements for assessing a single enantiomer of an approved racemate. However, the major deficiency of limited exposure ratios remained for studies of racemic modafinil, and was also a feature of the armodafinil studies.
- The primary pharmacology studies showed increased wakefulness and an equivalence of pharmacological effect between racemic modafinil and armodafinil, supporting the proposed indications.
- The mechanism of action of armodafinil and racemic modafinil remains unclear. Marked increases in heart rate were observed in dogs in a safety pharmacology study, but this observation was not replicated at the same doses in the repeat-dose toxicity study.
- The pharmacokinetic studies demonstrated a much shorter plasma half-life in rodents and dogs compared to humans which likely underlies the relatively low exposure ratios. A deficiency in the pharmacokinetic studies is the lack of metabolism data for armodafinil and the racemate.
- The bridging repeat dose toxicity studies demonstrated that the toxicity profile of armodafinil was very similar to that of racemic modafinil.
- Armodafinil has no demonstrated genotoxic potential. Due to deficiencies in exposure to armodafinil or racemic modafinil in the carcinogenicity studies, the carcinogenic potential of armodafinil has not been fully evaluated. The history of safe use of racemic modafinil suggests a limited carcinogenic liability for armodafinil.
- The proposed pregnancy category (B3) is consistent with the findings in the embryofoetal development studies in rats and rabbits, and with the category for modafinil (Modavigil). However, this categorisation requires consideration by the clinical evaluator, based on reported adverse pregnancy outcomes in humans.
- The deficiencies identified in the carcinogenicity studies and lack of metabolism data are offset by the bridging studies which demonstrate comparable effects of armodafinil and racemic modafinil, coupled with the history of safe use of the racemate in humans. Therefore, there are no nonclinical objections to registration of armodafinil.

# IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

## Introduction

### Clinical rationale

In the letter of application, the sponsor stated that the R- and S-enantiomers of modafinil appear to be identical with respect to the mechanism or action, with armodafinil having the longer half-life of the 2 enantiomers. Therefore, armodafinil was developed on the basis that a new formulation consisting solely of the R-enantiomer, although not significantly different from the racemic mixture with respect to safety or efficacy, would provide an improved plasma concentration profile and thus greater clinical benefit to patients.

In the clinical overview, the sponsor stated that PK studies demonstrated that systemic exposure to armodafinil following multiple daily doses of 150 mg or 250 mg was comparable to systemic exposure to modafinil following multiple daily doses of 200 mg or 400 mg. The sponsor goes on to state that, despite similar overall systemic exposure, armodafinil and racemic modafinil have distinct plasma concentration-time profiles due to different rates of clearance of the R- and S- enantiomers. Compared to modafinil, armodafinil exhibits a lower peak plasma concentration ($C_{max}$), which is offset by a higher plasma concentration at subsequent time points. Therefore, based on the PK of the two drugs the sponsor theorised that, compared to modafinil, armodafinil may have a better tolerability due to its lower $C_{max}$ and a more sustained effect due to its higher plasma concentrations subsequent to the $C_{max}$. In addition, the sponsor speculates that lower peak concentrations of armodafinil compared to modafinil might reduce the potential for drug-drug interactions. In view of the PK findings, the sponsor conducted a clinical program to assess the efficacy and safety of armodafinil for the treatment of patients with excessive sleepiness associated with OSAHS, SWSD, or narcolepsy.

> *Comment: The sponsor's rational for the armodafinil clinical development program is acceptable.*

### Contents of the clinical dossier

The submission contained the following clinical information:

- 11 Phase I clinical pharmacology studies, including pharmacokinetic data with or without pharmacodynamic data (9 in healthy subjects, 1 in patients with schizophrenia, and 1 in patients with OSAHS).
- 1 population pharmacokinetic report, 1 pharmacokinetic/pharmacodynamic modelling and simulation report.
- 4 pivotal Phase III, double blind, placebo controlled studies (2 in patients with OSAHS, 1 in patients with narcolepsy, 1 in patients with SWSD).
- 2 Phase III, open label studies each including patients with narcolepsy, OSAHS or SWSD.
- 2 Phase IIIb studies (1 double blind, placebo controlled study in patients with SWSD, 1 open label study in patients with OSAHS or narcolepsy).
- 4 in vitro bioanalytical reports; 2 human biomaterial reports.

- Literature references.

### Paediatric data

The sponsor has not applied to the EMA for a waiver relating to the submission of paediatric studies for the treatment of OSAHS, narcolepsy or SWSD.

The FDA has granted a waiver for paediatric studies in patients from birth to 17 years of age in OSAHS "on the basis that studies are highly impractical because the number of patients is so small or non-existent", and in SWSD "on the basis that very few, if any, paediatric patients experience excessive sleepiness associated with" this condition. The FDA granted a partial waiver for the paediatric study requirement for patients aged less than 6 years with narcolepsy "on the basis that studies are highly impractical because the number of patients is so small or non-existent". However, the FDA deferred the paediatric study requirement for patients aged 6 to 17 years with narcolepsy until November 2017 "on the basis that the other pediatric groups are subject to a waiver request".

### Good clinical practice

The sponsor states that the clinical studies were undertaken in compliance with the principles of Good Clinical Practice (GCP).

## Pharmacokinetics

### Studies providing pharmacokinetic data

#### *Clinical pharmacology studies providing PK (± PD) data for armodafinil*

The submission included 11 Phase I clinical pharmacology studies evaluating the PK of armodafinil in 383 healthy subjects, 38 patients with schizophrenia, and 42 patients with OSAHS. The studies are outlined below in Table 6.

**Table 6: Phase I clinical pharmacology studies containing PK and PD data for armodafinil.**

| Study | Objective | Design | Armodafinil Dose | N* |
|---|---|---|---|---|
| **Healthy subjects** | | | | |
| 1023 | Bioequivalence | Open-label, 2-way cross-over | SD x 250 mg | 25 |
| 1036 | Bioequivalence | Open-label, 3-way cross-over | SD x 250 mg | 28 |
| 101 | PK: Food effect | Double-blind, placebo-controlled | SD x 50-400 mg | 40 |
| 102 | PK: Multiple dose | Double-blind, placebo-controlled | MD x 14 days x 50-400 mg | 49 |
| 103 | PK, PD sleep deprivation | Double-blind, placebo- and active-controlled | SD x 100-300 mg | 107 |
| 1021 | DDI with CYP2C19 probe | Open-label, 2-way cross-over, omeprazole | SD x 400 mg | 24 |
| 1022 | DDI with CYP3A4 probe | Open-label, midazolam (iv and po) | MD x 31 days x 250 mg | 17 |
| 1025 | DDI with CYP1A2 probe | Open-label, caffeine | MD x 29 days x 250 mg | 24 |
| 1051 | PK: Effect of age | Open-label | MD x 10 days x 50-150 mg | 50 |
| **Schizophrenia** | | | | |
| 1056 | DDI with quetiapine | Open-label, quetiapine (CYP3A4 substrate) | MD x 39 days 100-250 mg | 25 |
| **OSAHS** | | | | |
| 1064 | PK: Comparative | Open-label, randomized, cross-over armodafinil versus modafinil | MD x 32-38 days x 200 mg | 38 |

N* = number of subjects in the PK analysis sets; SD = single dose; MD = multiple dose

### *Population pharmacokinetic (PPK) modelling and simulation studies*

The submission included population pharmacokinetic (PPK) and pharmacokinetic/pharmacodynamic (PK/PD) modelling and simulation analyses (report CP-05-001). The analyses were undertaken in order to assist in the design and dosage regimen selection for the armodafinil Phase III studies. The PPK and PK/PD analyses included data from modafinil (Provigil) and armodafinil studies. These analyses have been reviewed and the results discussed.

### *Pivotal Phase III armodafinil sleep disorder studies with PK data.*

Trough armodafinil plasma concentrations were determined from baseline through week 12 in the pivotal Phase III studies in patients with OSAHS and narcolepsy (Studies 3020, 3021, 3025).

### *Studies providing PK data for racemic modafinil*

The submission included summary data from three, Phase I studies investigating the PK of modafinil following single and multiple dose administration to healthy volunteers (C1538a/103/PK/US, C1538a/106/MD/US, and CEP-2101). The submission included comparative analyses of the PK of modafinil and armodafinil, and these analyses have been reviewed and the results discussed. Summaries of the three modafinil studies were provided by the sponsor in the Summary of Clinical Pharmacology (SCP), but complete

study reports were not included. Summaries of the three modafinil studies are provided. The three modafinil PK studies appear to have been previously evaluated by the TGA.

### *Analytical methods for calculation of pharmacokinetic parameters*

PK parameters from the individual studies were calculated using standard non-compartmental methods. PPK and PK/PD analyses were performed using standard statistical methods and computer software (that is, Nonlinear Mixed Effect Modeling (NONMEM) Version 5 Level 1.1 and SPlus 6.1 Professional Release 1).

### *Plasma concentration analytical methods*

The data included six in vitro reports validating the analytical methods used to measure plasma concentrations of the analytes investigated in the PK studies (that is, armodafinil, modafinil, R-modafinil acid, modafinil sulfone and quetiapine.). In the **armodafinil studies**, plasma samples were analyzed for R-modafinil and its two major circulating metabolites (R-modafinil acid and modafinil sulfone) using validated HPLC with ultraviolet (UV) detection methods (Reports DP-04-032, DP-2009-022, DP-2009-023). In each of the reports, the quantifiable range of the three analytes was stated to be 0.200 µg/mL through 50.0 µg/mL. In DP-04-006, DP-2009-023, modafinil, modafinil acid and modafinil sulfone plasma concentrations were also measured using a validated HPLC-UV method, with a quantifiable range for the analytes reported to be 0.200 µg/mL through 50 µg/mL. In the **modafinil studies**, plasma samples were analysed for R-modafinil and S-modafinil using an enantioselective HPLC-UV method, with the quantifiable range for the enantiomers reported be from 0.100 µg/mL to 15.0 µg/mL (report DP-95-003). In the **DDI studies**, quetiapine was measured in human plasma using a validated HPLC tandem mass spectrometric method with the quantifiable range reported to be 0.500 ng/mL to 1000 ng/mL (DP-2009-47, DP-2009-022).

### Evaluator's conclusions on PK

- The PK of armodafinil have been reasonable well characterized in healthy subjects following single and multiple dose administration. In addition, the PK data for armodafinil in patients with the conditions of interest are consistent with the PK data for healthy volunteers.
- There were deficiencies in the submitted PK data including: (a) no absolute bioavailability study; (b) no comparative bioequivalence study for the three proposed armodafinil tablet strengths 50, 150 and 250 mg; and (c) no mass balance study investigating elimination and metabolic pathways for armodafinil.
- In addition, there were no clinical DDI studies investigating the following interactions of potential clinical significance: (a) co-administration of armodafinil with Pgp inducers and inhibitors, armodafinil is reported to be a Pgp substrate in vitro; (b) co-administration of armodafinil with a CYP2B6 probe substrate, armodafinil is reported to induce CYP2B6 activity in vitro; (c) co-administration of armodafinil with a CYP2C9 probe substrate, armodafinil is reported to inhibit CYP2C9 in vitro; and (d) co-administration of armodafinil with CYP3A4 inducers and inhibitors, given that the formation of modafinil sulfone from R-modafinil is reported to be metabolized by CYP3A4/5.
- The submission included comparisons between the PK of armodafinil and modafinil in both healthy subjects and patients. The mean plasma concentration versus time profiles for R-armodafinil in healthy subjects were virtually superimposable following single dose armodafinil (50 mg) and modafinil (100 mg) in a dose normalised to 50 mg analysis. The sponsor states that this finding justifies the use of R-modafinil PK data from the modafinil (Provigil) studies to support the PK data for armodafinil provided in the submission. This is considered to be a reasonable inference.

- In a multiple dose analysis of PK data from healthy subjects (studies 102 and PROVIGIL-2101), systemic exposures to R-modafinil and modafinil were compared, based on $C_{max}$ and AUC values. The analyses included comparisons between armodafinil 150 mg/day versus modafinil 200 mg/day and armodafinil 250 mg versus modafinil 400 mg/day. The comparisons showed that $C_{max}$ values were lower for armodafinil compared to modafinil, while AUC values for the two analytes were similar. However, the plasma concentration versus time profiles for armodafinil and modafinil were significantly different. The decline from peak concentration of armodafinil was monoexponential, with a longer terminal half-life relative to a biexponential decline from peak concentration following administration of modafinil, with a shorter terminal half-life. The sponsor comments that the biexponential decline following administration of modafinil is the result of the differential rate of clearance of the R- and S- enantiomers (that is, clearance rate 3 fold higher for the S-compared to the R-enantiomer).
- Consistent with the data from the individual studies, the PPK analysis (CP-05-001) also indicated that the plasma concentration versus time profile for armodafinil notably differs from that for modafinil. The sponsor commented that the difference between the two drugs was expected to result in a more sustained effect (higher concentration later in the profile) and better tolerability (lower $C_{max}$) for armodafinil compared to modafinil. The difference between the two plasma concentration versus time profiles mean that equivalent exposures to armodafinil and modafinil cannot be achieved through dose adjustment. For example, if doses were selected to achieve comparable $C_{max}$ values then the plasma concentrations of armodafinil would be higher than modafinil at later time points, while if doses were selected to achieve comparable plasma concentrations at later time points then the $C_{max}$ value for armodafinil would be lower than for modafinil.
- The PK data showed that the median $T_{max}$ of armodafinil was approximately 2 h following administration in the fasted state (Study 101). In an in vitro study using MDR-MDCK cell monolayers, it was reported that armodafinil is a P-glycoprotein (Pgp) substrate but is not an inhibitor of Pgp (Study DP-2006-055).
- The sponsor states that the absolute bioavailability of armodafinil was not determined due to aqueous insolubility of armodafinil, which precluded IV administration. However, and IV preparation was used in the nonclinical intact animal studies.
- The effect of food on the bioavailability of armodafinil was studied following a single 100 mg dose (2 x 50 mg tablets) in the fasted and fed state in 6 healthy young males (Study 101). The mean $C_{max}$ and $AUC_{(0\text{-}inf)}$ for R-modafinil were ~ 11% lower and ~ 8% higher, respectively, in the fed compared to the fasted state. Apart from the median $T_{max}$, which was approximately 4 h longer in the fed compared to the fasted state (6.0 versus 2.3 h, respectively), other PK secondary parameters (that is, CL/F, VF, and t1/2) were similar in the fed and fasted states. The results suggest that the onset of action following administration might be longer when administered with food compared to fasting administration. This might be of clinical relevance where a rapid onset of action is required. There were no steady state data on the effect of food on the bioavailability of armodafinil, but based on similar single dose and steady state PK of the drug it can be predicted that the effect will be similar to that following single dose.
- In fasted healthy subjects, the single dose armodafinil 250 mg tablet proposed for registration was demonstrated to be bioequivalent to single dose armodafinil 5 x 50 mg tablets used in the clinical Phase III studies (Study 1023). Three armodafinil 250 mg tablets proposed for approval manufactured at different facilities in scale-up batches were found to be bioequivalent following single dose administration to healthy subjects (Study 1036). There was no comparative bioequivalence study comparing the three strengths of the armodafinil tablets being proposed for

registration (50, 150, 250 mg). However, based on Cmax and AUC values the PK of armodafinil were essentially linear over the dose range 50 mg to 400 mg following single dose and multiple dose over 7 and 14 days, and the apparent clearance was relatively constant over the dose range tested (Study 102).

- The mean apparent volume of distribution (V/F) of armodafinil following a single dose (dose normalised to 50 mg) was 42.4 L, based on pooled data from healthy subjects (n = 93) from Studies 1023, 101, and 102. Following multiple dosing of armodafinil (dose normalised to 50 mg), the mean V/F was 47.4 L on Day 14 in 30 healthy subjects (Study 102). The V/F indicates that armodafinil is well distributed. There were no data for armodafinil relating to protein binding, erythrocyte distribution, or tissue distribution in humans.
- The metabolic pathways for R-modafinil have not been specifically characterized in studies in humans. The sponsor states that a clinical mass balance and metabolism study of racemic modafinil suggests that the drug is nearly exclusively metabolized in the liver with less than 10% of the parent compound being excreted in the urine. The sponsor reports that interconversion of the R- and S-enantiomers of racemic modafinil has not been observed in vitro or in vivo.
- Two circulating metabolites of armodafinil were identified in the PK studies (R-modafinil acid and [achiral] modafinil sulfone). R-modafinil acid represents approximately 11% and 7% of parent drug exposure (based on AUC values), following single and multiple dose administration of armodafinil, respectively. These data indicate that there is relatively little accumulation of R-modafinil acid following multiple-dose treatment with armodafinil. Modafinil sulfone represents approximately 33% and 56% of parent drug exposure (based on AUC values), following single- and multiple dose administration of armodafinil, respectively. The data indicate that modafinil sulfone accumulates following multiple dose armodafinil. The sponsor reports that armodafinil is metabolised to modafinil sulfone via CYP3A4/5, indicating that this enzyme is responsible, at least in part, for the metabolism of armodafinil.
- After reaching peak plasma concentration following oral administration, the elimination of armodafinil appears to be monoexponential with a relatively long apparent half-life of approximately 15 h. The apparent mean terminal half-lives of R-modafinil acid and modafinil sulfone are approximately 15 and 38 h, respectively, following single dose administration of armodafinil (dose normalised to 50 mg) from pooled data (Studies 1023, 101, and 102). The mean apparent clearance (CL/F) of armodafinil following a single dose (dose normalised to 50 mg) was 38.6 mL/min, based on pooled data from healthy subjects (n = 93) from studies 1023, 101, and 102. Following multiple dose administration of armodafinil (dose normalised to 50 mg) in study 102, the mean CL/F was 32.4 ± 8.72 mL/min on Day 7 (n = 34) and 32.7 mL/min on Day 14 (n=30).
- The PK of armodafinil following single and multiple dose administration are similar, suggesting that the PK of the drug are time independent. In the multiple dose study (102), steady state appeared to have been reached after 7 days of administration, which is consistent with a half-life of approximately 15 h. The steady state accumulation ratio (Rss) for armodafinil (dose normalised to 50 mg) was 1.2 on both Days 7 and 14.
- In patients with OSAHS being treated with nCPAP (Study 1064), a multiple dose, 2 way crossover comparison between armodafinil 200 mg/day and modafinil 200 mg/day showed that the geometric $C_{max}$ and $AUC_{(0-\tau)}$ values for R-armodafinil were 37% and 69% higher relative to modafinil, while median $T_{max}$ values were similar for the two products (that is, 2 h). The plasma concentration versus time profile of R-armodafinil was higher at all time points than that for modafinil, with the difference between the

profiles being greater in the later part of the 24 h dosing interval than in the earlier part. The mean steady state accumulation ratio approximated unity for both R-armodafinil and modafinil, indicating time independent PK for both drugs.

- In a study investigating the effect of age on the PK of armodafinil in healthy volunteers (Study 1051), exposure to R-armodafinil following multiple dose armodafinil (150 mg/day) increased with age, particularly in subjects aged ≥ 75 years. Based on these data, dosage adjustment in patients aged ≥ 65 years should be considered, particularly in patients aged ≥ 75 years. In the PPK analysis (CP-05-001), no effect of age on clearance, volume of distribution, or absorption constant was observed. However, the effect of age in the PPK analyses may not have been fully characterised due to the limited number of patients aged ≥ 65 years in the analyses. The majority of patients in the PPK analysis were between 18 and 40 years of age.
- There were no specific studies on the effect of gender, weight, or race on the PK of armodafinil. However, in the PPK analysis (CP-05-001) no effect of gender on R-armodafinil on clearance, volume of distribution, or absorption rate was observed, and no effect of body weight on R-armodafinil clearance or absorption rate constant was observed, but the volume of distribution increased linearly with weight.
- In vitro data are reported to show that armodafinil has weak, but concentration-related inductive effects on CYP1A2, CYP2B6, and CYP3A4/5 activities. Clinical DDI studies have been undertaken investigating the effect of co-administration of armodafinil on CYP3A4 and CYP1A2 probe substrates, but not on CYP2B6 probe substrates.
- In vitro data are reported to show that armodafinil has a strong concentration related inhibitory effect on CYP2C9 activity and is an inhibitor of CYP2C19 activity. A clinical DDI study has been undertaken investigating the effects of co-administration of armodafinil on a CYP2C19 probe substrate, but not on a CYP2C9 probe substrate.
- The sponsor reports that, in vitro, armodafinil is a weak, concentration dependent inducer of CYP3A4 activity. In two DDI interaction studies with CYP3A4 substrates, multiple dose armodafinil (200 mg QD) reduced exposure to single IV and oral dose midazolam in healthy subjects and to steady state quetiapine in patients with schizophrenia. The results suggest that armodafinil is at least a moderate inducer of CYP3A4 activity and should be administered cautiously in patients being treated with drugs known to be CYP3A4 substrates. Upwards dose adjustment of CYP3A4 substrates co-administered with armodafinil might be required.
- The sponsor reports that, in vitro, armodafinil is a weak, concentration dependent inducer of CYP1A2 activity. However, in a clinical study in healthy subjects armodafinil administered at 250 mg QD for 4 weeks had no significant effect on exposure to caffeine (a CYP1A2 substrate) administered as a single 200 mg dose on Days 1 and 31 (Study 1025). The sponsor reports than, in vitro, armodafinil is an inhibitor of CYP2C19 activity. This was confirmed in Study 1021, which showed that single-dose armodafinil 400 mg significantly increased exposure to single dose omeprazole 40 mg (a CYP2C19 substrate) in healthy subjects who were extensive CYP2C19 metabolisers. Consequently, co-administration of armodafinil and drugs known to be metabolised by CYP2C19 should be undertaken cautiously, and downwards dose adjustment of CYP2C19 substrates might be required.

## Pharmacodynamics

### Studies providing pharmacodynamic data

#### *Study 103 - Healthy young men undergoing acute sleep deprivation*

*Objectives and design*

The primary objective this Phase I, double blind, randomised, active controlled (Provigil 200 mg) and placebo controlled study was to evaluate the pharmacodynamic (PD) profile over time of single doses of armodafinil (100, 150, 200, or 300 mg) in healthy young men undergoing acute sleep deprivation. The Provigil 200 mg (modafinil) group was included to assess study design sensitivity. The PD profile was measured using the Maintenance of Wakefulness Test (MWT). The study planned to enrol 108 subjects aged between 18 and 40 years, who were randomly assigned to 1 of 6 treatment groups (18 subjects/group), with randomisation assigned separately for each centre (1 in France and 1 in the UK).

*Methods*

Subjects were admitted to the study centre on Day -1 and slept from 2300 h on Day -1 until 0700 h on Day 1. On Day 1, subjects began Karolinska Sleepiness Scale (KSS) testing at 1 h intervals, and testing for attention and working memory using the Cognitive Drug Research (CDR) system and Psychomotor Vigilance Task (PVT) at 2 h intervals. After randomisation to one of the six treatment groups, a single dose of study drug was administered at 1925 h, immediately followed by a standardised dinner. Blood samples were collected before study drug administration, 30 minutes after administration, and then at 1 h intervals for up to 14 h. During the night of Day 1 (sleep deprivation period), KSS, CDR system, and PVT testing continued, and the MWT was conducted at 2 h intervals, starting at 2200 h.

On Day 2, MWT, KSS, CDR system testing, PVT testing and blood collection for PK continued at specified intervals until 1100 h. Subjects then underwent a sleep period that started at 1100 h, with polysomnography (PSG) until 1900 h. Subjects were awakened at 1900 h and underwent final assessments and end-of-study procedures between 2055 and 2130 h, after which they were discharged from the clinic. Follow-up telephone contact occurred 7 days after discharge from the clinic. The total duration of subject participation in the study was approximately 3 weeks.

Blood samples for drug plasma concentrations and PK profiling were collected prior to administration at 1925 h and after administration at times of 1955, 2025, 2125, 2225, and 2325 h on Day 1, and at times of 0025, 0125, 0225, 0325, 0425, 0525, 0625, 0725, 0825, and 0925 h on Day 2.

The armodafinil treatments were provided using 50 mg capsules, Provigil treatment was provided using 100 mg tablets, and placebo treatment was provided using matching armodafinil capsules or matching Provigil tablets. In order to maintain the double blind, each subject received 6 capsules and 2 tablets with the content depending on the randomised treatment group.

*Primary assessment of the PD profile and statistical methods*

For the primary assessment of the PD profile over time the MWT was performed every 2 h between 2200 and 0800 h of the second night in the clinic (evening of Day 1 to morning of Day 2, during a sleep deprivation period). The MWT is an objective assessment of sleepiness that measures the ability of a subject to remain awake. Subjects were instructed to try to remain awake in a darkened room while in a semi reclined position. Long sleep latencies are indicative of ability to remain awake. MWT sleep latency (minutes) (that is, time to 3 epochs of stage 1 sleep or 1 epoch of stages 2, 3, 4 or REM sleep) and latency to 10 seconds of sleep were analysed at 2 hour intervals from 2200 h on Day 1 to 0800 h on

Day 2. Each MWT session ended at 20 minutes if no sleep occurred and was counted as sleep latency of 20 minutes.

The MWT (and all other PD variables) were analysed at each time point. The null hypothesis was that the mean results for all treatments at all time points were equal. The alternate hypothesis was that at least two of the treatment means were not equal. The null hypothesis was to be rejected if $\alpha = 0.05$, pairwise treatment comparisons were also performed (Fisher's protective test). The testing was done using an ANOVA with treatment and centres as factors. In addition, tests for linear trends and nonlinear trends (quadratic trend test) using the placebo and armodafinil dose groups were performed. No adjustment for multiple comparisons was deemed necessary by the sponsor, as this was a Phase I PK/PD study in healthy normal subjects who were sleep deprived. Sample size was not based on statistical considerations. It was expected that a total sample size of 108 subjects with 18 subjects in each treatment group would provide sufficient information to test the null hypothesis.

*Results for PD endpoints*

Statistically significant results favouring single dose Provigil 200 mg compared to placebo were observed at most time points for MWT, PVT and CDR system testing. These results indicate that the test was sensitive enough to detect a PD effect of armodafinil over the dose range tested (100, 150, 200, 300 mg). The observed results for single dose armodafinil were similar to those observed for Provigil 200 mg. For MWT, PVT and CDR system testing, statistically significant differences favouring armodafinil (all doses) compared to placebo were observed at most time points over the testing period. All doses of armodafinil were observed to promote wakefulness (increased MWT) from 2000 to 0800 h. However, the two higher doses of armodafinil (200 mg and 300 mg), appeared to improve wakefulness (increased MWT) in the early morning (0600 and 0800 h) to a greater extent than Provigil 200 mg. The results for the primary PD endpoint of MWT, sleep latency and latency to 10 seconds of sleep, are summarised.

*Results for the pharmacokinetic/pharmacodynamic (PK/PD) relationship*

The study included PK/PD analyses. To evaluate the relationship between drug concentration and PD effect, plots of the mean values for the relevant PD measures for MWT, PVT, and CDR system tests overlaid with the mean plasma drug concentrations over time were generated for each treatment group. Statistically significant correlations between plasma concentration and PD outcome were observed for the Provigil 200 mg group for all PD variables tested. However, no statistically significant correlations were observed between plasma concentrations and PD outcomes for all PD variables tested for any of the armodafinil groups. The results for the correlation between the PD variables and the corresponding plasma drug concentration by treatment group are summarised.

***PK/PD modelling and simulations - Report Cephalon CP-05-001***

- The submission included PK/PD modelling and simulation data undertaken to select the armodafinil doses for the Phase III program in patients with the sleep disorders of interest. The main objectives of the analysis were to select armodafinil doses that would produce similar or superior responses compared to Provigil doses known to be efficacious, without increasing the potential for sleep disturbance. Modelling was carried out using the computer program NONMEM, Version 5 level 1.1. Figures were generated using Splus 6.1. Simulations were performed with Splus and TS2. Data preparation was performed in Splus or SAS. The analytical methodology underlying the PK/PD modelling and simulations was extensively described in the study report.
- The PD variables tested were MWT (MSLT [Multiple Sleep Latency Test] in SWSD) and two markers for sleep disturbance (PSG wake after sleep onset [WASO] and PSG sleep efficiency [SE]). Repeated MWT data were taken from the results at 2 h intervals from

2200 to 0800 h. MWT was censored at 20 minutes (that is, the duration of the MWT test). Plasma concentrations were simulated using PPK models in subject populations of interest.

- A multicomponent PK/PD model combining the effect of time of day and the effect of plasma concentration on MWT was developed for healthy subjects with acute sleep deprivation. The model produced nearly identical EC50 estimates for R- and S-modafinil (~ 0.6 µg/mL), supporting the hypothesis that the 2 enantiomers are equipotent. PK/PD simulation predicted that a 150 mg armodafinil dose should achieve comparable MWT to a 200 mg (near maximal effect) dose of Provigil at early times in the concentration-time profile with a potentially superior MWT at later times without causing sleep disturbance. WASO and SE (markers for sleep disturbance) were adequately described by simple regression models and changed as a function of the baseline value and drug concentration.
- Similar multiple component models were developed for patients and these models adequately described MWT in patients with OSAHS or narcolepsy treated with Provigil 200 mg and 400 mg, and MSLT in the patients with SWSD treated with Provigil 200 mg. PK/PD simulation predicted that a dosage of 150 mg/day of armodafinil was the lowest dosage that would achieve MWT/MSLT sleep latency values comparable to a dosage of 200 mg/day of modafinil early in the concentration-time profile, and potentially superior MWT/MSLT sleep latency values at later times in the concentration-time profile (representing a longer sustained effect), without an increased risk for sleep disturbance. In contrast to healthy subjects with acute sleep deprivation, no treatment effect on WASO or SE (markers for potential sleep disturbance) was detected in patients with excessive sleepiness associated with OSAHS, SWSD, or narcolepsy.

**Evaluator's conclusions on PD**

- Armodafinil at single doses of 100, 150, 200, and 300 mg appears to have a positive PD effect on promoting wakefulness, attention, and working memory in acutely sleep deprived healthy young men (Study 103). The duration of the PD effects appear to be longer with higher doses of armodafinil (200 mg and 300 mg) compared to lower doses of armodafinil (100 mg and 150 mg) and Provigil 200 mg.
- There were no statistically significant correlations between armodafinil plasma concentrations and any of the PD variables tested (MWT, PVT, CDR system test) following single dose armodafinil 100, 150, 200, and 300 mg in acutely sleep deprived healthy young men (Study 103). However, statistically significant correlations were observed between modafinil plasma concentrations and the PD variables tested (MWT, PVT, CDR system test) following single dose Provigil 200 mg.
- The results of PK/PD modelling and simulation reported in CP-05-001 predict that a dose of armodafinil 150 mg should achieve comparable MWT (OSAHS/narcolepsy) or MSLT (SWSD) to modafinil 200 mg at early times after administration, with superior MST/MSLT at later times.

## Dosage selection for the pivotal studies

In the pivotal Phase III studies in patients with OSAHS (Study 3021) and narcolepsy (Study 3020), the armodafinil dosages of 150 mg/day and 250 mg/day were selected on the basis of single dose PK study 101, multiple dose PK study 102 and single dose PK/PD Study 103. In Study 102, the maximum tolerated dosage following multiple dose administration was 300 mg/day. The sponsor stated that armodafinil doses of 150 mg/day and 250 mg/day were selected for the Phase III studies in patients with OSAHS and narcolepsy because

these doses were shown to be effective in study 103 and were anticipated to provide a balance between efficacy and tolerability.

The same Phase I PK and PK/PD studies used to select the doses (150 mg/day, 250 mg/day) for the pivotal Phase III studies for patients with OSAHS and narcolepsy were used to select the dose (150 mg/day) for the pivotal Phase III study for patients with SWSD (Study 3025). The sponsor stated that a dose of 150 mg/day of armodafinil was selected for the Phase III study in patients with SWSD because it was shown to be effective in Study 103, with low potential to disrupt daytime sleep.

*Comment: The sponsor's rationale for selecting the armodafinil doses for the pivotal Phase III studies is acceptable.*

## Efficacy

### Studies providing efficacy data

#### *Pivotal Phase III efficacy studies*

The submission included 4, pivotal, multinational, Phase III, double blind, placebo controlled, parallel group efficacy and safety studies of 12 weeks duration. The 4 pivotal studies included 2 studies in patients with OSAHS (C10953/3021/AP/MN and C10953/3025/AP/MN), 1 study in patients with SWSD (C10953/3022/CM/MN), and 1 study in patients with narcolepsy C10953/3020/NA/MN); the 4 studies are referred to in this clinical evaluation report as 3021, 3025, 3022 and 3020, respectively. The 4 pivotal studies are shown below in Table 7.

**Table 7: Pivotal Phase III efficacy and safety studies.**

| | Number of efficacy-evaluable patients (full analysis set)[a] | | | |
|---|---|---|---|---|
| Sleep disorder | Armodafinil | | | |
| Study number | 250 mg/day | 150 mg/day | Total | Placebo |
| OSAHS | | | | |
| Study 3021 | 121 | 120 | 241 | 124 |
| Study 3025 | — | 116 | 116 | 120 |
| SWSD | | | | |
| Study 3022 | — | 112 | 112 | 104 |
| Narcolepsy | | | | |
| Study 3020 | 60 | 58 | 118 | 58 |

a = The full analysis set included patients who received at least 1 dose of study drug, had a baseline and at least 1 post-baseline Maintenance of Wakefulness Test assessment (narcolepsy and OSAHS) or Multiple Sleep Latency Test assessment (SWSD), and at least 1 post-baseline Clinical Global Impression of Change assessment.

#### *Supportive efficacy studies*

The submission also included 2, Phase III, long term, open label safety and tolerability studies, including supportive efficacy data (C10953/3023/ES/MN and C10953/3024/ES/MN); the studies are referred to in this clinical evaluation report as 3023 and 3024, respectively. The patients who participated in Study 3023 had excessive sleepiness associated with OSAHS, SWSD, or narcolepsy and had not participated in another study with armodafinil. The patients who participated in Study 3024 had completed one of the 4 pivotal, double blind, placebo controlled studies. The submission also included 2, Phase IIIb studies providing supportive efficacy data (C10953/3045/CM/US, a double blind, placebo controlled study in patients with SWSD; and C10953/3046/ES/US, an open label study in patients with narcolepsy or OSAHS); the studies are referred to in this clinical evaluation report as 3045 and 3046, respectively. The 4 studies providing supportive efficacy data are summarised below in Table 8 and 9.

**Table 8: Supportive efficacy studies: Phase III, open label studies.**

| | Number of efficacy-evaluable patients (full analysis set) | | | |
|---|---|---|---|---|
| | Sleep disorder | | | |
| Study number | Narcolepsy | OSAHS | SWSD | Armodafinil overall |
| Study 3023[a] | 44 | 154 | 99 | 297 |
| Study 3024[b] | 150 | 459 | 106 | 715 |

a = The full analysis set (FAS) includes those patients in the safety analysis set who had at least 1 post-baseline efficacy assessment. b = The FAS included those patients in the safety analysis set who had at least 1 efficacy assessment during the open-label extension study.

**Table 9: Supportive efficacy studies: Phase IIIb studies.**

| Sleep disorder | Number of efficacy-evaluable patients (full analysis set)[a] | | | |
|---|---|---|---|---|
| Study number | Armodafinil | PROVIGIL | Placebo | Total |
| Study 3045 | | | | |
| SWSD | 73 | 27 | 26 | 126 |
| Study 3046 | | | | |
| OSAHS | 149 | — | — | 149 |
| Narcolepsy | 92 | — | — | 92 |

a = FAS includes those patients in the safety analysis set who had at least 1 post-baseline efficacy assessment.

### *Calculating sleep latency from MWT data – issues*

*Sponsor error in calculation of MWT*

In the three studies in which sleep latency calculated from the MWT was the primary efficacy variable (3021, 3021, 3025), the sponsor states that an error in the computer program that derives the primary efficacy variable from the raw scores of sleep stages for the MWT was discovered after unblinding of the data. The algorithm incorrectly calculated sleep latency from the MWT as the time to 6 consecutive epochs of sleep stage 1, 2, 3, or 4 or REM sleep, rather than protocol defined sleep latency calculated from the MWT as the time to onset of the first of 3 consecutive 30 second epochs of stage 1 sleep or to epoch 1 of stage 2, 3, or 4 or REM sleep. Consequently, the sponsor corrected the sleep latency algorithm to reflect the protocol specified definition, and the derived datasets were updated with corrected sleep latency values. The sponsor stated that this decision was deemed appropriate since the file containing the blinded raw scoring of sleep stages remained intact throughout the process, and these scores were not affected by the correction to the computer program. The correct sleep latencies from the MWT were analysed and presented in the relevant clinical safety reports.

*"Flawed" nap issue*

The "flawed" nap issue relates to the discrepancy identified by the FDA between assessment of sleep stage by local sleep technicians at the study sites and by central readers. For verification purposes, the FDA statistical reviewer of the Nuvigil new drug application (NDA) requested the raw score MWT data from 30 randomly selected patients. The FDA statistical reviewer identified some serious findings in the provided raw score data. In essence, sleep technicians who conducted the MWT in study centres were instructed to wake up patients and disconnect equipment when the patients were considered to have fallen asleep. The MWT tracings were then sent to a central laboratory for reading and calculation of sleep latency. The FDA statistical reviewer comments that this creates a problem between clinical judgement from sleep technicians and the reading from central readers. In particular, a patient can be disconnected by a local technician before the session ends and yet the central reader might not find the protocol defined sleep pattern in the "pruned" tracing. When this happened, the central reader assigned full session length to that patient, indicating that the patient did not fall asleep in that session.

This artificially prolongs sleep latency as some sessions were interrupted within a few minutes.

From the raw score data from 30 randomly selected patients, the FDA statistical reviewer found that 20 patients had at least one session affected by the discrepancy, and 7 patients had critical visits (baseline or last visit) affected. Consequently, the FDA statistical reviewer stated that "due to substantial changes to the observed data, the original analyses and results on the submitted data cannot be used for the regulatory decision". The FDA reviewer then requested the sponsor to undertake several ad hoc analyses to "understand the impact of this problem". The results of these ad hoc analyses were included in the FDA statistical review provided by sponsor, and taken into account by the FDA medical reviewer in undertaking her clinical evaluation. In this clinical evaluation report, the results of the sponsor's ad hoc analyses of the sleep latency based on the MWT have been discussed in the relevant sections of the report.

### Evaluator's conclusions on efficacy

#### *OSAHS*

The submission included 2 pivotal Phase III studies of similar design in patients with OSAHS (meeting ICSD criteria for sleep disorders) with residual daytime sleepiness despite regular and effective therapy with nCPAP (Studies 3021 and 3025). In Study 3021 (n = 395), patients were randomised to treatment with armodafinil 250 mg/day (n = 131), armodafinil 150 mg/day (n = 133) or placebo (n = 131). The mean age of the total patient population was 49.5 years (range: 26, 67 years), and the majority of patients were male (70%), and white (85%). In study 3025 (n = 263), patients were randomised to treatment with armodafinil 150 mg/day (n = 131) or placebo (n = 132). The mean age of the total patient population was 50.7 years (range: 25, 69 years), and the majority of patients were male (73%), and white (84%). In both studies, the majority of patients were white and both the mean weight and BMI were high, which is consistent for patients with OSAHS.

In both studies the duration of treatment was 12 weeks, and parallel group treatment was administered double-blind. The two primary efficacy variables in both studies were identical: an objective endpoint of change from baseline to endpoint (that is, last post baseline observation) in sleep latency from the 30 minute MWT (average of 4 naps at 0900, 1100, 1300, and 1500 h), tested in the FAS using an ANOVA model with treatment and country as factors; and a subjective endpoint of the proportion of patients with at least minimal improvement in the pre-treatment CGI-C rating (as related to the general condition) assessed at endpoint (that is, last post baseline observation), tested in the FAS using a CMH chi-square test adjusted for country.

Both studies included two primary efficacy variables, but no statistical adjustment was made in either study for multiplicity. In Study 3021, a closed testing method was used, with pairwise statistical comparisons between the two armodafinil dosage groups and placebo proceeding only if the initial pairwise statistical comparison between the combined armodafinil group and placebo was significant. The sponsor stated that due to the closed testing method, no adjustments due to multiple comparisons were deemed necessary. This is debatable. However, the statistical comparison for each pairwise comparison in both studies was robust and indicated that the comparisons would have remained significant irrespective of the method used to adjust for multiplicity, if one had been applied.

In Study 3021, mean sleep latency from the MWT increased from baseline to endpoint by 1.9 minutes in the combined armodafinil group (n = 241) and decreased by -1.7 minutes in the placebo group (n = 124); difference of 3.6 minutes statistically significantly in favour of combined armodafinil group, $p<0.0001$. In the armodafinil 150 mg/day group (n = 120), mean sleep latency from the MWT increased from baseline to endpoint by 1.7 minutes,

and was 3.4 minutes longer than placebo (p = 0.0008). In the armodafinil 250 mg/day group (n = 121), mean sleep latency from the MWT increased from baseline by 2.2 minutes, and was 3.9 minutes longer than placebo (p = 0.0001). In Study 3025, mean sleep latency from the MWT increased from baseline to endpoint by 2.3 minutes in the armodafinil 150 mg/day group (n = 116) and decreased by -1.3 minutes in the placebo group (n = 120); difference of 3.6 minutes statistically significantly in favour of combined armodafinil group, p = 0.0003.

In Study 3021, the proportion of patients with a least minimal improvement in CGI-C rating from pre-treatment to endpoint in the combined armodafinil group was 72% (174/241) compared to 37% (46/124) in the placebo group; p<0.0001. The proportion of patients with a least minimal improvement in CGI-C rating from pre-treatment to endpoint was 71% (85/120) in the armodafinil 150 mg/day group and 74% (89/121) in the armodafinil 250 mg/day group, and in both groups the difference compared to placebo was statistically significant (p<0.0001, both comparisons). The results for the combined armodafinil group and both of the armodafinil dosage groups are considered to be clinically meaningful. In study 3025, the proportion of patients with a least minimal improvement in CGI-C rating from pre-treatment to endpoint in the armodafinil 150 mg/day group was 71% (82/116) compared to 53% (64/120) in the placebo group; p<0.0069. The placebo response rate in this study was high, resulting in the difference between the two treatment groups being of doubtful clinical significance.

Both studies included a large number of secondary efficacy endpoints and the results of the endpoint analyses consistently numerically favoured the armodafinil compared to placebo group, and many of the pairwise comparisons were statistically significant. However, there was no statistically adjustment for multiplicity. In both studies, the sponsor nominated a key secondary efficacy outcome, with the nominated endpoint being different in the two studies. In both studies, no statistically significant difference between armodafinil and placebo were observed in the nominated key secondary efficacy endpoints.

In study 3021, the key secondary efficacy outcome was change from baseline to endpoint in the mean quality of episodic secondary memory from the CDR system (average of 4 tests at 0930, 1130, 1330, and 1530 h). There was no statistically significant difference between the combined armodafinil group and placebo in this outcome (mean change: 11.4 versus 5.4 units, p=0.1147). In Study 3025, the key secondary efficacy outcome was the change from baseline to endpoint in the mean power of attention from the tests of attention from the CDR system (average of 4 tests at 0930, 1130, 1330, and 1530 h). There was no statistically significant difference between armodafinil 150 mg/day and placebo in this outcome (mean change: 48.6 versus 43.6 msec, p = 0.8181).

Both studies included a number of other secondary efficacy outcomes including assessment of sleep latency from the MWT at later times in the day and at each visit, assessment of cognitive functioning including tests of memory and attention from the CDR system, assessment of sleepiness using the Epworth Sleepiness Scale (ESS) and additional CGI-C measures, assessment of fatigue on daily functioning using the Brief Fatigue Inventory (BFI), and assessment of the impact of sleepiness through the use of patient completed diaries and caffeine consumption. In general, the secondary efficacy endpoints numerically favoured armodafinil compared to placebo in both studies. The majority of the pairwise comparisons were analysed statistically, but no adjustment was made for multiplicity in either study. The results of the secondary efficacy outcomes are summarised below.

- In both studies, the mean change in sleep latency from MWT (average of 4 naps at 0900, 1100, 1300, and 1500 h) from baseline to Weeks 4, 8 and 12 statistically significantly favoured all armodafinil groups compared to placebo.

- Mean sleep latency from the MWT for later time points (average of 3 naps at 1500, 1700, and 1900 h) was tested at weeks 4, 8, and 12 and endpoint. In both studies, no statistically significant difference in mean change from baseline to endpoint was demonstrated for armodafinil and placebo.
- Descriptive results for mean change from baseline to endpoint in sleep latency from individual naps from the MWT (0900, 1100, 1300, 1500, 1700 and 1900 h) showed numerical differences in favour of the combined armodafinil group compared with placebo at all individual time points (apart from 1900 h) in both studies.
- In both studies, the proportion of patients with at least minimal improvement in the CGI-C rating at Weeks 4, 8 and 12 statistically significantly favoured all armodafinil groups compared to placebo.
- The mean change from baseline in the quality of episodic secondary memory from the CDR system (average of 4 tests at 0930, 1130, 1330, and 1530) was tested at Weeks 4, 8 and 12 and endpoint. In Study 3021, the mean change from baseline in this outcome statistically significantly favoured the combined armodafinil group compared to placebo at Week 4 ($p = 0.0064$) and Week 8 ($p = 0.0085$), but not at Week 12 ($p = 0.0910$) or endpoint ($p = 0.1147$). In Study 3025, the mean change from baseline in this outcome statistically significantly favoured the armodafinil 150 mg/day group at Week 12 ($p = 0.0055$), and endpoint ($p = 0.0102$), but not at Week 4 ($p = 0.5932$) or Week 8 ($p = 0.1697$).
- The mean change from baseline in the power of attention from the tests of attention from the CDR system (average of 4 tests at 0930, 1130, 1330, and 1530) was tested at Weeks 4, 8 and 12, and endpoint. In both studies, there were no statistically significant differences between armodafinil groups and placebo in this outcome at Weeks 4, 8 and 12 and endpoint.
- In both studies, no statistically significant differences were observed between the armodafinil and placebo groups in the mean change from baseline to endpoint in the quality of episodic secondary memory and power of attention at later time points (average of 3 tests at 1530, 1730, and 1930 h) from the CDR system.
- In both studies, no statistically significant differences were observed between armodafinil and placebo groups in mean change from baseline to endpoint in continuity of attention or speed of memory based on the relevant tests from the CDR system at earlier time points (average of 4 tests at 0930, 1130, 1330 and 1530 h) or later time points (average of 3 tests at 1530, 1730, and 1530 h).
- In both studies, the mean change from baseline to endpoint in the ESS scores statistically significantly favoured armodafinil compared with placebo.
- In both studies, mean change from baseline in the average BFI scores statistically significantly favoured armodafinil compared with placebo. In Study 3021, there was no statistically significant difference between armodafinil and placebo in mean change from baseline to endpoint in the worst fatigue score from the BFI. However, in Study 3025 there was a statistically significant difference between armodafinil 150 mg/day and placebo in mean change from baseline in the worst fatigue score from the BFI in favour of armodafinil.
- In both studies, descriptive data from the diaries showed that the number of daytime unintended sleep episodes and the number of naps decreased from baseline to endpoint to a greater extent in the armodafinil groups compared to placebo. In addition, in both groups the proportion of patients reporting mistakes, accidents or near misses post baseline was smaller in the armodafinil groups compared with placebo.

- In both studies, descriptive data relating to the number of caffeine drinks consumed each data decreased slightly by a similar amount in both the armodafinil and placebo group.

### *Narcolepsy*

The submission included one pivotal Phase III study in patients with excessive sleepiness associated with narcolepsy comparing treatment with armodafinil and placebo over 12 weeks (Study 3020). In this study, a total of 196 patients were randomised to armodafinil 150 mg/day (n = 65), armodafinil 250 mg/day (n = 67) or placebo (n = 64). The study design was similar to that for the two OSAHS studies (3021, 3025).

The mean age of the 194 patients in the safety set was 38.1 years (range: 18, 67 years), with the majority of patients (57%) being aged between 30 and 55 years. The study included a notable number of young patients aged from 18 to 29 years (32%, n = 63). The majority of patients were female (56%), with males accounting for 44% of the total population. The majority of patients were white (73%), with most of the remaining patients being black (16%). The distribution of the baseline Clinical Global Impression of Severity (CGI-S) ratings in the total safety population was 32% moderately ill, 49% markedly ill, 18% severely ill, 2% among the most extremely ill and no patients less than or equal to slightly ill. The baseline sleep latency from the MSLT in the FAS was similar for the armodafinil 250 mg/day group, armodafinil 150 mg/day group, combined armodafinil group, and placebo group (2.6, 2.5, 2.5, 2.6 minutes, respectively).

There were two primary efficacy variables, and for each variable the primary comparison was between the combined armodafinil group and the placebo group. The statistical analysis of each of the two armodafinil dosage groups compared to the placebo group only if the primary analysis was statistically significant (p = 0.05, two-tailed test). There was no statistical adjustment for multiplicity of the primary efficacy variables. However, if the most conservative option is adopted of both endpoints needing to be statistically significant for the primary comparison between the combined armodafinil group and the placebo group in order for the study to be deemed "positive", then the $\alpha$ should be 0.025 (two-tailed test) based on the Bonferroni correction. As described below, the primary efficacy comparison for both primary efficacy endpoints was ≤ 0.025.

The objective primary efficacy endpoint was the mean change from baseline to endpoint (last post baseline observation) in mean sleep latency from the 20 minute MWT (average of 4 naps at 0900, 1100, 1300, and 1500 h). The comparison between the treatment groups was tested in the FAS using an ANCOVA model with country and treatment as factors, and baseline sleep latency from the MWT as a covariate ($\alpha$ = 0.05, two tailed test). The mean sleep latency from the MWT increased by 1.9 minutes from baseline to endpoint in the combined armodafinil group (n = 118) and decreased by 1.9 minutes from baseline in the placebo group (n = 58), with the difference between groups being 3.8 minutes (p = 0.0024). In addition, the mean change in sleep latency from the MWT was statistically significantly greater in the armodafinil 150 mg/day (n=58) group compared to placebo (1.3 versus -1.9 minutes, $\Delta$ = 3.2 minutes, p = 0.0068), and in the armodafinil 250 mg/day group (n = 60) compared to placebo (2.6 versus -1.9 minutes, $\Delta$ = 4.5 minutes, p = 0.0099). The observed differences between each of the three armodafinil groups and the placebo group are considered to be clinically meaningful.

The subjective primary efficacy endpoint was the proportion of patients with at least minimal improvement in the CGI-C (as related to general condition) from baseline assessed at endpoint. The comparison was tested in the FAS using a CMH chi-square test adjusted for country. The proportion of patients meeting the endpoint was statistically significantly greater in the armodafinil combined group (n = 118) compared the placebo group (n = 58); 71% versus 33%, respectively, p<0.0001. In addition, the proportion of patients meeting the endpoint was statistically significantly greater in the armodafinil 150

mg/day group (n = 58) compared to placebo (69% versus 33%, respectively) and in the armodafinil 250 mg/day group (n = 60) compared to placebo (73% versus 33%, respectively, p <0.001). The observed differences between each of the three armodafinil groups and the placebo group are considered to be clinically meaningful.

There were a large number of secondary efficacy endpoints and the results of the endpoint analyses consistently numerically favoured the combined armodafinil group compared to the placebo group, and many of the pairwise comparisons were statistically significant. However, there was no statistically adjustment for multiplicity.

The key secondary efficacy endpoint was the change from baseline to endpoint in the mean quality of episodic secondary memory from the tests of memory from the CDR system (average of 4 tests at 0930, 1130, 1330, and 1530 h). The mean change from baseline to endpoint for this variable statistically significantly favoured the combined armodafinil group compared to placebo group (18.6 versus 1.0, respectively, p = 0.0032), the armodafinil 150 mg/day group compared to placebo group (20.7 versus 1.0, respectively, p = 0.0062), and the armodafinil 250 mg/day group compared to placebo group (16.5 versus 1.0, respectively, p = 0.0168).

Other secondary efficacy endpoints which statistically significantly favoured the combined armodafinil group compared to versus the placebo group were a:

- mean sleep latency from the MWT (average of 4 tests at 0900, 1100, 1300, and 1500 h), change from baseline to Week 4 (2.1 versus -1.1 minutes, p = 0.0054), Week 8 (1.7 versus -1.2 minutes, p = 0.0481), and Week 12 (1.8 versus -1.7 minutes , p = 0.0264);
- mean sleep latency from the MWT for later time points (average of 3 tests at 1500, 1700, and 1900 h), change from baseline at endpoint (1.5 versus -1.2 minutes, p=0.0286);
- proportion of patients with at least minimal improvement in the CGI-C ratings at Week 4 (73% versus 39%, p<0.0001), Week 8 (69% versus 38%, p=0.0001), and Week 12 (72% versus 30%, p<0.0001);
- mean power of attention (average of 4 tests at 0930, 1130, 1330, and 1530), change from baseline to endpoint (-41.5 versus 158.0 msec, p = 0.0498);
- mean power of attention for the later time points (average of 3 tests at 1530, 1730, and 1930), change from baseline to Week 12 (-9.8 versus 173.9 msec, p = 0.0219), and endpoint (3.5 versus 32.2 msec, p = 0.0413);
- mean speed of memory (average of 4 tests at 0930, 1130, 1330, and 1530), change from baseline to Week 4 (-144.8 versus 1.8 msec, p = 0.0141), Week 12 (-190.7 versus 92.7 msec, p = 0.0360), and endpoint (-199.7 versus -6.3 msec, p = 0.0178);
- mean quality of episodic secondary memory (average of 4 tests at 0930, 1130, 1330, and 1530 h), change from baseline to Week 4 (14.2 versus -2.2, p = 0.0071), Week 8 (19.4 versus -1.3, p = 0.0005) and Week 12 (18.1 versus 2.9, p = 0.0362);
- mean quality of episodic secondary memory for the later time points (average of 3 tests at 1530, 1730, and 1930), mean change from baseline at Week 12 (7.4 versus -8.8, p = 0.0344) and endpoint (8.5 versus -4.4 msec, p = 0.0256);
- mean change in total ESS score at Week 4 (-3.3 versus -2.2, p = 0.0282), Week 8 (-3.2 versus -1.4, p = 0.0014), Week 12 (-4.1 versus -1.4, p = 0.0002), and endpoint (-3.9 versus -1.9, p = 0.0006);
- mean change in worst fatigue score from the BFI scale from baseline to Week 12 (-0.9 versus -0.1, p = 0.0179); and

- mean change in average fatigue score from the BFI scale from baseline to Week 4 (-1.4 versus -0.2, p <0.0001), Week 8 (-1.5 versus -0.6, p = 0.0058), Week 12 (-1.5 versus -0.1, p <0.0001), and endpoint (-1.4 versus -0.3, p = 0.0002).

### *Shift Workers Sleep Disorder (SWSD)*

The submission included one pivotal Phase III study in patients with excessive sleepiness associated with chronic SWSD designed to determine whether armodafinil 150 mg/day was more effective than placebo for treatment of this disorder (study 3022). In this study, a total of 254 patients were randomised to treatment with armodafinil 150 mg/day (n = 127) or placebo (n = 127) to be taken 30 minutes to 1 h before a night shift (but no later than 2200 h) on the nights worked.

The mean age of the total population in the safety analysis set (n = 245) was 39.6 years (range: 18, 63 years), with the age distribution being 23% aged 18-29 years, 27% age 30-50 years, 44% aged 41-55 years and 7% aged > 55 years. The majority of patients were male (53%), with females accounting for 47% of the total population. Of the total population, 65% were white and 26% were black. Of note, 87% of the total population were permanent shift workers and 40% of the total population worked in "health care and social assistance". The distribution of the baseline CGI-S ratings in the total safety population was 56% moderately ill, 35% markedly ill, 8% severely ill, less than 1% among the most extremely ill and no patients less than or equal to slightly ill.

The objective primary efficacy endpoint was the mean change from baseline to endpoint in mean sleep latency from a 20 minute MSLT (average of 4 naps at 0200, 0400, 0600 and 0800 h). The comparison between the treatment groups was tested in the FAS using an ANOVA with treatment and country as factors. The mean ± SD baseline sleep latency from the MSLT was 2.3 ± 1.59 minutes in the armodafinil 150 mg/day group (n = 112) and 2.4 ± 1.60 minutes in the placebo group (n = 104). The mean ± SD change in sleep latency from the MSLT from baseline to endpoint was 3.1 ± 4.46 minutes in the armodafinil 150 mg group and 0.4 ± 2.87 minutes in the placebo group, with the 2.7 minutes difference between the two groups being statistically significantly in favour of armodafinil (p <0.0001). In addition, the difference of 2.7 minutes is considered to be clinically meaningful.

The subjective primary efficacy endpoint was the proportion of patients with at least minimal improvement in the CGI-C from baseline to endpoint. The comparison between treatments was tested in the FAS using a CMH chi-square test adjusted for country. The proportion of subjects with at least minimal improvement in the CGI-rating at endpoint was 79% (89/112) in the armodafinil 150 mg/day group and 59% (61/104) in the placebo group, with the difference between the two groups statistically significantly favouring armodafinil (p = 0.0010). The placebo response rate was unexpectedly high, resulting in the treatment difference between armodafinil 150 mg/day and placebo being of doubtful clinical significance.

No statistical adjustment was made for multiplicity of the two primary efficacy variables, with a separate $\alpha$ of 0.05 being tested for each pairwise comparison. Therefore, in order to be deemed "positive" it is considered that the both primary endpoints should be significant at an $\alpha$ of 0.025 (two tailed test), based on the Bonferroni correction for multiplicity. As can be seen above, the p values of both pairwise comparisons were ≤0.025.

There were a large number of secondary efficacy outcomes and the results of the endpoint analyses consistently numerically favoured the armodafinil 150 mg/day group compared to placebo. The pairwise comparisons for continuous efficacy variables used an ANOVA with treatment and country as factors, and the pairwise comparisons for the categorical CGI-C variables used CMH chi-square test adjusted for country. There was no statistically adjustment for multiplicity. Where pairwise comparisons were not tested using inferential statistics, the results were summarised using standard descriptive methods.

The key secondary efficacy endpoint was the mean change from baseline to endpoint in the mean quality of episodic secondary memory from the tests of memory from the CDR system (average of 4 tests at 0230, 0430, 0630 and 0830 h). The mean change from baseline to endpoint for this variable statistically significantly favoured the armodafinil 150 mg/day group compared to the placebo group (18.4 versus -3.3, respectively, p <0.0001). The difference between the two treatments was 21.7 units, which is notably higher than the 14 unit difference used in the power calculation. This suggests that the difference between the two treatments in the quality of episodic memory favouring armodafinil 150 mg/day can be considered to be clinically meaningful.

Other secondary efficacy endpoints of note which statistically significantly favoured armodafinil 150 mg/day compared to placebo group (p ≤0.05) were:

- mean sleep latency from the MSLT (average of 4 naps at 0200, 0400, 0600, and 0800) from baseline to Weeks 4, 8, and 12;
- proportion of patients with at least minimal improvement in CGI-C ratings from baseline to Weeks 4, 8, and 12;
- mean quality of episodic secondary memory (average of 4 tests at 0230, 0430, 0630, and 0830) from the CDR system from baseline to Weeks 4, 8, and 12 ;
- mean change in speed of memory (average of 4 tests at 0230, 0430, 0630, and 0830) from the CDR system from baseline to Weeks 8 and 12;
- mean change in power of attention (average of 4 tests at 0230, 0430, 0630, and 0830) from the CDR system from baseline to Weeks 4, 8, and 12; and
- mean change in KSS score (average of the 4 tests associated with the MSLT tests at 0200,0400, 0600, and 0800) from baseline to Weeks 4, 8, 12.

Other secondary efficacy outcomes compared descriptively and favouring armodafinil 150 mg/day compared to placebo from baseline to post baseline were:

- unintended sleep episodes during the night shift, and mean number of night naps during the night shift recorded by patient diaries; and
- the occurrence of sleepiness during the night shift based on KSS scores from patient diaries.

### *Long term efficacy and maintenance of effect*

The submission included long term, open label efficacy data relating to the use of flexible armodafinil dosage regimens (100 to 250 mg/day) for the treatment of excessive sleepiness in patients with narcolepsy, OSAHS or SWSD (Studies 3023 and 3024). The results from the two studies with long-term data suggest that armodafinil (100 to 250 mg/day) can maintain satisfactory efficacy in the three patient groups. However, the conclusions from the studies should be interpreted cautiously due to the lack of a control group. There were no controlled data in the submission assessing the effect of armodafinil treatment for longer than 12 weeks.

In study 3023, of the 323 enrolled patients with narcolepsy, OSAHS or SWSD, 217 (67%) were treated with armodafinil for > 6 months, 83 (26%) for > 12 months and 31 (10%) for > 18 months. The mean ± SD duration of exposure or participation in the study for the narcolepsy, OSAHS and SWSD groups was 311 ± 220, 309 ± 207, and 262 ± 163 days, respectively. The majority of patients in each sleep disorder group showed at least minimal improvement in the CGI-C rating beginning at Month 1 (range 86% to 92% of patients), which was maintained through to Month 12 (range 96% to 98% of patients). At endpoint, 84% (36/43) of patients with narcolepsy, 80% (123/153) of patients with OSAHS and 98% (97/99) of patients with SWSD showed at least minimal improvement in the CGI-rating. In addition, in the narcolepsy and OSAHS groups, improvements in mean

ESS scores were seen at month 1 (3.5 and 4.5 units, respectively), and were sustained through month 12 (3.5 and 10 units, respectively) and at endpoint (4.7 and 7.3 units, respectively).

In Study 3024, of the 731 enrolled patients, 508 (70%) were treated with armodafinil for >6 months, 378 (52%) were treated for >12 months, and 267 (37%) were treated for > 18 months. The mean ± SD duration of exposure or participation in the study for the narcolepsy, OSAHS and SWSD groups was 346 ± 222, 388 ± 250, and 342 ± 226 days, respectively. The majority of patients in each sleep disorder group showed at least minimal improvement in the CGI-C rating beginning at month 1 (87% to 94% of patients), which was maintained through to month 18 (range 93% to 100% of patients). At endpoint, 75% (113/150) of patients with narcolepsy, 80% (364/457) of patients with OSAHS and 92% (97/105) of patients with SWSD showed at least minimal improvement in the CGI-C rating. In addition, in the narcolepsy and OSAHS groups, improvements in mean ESS scores were seen at month 1 (5.0 and 8.0 units, respectively) and were sustained through to month 18 (4.0 and 8.0 units, respectively) and at endpoint (4.0 and 6.0 units, respectively). In the narcolepsy, OSAHS, and SWSD groups, fatigue improved from baseline to endpoint as assessed by the mean decrease from baseline in the average fatigue score (1.7, 1.7, and 2.3 units respectively), and the worst fatigue scores (1.5, 1.8, and 2.4 units, respectively) using the BFI.

In the open label study 3046, patient and clinician rated outcomes demonstrated that treatment with a flexible armodafinil dosage regimen (100 to 150 mg/day) reduced excessive sleepiness from baseline at week 8 in patients with narcolepsy or OSAHS, and that the observed improvement could be maintained through to Month 9. In addition, at each visit the majority of patients reported being at least moderately satisfied with armodafinil treatment and felt that armodafinil treatment helped them with regard to engaging in life activities. Furthermore, patients showed improvement in the global and worst fatigue scores from the BFI, while assessment of BFI functional factors using the GAS also indicated improvement in the impact of fatigue on daily functioning.

## Safety

### Studies providing safety data

The submission included safety data from 19 studies:11 Phase I clinical pharmacology studies (9 in healthy subjects, 1 in patients with schizophrenia, 1 in patients with OSAHS); 4 Phase III, double blind, placebo controlled studies (2 in patients with OSAHS and 1 each in patients with narcolepsy or SWSD); 2 Phase III uncontrolled studies in patients with OSAHS, narcolepsy or SWSD; 1 Phase IIIb, double blind, placebo controlled PK/PD study in patients with OSAHS; and 1 Phase IIIb, open label study in patients with OSAHS or narcolepsy.

The Summary of Clinical Safety (SCS) included an integrated summary of the safety data from the 4 Phase 3, double blind, placebo controlled studies (3020, 3021, 3022, 3025). In addition, the SCS included a separate integrated summary of the safety data from 7 completed clinical studies including the 4 pivotal, Phase III, double blind, placebo controlled studies (3020, 3021, 3022, 3025), in addition to 2 Phase III, open label studies (3023, 3024), and 1 Phase IIIb, open label study (3046). In these studies, patients with OSAHS or narcolepsy were scheduled to receive armodafinil continuously, and patients with SWSD were scheduled to receive armodafinil intermittently. In the 4 Phase III, double blind, placebo controlled studies the duration of armodafinil treatment was 12 weeks, while in the open label studies the duration of treatment was 12 months or more.

The SCS focused primarily on the combined safety data from the 4 Phase III, placebo controlled, double blind studies, supplemented by the integrated safety data from all

completed 7 clinical studies. The key safety data are considered to be from the 4 Phase III, double blind, placebo controlled studies. These studies, although relatively short term, allow an unbiased assessment of the safety of armodafinil due to presence of a randomised, double blinded placebo control. The safety data beyond 12 weeks were uncontrolled, which introduces a degree of uncertainty into the interpretation of the data. The submission also included approximately 6 years of extensive post marketing safety data for armodafinil consisting primarily of spontaneous reports and collected almost exclusively from patients treated in the USA.

Safety was assessed by AEs (including deaths, serious adverse events [SAEs], and withdrawals), results of clinical laboratory tests (serum chemistry, haematology, and urinalysis), vital signs (blood pressure and pulse), ECGs, physical examinations, and concomitant medication usage. In addition, for the purposes of assessing the effect of armodafinil on night-time sleep and cataplexy, nocturnal PSG (including sleep efficiency, time awake after sleep onset, sleep latency, time spread in stages 1-4, and REM sleep) was conducted at Week 12 or the last post baseline observation, and data from diaries were reviewed at Weeks 4, 8, and 12 or the last post baseline observation. For each safety variable, all findings (whether normal or abnormal) were recorded in the CRF. The investigator categorised the clinical severity of the AE data and its relationship to the study drug.

### Post marketing data

The sponsor submitted Periodic Adverse Drug Experience Reports (PADERs) relating to armodafinil covering the period from 15 June 2007 (date of first approval in the USA), though 31 May 2014. The sponsor stated that it has submitted PADERs to the FDA quarterly for the first 3 years following the US approval and annually thereafter. The sponsor submitted a copy of the most recent annual PADER covering the period from 01 June 2013 through 31 May 2014. In addition, the SCS included a summary of the post marketing data covering the period from the date of approval through 31 October 2013. The calculated post marketing exposure from June 2009 through 31 October 2013 based on US sales is summarised below in Table 10.

**Table 10: Estimated post-marketing armodafinil use in the USA; June 2009 through 31 October 2013.**

| Dose (mg) | Total number of tablets | Total (mg) | Average daily dose (mg) | Total patient treatment-days | Estimation of patients years |
|---|---|---|---|---|---|
| 50 | 7,059,600 | 352,980,000 | 70 | 5,042,571 | 13,815 |
| 150 | 59,785,110 | 8,967,766,500 | 155 | 57,856,558 | 158,511 |
| 250 | 70,276,560 | 17,569,140,000 | 261 | 67,314,713 | 184,424 |
| | | | **TOTAL** | 130,213,842 | 356,750 |

The post- marketing data identify serious skin reactions as being of particular concern with armodafinil treatment. There have been post marketing reports of Steven-Johnson Syndrome (SJS), dermatitis bullous, exfoliative rash, toxic epidermal necrolysis, erythema multiforme and drug reaction with eosinophilia and systemic symptoms (DRESS syndrome). Furthermore, there appears to have been at least one death associated with SJS and one death associated with the DRESS syndrome. It is noted that the USA prescribing information for armodafinil was updated in 2010 to include a warning relating to post marketing reports of serious rash including SJS. In response to a request from the FDA, the sponsor submitted an epidemiological study to the FDA in May 2011 further assessing the risk of serious rash and hypersensitivity reactions associated with Provigil and Nuvigil.

From the date of approval through 31 October 2013, skin reactions accounted for 198 (20%) out of a total or 987 post marketing reports received by the sponsor (spontaneous [n = 926], solicited [n = 61]). Of the total number of skin reaction reports, SJS accounted for 12.6% (25/198), and other skin reactions reported at least 10 times were rash (49 reports), skin exfoliation (12 reports), angioedema (12 reports), blister (11 reports), rash erythematous (11 reports), pruritus (10 reports), toxic epidermal necrolysis (10 reports), and urticaria (10 reports).

Other post marketing adverse drug reactions of concern reported from the approval date through 31 October 2013 included: psychiatric disorders (accounting for 160 [16.2%] of the reported 987 events), in particular suicidal ideation (24 reports), depression (14 reports), and mania (10 reports); and immune system disorders (accounting for 23 [2.3%] of the reported 1987 events), in particular hypersensitivity (11 reports), anaphylactic reaction (9 reports) and anaphylactic shock (1 report).

Preferred term post marketing adverse drug reactions each accounting for ≥ 1% of the total reports from the date of approval through 31 October 2013 were, in decreasing order of frequency: rash (49 reports); dyspnoea (27 reports); SJS (25 reports); convulsion (15 reports); suicidal ideation (14 reports); swollen tongue (15 reports); exposure during pregnancy (15 reports); depression (14 reports); death (13 reports); pharyngeal oedema (12 reports); skin exfoliation (12 reports); angioedema (12 reports); blister (11 reports); rash erythematous (11 reports); hypersensitivity (11 reports); mania (10 reports); pruritus (10 reports); urticaria (10 reports); toxic epidermal necrolysis (10 reports); and drug prescribing error (10 reports).

In the post marketing period from the date of approval through 31 October, there were 13 reports of death and 1 report each of brain death and sudden death. The most recent PADER summarising post marketing data from the date approval through 31 May 2014 identifies 6 further deaths associated with armodafinil (1x DRESS syndrome with possible causal association with armodafinil; 1x metastatic lung cancer considered unrelated to armodafinil; 1x metastatic prostate cancer considered unrelated to armodafinil; 1x cardio-respiratory arrest due to underlying condition including COPD; 2x death due to unknown cause). The sponsor is requested to provide a tabulated summary of all post marketing deaths reported from the date of approval through 31 May 2014, and narratives for each death.

Overall, the general pattern of reported adverse drug reactions in the most recent PADER is consistent with the reactions reported from date of approval through 31 October 2013. No revision to the USA prescribing information was proposed by the sponsor based on the most recent PADER.

**Evaluator's conclusions on safety**

The safety profile of armodafinil has been well characterized in the clinical trial program for armodafinil for the treatment of the three sleep disorders of interest (narcolepsy, OSAHS and SWSD), and in the post marketing data collected on the drug from first approval (USA) in June 2009 through 31 May 2014.

The limitations of the armodafinil safety data for the proposed population include: no placebo controlled or active controlled data for treatment longer than 12 weeks; no safety data in patients aged > 65 years; no safety data on disease rebound following discontinuation of treatment; and no safety data on the abuse potential of the drug including drug dependence.

The key clinical trial safety data relating to the use of the armodafinil for treatment of the proposed indications are provided by the 4, pivotal Phase III double blind, placebo controlled studies of 12 weeks duration for the three sleep disorders of interest (studies 3020, 3021, 3022, 3025). In these studies, 645 patients were exposed to armodafinil (150

mg/day [n = 447], 250 mg/day [n = 198]) and 445 patients were exposed to placebo. Based on the "rule of threes", the safety set of 645 patients exposed to armodafinil for 12 weeks in the pivotal Phase III studies is sufficient to detect adverse drug reactions occurring with an incidence of ≥ 0.5% with 95% certainty.

Supporting safety data are provided from the combined safety data from all 7 clinical studies for 1516 armodafinil treated patients (narcolepsy [n = 329], OSAHS [n = 902], SWSD [n = 285]). In all 7 clinical studies combined, the most common dose was 250 mg/day received by 52% (786/1516) of patients with a total exposure of 792 patient-treatment years, followed by 150 mg/day received by 28% (417/1516) of patients with a total exposure of 214 patient treatment years, 100 mg/day received by 13% (196/1516) of patients with a total exposure of 166 patient treatment years, and ≤ 100 mg/day received by 8% (117/1516) of patients with a total exposure of 71 patient treatment years. Based on the "rule of threes", the safety set of 1516 patients exposed to armodafinil in all 7 clinical studies combined is sufficient to detect adverse drug reactions occurring with an incidence of ≥ 0.2% with 95% certainty.

In addition to the key and supporting safety data from the clinical studies with armodafinil, the submission also included important post marketing safety data from 987 adverse drug reaction reports collected by the sponsor from the date of first approval of armodafinil in June 2009 through 31 October 2013 (926 spontaneous reports, 61 solicited reports). Based on US sales data from approval date through 31 October 2013, the estimated total patient treatment days for armodafinil is 130,213,842 and the estimated total patient treatment years of treatment is 356,750.

The post marketing data raise concerns relating to the association between armodafinil treatment and serious and potentially fatal skin conditions including SJS and DRESS syndrome. Both of these conditions have each been associated with at least one death in armodafinil treated patients. Other serious skin conditions reported in association with armodafinil treatment include dermatitis bullous, exfoliative rash, toxic epidermal necrolysis, erythema multiforme. Other safety concerns related to armodafinil treatment arising from the post- marketing data include psychiatric disorders, in particular, suicidal ideation, depression and mania, and immune system disorders, in particular, hypersensitivity disorders, anaphylactic reactions, and anaphylactic shock.

In the combined safety data from the pivotal Phase III studies, at least one AE was reported in 63% of patients in the armodafinil group and 48% of patients in the placebo group. AEs occurred more commonly in armodafinil treated patients than in placebo treated patients in each of the three sleep disorder populations. The greatest difference (Δ) between armodafinil and placebo in the incidence of patients with at least one AE was observed in narcolepsy patients (69% versus 46%, Δ = 23%), followed by SWSD patients (54% versus 40%, Δ = 14%) and OSAHS patients (64% versus 52%, Δ = 12%). The only AEs reported in ≥ 10% of armodafinil treated patients in at least one of the three sleep disorder populations were headache (22% [narcolepsy], 17% [OSAHS], 12% [SWSD]), and nausea (11% [narcolepsy], 7% [SWSD], 6% [OSAHS]).

In the narcolepsy group, AEs reported in ≥ 5% more armodafinil treated patients compared to placebo treated patients were headache (22% versus 11%), nausea (11% versus 0%), decreased appetite (5% versus 0%), and dizziness (5% versus 0%). In the OSAHS group, AEs reported in ≥ 5% more armodafinil treated patients compared to placebo treated patients were headache (17% versus 8%), insomnia (6% versus 1%), nausea (6% versus 4%), anxiety (5% versus <1%), and dizziness (5% versus 2%). In the SWSD group, AEs reported in ≥ 5% more armodafinil treated patients compared to placebo treated patients were headache (12% versus 10%), nausea (7% versus 3%), nasopharyngitis (6% versus 3%), and anxiety (5% versus 2%).

In the pivotal Phase III studies (combined safety data), AEs were reported more commonly in patients treated with 250 mg/day compared to patients treated with 150 mg/day (69% versus 60%), and more commonly in both dose groups compared to placebo (48% for each of the comparisons). AEs reported in ≥ 2% more patients in the 250 mg/day dose group compared to the 150 mg/day dose group were headache (23% versus 14%, Δ = 9%), dry mouth (7% versus 2%, Δ = 5%), nausea (9% versus 6%, Δ = 3%), rash (4% versus 1%, Δ = 3%), insomnia (6% versus 4%, Δ = 2%), depression (3% versus 1%, Δ = 2%), anorexia (3% versus < 1%, Δ = 2%), decreased appetite (3% versus < 1%, Δ = 2%), and pyrexia (2% versus 0%, Δ = 2%). The only AE reported in ≥ 2% more patients in the 150 mg/dose group compared to the 250 mg/day dose group was dyspepsia (3% versus 1%, Δ = 2%). The results demonstrate a dose response relationship between armodafinil and the incidence of commonly reported AEs.

In all 7 clinical studies combined (n = 1516), AEs reported in ≥ 5% of armodafinil treated patients were headache (24%), insomnia and nasopharyngitis (12% each), nausea (11%), upper respiratory tract infection (9%), anxiety (8%), dizziness and sinusitis (7% each), diarrhoea and dry mouth (6% each), and influenza, back pain, arthralgia, and hypertension (5% each). The incidence of patients with at least one AE was highest in the OSAHS group (89% [804/902]), followed by the narcolepsy (82% [270/329]) and SWSD (76% [217/285]) groups. Of the three AEs reported in ≥ 10% of armodafinil treated patients, headache, nasopharyngitis, and nausea were all reported more frequently in patients with narcolepsy (30%, 16%, and 15%, respectively) than in patients with OSAHS (23%, 12%, and 10%, respectively) or SWSD (19%, 10%, and 7%, respectively), while insomnia was reported more frequently in patients with OSAHS (14%) than in patients with narcolepsy or SWSD (7% and 11%, respectively).

In the pivotal Phase III studies (combined safety data), treatment-related AEs were reported in 38% of armodafinil treated patients compared to 21% of placebo treated patients. Treatment related AEs reported in ≥ 2% of patients in the combined armodafinil group (versus combined placebo group) were headache (14% versus 7%), nausea (6% versus 2%), insomnia (4% versus < 1%), dry mouth (4% versus < 1%), anxiety (3% versus < 1%), dizziness (3% versus < 1%), diarrhoea (2% versus < 1%), dyspepsia (2% versus < 1%), flatulence (2% versus 2%), and palpitations (2% versus < 1%). In all 7 clinical studies combined, treatment-related AEs reported in ≥ 2% of armodafinil treated patients were headache (19%), insomnia (10%), nausea (7%), anxiety (6%), dizziness (5%), dry mouth (5%), palpitations (3%), diarrhoea (3%), hypertension (3%), somnolence (2%), dyspepsia (2%), flatulence (2%), feeling jittery (2%), fatigue (2%), GGT increased (2%), heart rate increased (2%), decreased appetite (2%), nervousness (2%), irritability (2%), and tremor (2%).

In all 7 clinical studies combined, cumulative AE data from month 0 through month 24 showed that the majority of AEs were reported in first 3 months of treatment with armodafinil. Of the 1516 armodafinil treated patients, 47% reported at least one AE during the first 2 weeks of treatment, 72% reported at least one AE during the first 3 months of treatment, and 85% reported at least one AE during the first 24 months of treatment.

No patients in the pivotal Phase III studies died during treatment with armodafinil, and in all 7 clinical studies combined there was 1 death (0.1%) due to atherosclerotic cardiovascular disease considered by the investigator to be unrelated to treatment with armodafinil

In the pivotal Phase III studies (combined safety data), there were 6 (1%) armodafinil treated patients with SAEs compared to 2 (0.5%) placebo treated patients. In the narcolepsy population, SAEs were reported in 1 (0.8%) patient in the armodafinil group (angioneurotic oedema) and no patients in the placebo group. In the OSAHS population, SAEs were reported in 4 (1%) patients in the armodafinil group (1 x ulcerative colitis, 1 x duodenal haemorrhage, 1 x migraine, 1 x affective disorder, 1 x personality disorder) and

1 (0.4%) patient in the placebo group (1x GORD). In the SWSD population, SAES were reported in 1 (0.8%) patient in the armodafinil group (1x suicidal depression) and 1 (0.8%) patient in the placebo group (1 x viral meningitis). Of the reported SAEs, suicidal depression was considered to be related to treatment with armodafinil.

In all 7 clinical studies combined), SAEs were reported in 80 (5%) armodafinil treated patients, including 8 (2%) patients with narcolepsy, 62 (7%) patients with OSAHS, and 10 (4%) patients with SWSD. The following SAEs were considered by investigators to be related to treatment with armodafinil: pulmonary embolism (2x), chest pain (2x) and 1x each for myocardial infarction, ventricular tachycardia, headache, transient ischemic attack, depression, suicidal depression, asthma, hypertension, and thrombosis. All other SAEs were considered to be either not related or unlikely to be related to treatment with armodafinil.

In the pivotal Phase III studies (combined safety data), AEs leading to discontinuation were reported in 7% (44/645) of armodafinil treated and 4% (16/445) of placebo treated patients. In armodafinil treated patients, AEs reported in more than 2 patients leading to discontinuation were: headache (8 patients [1%]); nausea, anxiety, and depression (4 patients each [0.6%]); and palpitations, diarrhoea, alanine transaminase (ALT) increased, gamma glutamyltransferase (GGT) increased, agitation, and insomnia (3 patients each [0.5%]). No AEs leading to discontinuation were reported in more than 2 patients in the combined placebo group. AEs leading to discontinuation (armodafinil versus placebo) were reported in 5% versus 2% of patients, respectively, in the narcolepsy group, 8% versus 4% of patients, respectively, in the OSAHS group, and 6% versus 3% of patients, respectively, in the SWSD group. In general, the types of AEs leading to discontinuation were similar for the 3 sleep disorder populations.

In all 7 clinical studies combined, at least one AE leading to withdrawal in armodafinil treated patients was reported in 12% of patients with narcolepsy, 18% of patients with OSAHS, and 9% of patients with SWSD. The most frequently reported AEs leading to discontinuation (≥ 1% of patients) in armodafinil treated patients were headache (2%), anxiety (1%), and nausea (1%).

In the pivotal Phase 3studies, no clinically meaningful differences in clinical chemistry variables, haematological variables, or urinalysis results were observed between armodafinil and placebo. In particular, there was no evidence indicating that armodafinil is associated with haematological, hepatic or renal toxicity. In all 7 clinical studies combined, there was no evidence that armodafinil detrimentally affected the ECG (including QTc prolongation) or the PSG.

In the pivotal Phase III studies, based on pre specified criteria clinically significant elevated systolic and diastolic blood pressure were observed more frequently in patients treated with armodafinil (26% and 21%, respectively) compared to placebo (14% and 16%, respectively). In patients with narcolepsy, based of pre specified criteria clinically significant elevated systolic blood pressure was reported more frequently in patients in the armodafinil group compared to the placebo group (26% versus 14%, respectively), as was clinically significant elevated diastolic blood pressure (21% and 16%, respectively). In patients with SWSD, based on pre specified criteria clinically significant elevated systolic blood pressure was observed more frequently in armodafinil treated patients compared to placebo treated patients (23% versus 14%, respectively), while clinically significant elevated diastolic blood pressure was observed in a similar proportion of patients in both treatment groups (19% and 20%, respectively). In patients with OSAHS, based on pre specified criteria clinically significant elevated systolic blood pressure occurred in a similar proportion of armodafinil and placebo treated patients (32% and 34%, respectively), as did clinically significant elevated diastolic blood pressure (23% and 26%, respectively). No clinically significant increase in pulse rate was observed in either treatment group in the pivotal Phase III studies.

In the pivotal Phase III studies (combined safety data), AEs were reported more frequently in females compared to males in both armodafinil treated patients (67% versus 61%) and placebo treated patients (51% versus 46%). In particular, the incidence of nausea was higher in women (12% versus placebo 7%) compared to men (4% compared to placebo 0.7%). Other AEs occurring in ≥ 2% more women than men, and more frequently than placebo in both genders were: headache (18% [versus placebo 11%] versus 16% [versus placebo 8%], respectively); diarrhoea (5% versus [placebo 3%] versus 3% [versus placebo 1%], respectively); dry mouth (5% [versus placebo 0.6%] versus 3% [versus placebo 0.4%], respectively); and palpitations (3% [versus placebo 0.6%] versus 1% [versus placebo 1%], respectively).

In the pivotal Phase III studies (combined safety data), AEs were compared across four age groups (18-29, 30-40, 41-55, and > 55 years). In the four age groups from youngest to oldest, respectively, AEs were reported in the following proportions of armodafinil versus placebo treated patients, 67% versus 44% (Δ = 23%), 64% versus 51% (Δ = 13%), 62% versus 45% (Δ = 17%), and 61% versus 54% (Δ = 7%). The greatest difference in AEs between armodafinil and placebo treated patients was observed in the 18-29 years group. The only AEs reported in ≥ 10% of patients treated with armodafinil in at least one of the age groups were headache and nausea.

In pivotal Phase III studies (combined safety data), AEs were reported in a similar proportion of non-white and white patients in both armodafinil treated patients (66% versus 62% respectively) and placebo treated patients (55% versus 46%, respectively).

## First round benefit-risk assessment

### First round assessment of benefits

#### *OSAHS*

- The benefits of armodafinil for significantly improving wakefulness in patients with residual sleepiness associated with OSAHS have been satisfactorily demonstrated in two pivotal studies (3021, 3025). The available data suggests that the benefits of armodafinil treatment of this condition are similar to the benefits of modafinil.
- In both pivotal studies (3021, 3025), armodafinil compared to placebo significantly increased mean sleep latency time based on the 30 minute MWT (average of 4 tests at 0900, 1100, 1300 and 1500 h) from baseline to endpoint, and significantly increased the proportion of patients with at least minimal improvement in CGI-C rating at endpoint.
- In the armodafinil 150 mg/day group (Study 3021), mean sleep latency increased from baseline to endpoint by 1.7 minutes, and was 3.4 minutes longer than placebo (p = 0.0008). In the armodafinil 150 mg/day group (Study 3025), mean sleep latency increased from baseline to endpoint by 2.3 minutes, and was 3.6 minutes longer than placebo (p = 0.0003). In the armodafinil 250 mg/day group (Study 3021), mean sleep latency increased from baseline to endpoint by 2.2 minutes, and was 3.9 minutes longer than placebo (p = 0.0001). The increased sleep latency observed in each of the armodafinil groups compared to placebo is considered to be clinically meaningful.
- The increase in sleep latency observed for armodafinil compared to placebo in the two studies (3.4 to 3.9 minutes) was consistent with the increase in sleep latency observed for Modavigil 200 mg/day compared to placebo (2.7 minutes) and Modavigil 400 mg/day compared to placebo (2.6 minutes) reported in the Modavigil PI. The results suggest that the benefits of armodafinil 150 mg/day and 250 mg/day on increasing sleep latency in patients with OSAHS are similar to those reported for Modavigil 200 mg/day and 400 mg/day.

- The benefits of armodafinil in increasing sleep latency appear to be limited to earlier h following dosing rather than later h. In both studies, no statistically significant differences between armodafinil and placebo were observed in mean change from baseline to endpoint in sleep latency at later time points (average of 3 naps at 1500, 1700 and 1900 h).
- In Study 3021, the proportion of patients with a least minimal improvement in CGI-C rating from pre treatment to endpoint was 71% in the armodafinil 150 mg/day group, 74% in the armodafinil 250 mg/day group and 37% in the placebo group, and in both groups the difference compared to placebo was statistically significant ($p<0.0001$, both comparisons). The increased response rate in each of the armodafinil groups compared to placebo is considered to be clinically meaningful. Furthermore, the CGI-C results for the armodafinil versus placebo comparisons in study 3021 were comparable with the results for the comparisons between Modavigil 200 mg/day versus placebo (61% versus 37%, respectively) and Modavigil 400 mg/day versus placebo (68% versus 37%) reported in the Modavigil PI.
- In Study 3025, the proportion of patients with a least minimal improvement in CGI-C rating from baseline to endpoint in the armodafinil 150 mg/day group was 71% compared to 53% in the placebo group; $p = 0.0069$. The placebo response rate for patients reporting at least minimal improvement in CGI-C rating from baseline to endpoint in study 3025 was unexpectedly high. This results in the difference in the CGI-C rating from baseline to endpoint between armodafinil 150 mg/day and placebo in Study 3025 being of doubtful clinical significance. The placebo response rate in this study was notably higher than the placebo response rate reported in the Modavigil PI for patients with OSAHS (that is, 37%). However, the response rate for armodafinil 150 mg/day in study 3025 was comparable to the response rates for Modavigil 200 mg/day and 400 mg/day reported in the PI (that is, 71%, 61% and 68%, respectively).
- The effect of armodafinil in improving the quality of secondary episodic memory was equivocal. In study 3021, no statistically significant difference was observed from baseline to endpoint between the combined armodafinil group (150 mg/day and 250 mg/day) and placebo for the change in mean quality of secondary episodic memory from the CDR system (average of 4 tests at 0930, 1130, 1330 and 1530 h). In study 3021, this was a key secondary efficacy endpoint. However, in study 3025, there was a statistically significant improvement in this endpoint in the armodafinil 150 mg/day group compared to placebo.
- There was no evidence from the two studies that armodafinil improves the power of attention. In Study 3025, no statistically significance difference was observed between armodafinil 150 mg/day and placebo for the key secondary efficacy outcome of change in mean power of attention from the CDR system (average of 4 tests at 0930, 1130, 1330 and 1530 h) from baseline to endpoint. Similarly, in study 3021 no statistically significant difference was observed in this endpoint for the comparison between the combined armodafinil group and placebo. In addition, there was no evidence from the two studies that armodafinil improves continuity of attention or speed of memory.
- Armodafinil improves wakefulness, based on the ESS score. In study 3021, the change from baseline to endpoint in the mean total ESS score was statistically significantly greater in the armodafinil 150 mg/day group compared to placebo (-5.5 versus -3.3, $p = 0.0005$) and in the 250 mg/day group compared to placebo (-5.5 versus -3.3, $p = 0.0007$). In Study 3025, the change from baseline to endpoint in the mean total ESS score was statistically significantly greater in the armodafinil 150 mg/day group compared to placebo (-5.3 versus -3.0, $p = 0.0001$). The difference in the ESS total score for the armodafinil versus placebo comparisons were consistent with the results for the comparisons between Modavigil 200 mg/day ($\Delta = 2.7$) and Modavigil 400 mg/day ($\Delta = 2.7$) reported in the Modavigil PI. The results suggest that the benefits of

armodafinil 150 mg/day and 250 mg/day in improving wakefulness, based on the ESS total score, are similar to those of Modavigil 200 mg/day and 400 mg/day in patients with OSAHS,

- There was evidence from both studies that armodafinil improves fatigue, based on the average BFI score. However, improvement in worst fatigue scores with armodafinil treatment was equivocal. Descriptive subjective evidence from patient diaries shows that armodafinil reduces the number of daytime unintended sleep episodes, the number of daytime naps, and the number of mistakes, accidents or near misses. There is no evidence that armodafinil has a benefit greater than that observed with placebo on reducing the number of caffeine beverages consumed in a day.
- The benefits of armodafinil in patients with OSAHS appear to be maintained over the long term. In 2 open label studies, a flexible dosage regimen of armodafinil (100 to 250 mg/day) in patients with OSAHS, narcolepsy or SWSD decreased excessive sleepiness from baseline through to Month 12 (Study 3023) and through to Month 18 (Study 3024), with reductions in fatigue from baseline through to 18 months also being observed in Study 3024. In an open label study in patients with OSAHS or narcolepsy, improvements in excessive sleepiness, fatigue, and daily functioning observed at Week 8 were maintained through to Month 9 (Study 3046) with a flexible dosage regimen of armodafinil (100 to 250 mg/day.

***Narcolepsy***

- The benefits of armodafinil for significantly improving wakefulness in patients with excessive sleepiness due to narcolepsy have been satisfactorily demonstrated in one pivotal study (3020). The available data suggests that benefits of armodafinil treatment of this condition are similar to the benefits of modafinil.
- In the pivotal study (3020), armodafinil compared to placebo significantly increased mean sleep latency time based on the 20 minute MWT (average of 4 naps at 0900, 1100, 1300, and 1900) from baseline to endpoint, and significantly increased the proportion of patients with at least minimal improvement in CGI-C rating from baseline to endpoint.
- In the armodafinil 150 mg/day group, mean sleep latency increased from baseline to endpoint by 1.3 minutes, and was 3.2 minutes longer than placebo ($p = 0.0068$). In the armodafinil 250 mg/day group, mean sleep latency increased by 2.6 minutes, and was 4.5 minutes longer than placebo ($p = 0.0099$). The increase in sleep latency in both armodafinil groups compared to placebo is considered to be clinically meaningful.
- Furthermore, the increase in sleep latency observed for the two armodafinil dosage groups compared to placebo is consistent with the increase in sleep latency observed for Modavigil 200 mg/day compared to placebo from two studies ($\Delta = 3.1$ minutes, $\Delta = 2.9$ minutes) and for Modavigil 400 mg/day compared to placebo for two studies ($\Delta = 3.8$ minutes, $\Delta = 3.6$ minutes) reported in the Modavigil PI for patients with narcolepsy. The results suggest that the benefits of armodafinil 150 mg/day and 250 mg/day on improving wakefulness in patients with narcolepsy are similar to those reported for Modavigil 200 mg/day and 400 mg/day.
- Statistically significant benefits for armodafinil 150 mg/day on increasing mean sleep latency compared to placebo were observed at Week 4 and maintained at the Weeks 8 and 12. While a statistically significant benefit for armodafinil 250 mg/day on increasing mean sleep latency compared to placebo was observed at week 4, the differences at Week 8 and 12 were not statistically significant but were numerically superior. However, the difference from placebo in mean sleep latency was numerically greater in the armodafinil 250 mg/group compared to the 150 mg/day group at week

4 (3.3 versus 3.0 minutes), week 8 (3.2 versus 2.5 minutes) and week 12 (4.1 versus 2.8 minutes),

- A statistically significant benefit was observed for armodafinil 150 mg/day for increasing sleep latency at later time points (average of 3 naps at 1500, 1700 and 1900 h), with the mean increase from baseline to endpoint being 1.5 minutes compared with a decrease of 1.2 minutes in the placebo group (difference of 2.7 minutes, p = 0.0286). The difference between armodafinil 250 mg/day and placebo for this outcome was 2.8 minutes in favour of armodafinil, but was not statistically significant.
- The proportion of patients with a least minimal improvement in CGI-C rating from baseline to endpoint was 69% in the armodafinil 150 mg/day group, 73% in the armodafinil 250 mg/day group and 33% in the placebo group (p <0.0001 for both armodafinil versus placebo comparisons). The higher response rate in both armodafinil dosage groups compared to placebo is considered to be clinically meaningful. Furthermore, the results were consistent with those reported in the Modavigil PI for patients with narcolepsy for Modavigil 200 mg/day compared to placebo (64% versus 37%; 58% versus 38%) and for Modavigil 400 mg/day compared to placebo (72% versus 37%; 60% versus 38%). The results for the subjective CGI-C ratings suggest that the benefits of modafinil 150 mg/day and 250 mg/day on decreasing excessive sleepiness in patients with narcolepsy are consistent with those reported for Modavigil 200 mg/day and 400 mg/day.
- The proportion of patients with at least minimal improvement in CGI-C rating from baseline to endpoint statistically significantly favoured both armodafinil 150 mg/day and 250 mg/day groups compared to placebo at Weeks 4, 8, and 12.
- Both armodafinil dosage groups compared to placebo had a statistically significant beneficial effect on improving the quality of secondary episodic from the tests of memory from CDR system testing (average of 4 tests at 0930, 1130, 1330, and 1530 h) based on mean change from baseline to endpoint. This was the key secondary efficacy variable in Study 3020. In addition, the armodafinil 250 mg/day group also had a statistically significant beneficial effect on improving the quality of secondary episodic from the tests of memory from CDR system testing at later time points (average of 3 tests at 1530, 1730, and 1930 h) based on mean change from baseline to endpoint.
- The armodafinil 250 mg/day group (but not the 150 mg/day group) had a statistically significant beneficial effect on improving the speed of memory from CDR system testing (average of 4 tests at 0930, 1130, 1330, and 1530 h) based on mean change from baseline to endpoint compared to placebo. However, the benefit on the speed of memory was not observed at later time points.
- The armodafinil 150 mg/day group (but not the 250 mg/day group) had a statistically significant beneficial effect on improving the power of attention from CDR system testing (average of 4 tests at 0930, 1130, 1330, and 1530 h) based on mean change from baseline to endpoint compared to placebo. The armodafinil 250 mg/day group (but not the 150 mg/day group) had a statistically significant beneficial effect on improving the power of attention from CDR system testing at later time-points (average of 3 tests at 1530, 1730 and 1930 h) based on mean change from baseline to endpoint compared to placebo. Neither armodafinil dosage group had a beneficial effect on the continuity of attention from CDR system testing from baseline to endpoint at earlier or later time points compared to placebo.
- Both armodafinil dosage groups compared to placebo had a statistically beneficial effect on reducing excessive sleepiness as assessed by change in the mean ESS from baseline to endpoint. Both armodafinil dosage groups had a statistically significant beneficial effect on reducing fatigue based on the mean change in the average score from the BFI baseline to endpoint. The number of unintended sleep episodes and daily

naps summarized from patient daily diaries were numerically lower post-baseline compared to baseline for both armodafinil dosage groups compared to placebo.

- The benefits of armodafinil in patients with narcolepsy appear to be maintained over the long term. In 2 open label studies, a flexible dosage regimen of armodafinil (100 to 250 mg/day) in patients with OSAHS, narcolepsy or SWSD decreased excessive sleepiness from baseline through to Month 12 (Study 3023) and through to month 18 (Study 3024), with reductions in fatigue from baseline through to 18 months also being observed in Study 3024. In an open label study in patients with OSAHS or narcolepsy, improvements in excessive sleepiness, fatigue, and daily functioning observed at Week 8 were maintained through to Month 9 (Study 3046) with a flexible dosage regimen of armodafinil (100 to 250 mg/day).

***SWSD***

- The benefits of armodafinil for significantly improving wakefulness in patients with excessive sleepiness associated with chronic SWSD have been satisfactorily demonstrated in one pivotal study (3022). The available data suggests that benefits of armodafinil and modafinil for the treatment of this condition are likely to be similar.
- In the pivotal study (3022), armodafinil 150 mg/day compared to placebo significantly increased the objective primary efficacy endpoint of mean sleep latency time based on the 20 minute MSLT (average of 4 naps at 0200, 0400, 0600 and 0800 h) from baseline to endpoint, and significantly increased the subjective primary efficacy endpoint of the proportion of patients with at least minimal improvement in CGI-C rating from baseline to endpoint.
- In the armodafinil 150 mg/day group, mean sleep latency increased from baseline to endpoint by 3.1 minutes, and was 2.7 minutes longer than placebo ($p < 0.0001$). The increased in sleep latency is considered to be clinically meaningful. The difference in the mean change from baseline to endpoint in sleep latency of 2.7 minutes is greater than the corresponding difference reported in the Modavigil PI of 1.36 minutes for modafinil 200 mg. The results suggest that the benefit of armodafinil 150 mg/day on increasing sleep latency is at least as great as the benefits of modafinil 200 mg/day in patients with SWSD.
- The proportion of patients with a least minimal improvement in the CGI-C rating from baseline to endpoint was 79% in the armodafinil 150 mg/day group and 59% in the placebo group ($p = 0.0010$). The placebo response rate was unexpectedly high, resulting in the difference in response rate between the two treatments being of doubtful clinical significance. However, the response rate for the armodafinil 150 mg/day group for at least minimal improvement in the CGI-C rating from baseline to endpoint was similar to that reported in the Modavigil PI for Modavigil 200 mg/day for patients with SWSD (that is, 79% and 74%, respectively). The response rate for the comparator placebo control group for armodafinil 150 mg/day was notably higher than for the comparator placebo control group for Modavigil 200 mg/day (that is, 59% and 36%, respectively).
- Statistically significant benefits for armodafinil 150 mg/day compared to placebo were observed for both mean sleep latency and the proportion of patients with minimal improvement in the CGI-C rating from baseline to Weeks 4, 8 and 12.
- Armodafinil 150 mg/day compared to placebo statistically significantly improved the key secondary efficacy endpoint of change from baseline to endpoint in the mean quality of episodic secondary memory from the tests of memory from the CDR system (average of 4 tests at 0230, 0430, 0630, and 0830 h). In addition the mean change from baseline to Weeks 4, 8 and 12 in this outcome also statistically significantly favoured armodafinil 150 mg/day compared to placebo.

- Armodafinil 150 mg/day compared to placebo statistically significantly improved the mean change in the speed of memory (average of 4 tests at 0230, 0430, 0630, and 0830) from the CDR system from baseline to weeks 8 and 12, and the mean change in the power of attention (average of 4 tests at 0230, 0430, 0630, and 0830) from the CDR system from baseline to Weeks 4, 8, and 12.
- Armodafinil 150 mg/day compared to placebo statistically significantly reduced sleepiness based on the mean KSS from baseline to Weeks 4, 8, and 12. Patient reported outcomes from personal diaries numerically favouring armodafinil 150 mg/day compared to placebo included unintended sleep episodes during the night shift, mean number of night naps during the night shift, and sleepiness during the night shift based on KSS scores.
- The benefits of armodafinil in patients with SWSD appear to be maintained over the long term In 2 open label studies, a flexible dosage regimen of armodafinil (100 to 250 mg/day) in patients with OSAHS, narcolepsy or SWSD decreased excessive sleepiness from baseline through to Month 12 (Study 3023) and through to Month 18 (study 3024), with reductions in fatigue from baseline through to 18 months also being observed inS 3024.

**First round assessment of risks**

- The risks of treatment with armodafinil for the proposed indications have been adequately characterised based on the data from the clinical study program for the three sleep disorders of interest, and the post marketing data based on approximately 6 years of use relating to the drug. The safety profile of armodafinil for the proposed indications appears to be similar to the safety profile of modafinil for the same indications. While the use of armodafinil is not without risk, the safety profile of the drug for treatment of the proposed indications is considered to be satisfactory.
- The most commonly reported risks of note in the armodafinil clinical trial program for the sleep disorders of interest included AEs of headache, nausea, insomnia, dizziness, anxiety, and decreased appetite; all occurring in ≥ 5% more armodafinil treated patients compared to placebo treated patients in at least one of the pivotal Phase III sleep disorder studies. In addition, systolic and diastolic hypertension, based on pre-specified criteria, and detected by pre-specified blood pressure monitoring, were reported more frequently in armodafinil treated patients compared to placebo treated patients in the pivotal Phase III sleep disorder studies. Serious AEs were reported infrequently in armodafinil treated patients in the pivotal Phase III studies, as were discontinuations due to AEs.
- Adverse drug reactions of particular concern identified from the post marketing data include serious and potentially fatal skin condition (SJS, DRESS syndrome, dermatitis bullous, exfoliative rash, toxic epidermal necrolysis, and erythema multiforme), psychiatric disorders (suicidal ideation, depression, and mania), and immune system disorders (drug hypersensitivity reactions, anaphylactic reactions, and anaphylactic shock). Based on post marketing exposure the incidence of serious and potentially fatal skin reactions, serious psychiatric reactions and serious immune system disorders associated with armodafinil treatment appears to be rare and/or very rare.
- No patients in the pivotal Phase III studies died during treatment with armodafinil. There was 1 death (0.1%) due to atherosclerotic cardiovascular disease considered by the investigator to be unrelated to treatment with armodafinil in the safety data from all 7 clinical studies combined. In the post marketing data, it is estimated that there have been 21 fatal adverse drug reactions since armodafinil was first approved on 15 June 2009 through 31 May 2013, including at least one death each associated with SJS and DRESS syndrome.

- In the combined safety data from the pivotal Phase III studies, at least one AE during the 12 weeks of the study were reported in 63% of patients in the armodafinil group and 48% of patients in the placebo group. The risk of experiencing at least one AE with armodafinil treatment, relative to placebo, was greater in patients with narcolepsy (69% versus 46% [placebo]), while the risk of experiencing at least one AE with armodafinil treatment, relative to placebo, was similar in patients with OSAHS (64% versus 52% [placebo]) and SWSD (54% versus 40% [placebo]).
- The most frequently occurring risks of treatment in the pivotal Phase III studies, reported in ≥ 10% of patients in at least one of the three sleep disorders of interest, were headache (22% [narcolepsy], 17% [OSAHS], 12% [SWSD]), and nausea (11% [narcolepsy], 7% [SWSD], 6% [OSAHS]). In the narcolepsy group, AEs reported in ≥ 5% more armodafinil treated patients compared to placebo treated patients were headache (22% versus 11%), nausea (11% versus 0%), decreased appetite (5% versus 0%), and dizziness (5% versus 0%). In the OSAHS group, AEs reported in ≥ 5% more armodafinil treated patients compared to placebo treated patients were headache (17% versus 8%), insomnia (6% versus 1%), nausea (6% versus 4%), anxiety (5% versus <1%), and dizziness (5% versus 2%). In the SWSD group, AEs reported in ≥ 5% more armodafinil treated patients compared to placebo treated patients were headache (12% versus 10%), nausea (7% versus 3%), nasopharyngitis (6% versus 3%), and anxiety (5% versus 2%).
- In the pivotal Phase III studies, the risk of experiencing at least one AE was greater in patients in the 250 mg/day group compared to the 150 mg/day group. AEs reported in ≥ 2% more patients in the 250 mg/day dose group compared to the 150 mg/day dose group were headache, dry mouth, nausea, rash, insomnia, depression, anorexia, decreased appetite, and pyrexia.
- In all 7 clinical studies combined (n = 1516), AEs reported in ≥ 5% of armodafinil treated patients were headache (24%), insomnia (12%), nasopharyngitis (12%), nausea (11%), upper respiratory tract infection (9%), anxiety (8%), dizziness (7%), sinusitis (7%), diarrhoea (6%), dry mouth (6%), influenza (5%), back pain (5%), arthralgia (5%), and hypertension (5%). In all 7 clinical studies combined, cumulative AE data from month 0 through month 24 showed that the majority of AEs were reported in first 3 months of armodafinil treatment. Of the 1516 armodafinil treated patients, 47% reported at least one AE during the first 2 weeks of treatment, 72% reported at least one AE during the first 3 months of treatment, and 85% reported at least one AE during the first 24 months of treatment.
- In the pivotal Phase III studies, treatment related AEs reported in ≥ 2 % of patients (versus placebo) were headache (14% versus 7%), nausea (6% versus 2%), insomnia (4% versus < 1%), dry mouth (4% versus < 1%), anxiety (3% versus < 1%), dizziness (3% versus < 1%), diarrhoea (2% versus < 1%), dyspepsia (2% versus < 1%), flatulence (2% versus 2%), and palpitations (2% versus < 1%). In all 7 clinical studies combined, treatment-related AEs reported in ≥ 5% of armodafinil treated patients were headache (19%), insomnia (10%), nausea (7%), anxiety (6%), dizziness (5%), and dry mouth (5%).
- In the pivotal Phase III studies, SAEs were reported in 6 (1%) armodafinil treated patients compared to 2 (0.5%) placebo treated patients. In the narcolepsy population, SAEs were reported in 1 (0.8%) patient in the armodafinil group (angioneurotic oedema) and no patients in the placebo group. In the OSAHS population, SAEs were reported in 4 (1%) patients in the armodafinil group (1 x ulcerative colitis, 1 x duodenal haemorrhage, 1 x migraine, 1 x affective disorder, 1 x personality disorder) and 1 (0.4%) patient in the placebo group (1x GORD). In the SWSD population, SAEs were reported in 1 (0.8%) patient in the armodafinil group (1x suicidal depression) and 1 (0.8%) patient in the placebo group (1 x viral meningitis). One of the reported

SAEs (suicidal depression) was considered by the investigator to be related to treatment with armodafinil.

- In all 7 clinical studies combined, SAEs were reported in 80 (5%) armodafinil treated patients, including 8 (2%) patients with narcolepsy, 62 (7%) patients with OSAHS, and 10 (4%) patients with SWSD. The following SAEs were considered by investigators to be related to treatment with armodafinil: pulmonary embolism (2x), chest pain (2x) and 1x each for myocardial infarction, ventricular tachycardia, headache, transient ischaemic attack, depression, suicidal depression, asthma, hypertension, and thrombosis. All other SAEs were considered to be either not related or unlikely to be related to treatment with armodafinil.
- In the pivotal Phase III studies, AEs leading to discontinuation were reported in 7% of armodafinil treated and 4% of placebo treated patients. In armodafinil treated patients, AEs reported in more than 2 patients leading to discontinuation were: headache (8 patients [1%]); nausea, anxiety, and depression (4 patients each [0.6%]); and palpitations, diarrhoea, ALT increased, GGT increased, agitation, and insomnia (3 patients each [0.5%]). No AEs leading to discontinuation were reported in more than 2 patients in the combined placebo group. AEs leading to discontinuation (armodafinil versus placebo) were reported in 5% versus 2% of patients, respectively, in the narcolepsy group, 8% versus 4% of patients, respectively, in the OSAHS group, and 6% and 3% of patients, respectively, in the SWSD group. In general, the types of AEs leading to discontinuation were similar for the 3 sleep disorder populations.
- In all 7 clinical studies combined, at least one AE leading to withdrawal in armodafinil treated patients was reported in 12% of patients with narcolepsy, 18% of patients with OSAHS, and 9% of patients with SWSD. The most frequently reported AEs leading to discontinuation in all armodafinil treated patients (≥ 1 % of patients) were headache (2%), anxiety (1%), and nausea (1%).
- The clinical laboratory data suggest that armodafinil is not associated with clinically significant haematological, hepatic or renal toxicity. The vital sign data suggest that there is a risk or clinically significant elevations in both systolic and diastolic blood pressure with armodafinil. The ECG data suggest that armodafinil is not associated with clinically meaningful QTc prolongation.
- The risks of treatment with armodafinil are greater in female patients compared to male patients. The risks of treatment with armodafinil treatment appear to be similar for patients over the age range 18 to ≤ 65 years, but there are no data in patients aged ≥ 65 years.
- There are no data on the risks of armodafinil treatment in patients with cardiovascular disorders, but due to the risk of hypertension associated with armodafinil the drug should be used cautiously in patients with a history of myocardial infarction or unstable angina. There were no data on the risks of armodafinil treatment in patients with psychiatric disorders, but treatment of patients with significant psychiatric conditions such as mania, depression or psychosis should be avoided due to the potential risk of exacerbation of these conditions. There are no data on the risks of treatment with armodafinil in patients with hepatic or renal impairment.

**First round assessment of benefit-risk balance**

The benefit-risk benefit of armodafinil, given the proposed usage, is favourable.

The benefit-risk balance of armodafinil for the proposed indications appears to be comparable to that of modafinil. The European Medicines Agency (EMA) reviewed the safety and effectiveness of modafinil for the treatment of excessive sleepiness in patients with narcolepsy, OSAHS, and SWSD, and the Committee for Medicinal Products for Human

Use (CHMP) concluded in January 2011 that treatment should be restricted to patients with narcolepsy. In view of this decision, the TGA requested the Advisory Committee on the Safety of Medicines (ACSOM) to advise on the whether the benefit-risk evaluation of modafinil was adequate, due to safety concerns associated with the drug. Following review of the data, the ACSOM concluded that the benefit-risk balance for modafinil remained favourable, although the benefit appeared to be greater in narcolepsy than OSAHS or SWSD.

## First round recommendation regarding authorisation

It is recommended that armodafinil (Nuvigil) be approved:

- to improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy;
- to treat excessive sleepiness associated with moderate to severe chronic shift work sleep disorder where nonpharmacological interventions are unsuccessful or inappropriate; and
- use as an adjunct to continuous positive airways pressure (CPAP) in obstructive sleep apnoea/hypopnoea syndrome in order to improve wakefulness.

## Clinical questions

### Pharmacokinetics

Q1. Please provide a formal justification for not submitting an absolute oral bioavailability study for armodafinil. It is noted that an IV solution was used in nonclinical studies in rats and dogs. Why was this IV solution not suitable for use in human studies?

Q2. Please provide a formal justification for not submitting a bioequivalence study comparing the three proposed tablet strengths of armodafinil (that is, 50, 150 and 250 mg).

Q3. Please provide a formal justification for not submitting a mass balance and metabolism study for armodafinil in humans.

Q4. Please provide the $C_{max}$ and $AUC_{inf}$ ratios (fed:fasted) for armodafinil, with 90% Confidence Intervals (CIs), using standard bioequivalence methodology for the 6 subjects who received single dose armodafinil (100 mg) in the fasted and fed state in Study 101.

Q5. The Summary of Clinical Pharmacology included relative exposure data for R-armodafinil versus racemic modafinil following multiple doses of armodafinil and Provigil, respectively.

> (i) Please confirm that the data in the summary were based on the Day 7 results for subjects from armodafinil Study 102 and Provigil Study 2101.
>
> (ii) The summary refers to a 150 mg dose of armodafinil from Study 102. However, this study did not include an actual 150 mg dose of armodafinil. The data for the 150 mg dose provided in the Summary appears to be based on dose normalised to 150 mg data. Please clarify the source of the data for the 150 mg dose of armodafinil reported in the Summary
>
> (iii) The PK data from armodafinil Study 102 referred to in the summary were obtained following fasting on sample collection days, while the PK data from Provigil Study 2101 were obtained 1 h after a light breakfast on collection days. Given the different relationship between dose and meals on data collection days

for the two studies, please comment on the validity of the relative exposure data for R-modafinil and racemic modafinil provided in the Summary.

Q6. In vitro data are reported to show that armodafinil has weak, but concentration-related inductive effects on CYP1A2, CYP2B6, and CYP3A4/5 activities. Clinical DDI studies have been undertaken investigating the effect of co-administration of armodafinil on CYP3A4 substrates (midazolam and quetiapine) and a CYP1A2 substrate (caffeine), but not a CYP2B6 substrate. Please justify not undertaking a clinical DDI study assessing the effect of co-administration of armodafinil on a CYP2B6 substrate.

Q7. In vitro data are reported to show that armodafinil has inhibitory effects on CYP2C19 and CYP2C9. A clinical DDI studies has been undertaken investigating the effect of co-administration of armodafinil on a CYP2C19 substrate (omeprazole), but not a CYP2C9 substrate. Please justify not undertaking a clinical DDI study assessing the effect of co-administration of armodafinil on a CYP2C9 substrate.

Q8. In an in vitro study using MDR-MDCK cell monolayers it was reported that armodafinil is a P-glycoprotein (Pgp) substrate, but is not an inhibitor of Pgp (Study DP-2006-055). There were no clinical DDI studies investigating the effect of Pgp inhibitors or inducers on the bioavailability of armodafinil. The sponsor is requested to justify not submitting such studies. Does the sponsor have any data on whether armodafinil is an inducer of Pgp?

Q9. The sponsor states that the metabolic pathways of armodafinil have not been specifically characterised in the clinical studies, but reports that the formation of modafinil sulfone from R-modafinil is metabolised by CYP3A4/5. At steady state, modafinil sulfone represents approximately 56% of parent drug exposure. Therefore, in view of the involvement of CYP3A4/5 in at least part of the metabolism of armodafinil the sponsor should provide a justification for not submitting clinical DDI studies investigating the effects of CYP3A4 inhibition and CYP3A4 induction on systemic exposure to armodafinil.

Q10. Achiral modafinil sulfone was identified as a metabolite of R-modafinil. This suggests that R-modafinil sulfone resulting from the metabolism of R-modafinil undergoes interconversion with S-modafinil sulfone. Please provide the data supporting interconversion of the enantiomers of S-modafinil sulfone.

**Safety**

Q11. The Summary of Safety included an analysis of QTc changes in the 4 Phase III, double blind, placebo controlled studies using QTcF (that is, Fridericia correction) (Table 43). Please repeat the analysis using QTcB (that is, Bazett correction). Please comment on the significance of any observed differences between the two analyses.

Q12. In the post marketing period from the date of approval through 31 October, there were 13 reports of death and 1 report each of brain death and sudden death. The most recent PADER summarising post marketing data from the date approval through 31 May 2014 identifies 6 further deaths associated with armodafinil. Please provide a tabulated summary of all reported post marketing deaths and narratives for each of the post marketing deaths.

## Second round evaluation

### Pharmacokinetics

#### *Question 1*

- Please provide a formal justification for not submitting an absolute oral bioavailability study for armodafinil. It is noted that an IV solution was used in nonclinical studies in rats and dogs. Why was this IV solution not suitable for use in human studies?

*Sponsor's response*

As described in Question 52 (Biopharmaceutical section), data generated with modafinil was considered adequate to characterise the degree of absorption of armodafinil.

*Clinical evaluator's comment*

The sponsor's response is not entirely satisfactory. The sponsor justifies its decision not to undertake an absolute bioavailability study with armodafinil based on clinical data relating to Provigil from a mass balance study (C1538a/111/PK/US) and a relative bioavailability study (C1538a/110/BE/UK). The sponsor states that the data relating to Provigil are adequate to characterise the absorption of armodafinil. In the original submission, the sponsor stated that the absolute oral bioavailability was not determined in humans due to the aqueous insolubility of armodafinil, which precluded IV administration. However, an IV formulation was used in rats and dogs. It is not clear from the sponsor's response whether the use of an IV formulation would have been problematic in humans.

In the sponsor's response to Question 52 (Biopharmaceutical section) it was stated that:

> *Neither an absolute bioavailability study to compare Nuvigil tables to an IV solution, nor a relative bioavailability study to compare Nuvigil tables to an oral suspension as requested … were deemed necessary in view of the data generated with the racemic mixture. In the Provigil program, a mass balance study (C1538a/111/PK/US) conducted in 6 subjects receiving a single 200 mg dose of 14C-modafinil showed approximately 80% and [approximately] 1% of the total dose being recovered in the 11-days period [in] urine and feces, respectively, suggesting nearly complete absorption. In a relative bioavailability study comparing two 100 mg modafinil tablets and one 200 mg caplet versus an oral suspension (C1538a/110/BE/UK), the relative oral bioavailabilities were close to 100%. These results, together [support] armodafinil being considered [a] BCS Class I compound ... [and] demonstrate that high bioavailability of armodafinil following Nuvigil administration can be inferred without the need of an absolute or relative bioavailability study.*

It would have been preferable for a formal absolute bioavailability in humans to have been undertaken, unless precluded due to IV formulation issues, rather than infer the degree of absorption based on Provigil data. However, it is considered that the absence of an absolute bioavailability study in humans should not preclude approval of armodafinil. The totality of the clinical data submitted by the sponsor relating to the PK of armodafinil and the efficacy and safety of the drug for the proposed usage is considered to be adequate.

#### *Question 2*

- Please provide a formal justification for not submitting a bioequivalence study comparing the three proposed tablet strengths of armodafinil (that is, 50, 150 and 250 mg).

*Sponsor's response*

Bioequivalence was demonstrated between the 5 x 50mg film coated tablets employed in the Phase III clinical trials with the 1 x 250 mg uncoated to-be-marketed (TBM) tablet

(Study C10953/1023/BE/US). Teva considers that an in vivo BE study was not necessary for the lower strengths of the TBM tablets on the following basis:

- The 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 the 5 x 50 mg clinical trial formulation and the 1 x 250 mg TBM formulations.
- Similar dissolution profiles of all strengths of TBM tablets in multiple pH media.

*Clinical evaluator's comment*

The Australian Regulatory Guidelines for Prescription Medicines (ARGPM) state that bioequivalence among the different strengths of a new chemical entity are required (Section 15.4), unless a justification can be provided for not submitting such data (Section 15.9). The sponsor's justification provided in the response did not address the following clinical issues identified in the ARGPM Section 15.9:

- the PK characteristics of the drug substance(s), such as permeability (or absolute bioavailability), linearity, first pass effect (if any) and its significance;
- the clinical consequences of any potential differences in bioavailabilities of the products under consideration (for example, increased dose leading to toxicity or decreased dose leading to lack of efficacy); and
- the margin between the minimum effective and minimum toxic plasma concentration.

However, it is considered that the absence of clinical bioequivalence data for the different strengths of armodafinil should not preclude approval of the drug. The totality of the clinical data submitted by the sponsor relating to the PK of armodafinil and the efficacy and safety of the drug for the proposed usage is considered to be adequate.

***Question 3***

- Please provide a formal justification for not submitting a mass balance and metabolism study for armodafinil in humans.

*Sponsor's response*

A mass balance study was conducted in Provigil program (C1538a/111/PK/US). The similarities in metabolism between modafinil and armodafinil suggest that the modafinil disposition data would be adequate to describe the armodafinil disposition, and that exposing healthy subjects to a dose of a radiolabeled compound would be unnecessary. The results of a modafinil mass balance study suggest that the compound is nearly exclusively metabolised in the liver. Less than 10% of the parent compound and majority of the metabolites were excreted in the urine.

*Clinical evaluator's comment*

The sponsor's response is satisfactory.

***Question 4***

- Please provide the $C_{max}$ and $AUC_{inf}$ ratios (fed:fasted) for armodafinil, with 90% CIs, using standard bioequivalence methodology for the 6 subjects who received single-dose armodafinil (100 mg) in the fasted and fed state in Study 101.

*Sponsor's response*

As requested by TGA, assessment of bioequivalence for study $C_{max}$ and $AUC_{inf}$ ratios (fed:fasted) for armodafinil, with 90% CIs, using standard bioequivalence methodology for

the 6 subjects who received single dose armodafinil (100 mg) in the fasted and fed state in Study 101 are provided in Table 11.

**Table 11: Comparison of C10953 100 mg fed to C10953 100 mg fasted: R-Modafinil PK analysis set.**

| Parameter | Statistic | Fed | Fasted | GMR (Fed/Fasted) | 90% CI for GMR |
|---|---|---|---|---|---|
| AUC[0-inf] (mcg*hr/mL) | n | 6 | 6 | | |
| | Mean | 43.80 | 40.58 | | |
| | SD | 8.175 | 7.370 | | |
| | SE of mean | 3.337 | 3.009 | | |
| | Geometric Mean | 43.175 | 39.977 | 1.080 | 1.018, 1.146 |
| | CV | 18.7 | 18.2 | | |
| | Median | 42.90 | 42.80 | | |
| | Min, max | 33.30, 56.60 | 29.00, 47.90 | | |
| Cmax (mcg/mL) | n | 6 | 6 | | |
| | Mean | 2.17 | 2.44 | | |
| | SD | 0.092 | 0.384 | | |
| | SE of mean | 0.038 | 0.157 | | |
| | Geometric Mean | 2.168 | 2.416 | 0.897 | 0.795, 1.013 |
| | CV | 4.2 | 15.7 | | |
| | Median | 2.18 | 2.46 | | |
| | Min, max | 2.05, 2.29 | 1.97, 2.94 | | |

*Clinical evaluator's comment*

The provided data indicate that the geometric mean $AUC_{inf}$ of armodafinil is 8% higher in the fed state compared to the fasted state, with the 90% CI of the geometric mean ratio (GMR) (1.018, 1.146) not being enclosed completely within the standard bioequivalence interval of 0.80 to 1.25. The geometric $C_{max}$ of armodafinil is 10% lower in the fed state compared to the fasted state, with the 90% CI of the GMR (0.795, 1.013) not being enclosed completely within the standard bioequivalence interval of 0.80 to 1.25. The results indicate that armodafinil is not bioequivalent when administered in the fed and fasted states. However, the data should be interpreted cautiously as only 6 subjects were included in the fed versus fasted analysis. The recommended number of subjects for formal bioequivalence studies is stated to be not less than 12.[29]

Overall, the difference in bioavailability between armodafinil in the fasted state and fed state (based on the $C_{max}$ and $AUC_{inf}$) is unlikely to be clinically significant. However, the median $T_{max}$ was notably shorter in the fasted state compared to the fed state (2.3 versus 6 h, respectively). This is of potential clinical significance as the onset of effect might be delayed when the drug is administered in the fed state. The *Dosage and Administration* section of the proposed PI has no specific recommendation relating to the administration of armodafinil with or without food. The *Pharmacokinetics* section of the PI comments that the effect of food on overall bioavailability is minimal, but notes that the $T_{max}$ may be delayed by approximately 2 to 4 h in the fed state. This section of the PI also states that

> *[s]ince the delay in $t_{max}$ is also associated with elevated plasma concentrations later in time, food can potentially affect the onset and time course*

of the pharmacological action of armodafinil. Information on the potential effect of food on the time course of action of armodafinil should be included in the *Dosage and Administration* section of the PI. It would be reasonable to include a statement in the *Dosage and Administration* section indicating that, while armodafinil can be taken with or without food, administration with food may delay the onset of action and prolong the effect of the drug.

[29] European Medicines Agency, Committee for Medicinal Products for Human Use, "Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **)", 20 January 2010.

### *Question 5*

- The Summary of Clinical Pharmacology included relative exposure data for R-armodafinil versus racemic modafinil following multiple doses of armodafinil and Provigil, respectively.
  - Please confirm that the data in the summary were based on the Day 7 results for subjects from armodafinil Study 102 and Provigil Study 2101.
  - The summary refers to a 150 mg dose of armodafinil from Study 102. However, this study did not include an actual 150 mg dose of armodafinil. The data for the 150 mg dose provided in the Summary appears to be based on dose normalised to 150 mg data. Please clarify the source of the data for the 150 mg dose of armodafinil reported in the Summary
  - The PK data from armodafinil Study 102 referred to in the summary were obtained following fasting on sample collection days, while the PK data from Provigil Study 2101 were obtained 1 h after a light breakfast on collection days. Given the different relationship between dose and meals on data collection days for the two studies, please comment on the validity of the relative exposure data for R-modafinil and racemic modafinil provided in the Summary.

*Sponsor's response*

- The sponsor confirms that the data in the summary were based on the Day 7 results for subjects from armodafinil Study 102 and Provigil Study 2101.
- The armodafinil values are based on data from the pooled analysis (dose normalised to 50 mg) that is presented below in Table 12 from the Summary of Clinical Pharmacology provided to the FDA. This methodology was considered adequate based on the lack of deviation from dose linearity, and was intended to increase the dataset on which the PK parameters were calculated. The corresponding values for 150 and 250 mg/day were calculated by multiplying the values in the table below by factors of 3 and 5, respectively.

**Table 12: Mean PK parameters of R-modafinil following single and multiple doses of armodafinil in healthy subjects (dose dependent parameters normalised to a 50 mg dose armodafinil).**

| Parameter (unit) Statistic | Single dose (N=93) | Multiple dose Day 7 (N=34) | Multiple dose Day 14 (N=30) |
|---|---|---|---|
| $AUC_{0-\infty}$ (µg•h/mL) | | | |
| n | 93 | NA | NA |
| Mean±SD | 24.1±6.89 | NA | NA |
| $AUC_{0-\tau}$ (µg•h/mL) | | | |
| n | NA | 34 | 30 |
| Mean±SD | NA | 27.1±5.75 | 26.1±4.03 |
| $C_{max}$ (µg/mL) | | | |
| n | 93 | 34 | 30 |
| Mean±SD | 1.3±0.36 | 1.8±0.36 | 1.9±0.37 |
| $t_{max}$ (h) | | | |
| n | 93 | 34 | 30 |
| Median (range) | 1.5 (0.5, 6.0) | 2.0 (0.5, 6.0) | 1.8 (0.0, 4.0) |
| $t_{½}$ (h) | | | |
| n | 87 | 4 | 30 |
| Mean±SD | 13.8±3.31 | 15.3±3.04 | 16.9±3.13 |
| V/F (L) | | | |
| n | 93 | 4 | 30 |
| Mean±SD | 42.4±12.54 | 54.5±31.42 | 47.4±8.66 |
| CL/F (mL/min) | | | |
| n | 93 | 34 | 30 |
| Mean±SD | 38.6±9.86 | 32.4±8.72 | 32.7±5.16 |
| $R_{ss}$ | | | |
| n | NA | 34 | 30 |
| Mean±SD | NA | 1.2±0.18 | 1.2±0.19 |
| $R_{obs}$ | | | |
| n | NA | 34 | 30 |
| Mean±SD | NA | 1.8±0.27 | 1.7±0.20 |

Pooled analysis: armodafinil studies 1023, 101, and 102 combined (single dose) and armodafinil study 102 (multiple dose).
$AUC_{0-\infty}$=area under the plasma concentration by time curve from time zero to infinity; $AUC_{0-\tau}$=area under the plasma concentration by time curve over 1 dosing interval; $R_{ss}$=steady-state accumulation ratio (ratio of $AUC_{0-\tau}$ on day 7 or 14 to $AUC_{0-\infty}$ on day 1); CL/F=total oral clearance; $C_{max}$=maximum observed plasma drug concentration; n=number of subjects included in the analysis; NA=not applicable; $R_{obs}$=observed accumulation ration (ratio of $AUC_{0-\tau}$ on day 7 or 14 to $AUC_{0-24}$ on day 1); $t_{½}$=elimination half-life; SD=standard deviation; $t_{max}$=time to maximum observed drug concentration; V/F=apparent volume of distribution.

- The sponsor acknowledges that a direct comparison between fed or fasted states is ideal, but these data are the most appropriate available for comparison. The PK data from armodafinil Study 102 referred to in the summary were obtained following fasting on sample collection days, while the PK data from Provigil Study 2101 were obtained 1 h after a light breakfast on collection days. Food has been shown to be significantly related to the rate, but not the extent of absorption of modafinil. Therefore, a light meal is expected to have minimal effect on exposure ($C_{max}$ and AUC) of these 2101 modafinil data.

*Clinical evaluator's comment*

The sponsor's response is satisfactory.

### *Question 6*

- In vitro data are reported to show that armodafinil has weak, but concentration-related inductive effects on CYP1A2, CYP2B6, and CYP3A4/5 activities. Clinical DDI studies have been undertaken investigating the effect of co-administration of armodafinil on CYP3A4 substrates (midazolam and quetiapine) and a CYP1A2 substrate (caffeine), but not a CYP2B6 substrate. Please justify not undertaking a clinical DDI study assessing the effect of co-administration of armodafinil on a CYP2B6 substrate.

*Sponsor's response*

Modafinil and armodafinil produces modest, but concentration dependent, induction of CYP3A4, CYP1A2 and CYP2B6 activity in primary human hepatocytes in vitro. The observation that CYP2B6 activity is increased under the same conditions as CYP3A4 was not surprising given the high correlation in the responses of the two enzymes to CYP3A4 inducers.[30] CYP3A4, however, is the more important CYP enzyme due to its high levels in liver and its wide range of substrates. Several armodafinil DDI studies were conducted in healthy subjects to investigate the potential of armodafinil to induce the activity of CYP1A2 (using caffeine as a probe substrate); the potential of armodafinil to induce activity of gastrointestinal and hepatic CYP3A4 activity (using IV and oral midazolam as the probe substrate); and the potential for repeated doses of armodafinil to induce activity of CYP3A4 using quetiapine, carbamazepine, ziprasidone, aripiprazole, and risperidone as substrates. While induction of CYP1A2 was ruled out in vivo, treatment with armodafinil caused moderate induction of CYP3A activity in vivo and consequently reduced systemic exposures to co-medications that are substrates for CYP3A. Quantitatively, CYP2B6 is a less important CYP enzyme, and therefore no formal DDI study was undertaken.

*Clinical evaluator's comment*

The sponsor's response is unsatisfactory. No quantitative in vitro data were presented in the response to Question 6 supporting the decision not to undertake a clinical DDI investigating the potential PK effects of co-administration of armodafinil and a CYP2B6 substrate. It is recommended that the nonclinical evaluator review the in vitro data provided in the original submission and specifically comment on the interaction between armodafinil and the CYP2B6 substrate probe. In particular, the nonclinical evaluator should compare the in vitro interaction results between armodafinil and a CYP2B6 substrate probe and armodafinil and a CYP3A4/5 substrate probe. If in vitro induction of CYP2B6 and CYP3A4/5 by armodafinil is quantitatively similar then the sponsor should be requested to undertake a clinical DDI study between armodafinil and a CYP2B6 substrate. The PI should include a statement on the potential of armodafinil to induce CYP2B6 activity, unless it can be satisfactorily determined from the in vitro data that a clinically significant interaction is unlikely.

### *Question 7*

- In vitro data are reported to show that armodafinil has inhibitory effects on CYP2C19 and CYP2C9. A clinical DDI studies has been undertaken investigating the effect of co-administration of armodafinil on a CYP2C19 substrate (omeprazole), but not a CYP2C9 substrate. Please justify not undertaking a clinical DDI study assessing the effect of co-administration of armodafinil on a CYP2C9 substrate.

*Sponsor's response*

Racemic modafinil was shown to suppress CYP2C9 activity in vitro in human hepatocytes but armodafinil did not. In a subsequent in vivo clinical DDI study (Study

[30] Faucette SR, et al. Regulation of CYP2B6 in primary human hepatocytes by prototypical inducers. *Drug Metab Dispos.* 32: 348-358 (2004).

C1538a/410/PK/US), there was no significant effect of repeated administration of 400 mg racemic modafinil on the PK of S-warfarin (a CYP2C9 substrate) following a single dose of racemic warfarin.

*Clinical evaluator's comment*

The sponsor's response is satisfactory. The proposed PI (Interactions with other drugs) includes the following statement:

> *Concomitant administration of modafinil with warfarin did not produce significant changes in the pharmacokinetic profiles of (R)- and (S)-warfarin. However, since only a single dose of warfarin was tested in this study, an interaction cannot be ruled out. Therefore, more frequent monitoring of prothrombin times/INR should be considered whenever Nuvigil is co-administered with warfarin.*

### *Question 8*

- In an in vitro study using MDR-MDCK cell monolayers it was reported that armodafinil is a P-glycoprotein (Pgp) substrate, but is not an inhibitor of Pgp (Study DP-2006-055). There were no clinical DDI studies investigating the effect of Pgp inhibitors or inducers on the bioavailability of armodafinil. The sponsor is requested to justify not submitting such studies. Does the sponsor have any data on whether armodafinil is an inducer of Pgp?

*Sponsor's response*

There are no Pgp induction data available for armodafinil. At the request of the FDA, a comprehensive literature search was performed for:

- information on the Pgp induction potential of modafinil in vivo; and
- any in vivo Pgp drug-drug interaction information as an alternative to conducting an in vivo study with a Pgp inhibitor.

These searches provided no suggestion of effects of modafinil or armodafinil on the PK or safety/efficacy of concomitant medications in vivo through modulation of the activity of the Pgp transporter system. A more recent search of transporter queries using the University of Washington Drug Interaction Database provided no additional literature references.

*Clinical evaluator's comment*

The sponsor's response is adequate. The proposed PI (Interaction with P-Glycoprotein) includes the following statement:

> *An in vitro study demonstrated that armodafinil is a substrate, but not inhibitor, of P-glycoprotein.*

However, the proposed PI submitted with the Section 31 response deleted the following statement:

> *The impact of inhibition of P glycoprotein is not known.*

This statement was included in the PI provided with the original submission and is found in the US prescribing information. It is considered that this statement be amended to read:

> *The clinical impact of inhibition of P-glycoprotein on the bioavailability of armodafinil is not known.*

### *Question 9*

- The sponsor states that the metabolic pathways of armodafinil have not been specifically characterised in the clinical studies, but reports that the formation of modafinil sulfone from R-modafinil is metabolised by CYP3A4/5. At steady state,

modafinil sulfone represents approximately 56% of parent drug exposure. Therefore, in view of the involvement of CYP3A4/5 in at least part of the metabolism of armodafinil the sponsor should provide a justification for not submitting clinical DDI studies investigating the effects of CYP3A4 inhibition and CYP3A4 induction on systemic exposure to armodafinil

*Sponsor's response*

Armodafinil is indeed a substrate for cytochrome P450 3A4/5 (CYP3A4/5), however the existence of multiple pathways for metabolism and the fact that a non CYP450 related pathway is the most rapid in metabolising armodafinil suggest a low probability that concomitant medications that inhibit CYP450 will significantly affect the overall PK profile of armodafinil. The impact of CYP3A4/5 inducers on armodafinil was investigated from January to May of 2011 in a study entitled "An Open Label, Parallel Group Study to Evaluate the Effect of Multiple Dose Administration of Armodafinil (250 mg/day) on the Pharmacokinetics of Carbamazepine (200 mg) and the Effect of Multiple-Dose Administration of Carbamazepine (400 mg/day) on the Pharmacokinetics of Armodafinil (250 mg) in Healthy Male Subjects". The details of this study are published.[31] At steady state, carbamazepine caused a decrease in systemic exposure to armodafinil. Armodafinil $C_{max}$ is approximately 11% lower and armodafinil AUC is approximately 37% lower when administered in combination with carbamazepine as compared to when administered alone. Dose adjustment for armodafinil may be required when co-administered with CYP3A4/5 inducers as carbamazepine.

*Clinical evaluator's comment*

The published study referred to in the sponsor's response has been reviewed. The study was not provided by the sponsor, but was obtained independently by the evaluator. The study was a single site (USA), open label, parallel group study designed to evaluate the potential PK interaction between armodafinil and extended release carbamazepine. Carbamazepine is a substrate for CYP3A4 and a potent inducer of this enzyme. The study was conducted in accordance with relevant ICH and FDA guidelines and the Declaration of Helsinki. The study protocol and informed consent form were reviewed and approved by an IRB. The study was sponsored by Teva Pharmaceuticals, Inc.

The study included 81 healthy adult men aged 18 to 45 years inclusive, of whom 79 were evaluable for PK (group 1 = 40; group 2 = 41), and 80 were evaluable for safety (40 in each group). Subjects were assigned (not randomized) to study group 1 (effect of pre-treatment with armodafinil on the single dose PK of carbamazepine) or study group 2 (effect of pre-treatment with carbamazepine on the single dose PK of armodafinil). In both groups, sampling for PK analysis was undertaken following single dose carbamazepine (group 1) or single-dose armodafinil (group 2). The PK sampling following single dose carbamazepine (8 days) was approximately 5 half-lives of the drug (that is, average half-life following single dose of 36 h [carbamazepine PI]). The PK sampling following single dose armodafinil (3 days) was approximately 5 half-lives of the drug (that is, half-life of 15 h). Therefore, the sampling time was sufficient to characterise the elimination phase of each drug following single dose administration. In addition, the mean extrapolation percentage (that is, percentage of $AUC_{inf}$ that was extrapolated from the time of the last measurable plasma concentration to infinite time) was < 10% for carbamazepine (alone and in combination with armodafinil) and for armodafinil (alone and in combination with carbamazepine) confirming the adequacy of the sampling schedule for the two drugs.

PK parameters of armodafinil and carbamazepine were estimated using non-compartmental methods. The parameters included $C_{max}$, AUC, $AUC_{inf}$, $AUC_{0-t}$, $AUC_{0-\tau}$, $T_{max}$,

[31] Darwish M, et al. Evaluation of the potential for pharmacokinetic drug-drug interaction between armodafinil and carbamazepine in healthy adults. *Clin Ther.* 37: 325-337 (2015).

λz, and t1/2. These parameters were also calculated as appropriate and where possible for the metabolites of armodafinil and carbamazepine.

The results for armodafinil and its two metabolites are summarised below in Table 13. The geometric mean for armodafinil Cmax was 11% lower when armodafinil was co-administered with carbamazepine compared to armodafinil alone, with the 90% CI of the GMR being enclosed entirely within the bioequivalence interval of 0.80 to 1.25. The geometric mean for armodafinil AUCinf was 37% lower when armodafinil was co-administered with carbamazepine compared to armodafinil alone, with the 90% CI for the GMR being completely outside the bioequivalence interval of 0.80 to 1.25. The results suggest that the efficacy of armodafinil might be reduced when the drug is co-administered with CYP3A4/5 inducers.

**Table 13: PK parameters for armodafinil, R-modafinil, and modafinil sulfone after administration of 250 mg armodafinil alone and pre-treatment with carbamazepine 400 mg/day.**

| Analyte/Variable* | Armodafinil Alone (n = 38)† | Armodafinil + Carbamazepine (n = 38) | Geometric Mean Ratio (90% CI) |
|---|---|---|---|
| Armodafinil | | | |
| $C_{max}$ (µg/mL) | 6.0 (1.1) | 5.3 (0.9) | 0.89 (0.86–0.92) |
| $AUC_{0-\infty}$ (µg · h/mL) | 124.0 (34.9) | 75.6 (12.8) | 0.63 (0.60–0.65) |
| $AUC_{0-t}$ (µg · h/mL) | 114.9 (31.2) | 72.0 (13.4) | 0.64 (0.61–0.66) |
| $T_{max}$ (h) | 2.0 (1.0, 4.0) | 2.0 (0.5, 6.0) | ND |
| $t_{½}$ (h) | 15.3 (4.3) | 9.9 (1.2) | ND |
| Extrapolation (%) | 7.1 (2.9) | 5.9 (2.2) | ND |
| $\lambda_z$ (1/h) | 0.048 (0.011) | 0.71 (0.009) | ND |
| *R*-modafinil acid | | | |
| $C_{max}$ (µg/mL) | 0.5 (0.1) | 0.5 (0.1) | ND |
| $AUC_{0-\infty}$ (µg · h/mL) | 11.3 (3.5) | 8.2 (2.2) | ND |
| $AUC_{0-t}$ (µg · h/mL) | 6.4 (2.7) | 4.4 (1.2) | ND |
| $T_{max}$ (h) | 1.5 (1.0, 4.0) | 2.0 (0.5, 72.0) | ND |
| Modafinil sulfone | | | |
| $C_{max}$ (µg/mL) | 0.5 (0.2) | 1.3 (0.4) | ND |
| $AUC_{0-\infty}$ (µg · h/mL) | 44.3 (12.7) | 72.6 (28.8) | ND |
| $AUC_{0-t}$ (µg · h/mL) | 26.3 (14.9) | 57.4 (23.4) | ND |
| $T_{max}$ (h) | 24.0 (10, 48) | 21.0 (8, 24) | ND |

ND = not determined.
*Mean (SD) for all variables except $T_{max}$, which is median (minimum, maximum).
†Three subjects were excluded from the pharmacokinetic analysis.

The GMR for carbamazepine Cmax was 0.88 (90% CI: 0.83, 0.92) when co-administered with armodafinil compared with carbamazepine alone. The GMR for carbamazepine $AUC_{inf}$ was 0.75 (90% CI: 0.71, 0.80) when co-administered with armodafinil compared with carbamazepine alone. The results indicate that armodafinil is an inducer of CYP4A4.

The sponsor's justification for not submitting a PK study investigation co-administration of armodafinil with a CYP3A4 inhibitor is unsatisfactory. It is recommended that the nonclinical evaluator review the in vitro data relating to a co-administration of armodafinil and a CYP3A4 inhibitor. If the data predict a potentially significant DDI, then the sponsor should be requested to undertake a formal clinical PK interaction study investigating co-administration of armodafinil and a CYP3A4 inhibitor.

### *Question 10*

- Achiral modafinil sulfone was identified as a metabolite of R-modafinil. This suggests that R-modafinil sulfone resulting from the metabolism of R-modafinil undergoes

interconversion with S-modafinil sulfone. Please provide the data supporting interconversion of the enantiomers of S-modafinil sulfone.

*Sponsor's response*

Modafinil sulfone is an achiral molecule. Once armodafinil (or S-modafinil) undergoes oxidation on the chiral sulfur atom to form modafinil sulfone, the molecule loses its chirality.

*Clinical evaluator's comment*

The sponsor's response is satisfactory.

## Safety

### *Question 11*

- The Summary of Safety included an analysis of QTc changes in the 4 Phase III, double blind, placebo controlled studies using QTcF (that is, Fridericia correction) (Table 43). Please repeat the analysis using QTcB (that is, Bazett correction). Please comment on the significance of any observed differences between the two analyses.

*Sponsor's response*

An analysis of QTc changes in the 4 Phase III, double blind, placebo controlled studies using QTcB (that is, Bazett correction) has been performed (Table 14). Values of QTc more than 450 msec were observed with similar frequency for the armodafinil and placebo treatment groups across sleep disorder populations. Five patients with OSAHS (4 armodafinil treated, 1 placebo treated) and one patient with Narcolepsy (armodafinil treated) had QTc values more than 480 msec. Only 2 armodafinil treated patients (with OSAHS) had a QTc value more than 500 msec. Changes from baseline of more than 60 msec were observed in no more than 4% of patients in any treatment group.

**Table 14: Categorical changes from baseline in QTc interval (Bazett) by sleep disorder and treatment group in double blind, placebo controlled studies.**

| | Narcolepsy | | OSAHS | | SWSD | |
|---|---|---|---|---|---|---|
| | Number (%) of patients[a] | | | | | |
| **QTc interval (Bazzet)** | **Armodafinil (n=131)** | **Placebo (N=63)** | **Armodafinil (N=391)** | **Placebo (N=260)** | **Armodafinil (N=123)** | **Placebo (N=122)** |
| **Absolute value, msec** | | | | | | |
| >450 | 6 (5) | 3 (5) | 37 (9) | 20 (8) | 7 (6) | 9 (7) |
| >480 | 1 (<1) | 0 | 4 (1) | 1 (<1) | 0 | 0 |
| >500 | 0 | 0 | 2 (<1) | 0 | 0 | 0 |
| **Change from baseline, msec** | | | | | | |
| <30 | 74 (56) | 46 (73) | 277 (71) | 183 (70) | 89 (72) | 72 (59) |
| 30-60 | 49 (37) | 13 (21) | 90 (23) | 68 (26) | 25 (20) | 38 (31) |
| >60 | 2 (2) | 0 | 11 (3) | 7 (3) | 5 (4) | 4 (3) |

[a] Includes only patients with post baseline QTc values
OSAHS=obstructive sleep apnea hypopnea syndrome; SWSD=shift work sleep disorder; msec=milliseconds

In the double blind, placebo controlled studies, there were no clinically meaningful changes from baseline to endpoint and no marked differences between the armodafinil and placebo treatment groups in mean ventricular rate or in mean PR, QRS, QT, QTc (Bazett or Fridericia), or RR intervals across the sleep disorder populations.

In all sleep disorder studies combined, small mean increases in ventricular rate and decreases in uncorrected QT interval and RR interval were observed over time. These changes were consistent with the mean increase in pulse over time. Mean changes in corrected QT interval did not indicate any clinically meaningful trends at any time point.

*Clinical evaluator's comment*

The sponsor's response is satisfactory. Overall, the number of patients in both armodafinil and placebo groups with categorical increases in QTcB from baseline was greater than the corresponding number of patients with categorical increases in QTcF from baseline. In general:

> *Bazett's correction overcorrects at elevated heart rates and under corrects at heart rates below 60 bpm and hence is not an ideal correction. Fridericia's correction is more accurate than Bazett's correction in subjects with such altered heart rates.*[32]

### *Question 12*

- In the post marketing period from the date of approval through 31 October, there were 13 reports of death and 1 report each of brain death and sudden death. The most recent PADER summarising post marketing data from the date approval through 31 May 2014 identifies 6 further deaths associated with armodafinil. Please provide a tabulated summary of all reported post marketing deaths and narratives for each of the post marketing deaths.

*Sponsor's response*

A search was conducted in Teva's Pharmacovigilance global database (MedDRA version 17.1) using the following criteria:

- Preferred Product description – armodafinil
- Initial received date – Cumulative data through 27 February 2015
- Cases with Fatal outcome
- All sources excluding Clinical trials

Since the following search includes all fatal cases from all sources regardless of the relatedness of the death to armodafinil, the overall number of cases is different from PADER's count which takes into consideration only related cases (48 cases versus 21 cases, respectively).

In 2012, Teva's Pharmacovigilance global database was merged with the Cephalon pharmacovigilance database.

**Search outcome**

A total of 48 armodafinil fatal cases reported post marketing were retrieved in the search. There were a total of 53 reported AEs with a fatal outcome (Tables 15-16).

**Table 15: A summary of death cases of patients taking armodafinil defined by the source of reporting.**

| Source | No. of cases | Related cases according to company assessment | Not-related cases according to company assessment |
|---|---|---|---|
| Solicited | 12 | 2 | 10 |
| Spontaneous | 36 | 13 | 23 |
| Total | 48 | 15 | 33 |

[32] European Medicines Agency, Committee for Medicinal Products for Human Use, "ICH note for guidance on the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs (ICH E14) (CHMP/ICH/2/04)", November 2005.

**Table 16: A summary of total death cases according to SOC of the reported fatal PT.**

| SOC | PT | Count of fatal events | Company causality |
|---|---|---|---|
| Injury, poisoning and procedural complications | Alcohol poisoning | 1 | Unlikely |
| | Overdose | 2 | 1 not related;<br>1 unlikely |
| | Road traffic accident | 1 | Unlikely |
| skin and subcutaneous tissue disorder | Stevens-Johnson syndrome | 1 | Not assessable |
| | DRESS Syndrome | 1 | Possible |
| General disorders and administration site conditions | Brain death | 1 | Unlikely |
| | Sudden death | 1 | Possible |
| | Death | 23 | 8 not assessable; 1 possible;<br>13 not related;<br>1 unlikely |
| | Organ failure | 1 | Not assessable |
| | multi-organ failure | 1 | Possible |
| Cardiac disorders | Cardiac disorder | 1 | Not related |
| | Cardiac failure | 1 | Possible |
| | Cardio-respiratory arrest | 1 | Not related |
| | Myocardial infarction | 2 | 1 possible;<br>1 not related |
| Neoplasms benign, malignant and unspecified (incl. cysts and polyps) | Lung cancer metastatic | 1 | Not related |
| | Lung neoplasm malignant | 1 | Not related |
| | Pancreatic carcinoma | 2 | Not related |
| | Prostate cancer metastatic | 1 | Not related |
| Respiratory, thoracic and mediastinal disorders | Pulmonary fibrosis | 1 | Not related |
| Renal and urinary disorders | Renal failure chronic | 1 | Not related |
| Nervous system disorders | Status epilepticus | 1 | Unlikely |
| Psychiatric disorders | Drug abuse | 1 | Not related |
| | Completed suicide | 5 | 3 possible,<br>1 not assessable,<br>1 not related |
| Social circumstances | Dependence on enabling machine | 1 | Not related |
| **Total** | | **53** | |

Twelve cases were received from solicited sources such as AccessMed, a part of the Cephalon CARES Patient Assistant Program, and the Teva Patient Assistance Program. It has often been observed that solicited sources, in which patients are closely monitored, generate much higher reporting rates than are generally received from spontaneous sources. In addition, the Teva Patient Assistance Program treated disadvantaged patients who could not otherwise afford their medications. A contribution of the social

circumstances of this patient population to death outcomes from unknown reasons cannot be excluded.

In order to further analyse the causes of death in the 48 reported death cases the cases are summarised below based on the System Organ Class (SOC) of the reported fatal adverse events. There were a total of 53 reported PTs with a fatal outcome.

**Review of death cases**

**Injury, poisoning and procedural complications.** SOC includes a total of 4 cases: 1 case of alcohol poisoning, 2 cases of overdose and 1 case of a road accident. The patient who died from alcohol poisoning also had previous history of medication abuse and bipolar disorder. Reporter suggested causality between armodafinil use and the death and company assessed the causality as unlikely. One of the patients who died from overdose had an underlying history of depression and use of concomitant medications that may have contributed to the event. It was later confirmed that the patient had died from acute fentanyl intoxication. In the second overdose case the patient had a history of depression, anxiety and accidental overdose of dilaudid and eventually died from methamphetamine overdose. The company's causality was assessed as not related to armodafinil in both cases. The car driver who died in a fatal road accident was assessed originally as possibly related to armodafinil use. Further information revealed changed the company causality to unlikely related to armodafinil. The patient's underlying medical history of uterine and ovarian cancer and unspecified pain medications provided an alternate etiology for the event.

**Skin and subcutaneous tissue disorders.** SOC includes 1 case of SJS and 1 case of DRESS syndrome. Serious skin reactions including SJS have been identified as risks of armodafinil and are highly monitored by Teva. The patient took armodafinil for shift work disorder. Due to lack of further information causality was not assessable by the company. A case from the literature described a patient who was taking armodafinil for fatigue related to methadone. The patient eventually died of DRESS syndrome accompanied by fatal multi organ failure and a cardiac function failure. Both reporter and the company assessed the death as possibly related.

**General disorders and administration site conditions.** SOC contains 27 reports in total; 23 of these cases list no specific cause of death. Of the reported deaths, 13 were assessed by company as not related to armodafinil, 1 was assessed as possible; and 8 could not be assessed due to insufficient information, and 1 was assessed as unlikely. A review of the narrative of the death cases with unspecified cause did not reveal any special circumstances or cumulative findings to connect the cases. Most cases had a sudden unexplained death in which patients did not have any medical history thought to contribute to the death. In these cases, armodafinil was assessed as not causally related to the deaths. In three cases the death was later explained as a result of chronic renal failure, cardiomegaly and AIDS.

**Cardiac disorders.** SOC includes 5 cases including 2 cases of myocardial infarction. One of the cardiac cases has been described above; that is, DRESS syndrome. In a second case a patient was using a CPAP machine and had a cardiac arrest while away from the machine. The case was assessed by the company as not related. In a third case the patient had a medical history of heart condition and coronary artery bypass graft among other conditions which led to his death. The case was assessed by the company as not related. Two patients died due to myocardial infarction. One patient with multiple sclerosis took armodafinil and later felt palpitations, chest pain, and developed asystole. A relationship to armodafinil could not be excluded due to the proximity of treatment to the events. In another case a patient known to suffer from cardiac illness died of a massive myocardial infarction. He was not receiving armodafinil at the time of his death and causality was assessed as not related.

**Neoplasms benign, malignant and unspecified (including cysts and polyps).** SOC includes 5 cases. In two cases of lung cancer metastatic, patients died from terminal or metastatic lung cancer. There is no further information on whether the cancer preceded armodafinil use however both cases were assessed by the company as not related. In 1 case of pancreatic carcinoma cancer was diagnosed shortly after starting armodafinil and both the reporter and the company concluded there were no relationship between armodafinil and the cause of death. In the second case pancreatic cancer predated armodafinil treatment and patient died of disease progression. The case was assessed by the company as not related to armodafinil. In a report of prostate cancer metastatic, the disease began a few years prior to armodafinil therapy. Armodafinil was taken in order to fight fatigue and difficulty staying awake. The case was assessed by the company as not related to the drug armodafinil.

**Respiratory, thoracic and mediastinal disorders.** SOC included 1 case of pulmonary fibrosis. In this case the patient suffered from obstructive sleep apnea and died of intercurrent illness of severe end stage pulmonary fibrosis. Death was assessed as not related to use of armodafinil by both the reporter and the company.

**Renal and urinary disorders**. SOC included one case of chronic renal failure. The patient suffered from renal failure prior to her treatment with armodafinil. Her death was assessed by both the reporter and the company as the result of complications of her chronic renal failure and as not related to armodafinil.

**Nervous system disorders.** SOC includes one case of status epilepticus with secondary brain death event. Both fatal events occurred 4 months after starting treatment. The patient had a medical history of depression, post traumatic stress disorder (PTSD), tremor and familial migraines. Multiple conditions such as respiratory failure, serotonin syndrome, anaemia, altered mental status and renal and liver failures were reported as adverse events. The reporter and the company could not rule out a temporal relation to armodafinil however follow-up information on both patient's history and negative lab results contribute to a change in assessment to unlikely.

**Psychiatric disorders.** SOC includes one case of drug abuse and 5 cases of completed suicide. In the first case the patient died of methamphetamine drug abuse and overdose as was previously discussed. The 5 cases of successful suicide are listed below:

- One patient suffered from mental illness and severe fatigue. They discontinued armodafinil after 3 days of therapy. As there is no medication start date and no further information on their death, causality was assessed as related by both the reporter and the company.
- Another patient was taking armodafinil as an only drug. As no further information is available, causality could not be determined.
- A third patient suffered from hallucinations, massive mood swings, episodes of confusion and abnormal behaviour on the morning prior to the suicide. Therapy with armodafinil was discontinued but it was not clear whether it stopped prior to the suicide or not. As no further information was available, the company assessed the death as possibly related.
- A fourth patient suffered from drug addiction. They were also taking buprenorphine HCl and naloxone HCl. The company assessed the case as not related.
- A fifth patient had a long history of suicidality (beginning 2 years pre armodafinil use), depression and anxiety. Armodafinil was taken to treat depression. In April 2011, the patient discontinued armodafinil due to insurance issue and committed suicide in June 2011. Although the physician ruled out a relationship between the suicide and armodafinil, both reporter and the company assessed causality as possible.

Narratives of all cases with fatal outcome presented in the analysis were provided in the sponsor's response.

**Conclusions**

The majority of patients who died while on armodafinil had previously existing conditions which deteriorated thus contributing to the cause of death. All of these patients were on armodafinil doses within the recommended range.

*Clinical evaluator's comment*

The sponsor's response is satisfactory. The case narratives have been examined.

### Second round benefit-risk assessment

#### Second round assessment of benefits

After consideration of the responses to the clinical questions, the benefits of armodafinil (Nuvigil) for the proposed usages are unchanged from those identified in the first round.

#### Second round assessment of risks

After consideration of the responses to the clinical questions, the risks of armodafinil (Nuvigil) for the proposed usages are unchanged from those identified in the first round.

#### Second round assessment of benefit-risk balance

After consideration of the responses to the clinical questions, the benefit-risk balance of armodafinil (Nuvigil) for the proposed usages remains favourable and is unchanged from that discussed in the first round.

### Second round recommendation regarding authorisation

It is recommended that armodafinil (Nuvigil) be approved:

- to improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy;
- to treat excessive sleepiness associated with moderate to severe chronic shift work sleep disorder where nonpharmacological interventions are unsuccessful or inappropriate; and
- use as an adjunct to continuous positive airways pressure (CPAP) in obstructive sleep apnoea/hypopnoea syndrome in order to improve wakefulness.

# V. Pharmacovigilance findings

### Risk management plan

The sponsor submitted an Australian RMP Version 1.0 (dated 20 March 2014, DLP 31 October 2013) which was reviewed by the RMP evaluator.

#### Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 17.

**Table 17: Ongoing safety concerns.**

| | |
|---|---|
| **Important identified risks** | • Serious skin reactions<br>• Cardiovascular disorders<br>• Psychiatric disorders<br>• Hypersensitivity |
| **Important potential risks** | • Misuse, abuse and diversion |
| **Missing information** | • Exposure during pregnancy |

### *RMP reviewer comment*

There is a moderate risk that armodafinil will be used outside of its approved indications. There are known DDI of armodafinil, including effects on CYP3A substrates, CYP2C19 substrates, and CNS active drugs. Interaction effects with p-gp substrates are unknown. Given that patient characteristics of armodafinil users include patients on antidepressants, hypnotics, or cardiovascular medication, any effects of an interaction with these compounds needs to be reported. There is no or limited data to exposure in lactating women and paediatric patients.

Notwithstanding the evaluation of the nonclinical and clinical aspects of the Safety Specification, the following recommendations are made. The following should be added as Safety Concerns and become part of the pharmacovigilance plan and risk minimisation plan:

- 'Off-label use' should be added as an Important Potential Risk.
- 'Drug-drug interactions' should be added as an Important Potential Risk.
- 'Exposure during lactation' should be added as Missing information.
- 'Paediatric patients' should be added as Missing information.

## Pharmacovigilance plan

The sponsor proposes routine pharmacovigilance activities for important identified and potential risks and missing information. Furthermore, additional activities are planned for some of the risks. These activities are summarised in Table 18.

**Table 18: Additional pharmacovigilance activities planned by the sponsor.**

| Additional activity | Assigned safety concern | Actions/outcome proposed | Estimated planned submission of final data |
|---|---|---|---|
| Pregnancy registry (non-interventional)<br>The Nuvigil (armodafinil) Tablets [C-IV]/Provigil (modafinil) Tablets [C-IV] Pregnancy Registry<br>Ongoing study | Exposure during pregnancy | To characterise and assess pregnancy outcomes in clinical practice should a pregnancy occur | Annual interim reports<br>Final CSR date not given. |

***RMP reviewer comment***

There is no definite objection to the pharmacovigilance plan proposed by the sponsor in the context of this application, if the RMP evaluator recommendations are implemented.

The sponsor should provide off-label use, misuse, abuse, and diversion data of modafinil in Australia (from a drug utilisation study, sales data, or another source) to enable a reasonably accurate prediction of off-label use, misuse, abuse, and diversion of armodafinil in Australia. This will enable assessment for the need to perform further additional pharmacovigilance activities.

### Risk minimisation activities

The sponsor is not proposing any additional risk minimisation activities.

***RMP reviewer comment***

The sponsor's conclusion is adequate in the context of this submission, if the requests made by the RMP evaluator are implemented.

### Reconciliation of issues outlined in the RMP report

The following section summarises the OPR's first round evaluation of the RMP, the sponsor's responses to issues raised by the OPR and the OPR's evaluation of the sponsor's responses.

***Recommendation #1 in RMP evaluation report***

Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated Section 31 request and/or the nonclinical and clinical evaluation reports, respectively. It is important to ensure the information provided in response to these includes a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.

***Sponsor response***

We acknowledge the recommendation to update the RMP where relevant when addressing matters that have been raised in the nonclinical and clinical evaluation reports. At this stage, no safety matters have been raised in either the nonclinical or clinical evaluations that might affect the RMP.

***Evaluator's comment***

The response has been noted.

***Recommendation #2 in RMP evaluation report***

'Off-label use' should be added as an Important Potential Risk.

***Sponsor response***

Off-label use was added as an Important Potential Risk to the RMP.

***Evaluator's comment***

This is considered acceptable in the context of this application.

***Recommendation #3 in RMP evaluation report***

'Drug-drug interactions' should be added as an Important Potential Risk.

***Sponsor response***

Drug-drug interaction with CYP3A and CYP2C19 inducing/inhibiting substances and CNS active drugs was added as an Important Potential Risk to the RMP.

***Evaluator's comment***

This is considered acceptable in the context of this application.

***Recommendation #4 in RMP evaluation report***

'Exposure during lactation' should be added as Missing information.

***Sponsor response***

Exposure during lactation was added as Missing information to the RMP.

***Evaluator's comment***

This is considered acceptable in the context of this application.

***Recommendation #5 in RMP evaluation report***

'Paediatric patients' should be added as Missing information.

***Sponsor response***

Usage in Paediatric patients was added as Missing information to the RMP.

***Evaluator's comment***

This is considered acceptable in the context of this application.

***Recommendation #6 in RMP evaluation report***

The sponsor should provide off-label use, misuse, abuse, and diversion data of modafinil in Australia.

***Sponsor response***

Analysis of off-label use, misuse, abuse, and diversion data of modafinil in Australia is provided in the updated RMP and below.

*Off-label use*

Teva's Global Pharmacovigilance Database includes individual case safety reports from postmarketing sources (spontaneous, solicited and literature reports) and clinical trials reports of serious and non-serious cases from all over the world. The database was searched for all modafinil cases from all sources originating in Australia which suggested off-label use of modafinil through 17 February 2015. The search criteria included the following MedDRA (version 17.1) PTs: Drug ineffective for unapproved indication, Drug prescribing error, off-label use and therapeutic product ineffective for unapproved indication. Table 19 summarises the number of cases identified in Australia for off-label use.

**Table 19: Summary of total cases identified for Australia out of total cases found for off-label use.**

| | Entire world | Australia |
|---|---|---|
| Total cases found | 1074 | 13 |

All thirteen cases were spontaneous, non-serious reports. The following analysis focusses on three areas of off-label use: Use for unapproved indications, paediatric use and use outside the recommended dosing parameters.

*Off-label Indications*

In Australia, modafinil is indicated in adults for the treatment of excessive sleepiness associated with narcolepsy with or without cataplexy.

Off-label indications for which modafinil was reported to have been taken in Australia include:

- Hypersomnia (4 cases): In one case, a subject was taking modafinil for 6 months. On the third month she developed tremors. Although modafinil had good response she was considering terminating the treatment due to the tremor. In other case patient started having headaches while on modafinil. There was no company causality and outcome was not known. No other adverse events were reported.
- Fatigue (3 cases) which in one case was described as chronic fatigue syndrome and was associated with obsessive compulsive disorder. In one case gain weight of 6 pounds within 12 days was additionally reported.
- Loss of energy (1 case) in a patient with a history of bipolar disorder with depression and attention deficit disorder.
- Stroke (1 case) without any further detail provided,
- Attention deficit hyperactivity disorder (1 case), and Multiple Sclerosis (1 case) without any further explanation.

Table 20 summarises the off-label indications reported as the reason for modafinil treatment.

**Table 20: Summary of off-label use indication in patients on modafinil in Australia.**

| SOC | PT | No. of cases |
|---|---|---|
| General disorders and administration site conditions | Fatigue (Of which 1 included both fatigue and depression) | 2 |
| | Chronic fatigue syndrome | 1 |
| | Loss of Energy | 1 |
| Nervous system disorder | Hypersomnia | 4 |
| | MS | 1 |
| Psychiatric disorders | ADHD | 1 |
| Nervous system disorder | Stroke | 1 |
| | **Total** | 11 |

*Off-label Uses Related to Age or Dose*

The database search for off-label use cases also revealed one case of paediatric use. A child had a medical history of brain injury, epilepsy, nacrolepsy and cataplexy. The child received a dose of 100 mg/d. The child's physician stated that he and his colleagues (paediatricians) have used modafinil for the past 10 years in approximately 150 children

as a treatment for nacrolepsy and idiopathic hypersomnolence as the alternative dexamphetamine has too many side effects.

And one case of higher than recommended dose being given to a subject who suffered from Hypersomnia received 400 mg/d which was later increased to 1000 mg/d by his neurologist. His state improved substantially.

In both cases no additional AEs were reported.

*Misuse, Abuse and Dependence*

The Teva pharmacovigilance database was searched for modafinil cases originating in Australia with events falling within the Drug Abuse and Dependence SMQ (broad and narrow). This SMQ contains search terms covering misuse, abuse, dependence and diversion.

The total number of cases which were identified in Australia in the broad search is summarised in Table 21.

**Table 21: Total number of cases identified for Australia out of total cases found in regards to drug abuse and dependence SMQ - Broad.**

| | Worldwide | Australia |
|---|---|---|
| Total cases found | 937 | 6 |

Of the 6 cases identified, 5 cases were spontaneous non-serious cases and one literature serious case. Three cases had only drug tolerance as a reported event. One case had overdose and drug tolerance reported terms. One case had misuse and overdose reported terms and a final literature case of overdose and drug-induced psychosis reported terms.

*Abuse and Dependence*

No cases of abuse and dependence were identified both in the wide and narrow searches.

*Diversion*

A search of post-marketing reports originating in Australia in the Teva pharmacovigilance database revealed no cases of diversion of modafinil.

*Misuse and Overdose*

Of the 6 cases mentioned above in the Drug Abuse and Dependence SMQ search, 3 cases reported overdose. In the narrow SMQ search only one case of intentional misuse was revealed (the second case below):

- A case describing a subject with a medical history of paranoid personality disorder, narcolepsy and cataplexy, who had taken an overdose of modafinil in 2 occasions in order to stay awake and pass a renewal driving license test. On the first occasion the patient was on 200 mg/d modafinil and it is unknown how much overdose he took. On the second occasion patient was on 400 mg/d dose and was taking at least 500mg/d before the test. The subject experienced modafinil induced psychosis associated with agitation, orofacial dystonia, unusual behaviour, paranoid delusions, hypertension, and tachycardia. The subject showed poorly formed persecutory delusions and auditory hallucinations. The subject was hypertensive and experienced tachycardia. By the next day, the subject was considerably settled and his florid symptomatology had resolved.
- A case of a subject suffering from narcolepsy. The subject took modafinil 400 mg for 2 months which allowed the subject to stay awake for 3 h a day only. The subject intentionally changed her dose of modafinil to as much as 600 mg daily in order to help the subject stay awake longer.

- Another case described a patient who took modafinil for the treatment of idiopathic hypersomnia described as secondary to a year of severe stress. The patient increased his dose on the recommendation of his neurologist from 400 mg/d to 1000 mg/d with clinical improvement.

### *Evaluator's comment*

There is an inconsistency between Table 19 and Table 20 with regard to the number of off-label use cases.

The sponsor should provide an explanation for the discrepancy in the response and provide information on the extra cases of off-label use.

## Summary of recommendations

### *Outstanding issues*

*Issues in relation to the RMP*

It is considered that the sponsor's response to the TGA Section 31 Request has adequately addressed most of the issues identified in the RMP evaluation report.

*Outstanding issues*

- With regard to off-label, the sponsor should provide an explanation for the discrepancy in the response given by the sponsor and provide information on the extra cases of off-label use.
- The nonclinical section of the RMP should be updated to reflect the non-clinical findings with regard to toxicity in bone marrow, kidney and urinary bladder.
- Based on the recommendation in the nonclinical evaluation report, 'Carcinogenicity' should be added as Missing Information.
- With regard to Developmental Toxicity, the sponsor should make the changes to the RMP requested by the Nonclinical Evaluator, including the addition of 'Developmental toxicity' as Important Potential Risk. The nonclinical section of the RMP should be updated to reflect the nonclinical findings.

### *Comments on the safety specification of the RMP*

*Clinical evaluation report*

The clinical evaluator made the following first round comment in regard to safety specifications in the draft RMP:

> *The safety specification in the draft Risk Management Plan is satisfactory.*

The clinical evaluator made the following second round comment in regard to safety specifications in the draft RMP:

> *The clinical aspects of the Safety Specification in the draft RMP with the sponsor's s31 response to the first round evaluation are satisfactory.*

*Nonclinical evaluation report*

The nonclinical evaluator made the following comment in regard to safety specifications in the draft RMP:

> *Module SII of the RMP concluded that there are no "important identified risks" or "important potential risks" regarding clinical armodafinil use based on the nonclinical data. This is inaccurate as the nonclinical data identified toxicity in bone marrow, kidney and urinary bladder which may have clinical relevance. These should be discussed in the RMP and included as "important potential risks". The sponsor has*

*objected to this recommendation and provided data from clinical experience, which requires consideration by the RMP and/or clinical evaluators (see Module 1-0-2 Response Non-S31). Based on the low relative exposures at which the adverse bone marrow, kidney and urinary bladder changes were observed in animal studies, the Nonclinical Evaluator considers these findings should be listed in the RMP.*

*The carcinogenic potential has not been adequately assessed it is recommended that carcinogenicity be identified as "missing information". In the "Non-S31 Response" the sponsor argued that the total of 4 carcinogenicity studies compensates for the deficiencies of these studies. It is acknowledged that the sponsor has made extensive efforts to assess the carcinogenic potential of armodafinil and racemic modafinil. However, the exposures achieved in the studies remain insufficient to conclude that the carcinogenic potential has been adequately assessed. Therefore, the Nonclinical Evaluator recommends that carcinogenicity be identified as "missing information". The clinical data on carcinogenicity should be considered by the RMP and/or clinical evaluators.*

*Exposure during pregnancy is currently identified as "missing information". However, the conclusions regarding reproductive toxicity in the RMP do not accurately reflect the nonclinical findings. The RMP states that neither "modafinil or R-modafinil is a reproductive toxin, a selective developmental toxin, a developmental toxicant or a teratogenic agent." These statements were based on an independent expert review, which was considered by the TGA. As discussed above, the nonclinical data indicate that armodafinil is a selective developmental toxicant, which is consistent with the conclusions in the FDA evaluation of armodafinil. The proposed PI information on use in pregnancy also discusses the developmental toxicity observed in the reproductive toxicity tests. Therefore, the "relevance to human usage" in module SII of the RMP should be amended to be an "important potential risk" in order to accurately reflect the nonclinical findings. The clinical data located in Appendix II of the "Non-S31 Response" in Module 1.0.2 should be considered by the RMP and/or clinical evaluators.*

**RMP Evaluator comment**

It is noted that the sponsor has responded to the recommendations raised in the Nonclinical Evaluation Report.

- Toxicity in bone marrow, kidney and urinary bladder

For RMP purposes, the RMP evaluator is satisfied with the response provided by the sponsor. However, the nonclinical section of the RMP should be updated to reflect the non-clinical findings.

- Carcinogenicity

Based on the recommendation in the nonclinical evaluation report, 'Carcinogenicity' should be added as Missing Information. For RMP purposes, the PI wording with regard to this issue is acceptable. The current PI wording regarding exposure is:

> *These results indicate that the exposure of armodafinil or modafinil was insufficient to adequately assess carcinogenic potential.*

- Developmental Toxicity

The sponsor should make the changes to the RMP requested by the nonclinical evaluator, including the addition of 'Developmental toxicity' as Important Potential Risk. However, the nonclinical section of the RMP should be updated to reflect the nonclinical findings. For RMP purposes, the PI wording with regard to this issue is acceptable.

### *Key changes to the updated RMP*

Australian RMP Version 1.0 (dated 20 March 2014, DLP 31 October 2013) has been superseded by:

> *Australian Risk Management Plan Version 1.1 (dated 5 March 2015, DLP 31 October 2013).*

Table 22 shows a summary of key changes between RMP (in EU-RMP format) Version 1.0 and RMP (in EU-RMP format) Version 1.1.

**Table 22: Summary of key changes between RMP (in EU-RMP format) Version 1.0 and RMP (in EU-RMP format) Version 1.1.**

| Summary of key changes between RMP (in EU-RMP format) Version 1.0 and RMP (in EU-RMP format) Version 1.1 | |
|---|---|
| **Safety specification** | Important Potential Risk changes:<br>• Added Important Potential Risks:<br>o Off-label use<br>o Drug-drug interaction with CYP3A and CYP2C19 inducing/inhibiting substances and CNS active drugs<br>Missing inform ation changes:<br>• Added Missing Information:<br>o Exposure during lactation<br>o Paediatric patients |
| **Pharmacovigilance activities** | • Updates to accommodate changes to Safety Concerns/Missing Information |
| **Risk minimisation activities** | • Updates to accommodate changes to Safety Concerns/Missing Information |

*Summary of Safety Concerns*

Table 23 compares the Safety Concerns and Missing Information in RMP Versions 1.0 and 1.1.

**Table 23: Comparing the Safety Concerns and Missing Information in RMP Versions 1.0 and 1.11.**

RMP Version 1.0

| | |
|---|---|
| **Important identified risks** | • Serious skin reactions<br>• Cardiovascular disorders<br>• Psychiatric disorders<br>• Hypersensitivity |
| **Important potential risks** | • Misuse, abuse and diversion |
| **Missing information** | • Exposure during pregnancy |

RMP Version 1.1

| | |
|---|---|
| **Important identified risks** | • Serious skin reactions<br>• Cardiovascular disorders<br>• Psychiatric disorders<br>• Hypersensitivity |
| **Important potential risks** | • Misuse, abuse and diversion<br>• Off-label use<br>• Drug-drug interaction with CYP3A and CYP2C19 inducing/inhibiting substances and CNS active drugs |
| **Missing information** | • Exposure during pregnancy<br>• Exposure during lactation<br>• Paediatric patients |

### *Suggested wording for conditions of registration*

*RMP*

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

The suggested wording is:

> *Implement Australian Risk Management Plan Version 1.1 (dated 5 March 2015, DLP 31 October 2013) and any future updates as a condition of registration.*

# VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

## Quality

- Initially, the conclusion was that there are no objections in respect of Biopharmaceutics to registration of these products. However, a number of matters

relating to the quality control of the drug substance and the finished products require resolution before approval can be recommended from a Quality perspective.

- The final conclusion stated that the company has provided a response to the Quality/Biopharmaceutics evaluation report that has satisfactorily addressed all matters relating to the quality control of the drug substance and the finished products. There are now no objections in respect of Quality or Biopharmaceutics to registration of these products.

### Nonclinical

- The studies included met most of the requirements for assessing a single enantiomer of an approved racemate. However, the major deficiency of limited exposure ratios remained for studies of racemic modafinil, and was also a feature of the armodafinil studies.
- The primary pharmacology studies showed increased wakefulness and an equivalence of pharmacological effect between racemic modafinil and armodafinil, supporting the proposed indications.
- The mechanism of action of armodafinil and racemic modafinil remains unclear. Marked increases in heart rate were observed in dogs in a safety pharmacology study, but this observation was not replicated at the same doses in the repeat-dose toxicity study.
- The PK studies demonstrated a much shorter plasma half-life in rodents and dogs compared to human which likely underlies the relativity low exposure ratios. A deficiency in the PK studies is the lack of metabolism data for armodafinil and the racemate.
- The bridging repeat-dose toxicity studies demonstrated that the toxicity profile of armodafinil was very similar to that of racemic modafinil.
- Armodafinil has no demonstrated genotoxic potential. Due to deficiencies in exposure to armodafinil or racemic modafinil in the carcinogenicity studies, the carcinogenic potential of armodafinil has not been fully evaluated. The history of safe use of racemic modafinil suggests carcinogenic liability for armodafinil.
- The proposed pregnancy Category (B3) is consistent with the findings in the embryofoetal development studies in rats and rabbits, and with the category for modafinil (Modavigil). However, this categorisation requires consideration by the clinical evaluator, based on reported adverse pregnancy outcomes in humans.
- The deficiencies identified in the carcinogenicity studies and lack of metabolism data are offset by the bridging studies which demonstrate comparable effects of armodafinil and racemic modafinil, coupled with the history of safe use of the racemate in humans. Therefore, there are no nonclinical objections to registration of armodafinil.

    *Note: The toxicology evaluator has stated that the nonclinical recommendations have all been adopted by the sponsor and that the minor change in the statement on induction of CYP2B6 is acceptable. There are therefore no further changes required from the nonclinical perspective.*

## Clinical

### Pharmacokinetics

#### *Clinical pharmacology studies providing PK (± PD) data for armodafinil*

The submission included 11 Phase I clinical pharmacology studies evaluation the PK of armodafinil in 383 healthy subjects, 38 patients with schizophrenia, and 42 patients with OSAHS.

#### *Population pharmacokinetic (PPK) modelling and simulation studies*

The submission included population pharmacokinetic (PPK) and pharmacokinetic/pharmacodynamics (PK/PD) modelling and simulation analyses (report CP-05-001).

#### *Pivotal Phase III armodafinil sleep disorder studies with PK data*

Trough armodafinil plasma concentrations were determined from baseline through week 12 in the pivotal Phase III studies in patients with OSAHS and narcolepsy (Studies 3020, 3021, 3025).

#### *Studies providing PK data for racemic modafinil*

The submission included summary data from three, Phase I studies investigating the PK of modafinil following single and multiple dose administration to healthy volunteers (C1538a/103/PK/US, C1538a/106/MD/US, and CEP-2101).

> *Note: PK parameters from the individual studies were calculated using standard non-compartmental methods. PPK and PK/PD analyses were performed using standard statistical methods and computer software (that is, Nonlinear Mixed Effect Modeling (NONMEM) Version 5 Level 1.1 and SPlus 6.1 Professional Release 1).*

Overall, the clinical evaluator concluded on PK that:

- The PK of armodafinil has been reasonably well characterised in healthy subjects following single and multidose administration. In addition, the PK data for armodafinil in patients with the conditions of interest are consistent with the PK data for healthy volunteers.
- There were deficiencies in the submitted PK data including: (a) no absolute bioavailability study; (b) no comparative bioequivalence study for the three proposed armodafinil tablet strengths 50, 150 and 250 mg; and (c) no mass balance study investigating elimination and metabolic pathways for armodafinil.
- In addition, there were no clinical DDI studies investigating the following interactions of potential clinical significance: (a) co-administration of armodafinil with Pgp inducers and inhibitors, armodafinil is reported to be a Pgp substrate in vitro; (b) co-administration of armodafinil with a CYP2B6 probe substrate, armodafinil is reported to inhibit CYP2C9 probe substrate, armodafinil is reported to inhibit CYP2C9 in vitro; and (c) co-administration of armodafinil with CYP3A4 inducers and inhibitors, given that the formation of modafinil sulfone from R-modafinil is reported to be metabolized by CYP3A4/5.
- The submission included comparisons between the PK of armodafinil and armodafinil in both healthy subjects and patients. The mean plasma concentration versus time profiles for R-armodafinil in healthy subjects were virtually superimposable following single dose armodafinil (50 mg) and modafinil (100 mg) in a dose normalised to 50 mg analysis. The sponsor states that this finding justifies the use of R-modafinil PK data from the modafinil (Provigil) studies to support the PK data for armodafinil provided in the submission. This is considered to be a reasonable inference.

- In a multiple dose analysis of PK data from healthy subjects (Studies 102 and PROVIGIL-2101), systemic exposure to R-modafinil and modafinil were compared, based on $C_{max}$ and AUC values. The analyses included comparisons between armodafinil 150 mg/day versus modafinil 200 mg/day and armodafinil 250 mg versus modafinil 400 mg/day. The comparisons showed that $C_{max}$ values were lower for armodafinil compared to modafinil, while AUC values for the two analytes were similar. However, the plasma concentration versus time profiles for armodafinil and modafinil was monoexponential, with a longer terminal half-life relative to a biexpontial decline from peak concentration following administration of modafinil, with a shorter terminal half-life. The sponsor comments that the biexponential decline following administration of modafinil is the result of the differential rate of clearance of the R- and S- enantiomers (that is, clearance rate 3 fold higher for the S-compared to the R-enantiomer).
- Consistent with the data from the individual studies. The PPK analysis (CP-05-001) also indicated that the plasma concentration versus time profile for armodafinil notably differs from that for modafinil. The sponsor commented that the difference between the two drugs was expected to result in a more sustained effect (higher concentration later in the profile) and better tolerability (lower $C_{max}$) for armodafinil compared to modafinil. The difference between the two plasma concentration versus time profiles mean the equivalent exposures to armodafinil and modafinil cannot be achieved through dose adjustment. For example, if doses were selected to achieve comparable $C_{max}$ values then the plasma concentrations of armodafinil would be higher than modafinil at later time points, while if doses were selected to achieve comparable plasma concentrations at later time points then the $C_{max}$ value of armodafinil would be lower than for modafinil.
- The PK data showed that the median $T_{max}$ of armodafinil was approximately 2 h following administration in the fasted state (Study 101). In an in vitro study using MDR-MDCK cell monolayers it was reported that armodafinil is a P-glycoprotein (Pgp) substrate, but is not an inhibitor of Pgp (Study DP-2006-055).
- The sponsor states that the absolute bioavailability of armodafinil was not determined due to aqueous insolubility of armodafinil, which precluded IV administration. However, IV preparation was used in the nonclinical intact animal studies.
- The effect of food on the bioavailability of armodafinil was studied following a single 100 mg dose (2 x 50 mg tablets) in the fasted and fed state in 6 healthy young males (Study 101). The mean $C_{max}$ and $AUC_{(0\text{-inf})}$ for R-modafinil were ~ 11% lower and ~ 8% higher, respectively, in the fed compared to the fasted state. Apart from the median $T_{max}$, which was approximately 4 h longer in the fed compared to the fasted state (6.0 versus 2.3 h, respectively), other PK secondary parameters (that is, CL/F, VF, and t1/2) were similar in the fed and fasted states. The results suggest that the onset of action following administration might be longer when administered with food compared to fasting administration. This might be of clinical relevance where a rapid onset of action is required. There were no steady state data on the effect of food on the bioavailability of armodafinil, but based on similar single dose and steady state PK of the drug it can be predicted that the effect will be similar to that following single dose.
- In fasted healthy subjects, the single dose armodafinil 250 mg tablet proposed for registration was demonstrated to be bioequivalent to single dose armodafinil 5 x 50 mg tablets used in the clinical Phase III studies (Study 1023). Three armodafinil 250 mg tablets proposed for approval manufactured at different facilities in scale up batches were found to be bioequivalent following single dose administration to healthy subjects (Study 1036). There was no comparative bioequivalence study comparing the three strengths of the armodafinil tablets being proposed for registration (50, 150, 250 mg). However, based on $C_{max}$ and AUC values the PK of

armodafinil were essentially linear over the dose range 50 mg to 400 mg following single dose and multiple dose over 7 and 14 days, and the apparent clearance was relatively constant over the dose range tested (Study 102).

- The mean apparent volume of distribution (V/F) of armodafinil following a single dose (dose normalised to 50 mg) was 42.4 L, based on pooled data from healthy subjects (n = 93) from Studies 1023, 101, and 102. Following multiple dosing of armodafinil (dose normalised to 50 mg), the mean V/F was 47.4 L on Day 14 in 30 healthy subjects (Study 102). The V/F indicates that armodafinil is well distributed. There were no data for armodafinil relating to protein binding, erythrocyte distribution, or tissue distribution in humans.
- The metabolic pathways for R-modafinil have not been specifically characterized in studies in humans. The sponsor states that a clinical mass balance and metabolism study of racemic modafinil suggests that the drug is nearly exclusively metabolised in the liver with less than 10% of the parent compound being excreted in the urine. The sponsor reports that interconversion of the R and S enantiomers of racemic modafinil have not been observed in vitro or in vivo.
- Two circulating metabolites of armodafinil were identified in the PK studies (R-modafinil acid and [achiral] modafinil sulfone). R-modafinil acid represents approximately 11% and 7% of parent drug exposure (based on AUC values), following single and multiple dose administration of armodafinil, respectively. These data indicate that there is relatively little accumulation of R-modafinil acid following multiple dose treatment with armodafinil. Modafinil sulfone represents approximately 33% and 56% of parent drug exposure (based on AUC values), following single and multiple dose administration of armodafinil, respectively. The data indicate that modafinil sulfone accumulates following multiple dose armodafinil. The sponsor reports that armodafinil is metabolised to modafinil sulfone via CYP3A4/5, indicating that this enzyme is responsible, at least in part, for the metabolism of armodafinil.
- After reaching peak plasma concentration following oral administration, the elimination of armodafinil appears to be monoexponential with a relatively long apparent half-life of approximately 15 h. The apparent mean terminal half-lives of R-modafinil acid and modafinil sulfone are approximately 15 and 38 h, respectively, following single dose administration of armodafinil (dose normalised to 50 mg) from pooled data (Studies 1023, 101, and 102). The mean apparent clearance (CL/F) of armodafinil following a single dose (dose normalised to 50 mg) was 38.6 mL/min, based on pooled data from healthy subjects (n = 93) from studies 1023, 101, and 102. Following multiple-dose administration of armodafinil (dose normalised to 50 mg) in Study 102, the mean CL/ was 32.4 ± 8.72 mL/min on Day 7 (n = 34) and 32.7 mL/min on Day 14 (n = 30).
- The PK of armodafinil following single and multiple dose administration are similar, suggesting that the PK of the drug are time-independent. In the multiple dose study (102), steady state appeared to have been reached after 7 days of administration, which is consistent with a half-life of approximately 15 h. The steady state accumulation ratio (Rss) for armodafinil (dose normalised to 50 mg) was 1.2 on both days 7 and 14.
- In patients with OSAHS being treated with nCPAP (Study 1064), a multiple dose, 2 way crossover comparison between armodafinil 200 mg/day and modafinil 200 mg/day showed that the geometric $C_{max}$ and $AUC_{(0-\infty)}$ values for R-armodafinil were 37% and 69% higher relative to modafinil, while median $T_{max}$ values were similar for the two products (that is, 2 h). The plasma concentration versus time profile of R-armodafinil was higher at all time points than that for modafinil, with the difference between the profiles being greater in the later part of the 24 h dosing interval than in the earlier

part. The mean steady state accumulation ratio approximated unity for both R-armodafinil and modafinil, indicating time independent PK for both drugs.

- In a study investigating the effect of age on the PK of armodafinil in healthy volunteers (Study 1051), exposure to R-armodafinil following multiple dose armodafinil (150 mg/day) increased with age, particularly in subjects aged ≥ 75 years. Based on these data, dosage adjustment in patients aged ≥ 65 years should be considered, particularly in patients aged ≥ 75 years. In the PPK analysis (CP-05-001), no effect of age on clearance, volume of distribution, or absorption constant was observed. However, the effect of age in the PPK analyses may not have been fully characterised due to the limited number of patients aged ≥ 65 years in the analyses. The majority of patients in the PPK analysis were between 18 and 40 years of age.
- There were no specific studies on the effect of gender, weight, or race on the PK of armodafinil. However, in the PPK analysis (CP-05-001) no effect of gender on R-armodafinil on clearance, volume of distribution, or absorption rate was observed, and no effect of body weight on R-armodafinil clearance or absorption rate constant was observed, but the volume of distribution increased linearly with weight.
- In vitro data are reported to show that armodafinil has weak, but concentration-related inductive effects on CYP1A2, CYP2B6, and CYP3A4/5 activities. Clinical DDI studies have been undertaken investigating the effect of co-administration of armodafinil on CYP3A4 and CYP1A2 probe substrates, but not on CYP2B6 probe substrates.
- In vitro data are reported to show that armodafinil has a strong concentration-related inhibitory effect on CYP2C9 activity and is an inhibitor of CYP2C19 activity. A clinical DDI study has been undertaken investigating the effects of co-administration of armodafinil on a CYP2C19 probe substrate, but not on a CYP2C9 probe substrate.
- The sponsor reports that, in vitro, armodafinil is a weak, concentration-dependent inducer of CYP3A4 activity. In two DDI interaction studies with CYP3A4 substrates, multiple dose armodafinil (200 mg QD) reduced exposure to single IV and oral dose midazolam in healthy subjects and to steady-state quetiapine in patients with schizophrenia. The results suggest that armodafinil is at least a moderate inducer of CYP3A4 activity and should be administered cautiously in patients being treated with drugs known to be CYP3A4 substrates. Upwards dose adjustment of CYP3A4 substrates co-administered with armodafinil might be required.
- The sponsor reports that, in vitro, armodafinil is a weak, concentration dependent inducer of CYP1A2 activity. However, in a clinical study in healthy subjects armodafinil administered at 250 mg QD for 4 weeks had no significant effect on exposure to caffeine (a CYP1A2 substrate) administered as a single 200 mg dose on Days 1 and 31 (Study 1025). The sponsor reports than, in vitro, armodafinil is an inhibitor of CYP2C19 activity. This was confirmed in Study 1021, which showed that single-dose armodafinil 400 mg significantly increased exposure to single dose omeprazole 40 mg (a CYP2C19 substrate) in healthy subjects who were extensive CYP2C19 metabolisers. Consequently, co-administration of armodafinil and drugs known to be metabolized by CYP2C19 should be undertaken cautiously, and downwards dose adjustment of CYP2C19 substrates might be required.

## Pharmacodynamics

### *Study 103*

The primary objective of this Phase I, double blind, randomised, active controlled (Provigil 200 mg) and placebo controlled study was to evaluate the PD profile over time of single doses of armodafinil (100, 150, 200, or 300 mg) in healthy young men undergoing acute

sleep deprivation. The Provigil 200 mg (modafinil) group was included to assess study design sensitivity. The PD profile was measured using the MWT. The study planned to enrol 108 subjects aged between 18 and 40 years, who were randomly assigned to 1 of 6 treatment groups (18 subjects/group), with randomisation assigned separately for each centre (1 in France and 1 in the UK).

The MWT (and all other PD variables) were analysed at each time point. The null hypothesis was that the mean results for all treatments at all time points were equal. The alternate hypothesis was that at least two of the treatment means were not equal. The null hypothesis was to be rejected if $\alpha = 0.05$, pairwise treatment comparisons were also performed (Fisher's protective test). The testing was done using an ANOVA with treatment and centres as factors. In addition, tests for linear trends and nonlinear trends (quadratic trend test) using the placebo and armodafinil dose groups were performed. No adjustment for multiple comparisons was deemed necessary by the sponsor, as this was a Phase I PK/PD study in healthy normal subjects who were sleep deprived. Sample size was not based on statistical considerations. It was expected that a total sample size of 108 subjects with 18 subjects in each treatment group would provide sufficient information to test the null hypothesis.

Overall, the clinical evaluator concluded on PD that:

- Armodafinil at single doses of 100, 150, 200, and 300 mg appears to have a positive PD effect on promoting wakefulness, attention, and working memory in acutely sleep deprived healthy young men (Study 103). The duration of the PD effects appear to be longer with higher doses of armodafinil (200 mg and 300 mg) compared to lower doses of armodafinil (100 mg and 150 mg) and Provigil 200 mg.
- There were no statistically significant correlations between armodafinil plasma concentrations and any of the PD variables tested (MWT, PVT, CDR system test) following single dose armodafinil 100, 150, 200, and 300 mg in acutely sleep deprived healthy young men (Study 103). However, statistically significant correlations were observed between modafinil plasma concentrations and the PD variables tested (MWT, PVT, CDR system test) following single dose Provigil 200 mg.
- The results of PK/PD modelling and simulation reported in CP-05-001 predict that a dose of armodafinil 150 mg should achieve comparable MWT (OSAHS/narcolepsy) or MSLT (SWSD) to modafinil 200 mg at early times after administration, with superior MST/MSLT at later times.

## Efficacy

### *Pivotal Phase III efficacy studies*

The submission included 4, pivotal, multinational, Phase III, double blind, placebo controlled, parallel group efficacy and safety studies of 12 weeks duration (Table 24). The 4 pivotal studies included 2 studies in patients with OSAHS (C10953/3021/AP/MN and C10953/3025/AP/MN), 1 study in patients with SWSD (C10953/3022/CM/MN), and 1 study in patients with narcolepsy (C10953/3020/NA/MN).

**Table 24: Number of efficacy evaluable patients (FAS): pivotal studies.**

| Sleep disorder | Number of efficacy-evaluable patients (full analysis set)[a] | | | |
|---|---|---|---|---|
| | Armodafinil | | | |
| Study number | 250 mg/day | 150 mg/day | Total | Placebo |
| OSAHS | | | | |
| Study 3021 | 121 | 120 | 241 | 124 |
| Study 3025 | — | 116 | 116 | 120 |
| SWSD | | | | |
| Study 3022 | — | 112 | 112 | 104 |
| Narcolepsy | | | | |
| Study 3020 | 60 | 58 | 118 | 58 |

a = The full analysis set included patients who received at least 1 dose of study drug, had a baseline and at least 1 post-baseline Maintenance of Wakefulness Test assessment (narcolepsy and OSAHS) or Multiple Sleep Latency Test assessment (SWSD), and at least 1 post baseline Clinical Global Impression of Change assessment.

### *Supportive efficacy studies*

The submission also included two Phase III long term, open label safety and tolerability studies, including supportive efficacy data (C10953/3023/ES/MN and C10953/3024/ES/MN); the studies are referred to in this clinical evaluation report as 3023 and 3024, respectively. The patients who participated in study 3023 had excessive sleepiness associated with OSAHS, SWSD, or narcolepsy and had not participated in another study with armodafinil. The patients who participated in study 3024 had completed one of the 4 pivotal, double blind, placebo controlled studies. The submission also included 2, Phase IIIb studies providing supportive efficacy data (C10953/3045/CM/US, a double blind, placebo controlled study in patients with SWSD; and C10953/3046/ES/US, an open label study in patients with narcolepsy or OSAHS).

**Table 25: Number of efficacy evaluable patients (FAS): supportive studies.**

| | Number of efficacy-evaluable patients (full analysis set) | | | |
|---|---|---|---|---|
| | Sleep disorder | | | |
| Study number | Narcolepsy | OSAHS | SWSD | Armodafinil overall |
| Study 3023[a] | 44 | 154 | 99 | 297 |
| Study 3024[b] | 150 | 459 | 106 | 715 |

a = The FAS includes those patients in the safety analysis set who had at least 1 post baseline efficacy assessment. b = The FAS included those patients in the safety analysis set who had at least 1 efficacy assessment during the open label extension study.

**Table 26: Number of efficacy evaluable patients (FAS): Phase IIIb studies.**

| Sleep disorder | Number of efficacy-evaluable patients (full analysis set)[a] | | | |
|---|---|---|---|---|
| Study number | Armodafinil | PROVIGIL | Placebo | Total |
| Study 3045 | | | | |
| SWSD | 73 | 27 | 26 | 126 |
| Study 3046 | | | | |
| OSAHS | 149 | — | — | 149 |
| Narcolepsy | 92 | — | — | 92 |

a = FAS includes those patients in the safety analysis set who had at least 1 post baseline efficacy assessment.

### *Pivotal studies*

*OSAHS*

- Study 3021 – A randomised, double blind, placebo controlled, parallel group Phase III study of 12 weeks duration designed to evaluate the efficacy and safety of armodafinil

(150 mg/day and 250 mg/day) for the treatment of residual excessive sleepiness associated with OSAHS in adults.

Approximately 360 men and women aged 18 to 65 years (inclusive) with a diagnosis of OSAHS, according to ICSD criteria, were scheduled for inclusion in order to obtain 324 evaluable patients (that is, patients with at least 1 post baseline assessment of MWT). The inclusion criteria required that patients had residual excessive sleepiness despite effective and regular nCPAP therapy. In addition, patients were required to have a baseline CGI-S rating score of 4 or more (that is, 1 = normal [shows no signs of illness]; 2 = borderline ill; 3 = mildly [slightly] ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; 7 = among the most extremely ill patients), and an ESS Score of 10 or more. A patient was enrolled in the study only if all inclusion criteria and none of the exclusion criteria were fulfilled. To undertake the inclusion tests, patients had washout periods from medications prohibited by the study protocol.

Patients meeting the above criteria/assessment were randomised 1:1:1 to 12 weeks treatment with once daily armodafinil 150 mg, armodafinil 250 mg or placebo. Baseline assessments were in the morning at the clinic with the patients' arrival the night before. The assessments included MWT administered 6 times at 2 h intervals from 0900 h through 1900 h (inclusive), CDR system testing administered between MWT naps, and the BFI administered prior to the first MWT. Patients were discharged from the clinic the morning after baseline assessments.

During the 12 week, double blind, treatment period, patients were instructed to take study medications once daily before 0800 h and about 30 minutes before breakfast. The exceptions from the dosage regimen took place at Weeks 4, 8, and 12 visit days when the study drug was taken in the clinic within 15 minutes of 0700 h and about 30 minutes before breakfast. The sponsor stated that armodafinil was administered in the fasted state (defined as 30 minutes before breakfast) in order to avoid potential food effects. Armodafinil dosage was titrated as follows: 50 mg on the first day and then an additional 50 mg for two consecutive days until the target dose of 150 mg/day or 250 mg/day were reached. The daily armodafinil dose was given using 50 mg tablets. In order to maintain the double blind, 5 tablets were taken daily with the mixture of placebo and/or armodafinil being determined by the randomisation group and the titration day. With treatment, the MWT was administered 6 times at 2 hour intervals from 0900 to 1900 h (inclusive) at weeks 4, 8 and 12. The CGI-C, the ESS and the BFI were administered before the first MWT and CDR system testing (between MWT naps) sessions at Weeks 4, 8 and 12. In order to assess night time sleep, the week 12 visit or the last post baseline observation visit also included a nocturnal PSG.

> *Note: Study days were numbered relative to the first day of drug administration. Efficacy and safety data were assigned to study windows. The visit windows were: baseline, nominal Day 1, window ≤ 1 day; Week 4, nominal Day 28, visit window 2 to 42 days; Week 8, nominal Day 56, visit window 43 to 70 days; Week 12, nominal day 84, visit window ≥ 71 days; endpoint, visit window ≤ 1 day. If multiple data fell in the same visit window then the value closest to the nominal day in the visit window was used for the analysis.*

The primary objective was to determine whether treatment with armodafinil is more effective than placebo for patients with residual excessive sleepiness associated with OSAHS by measuring sleep latency from the MWT (30 minute version) (average of 4 naps at 0900, 1100, 1300, and 1500 h), and by CGI-C ratings (as related to general condition) at Week 12 or the last post baseline observation.

The secondary objectives were:

- To determine effect on attention and memory as assessed by CDR system testing (0930, 1130, 1330, 1530, 1730 and 1930) at Weeks 4, 8 and 12 and the last post baseline observation
- To determine mean sleep latency from the MWT assessed at later time points (average of 3 naps at 1500, 1700, and 1900) at Weeks 4, 8 and 12 and the last post baseline observation
- To determine the effects on sleepiness as measure by ESS scores at weeks 4, 8, and 12 and the last post baseline observation
- To determine CGI-C ratings at Weeks 4, 8, and 12
- To determine mean sleep latency from the MWT assessed at Weeks 4, 8, and 12 (average of 4 naps at 0900, 1100, 1300 and 1500)
- To determine mean sleep latency from the MWT assessed at Weeks 4, 8, and 12 and the last post baseline observation (results for individual tests at 0900, 1100, 1300, 1500, 1700 and 1900)
- To determine the effect on daytime sleepiness (from diaries reviewed at Weeks 4, 8, and 12 or the last post baseline observation)
- To determine the effect on fatigue as measured by the BFI at Weeks 4, 8, and 12 and the last post baseline observation.

The primary efficacy variables were:

- Mean change from baseline to endpoint in the MWT mean sleep latency (average of 4 naps at 0900, 0110, 1300 and 1500 h); and
- The proportion of patients with at least minimal improvement in the CGI-C ratings (related to general condition) as assessed at the last post baseline observation.

> *Note: The MWT is a validated objective assessment of sleepiness that measures the ability of a subject to remain awake. Patients were instructed to try to remain awake in a darkened room during a series of 30 minute periods while in a semi reclined position. Long latencies to sleep are indicative of the ability to remain awake. Sleep latency was defined as the time to onset of 3 consecutive epochs (that is, epoch = 30 second segment) of stage 1 sleep, or the time to onset of any epoch of stages 2, 3, 4 or REM sleep. Each sleep epoch is scored for both stage of sleep and any abnormalities occurring within that epoch. In order to score an epoch as belonging to a certain stage of sleep or any abnormality, more than half of the epoch is required to have the observed finding (that is, epochs individually scored using the 50% [16 second] rule). If a patient fell asleep during a 30 minute period, then the patient was immediately awakened and was prevented from falling asleep for the remainder of that period, but could remain in bed. If a patient did not fall asleep during the 30 minute MWT, then a sleep latency value of 30 minutes was assigned. The sponsor states that the method used to assess sleep latency for MWT is the accepted standard and was used in the Provigil narcolepsy and OSAHS studies, in which MWT was also one of the co-primary efficacy endpoints. The electronic files of the tracings were sent to a central laboratory and the tracings were scored by central readers.*
>
> *The CGI-C is a subjective measure of the patient's global health made by the clinician based on assessment of improvement in response to treatment compared to baseline. The CGI-C uses the following categories and scoring assignments: 1 = very much improved; 2 = much improved; 3 = minimally improved; 4 = no change; 5 = minimally worse; 6 = much worse; and 7 = very much worse. The CGI-C reflects the clinician's subjective assessment of the effect of treatment on the residual daytime sleepiness resulting from OSAHS.*

The key secondary efficacy variable was defined as the change from baseline in mean quality of episodic secondary memory from the tests of memory from the CDR system (average of 4 tests at 0930, 1130, 1330, and 1530 h) at endpoint.

> *Note: The CDR system is a computerised assessment system that can detect alterations in cognitive function (that is, attention and memory). The CDR battery of cognitive tests took approximately 25 minutes to complete, and during this time patients completed 3 attention tests and 5 memory tests. Attention tasks included simple reaction time, digit vigilance, and choice reaction time. The working memory task included numeric working memory. Episodic secondary memory tasks included immediate word recall, delayed word recall, word recognition, and picture recognition. The results of the tests are combined to create derived measures of power of attention, continuity of attention, speed of memory, and quality of episodic memory.*

Other secondary efficacy variables included:

- The change from baseline for the following:
  - Total score from the ESS at Weeks 4, 8, 12 and endpoint
  - Worst fatigue score from the BFI scale at Weeks 4, 8, 12 and endpoint
  - Average score from the BFI scale at Weeks 4, 8, 12 and endpoint.

    *Note: The ESS measures subjective evaluation of excessive daytime sleepiness. The ESS score is based on response to 8 everyday situations and is derived from the sum of the values for the 8 situations. The ESS scores range from 0 to 24, with a higher score indicating greater daytime sleepiness. The test is self-administered.*

    *The BFI measures the effects of the study drug on daytime sleepiness, with simple numeric rating scales from 0 to 10 being used, with 0 indicating no fatigue and 10 indicating fatigue that completely interferes with functioning.*
- The change from baseline for the following:
  - Mean sleep latency from the MWT (average of 4 naps at 0900, 1100, 1300, and 1500) at Weeks 4, 8, and 12
  - Mean sleep latency from the MWT for the later time points (average of 3 naps at 1500, 1700, and 1900) at Weeks 4, 8, and 12 and endpoint
  - Sleep latency for the individual tests from the MWT (0900, 1100, 1300, 1500, 1700, and 1900) at Weeks 4, 8, and 12 and endpoint
- The proportion of patients with at least minimal improvement in the CGI-C rating at Weeks 4, 8, and 12
- CGI-C ratings at Weeks 4, 8, and 12 and endpoint
- The change from baseline for the following variables from tests of attention from the CDR system
  - Mean power of attention (average of 4 tests at 0930, 1130, 1330, and 1530) at Weeks 4, 8, and 12
  - Mean power of attention for the later time points (average of 3 tests at 1530, 1730 and 1930) at Weeks 4, 8, and 12 and endpoint
  - Power of attention for the individual tests (0930, 1130, 1330, 1530, 1730, and 1930) at Weeks 4, 8, and 12 and endpoint
  - Mean continuity of attention (average of 4 tests at 0930, 1130, 1330, and 1530) at Weeks 4, 8 and 12 and endpoint

  - Mean continuity of attention for the later time points (average of 3 tests at 1530, 1730, and 1930) at Weeks 4, 8 and 12 and endpoint
  - Continuity of attention for the individual tests (0930, 1130, 1330, 1530, 1730, and 1930) at Weeks 4, 8, and 12 and endpoint
- The change from the baseline for the following variables from tests of memory from the CDR system
  - Mean speed of memory (average of 4 tests at 0930, 1130, 1330, and 1530) at Weeks 4, 8, and 12 and endpoint
  - Means speed of memory for the later time points (average of 3 tests at 1530, 1730, and 1930) at Weeks 4, 8, and 12 and endpoint
  - Speed of memory for the individual tests (0930, 1130, 1330, 1530, 1730 and 1930) at Weeks 4, 8, and 12 and endpoint
  - Mean quality of episodic secondary memory (average of 4 tests at 0930, 1130, 1330, and 1530) at Weeks 4, 8, and 12 and endpoint
  - Mean quality of episodic secondary memory for the later time points (average of 3 tests at 1530, 1730, and 1930) at Weeks 4, 8, and 12 and endpoint
  - Quality of episodic secondary memory for the individual tests (0930, 1130, 1330, 1530, 1730 and 1930) at Weeks 4, 8, and 12 and endpoint.

Sample size estimates were based on the PK/PD data derived from the armodafinil Phase I clinical pharmacology studies in healthy volunteers and the modafinil clinical trials in patients with sleep disorders, under the assumption that both primary treatment comparisons (that is, MWT and CGI-C) would be with a 2 sided test at an alpha level of 0.05. On this basis, a sample size of 108 patients per group would provide at least 90% power to detect a 2.5 minute difference in the mean sleep latency from the MWT (tests at 0900, 1100, 1300, and 1500), between the combined armodafinil and placebo groups, assuming a common standard deviation of 6.5 minutes. This sample size would also have a 90% power to detect a difference of 25% between the combined armodafinil and placebo groups in the proportion of patients reporting at least minimal improvement in CGI-C ratings, assuming a 36% rate in the placebo group. In addition, for the key secondary efficacy variable memory (quality of episodic secondary memory from test of memory in the CDR system battery), this sample size would also provide at least 80% power to detect a 14 unit difference between armodafinil and placebo, assuming a common standard deviation of 42.

> *Note: The CE commented that the study actually recruited 395 patients and that 365 patients were eligible for the full analysis of efficacy (FAE). The number of evaluable patients in each of the three treatment groups was >108. Therefore, the study was adequately powered to test the two primary treatment comparisons, based on the assumptions on which the sample size calculations were made.*

Statistical methods included the pre specified: ANOVA model (for the primary analysis) and non parametric Wilcoxon rank sum test (to compare the combined armodafinil dose group to the placebo group in order to assess the robustness of the findings). Actual values and changes from the baseline to endpoint in the mean sleep latency from the MWT were summarised using descriptive statistics. Ninety-five percent confidence intervals (95% CIs) for the treatment differences (using LS means) were also presented. CGI-C was tested subjectively and summarised, using descriptive statistics for the proportion of patients with at least minimal improvements in the CGI-C rating (as related to general condition) at endpoint. The comparison between treatment groups was tested using the CMH chi-square test adjusted for country.

*Note: The CE commented that for a comparison of the two primary efficacy end points to be statistically significant and for the study outcome to be positive, then the $\alpha$ should be 0.025 (that is, adjusted for multiplicity using the Bonferroni correction) for each of the two primary comparisons. The CE also commented that the primary efficacy variables were assessed at endpoint, last post baseline observation using the LOCF approach. In order to assess the effect of LOCF methodology on the analyses, the primary efficacy variables were also analysed using the observed Week 12 results for patients who had completed the study.*

The continuous secondary efficacy variables were analysed using an ANOVA model with country and treatment as factors. Secondary efficacy variables based on CGI-C ratings were analysed using a CMH chi-square test adjusted for country. All statistical testing for other secondary variables was at $\alpha = 0.05$ (using a two-tailed test) and followed the closed testing methodology used for the primary efficacy analyses. Treatment differences (using LS means) with 95% CIs were also presented. There was no statistical adjustment for multiplicity of secondary efficacy outcome testing.

A total of 395 patients were randomised (n = 131 for armodafinil 250mg/day, n = 133 for armodafinil 150mg/day and n = 131 for placebo).

*Note: The CE commented that the patient disposition profiles were generally similar for the armodafinil combined and placebo groups. However, discontinuations due to adverse events were 2-fold higher in the armodafinil combined group than in the placebo group.*

Overall, the baseline demographic characteristics were well balanced between the combined armodafinil and placebo groups, and between the two armodafinil dosage groups. Patients were required to have ESS scores ≥10 and the mean baseline ESS scores for the three patient groups (armodafinil 150 mg/day, 250 mg/day and placebo) were 15.4 (range: 10-15), 15.3(range: 5-13) and 15.9 (range: 10-24), respectively. The baseline CGI-S ratings were similar for the two armodafinil dosage groups and the placebo group. Medical history was similar for the two armodafinil dosage groups and placebo group. There were some differences in the prior medication profiles of the treatment groups, but these differences are unlikely to have affected the validity of the efficacy and safety analyses.

- Study 3025 – A randomised, double blind, placebo controlled, parallel group Phase III study of 12 weeks duration designed to evaluate the efficacy and safety of armodafinil (150 mg/day) for the treatment of residual excessive sleepiness associated with OSAHS in adults.

Approximately 240 patients were scheduled to be included in the study in order to obtain 216 evaluable patients (that is, who have at least 1 post baseline MWT assessment). The study actually enrolled 263 patients and 236 patients were evaluable for efficacy (FAS). The number of evaluable patients in each of the two treatment groups was > 108. The CE commented therefore, that the study was adequately powered to test the two primary treatment comparisons, based on the assumptions on which the sample size calculations were made. Patients with a current diagnosis of OSAHS were randomised 1:1 to 12 weeks treatment with once daily dose of armodafinil 150 mg or placebo.

The CE stated that Study 3025 was similar to Study 3021 in all aspects of inclusion/exclusion criteria, study treatments, primary/secondary objectives and variables, randomisation/blinding methods, analysis populations and sample size considerations/power calculations on the two primary efficacy endpoints. The clinical evaluator stated that calculations were provided for 108 patients in each of the armodafinil 150 mg/day and placebo groups and that, as the key secondary efficacy endpoint in this study was attention (power of attention in the CDR system battery), a sample size of 108 patients would provide at least 80% power to detect a 70 msec

difference between the two treatment groups, assuming a common standard deviation of 160 msec. The study actually enrolled around 131 patients for each arm of treatment.

The statistical methods used were identical to those in Study 3021. 263 patients were randomised (n = 131 for armodafinil 150 mg/day and n = 132 for placebo). The clinical evaluator commented that the patient disposition profiles were similar for the two treatment groups and that the reported protocol violations/deviations are considered not to have invalidated the efficacy or safety analyses. The clinical evaluator stated that:

- Overall, the baseline demographic characteristics were well balanced between the armodafinil and placebo groups, and were consistent with the baseline demographic characteristics of patients in Study 3021.
- The baseline CG1-S ratings were similar for armodafinil and placebo groups, with the proportion of moderately ill patients been 56% (72/129) and 58% (75/130), respectively, and the proportion of markedly, severely, or extremely ill patients been 44% (57/129) and 42% (55/130), respectively. The disease characteristics were similar for the two treatment groups, and were consistent with those observed in study 3021.
- The medical history profiles were similar for the two treatment groups.
- Overall, the prior medication profiles of the two treatment groups were similar.

*Narcolepsy*

- Study 3020 – a randomised, double blind, placebo controlled, parallel group Phase III study of 12 weeks duration designed to evaluate the efficacy and safety of armodafinil (150 mg/day and 250 mg/day) in adult patients with excessive sleepiness due to narcolepsy.

A total of 196 patients, aged 18 to 65 years, with a current diagnosis of narcolepsy according to ICSD criteria and fulfilling all inclusion but no exclusion criteria were enrolled and randomised. The inclusion criteria included the requirement that patients have a mean sleep latency of 6 minutes or less as determined by the MSLT (performed at 0900, 1100, 1300 and 1500 h), CGI-S rating of 4 or more (assessed after washout of medication disallowed by the protocol) and a screening for ESS. After randomisation, patients went to the clinic the evening before the morning baseline assessments.

Baseline assessments included the MWT administrated 6 times (naps at 0900, 1100, 1300, 1500, 1700 and 1900 h), CDR system testing (tests of attention and memory) administrated between MWT naps, and the BFI assessed prior to the first MWT nap. Nocturnal PSG started (that is, lights out) within 30 minutes of the patients habitual bedtime (as determined by sleep history), but no earlier than 2130 h and after other procedures/assessments were performed. Patients were discharged the following morning.

For each remaining clinic visit, patients arrived at the clinic the evening before, stayed overnight, and were administrated study drug at 0700 (± 15 minutes) the next day, about 30 minutes before breakfast. The MWT was administrated 6 times (naps at 0900, 1100, 1300, 1500, 1700 and 1900 h) at weeks 4, 8, and 12. The CGI-C (as related to general condition), the ESS, and the BFI were administered before the first MWT and CDR system testing session at Weeks 4, 8 and 12. Between MWT naps, CDR system testing was administered at Weeks 4, 8 and 12. Data from diaries on the effect on daytime sleepiness, night time sleep, and cataplexy were reviewed at Weeks 4, 8 and 12. For the purposes of assessing the effect on night time sleep, the week 12 visit or the last post baseline observation also included a nocturnal PSG (conducted overnight after other procedures and assessment were performed. Numbering of study days and allocation of visit windows and nominal visit days (with ranges) was the same as for the two OSAHS studies.

*Note: The CE commented that the second amendment (21.10.04) made after 196 patients were enrolled has no negative impacts on the efficacy and safety assessments of those patients.*

The primary objective of the study was to determine whether treatment with armodafinil was more effective than placebo for patients with excessive sleepiness associated with narcolepsy by measuring sleep latency from the MWT (20 minute version) (average of 4 naps at 0900, 1100, 1300, and 1500 h), and by CGI-C ratings (as related to general condition) at Week 12 (or the last post-baseline observation).

The secondary objectives were:

- To determine mean sleep latency from the MWT assessed at later time points (average of 3 naps at 1500, 1700, and 1900) at Weeks 4, 8 and 12 and the last post baseline observation
- To determine effect on attention and memory as assessed by CDR system testing (0930, 1130, 1330, 1530, 1730, and 1930) at Weeks 4, 8 and 12 and the last post baseline observation
- To determine the effects on sleepiness as measured by ESS scores at Weeks 4, 8 and 12 and the last post baseline observation
- To determine CGI-C ratings at weeks 4, 8, and 12
- To determine mean sleep latency from the MWT assessed at Weeks 4, 8 and 12 (average of 4 naps at 0900, 1100, 1300, and 1500)
- To determine mean sleep latency from the MWT assessed at Weeks 4, 8 and 12 and the last post baseline observation (results for individual naps at 0900, 1100, 1300, 1500, 1700, and 1900)
- To determine the effect on daytime sleepiness from diaries reviewed at Weeks 4, 8 and 12 or the last post baseline observation
- To determine the effect on fatigue as measured by the BFI at Weeks 4, 8 and 12 and the last post baseline observation

*Note: The clinical evaluator commented that the efficacy objectives of the narcolepsy study were consistent with the efficacy objectives of the two OSAHS studies.*

The primary efficacy variables were:

- The mean change from the baseline assessment in MWT (20 minute version) mean sleep latency (average of 4 naps at 0900, 1100, 1300, and 1500 h), to the last post-baseline assessment; and
- The proportion of patients with at least minimal improvement in the CGI-C ratings (as related to general condition), assessed at the last post baseline observation.

The MWT was administered in an identical fashion to the two OSAHS studies (3021, 3025), except the narcolepsy study used 20 minute sessions while the two OSAHS studies used 30 minute sessions. The CGI-C ratings were identical those used in the two OSAHS studies.

The secondary efficacy variables were identical to the secondary efficacy variables in the two OSAHS studies, except the sleep latency variables from the MWT used 20 minute sessions in the narcolepsy study while the two OSAHS studies used 30 minute sessions.

Sample size estimates were made on the basis of the results of PK/PD modelling and clinical trial simulation applied to data from the Phase I clinical studies with armodafinil and from clinical trials in sleep disorders with Provigil, under the assumption that both primary treatment comparisons would be with a 2 sided test at an alpha level of 0.05.

On this basis, a sample size of 64 per group would provide 80% power to detect a 2.5 minute difference in the mean sleep latency from the MWT (naps at 0900, 1100, 1300, and 1500 h) between either dose of armodafinil and placebo, assuming a common standard deviation of 5.0 minutes. This sample size would also have at least 80% power to detect a difference of 25% between either dose of armodafinil and placebo in the proportion of patients reporting at least minimal improvement in CGI-C ratings, assuming a 37% rate in the placebo treated group.

> *Note: The clinical evaluator commented that approximately 210 patients were planned to be enrolled in order to obtain 192 evaluable patients (that is, patients with at least 1 post baseline MWT assessment and 1 post baseline CGI-C assessment). The study enrolled a total of 196 patients, and the number of patients in each group in the FAS was < 64, suggesting that the study might not have been adequately powered to have detected a difference in the primary efficacy outcomes between either dose of armodafinil and placebo, based on the assumptions used to calculate the sample size.*

Statistical methods included the pre-specified: ANCOVA model (with country and treatment as factors, and baseline sleep latency from MWT as a covariate and non-parametric test (Wilcoxon rank-sum test for the continuous primary efficacy variables in the study. Actual values and changes from baseline to endpoint in the mean sleep latency from the MWT were summarised using descriptive statistics. Ninety-five percent confidence intervals for the treatment differences (using LS means) were also presented. CGI-C comparison between treatments groups were tested subjectively using the CMH chi-square test adjusted for country. The proportion of patients with at least minimal improvement in the CGI-C rating at endpoint was summarized using descriptive statistics.

> *Note: The primary comparison of both efficacy outcomes was between the combined armodafinil group and placebo. If the primary comparison was statistically significant at $\alpha = 0.05$ using a two tailed test (that is, the null hypothesis of no difference between treatment groups was rejected), then each armodafinil dosage group was separately compared with placebo. The sponsor described the sequential testing procedure as being a closed method. There was no statistical adjustment for multiplicity arising from having two primary efficacy endpoints. If the most conservation position is adopted of requiring both endpoints to be statistically significant in order for the study to be deemed "positive", then it is considered that for each of the two primary comparisons (combined armodafinil group versus placebo), the $\alpha$ should be 0.025 (that is, adjusted for multiplicity using the Bonferroni correction).*

Randomisation wise, n = 67, 65 and 64 respectively for armodafinil 250 mg/day, armodafinil 150 mg/day and placebo respectively.

> *Note: The clinical evaluator commented that (1) the patient disposition was similar in the armodafinil and placebo groups, (2) there were some differences in the baseline demographic characteristics of the patient groups (e.g., mean age, age distribution profile), but it is considered that these are unlikely to have invalidated the efficacy or safety analyses, (3) baseline characteristics of narcolepsy were generally similar among patients in each treatment group, (4) the only medical conditions for which the difference in incidence between the combined armodafinil and placebo groups was ≥10% of patients were respiratory disease (18% versus 6%, respectively) and allergy drug sensitivity (34% versus 44% respectively) and (5) the prior medication profiles was similar across the treatment groups, and the only prior medications reported for which the differences in incidence between the combined armodafinil and placebo groups was ≥5% of patients were respiratory agents (13% versus 3%, respectively) and gastrointestinal agents (9% and 14%, respectively).*

*SWSD*

- Study 3022 – A randomised, double blind, placebo controlled, parallel group Phase III study designed to evaluate the efficacy and safety of armodafinil (150 mg/day) for the treatment of excessive sleepiness associated with chronic SWSD.

Patients, aged 18 to 65 years, with a diagnosis of SWSD according to ICSD criteria were enrolled. As part of the inclusion criteria, patients were required to have had excessive sleepiness during the night shifts for at least 3 months, and to have worked at least 5 nights shifts per month (of which at least 3 shifts were consecutive) and planned to maintain this schedule. In addition, patients were required to have had no more than 87.5% sleep efficiency (that is, sleep duration/time in bed x 100%) as determined by 8 hour daytime PSG. Furthermore, patients were required to have a mean sleep latency of 6 minutes or less from the MSLT (performed at 0200, 0400, 0600 and 0800 h ± 30 minutes), and a CGI-S rating of 4 or more relating to sleepiness during night shifts including the commute to and from work.

254 patients were randomised (1:1) to armodafinil 150 mg/day (n = 127) or placebo (n = 127) to be taken 30 minutes to 1 hour before the start of a shift, but no later than 2300 h and only on nights worked. The duration of the double blind treatment period was 10 to 12 weeks. Depending on the shift work schedule, a patient could be considered to have completed the study after 10 weeks of double blind treatment.

Potential patients came to the clinic for preliminary screening assessments, including administration of the CGI-S. If the CGI-S criteria were met (that is, CGI-S rating of at least 4), patients returned to the clinic (at approximately 1900) for additional screening/baseline assessments, including the MSLT and 8 h daytime PSG. There had to be at least 7 days between the preliminary screening visit and the study drug dispensing visit (visit 3) in order to collect 7 days of diary data. If a patient was taking medication excluded by the protocol, there had to be a washout period before collection of baseline diary data and before the screening/baseline assessments of CGI-S, MSLT, and 8 h daytime PSG.

Patients who met the inclusion/exclusion and screening criteria were dispensed study drug at a subsequent visit. With the exception of the initial screening visit and the dispensing visit, all visits included an overnight stay in the clinic, which took place immediately following the last night worked for the night shift work period (that is, at least 3 consecutive night shifts). For each overnight clinic visit, with the exception of the screening/baseline visit, patients refrained from eating/drinking (except bottled water) after 1900 h. Study drug was administered within 30 minutes of 2200 h, followed by a meal. Outcome assessments included the MSLT administered 5 times (at 2400, 0200, 0400, 0600, and 0800 h), the BFI was assessed before the first MSLT nap, the KSS was administered before each MSLT nap, CDR system testing was administered after MSLT naps, and the CGI-C was assessed after the last CDR system testing session.

During the double blind treatment period, patients were instructed to take a single dose of armodafinil 150 mg or placebo 30 minutes to 1 h before the start of the night shift on nights worked, but no later than 2300 h. It was recommended that patients refrain from eating/drinking (except bottled water) for at least 2 h before taking study drug.

Armodafinil treatment was titrated as follows (only on nights worked): the first dose was 50 mg, the second and third doses were 100 mg, and the fourth and subsequent doses were 150 mg. Each dose of armodafinil was administered using 50 mg tablets.

Investigators were responsible for monitoring patient compliance. Patients could be withdrawn from the study at any time if the investigator or the sponsor determined that the patient was not compliant with the study protocol. Compliance checks involved reviews of electronic patient diaries and work schedules, counts of total tablets dispensed and totals returned, and verification of source documents.

*Note: The clinical evaluator commented that:*

- *The inclusion and exclusion criteria are satisfactory. The criteria are considered to be sufficient to capture only patients with severe morbidity arising from the condition.*
- *The study was well designed and provided pivotal short term efficacy and safety data. There were two amendments to the protocol, the first was issued prior to the enrolment of any patients into the study (2 March 2004) and the second was made after all patients had been enrolled in the study (21 October 2004). The changes made in Amendment 2 have been examined and are considered not to have negatively impacted on the safety and efficacy analyses based on data from the enrolled patients.*
- *Prohibited concomitant medications were consistent with those from the previously described OSAHS and narcolepsy studies.*

The primary objective of the study was to determine whether treatment with armodafinil was more effective than placebo for patients with excessive sleepiness associated with chronic SWSD by measuring mean sleep latency from the 20 minute MSLT (average of 4 naps at 0200, 0400, 0600, and 0800 h), and by CGI-C ratings (for sleepiness during night shifts including the commute to and from work) at Week 12 or the last post baseline observation.

The secondary objectives were:

- To determine effect on attention and memory as assessed by CDR system testing (at 0030, 0230, 0430, 0630, and 0830) at Weeks 4, 8, and 12 and the last post baseline observation;
- To determine the effects on sleepiness as measured by KSS scores at weeks 4, 8, and 12 and the last post baseline observation (administered before each MSLT test);
- To determine CGI-C ratings at Weeks 4, 8, and 12;
- To determine mean sleep latency from the MSLT assessed at Weeks 4, 8, and 12 (average of 4 naps at 0200, 0400, 0600, and 0800)
- To determine mean sleep latency from the MSLT assessed at Weeks 4, 8, and 12 and the last post baseline observation (results for the individual naps at 2400 [midnight], 0200, 0400, 0600, and 0800);
- To determine the mean sleep latency profile from the MSLT over the duration of the study;
- To determine the effect of sleepiness and its consequences during the night shift and the commute home (from diaries reviewed at Weeks 4, 8, and 12 and the last post baseline observation); and
- To determine the effect on fatigue as measured by the BFI at weeks, 4, 8, and 12 and the last post baseline observation.

The primary efficacy variations were:

- the mean change from the baseline to endpoint assessment in MSLT mean sleep latency (average of 4 naps at 0200, 0400, 0600, and 0800 h); and
- the proportion of patients with at least minimal improvement in the CGI-C ratings (for sleepiness during night shifts including the commute to and from work) as assessed at week 12 or the last post baseline observation. The CGI-C rating used in this study was identical to that used in the pivotal OSAHS and narcolepsy studies.

*Note: The MSLT is a validated objective assessment of sleepiness that measures the likelihood of falling asleep, rather than the ability to stay awake for a defined period of time as objectively measured by the MWT used in the pivotal OSAHS and narcolepsy studies. The MSLT is based on the premise that the degree of sleepiness is reflected by sleep latency. The MSLT involved five 20 minute (maximum) naps performed at 2 hour intervals at scheduled visits (2400, 0200, 0400, 0600, and 0800 h). The patient was dressed in non-constricting clothes and was instructed to lie quietly and attempt to sleep. Each MSLT nap continued until (a) 3 consecutive 30 second epochs of stage 1 sleep were reached, or (b) any single, 30 second episode of stage 2, 3, 4 or REM sleep was reached. Sleep latency for each nap and average sleep latency for the 4 naps were tabulated. According to the clinical protocol for the MSLT, each nap was terminated after 20 minutes if no sleep occurred. Sleep latency was measured as the elapsed time from lights out to the first epoch scored as sleep. With a 30 second scoring epoch, this criterion was reached when sleep occupied at least 16 seconds of any epoch. If a patient fell asleep, he or she was awakened and kept awake but remained in bed.*

The secondary efficacy variables:

- The key secondary variable was the change from baseline to endpoint in the mean quality of episodic secondary memory derived from the tests of memory from the CDR system (average of 4 tests at 0230, 0430, 0630, and 0830 h).

The secondary efficacy variables were:

- The change from baseline for the following:
  - Mean sleep latency from the MSLT (average of naps at 0200, 0400, 0600, and 0800) at Weeks 4, 8, and 12
  - Sleep latency for individual naps from the MSLT (2400 [midnight], 0200, 0400, 0600, and 0800) at Weeks 4, 8, and 12 and endpoint
  - Mean sleep latency from the MSLT (all 5 naps) profile over the duration of the study
- Profile of the change from baseline in the mean sleep latency from the MSLT over the duration of the study
- The proportion of patients with at least minimal improvement in the CGI-C rating at Weeks 4, 8 and 12
- CGI-C ratings at Weeks 4, 8 and 12 and endpoint
- The change from the baseline for the following variables from tests of attention from the CDR system:
  - Mean power of attention (average of 4 tests at 0230, 0430, 0630, and 0830) at Weeks 4, 8 and 12
  - Power of attention for the individual tests (0030, 0230, 0430, 0630, and 0830) at Weeks 4, 8 and 12 and endpoint
  - Mean continuity of attention (average of 4 tests at 0230, 0430, 0630, and 0830) at Weeks 4, 8 and 12 and endpoint
  - Continuity of attention for the individual tests (0030, 0230, 0430, 0630, and 0830) at Weeks 4, 8 and 12 and endpoint
- The change from baseline for the following variables from tests of memory from the CDR system:

  - Mean speed of memory (average of 4 tests at 0230, 0430, 0630, and 0830) at Weeks 4, 8 and 12 and endpoint
  - Speed of memory for the individual tests (0030, 0230, 0430, 0630, and 0830) at Weeks 4, 8 and 12 and endpoint
  - Mean quality of episodic secondary memory (average of 4 tests at 0230, 0430, 0630, and 0830) at Weeks 4, 8 and 12 and endpoint
  - Quality of episodic secondary memory for the individual tests (0030, 0230, 0430, 0630, and 0830) at weeks 4, 8, and 12 and endpoint
- The change from baseline for the following:
  - Mean KSS score (average of the 4 tests associated with the MSLT tests at 0200, 0400, 0600, and 0800) at weeks 4, 8, and 12 and endpoint
  - Worst fatigue score from the BFI scale at Weeks 4, 8 and 12 and endpoint
  - Average score from the BFI scale at Weeks 4, 8 and 12 and endpoint

Sample size estimates were made on the basis of the results of PK/PD modelling and simulation applied to data from the Phase I clinical studies with armodafinil and from clinical trials in sleep disorders with Provigil, under the assumption that both primary treatment comparisons would be with a 2-sided test at an alpha level of 0.05.

On this basis, a sample of size 108 per treatment group would provide 85% power to detect a 1.5 minute difference in the mean sleep latency from the MSLT between armodafinil and placebo, assuming a common standard deviation of 3.65 minutes. This sample size would also have at least 90% power to detect a difference of 25% between armodafinil and placebo in the proportion of patients reporting at least minimal improvement in CGI-C ratings, assuming a 37% rate in the placebo group. In addition, for the key secondary variable of memory (defined as the quality of episodic secondary memory from tests of memory in the CDR system battery), this sample size would provide at least 68% power to detect a 14 unit difference between armodafinil and placebo, assuming a common standard deviation of 42.

*Note: The clinical evaluator commented that:*

- *Approximately 250 patients were planned to be enrolled in this study in order to obtain 216 evaluable patients (that is, who have at least 1 post baseline MSLT assessment). The study actually enrolled 254 patients and 216 were evaluable for efficacy (FAS). There were 112 patients evaluable for efficacy in the armodafinil 150 mg/day group and 104 patients evaluable for efficacy in the placebo group. Therefore, the number of patients in each treatment group was similar to the number of patients in each treatment group on which the study was powered.*
- *The full analysis set (FAS) included those patients in the safety analysis set who have a baseline and at least 1 post baseline MSLT assessment, and at least 1 post-baseline CGI-C assessment. The FAS was used for all efficacy analyses.*
- *The baseline demographic data for the armodafinil 150mg and placebo treatment groups were generally well matched.*
- *Baseline CGI-S ratings were similar between the armodafinil 150mg and placebo groups, with 90% and 91% of patients, respectively, being moderately or markedly ill.*
- *The majority of patients in both the armodafinil 150 mg and placebo group were permanent shift workers (87% and 86%, respectively), and the most frequently occurring shift worker occupation in both groups was "health care social assistance" (41% and 39%, respectively).*

- *Patients in both treatment groups had similar medical histories.*
- *Prior medication use was similar for patients in both treatment groups (67% in the armodafinil 150 mg group and 68% in the placebo group).*
- *Protocol violations (non-adherence to inclusion and/or exclusion criteria, primary endpoint criteria, and/or CGP guidelines) were acknowledged for 12 patients' safety analyses.*

Statistical methods included parametric ANOVA test with treatment and country as a factor for MSLT using 2 tailed or $\alpha = 0.05$ and pre-specified non parametric Wilcoxon rank sum test.

> *Note: the protocol specified ANCOVA but was changed to ANOVA because of an interaction between treatment and baseline MSLT sleep latency (p <0.011). This change in the analytical methods was specified in the SAP approved before unbinding of the data.*

As both the parametric and non-parametric tests revealed same inferences, only the p-values from the parametric procedure were reported for the primary efficacy outcome comparison and the latter, was also applied to the secondary continuous efficacy variables. CGI-C was assessed at week 12 or the last post baseline observation using a CMH chi-square test adjusted for the country. The statistical test was 2 tailed using $\alpha = 0.05$.

> *Note: The CE commented that if efficacy in CGI-C was analysed using both observed cases and LOCF methods and that, the most conservative position is adopted of requiring both endpoints to be statistically significant in order for the study to be deemed "positive", then it is considered that each two endpoints should have been tested at $\alpha = 0.25$ (that is, adjusted for multiplicity using the Bonferroni correction).*

***Supportive Studies: Phase III, open label, long term studies***

- Study 3023 – A Phase III, open label, study designed to evaluate the safety and tolerability (primary objective) and the long term efficacy (secondary objective) of a flexible armodafinil dosage regimen (100 to 250 mg/day) administered for up to 12 months or more for the treatment of excessive sleepiness associated with a current diagnosis of narcolepsy, OSAHS (with regular use of nCPAP) or chronic SWSD.

The inclusion and exclusion criteria have been examined and are consistent with those for the pivotal Phase III studies for each of the three conditions. The distribution of enrolled patients among the three groups was approximately 1:2:3 for narcolepsy (n = 50), SWSD (n = 108), and OSAHS (n = 170). The percentage of patients completing the study was similar for the narcolepsy, SWSD and OSAHS groups (46%, 42% and 49%, respectively). The most commonly used dose of armodafinil was 250 mg/day (46% [148/323] of patients). Of the total number of patients in the safety set (n = 323), 67% (n = 217) received armodafinil daily or intermittently for 6 months and 26% (n = 83) of patients received armodafinil for more than 12 months.

The mean ± SD age at baseline in the safety analysis set was 44.8 ± 14.5 years (range: 20, 70 years) in the narcolepsy group, 48.9 ± 8.68 years (range: 12, 65 years) in the OSAHS group and 45.2 ± 11.27 years (range: 19, 70 years) in the SWSD group.

The majority of patients in each of the three groups were moderately or markedly ill. A greater percentage of patients were severely ill in the narcolepsy and OSAHS groups compared to the SWSD group (14%, 10% and 4%, respectively). No patients in the study were CGI-S rated as normal, borderline, or slightly ill, suggesting that all patients in the study had significant morbidity arising from the condition.

The secondary objective was to evaluate long term efficacy by using CGI-C ratings for all patients, and the ESS at baseline evaluations and at Months 1, 3, 6, 9, and 12, and every 3

months thereafter (or at the early termination visit) for patients with narcolepsy or OSAHS. For patients with narcolepsy or OSAHS, CGI-C was evaluated to assess general clinical condition. For patients with SWSD, CGI-C was evaluated to assess sleepiness during night shifts, including the commute to and from work.

The FAS was used for all efficacy analyses. The FAS included patients in the safety set (enrolled patients who took 1 or more doses of study drug) who had at least 1 post-baseline efficacy assessment.

Study was open labelled with no formed sample size and power calculations undertaken.

- Study 3024: A Phase III, multinational, multicentre, open label, study designed to evaluate the safety and tolerability (primary objective) and the long term efficacy (secondary objective) of a flexible armodafinil dosage regimen (100 to 250 mg/day) administered for up to 12 months or more for the treatment of excessive sleepiness associated with a current diagnosis of narcolepsy, OSAHS (with regular use of nCPAP) or chronic SWSD.

All patients in this study had completed one of the 4 pivotal Phase III studies (that is, Study 3020 [narcolepsy], Study 3021 [OSAHS], Study 3022 [SWSD], or Study 3025 [OSAHS]). Patients who had completed one these studies, met inclusion/exclusion criteria. Of the 743 enrolled patients, 474 (64%) had OSAHS, 156 (21%) had narcolepsy and 113 (15%) had SWSD. The mean ± SD age at baseline in the safety analysis set was 38.9± 12.55 years (range: 18, 67 years) in the narcolepsy group, 50.2 ± 8.80 years (range: 25, 69 years) in the OSAHS group and 42.7 ± 10.97 years (range: 19, 63 years) in the SWSD group.

The majority of patients in each of the three groups were moderately or markedly ill. A greater percentage of patients with narcolepsy (67%) were considered markedly, severely, or extremely ill compared to patients with OSAHS (46%) or SWSD (49%). No patients in the groups were CGI-S rated as normal, borderline, or slightly ill, suggesting that all patients in the study had significant morbidity arising from the condition.

The used doses of armodafinil for the overall population were 250 mg for 67% of patients, 200 mg for 10%, 150 mg for 14%, 100mg for 8%, and 50 mg for less than 1% of patients. The sponsor reported that similar patterns were observed for each of the three sleep disorder populations.

The mean ± SD duration of exposure for patients with narcolepsy was 346.2 ± 222.05 days.

The mean ± SD duration of exposure for patients with OSAHS was 387.9 ± 249.91 days.

The mean ± SD duration of exposure for patients with SWSD was 342.1 ± 226.33 days.

The primary objective was to evaluate the safety and tolerability of armodafinil administered on a flexible dosage regimen of 100 to 250 mg/day for up to 12 months or more in patients with excessive sleepiness associated with a current diagnosis of narcolepsy, OSAHS (regular users of nCPAP therapy), or chronic SWSD.

The secondary objectives were to evaluate long term efficacy by assessing the following outcomes at months 1, 3, 6, 9, and 12, and every 3 months thereafter (or at the early termination visit): CGI-C ratings (with respect to general condition for patients with narcolepsy or OSAHS [regular users of nCPAP therapy], or to sleepiness during night shifts, including the commute to and from work, for patients with chronic SWSD); BFI scores; and ESS scores for patients with narcolepsy or OSAHS.

The FAS was used for all efficacy analyses as in Study 3023. As the study was open labelled without a control group, no statistical inference procedures were applied to the data and the determination of sample size was not based on statistical considerations.

- Study 3046: A Phase IIIb, single nation, multicentre, open label study of 8 weeks initial treatment followed by a long term treatment period designed to assess the effect of a flexible armodafinil dosage regimen (150 to 250 mg/day) for the treatment of excessive sleepiness in patients with narcolepsy or OSAHS.

The study included men and women aged 18 through 65 years (inclusive) with excessive sleepiness associated with a diagnosis of narcolepsy or OSAHS, with a CGI-S rating at baseline of 4 or more (that is, at least moderately ill). In addition, patients with OSAHS were required to be regular users of effective nCPAP (at least 4 h/night on at least 70% of nights), with treatment being stable for at least 4 weeks prior to study entry. The inclusion and exclusion criteria have been examined and are considered to be consistent with the criteria for the pivotal Phase III studies.

Overall, CGI-S ratings at baseline indicated that 115 (47%) of the patients in the study were moderately ill, and 130 (53%) were markedly, severely, or among the most extremely ill. A greater proportion of patients with narcolepsy (60%) were considered markedly, severely, or extremely ill compared to patients with OSAHS (48%). In general, subjective ratings of severity of illness at baseline (PGI-S) by patients were similar to the baseline ratings (CGI-S) by investigators, although 15% of patients considered themselves normal, borderline, or slightly ill, while investigators considered all but 1 patient to be at least moderately ill.

The mean SD age at baseline in the safety analysis set was 40.1± 13.87 years (range: 18, 64 years) in the narcolepsy group and 50.6 ± 9.62 years (range: 24, 67 years) in the OSAHS group. In the narcolepsy group (n = 95), the mean ± SD armodafinil dose was 147.0 ± 77.00 mg/day, with 79 (83%) patients being exposed for more than 8 weeks, 64 (67%) for more than 12 weeks, 39 (41%) for more than 6 months and no patients for more than 9 months. In the OSAHS group (n = 151), the mean SD armodafinil dose was 146.7 ± 81.55 mg/day, with 121 (81%) patients being exposed for more than 8 weeks, 105 (69%) for more than 12 weeks, 55 (36%) for more than 6 months, and 2 (1%) for more than 9 months.

The study included a number of objectives, but none was defined as being primary or secondary.

All outcome variables were analysed using descriptive statistics. No inferential statistical were used to analyse the data from this open label study without a control group and the determination of sample size was not based on statistical considerations.

### *Short term (12 weeks) studies*

*OSAHS*

**Primary**

- In study 3021, mean sleep latency from the MWT increased from baseline to endpoint by 1.9 minutes in the combined armodafinil group (n = 241) and decreased by -1.7 minutes in the placebo group (n = 124); difference of 3.6 minutes statistically significantly in favour of combined armodafinil group, p <0.0001. In the armodafinil 150 mg/day group (n = 120), mean sleep latency from the MWT increased from baseline to endpoint by 1.7 minutes, and was 3.4 minutes longer than placebo (p = 0.0008). In the armodafinil 250 mg/day group (n = 121), mean sleep latency from the MWT increased from baseline by 2.2 minutes, and was 3.9 minutes longer than placebo (p = 0.0001). In Study 3025, mean sleep latency from the MWT increased from baseline to endpoint by 2.3 minutes in the armodafinil 150 mg/day group (n = 116) and decreased by -1.3 minutes in the placebo group (n = 120); difference of 3.6 minutes statistically significantly in favor of combined armodafinil group, p = 0.0003.
- In study 3021, the proportion of patients with a least minimal improvement in CGI-C rating from pre-treatment to endpoint in the combined armodafinil group was 72%

(174/241) compared to 37% (46/124) in the placebo group; p<0.0001. The proportion of patients with a least minimal improvement in CGI-C rating from pre-treatment to endpoint was 71% (85/120) in the armodafinil 150 mg/day group and 74% (89/121) in the armodafinil 250 mg/day group, and in both groups the difference compared to placebo was statistically significant (p <0.0001, both comparisons). The results for the combined armodafinil group and both of the armodafinil dosage groups are considered to be clinically meaningful. In Study 3025, the proportion of patients with a least minimal improvement in CGI-C rating from pre-treatment to endpoint in the armodafinil 150 mg/day group was 71% (82/116) compared to 53% (64/120) in the placebo group; p <0.0069. The placebo response rate in this study was high, resulting in the difference between the two treatment groups being of doubtful clinical significance.

**Secondary**

- In Study 3021, the key secondary efficacy outcome was change from baseline to endpoint in the mean quality of episodic secondary memory from the CDR system (average of 4 tests at 0930, 1130, 1330, and 1530 h). There was no statistically significant difference between the combined armodafinil group and placebo in this outcome (mean change: 11.4 versus 5.4 units, p = 0.1147). In Study 3025, the key secondary efficacy outcome was the change from baseline to endpoint in the mean power of attention from the tests of attention from the CDR system (average of 4 tests at 0930, 1130, 1330, and 1530 h). There was no statistically significant difference between armodafinil 150 mg/day and placebo in this outcome (mean change: 48.6 versus 43.6 msec, p = 0.8181).
- In both studies, the mean change in sleep latency from MWT (average of 4 naps at 0900, 1100, 1300, and 1500 h) from baseline to Weeks 4, 8 and 12 statistically significantly favoured all armodafinil groups compared to placebo.
- Mean sleep latency from the MWT for later time points (average of 3 naps at 1500, 1700, and 1900 h) was tested at Weeks 4, 8, and 12 and endpoint. In both studies, no statistically significant difference in mean change from baseline to endpoint was demonstrated for armodafinil and placebo.
- Descriptive results for mean change from baseline to endpoint in sleep latency from individual naps from the MWT (0900, 1100, 1300, 1500, 1700 and 1900 h) showed numerical differences in favour of the combined armodafinil group compared with placebo at all individual time points (apart from 1900 h) in both studies.
- In both studies, the proportion of patients with at least minimal improvement in the CGI-C rating at Weeks 4, 8 and 12 statistically significantly favoured all armodafinil groups compared to placebo.
- The mean change from baseline in the quality of episodic secondary memory from the CDR system (average of 4 tests at 0930, 1130, 1330, and 1530) was tested at Weeks 4, 8 and 12 and endpoint. In Study 3021, the mean change from baseline in this outcome statistically significantly favoured the combined armodafinil group compared to placebo at Week 4 (p=0.0064) and Week 8 (p = 0.0085), but not at Week 12 (p = 0.0910) or endpoint (p = 0.1147). In Study 3025, the mean change from baseline in this outcome statistically significantly favoured the armodafinil 150 mg/day group at week 12 (p = 0.0055), and endpoint (p = 0.0102), but not at Week 4 (p = 0.5932) or week 8 (p = 0.1697).
- The mean change from baseline in the power of attention from the tests of attention from the CDR system (average of 4 tests at 0930, 1130, 1330, and 1530) was tested at weeks 4, 8 and 12, and endpoint. In both studies, there were no statistically significant

differences between armodafinil groups and placebo in this outcome at weeks 4, 8 and 12 and endpoint.

- In both studies, no statistically significant differences were observed between the armodafinil and placebo groups in the mean change from baseline to endpoint in the quality of episodic secondary memory and power of attention at later time points (average of 3 tests at 1530, 1730, and 1930 h) from the CDR system.
- In both studies, no statistically significant differences were observed between armodafinil and placebo groups in mean change from baseline to endpoint in continuity of attention or speed of memory based on the relevant tests from the CDR system at earlier time points (average of 4 tests at 0930, 1130, 1330 and 1530 h) or later time points (average of 3 tests at 1530, 1730, and 1530 h).
- In both studies, the mean change from baseline to endpoint in the ESS scores statistically significantly favoured armodafinil compared with placebo.
- In both studies, mean change from baseline in the average BFI scores statistically significantly favoured armodafinil compared with placebo. In Study 3021, there was no statistically significant difference between armodafinil and placebo in mean change from baseline to endpoint in the worst fatigue score from the BFI. However, in Study 3025 there was a statistically significant difference between armodafinil 150 mg/day and placebo in mean change from baseline in the worst fatigue score from the BFI in favour of armodafinil.
- In both studies, descriptive data relating to the number of caffeine drinks consumed each data decreased slightly by a similar amount in both the armodafinil and placebo group.

*Narcolepsy*

**Primary**

- The objective primary efficacy endpoint was the mean change from baseline to endpoint (last post baseline observation) in mean sleep latency from the 20-minute MWT (average of 4 naps at 0900, 1100, 1300, and 1500 h). The comparison between the treatment groups was tested in the FAS using an ANCOVA model with country and treatment as factors, and baseline sleep latency from the MWT as a covariate ($\alpha = 0.05$, two tailed test). The mean sleep latency from the MWT increased by 1.9 minutes from baseline to endpoint in the combined armodafinil group (n = 118) and decreased by 1.9 minutes from baseline in the placebo group (n = 58), with the difference between groups being 3.8 minutes (p = 0.0024). In addition, the mean change in sleep latency from the MWT was statistically significantly greater in the armodafinil 150 mg/day (n = 58) group compared to placebo (1.3 versus -1.9 minutes, $\Delta = 3.2$ minutes, p = 0.0068), and in the armodafinil 250 mg/day group (n = 60) compared to placebo (2.6 versus -1.9 minutes, $\Delta = 4.5$ minutes, p = 0.0099). The observed differences between each of the three armodafinil groups and the placebo group are considered to be clinically meaningful.
- The subjective primary efficacy endpoint was the proportion of patients with at least minimal improvement in the CGI-C (as related to general condition) from baseline assessed at endpoint. The comparison was tested in the FAS using a CMH chi-square test adjusted for country. The proportion of patients meeting the endpoint was statistically significantly greater in the armodafinil combined group (n = 118) compared the placebo group (n = 58); 71% versus 33%, respectively, p<0.0001. In addition, the proportion of patients meeting the endpoint was statistically significantly greater in the armodafinil 150 mg/day group (n = 58) compared to placebo (69% versus 33%, respectively) and in the armodafinil 250 mg/day group (n = 60) compared to placebo (73% versus 33%, respectively, p <0.001). The observed

differences between each of the three armodafinil groups and the placebo group are considered to be clinically meaningful.

**Secondary**

- The key secondary efficacy endpoint was the change from baseline to endpoint in the mean quality of episodic secondary memory from the tests of memory from the CDR system (average of 4 tests at 0930, 1130, 1330, and 1530 h). The mean change from baseline to endpoint for this variable statistically significantly favoured the combined armodafinil group compared to placebo group (18.6 versus 1.0, respectively, p = 0.0032), the armodafinil 150 mg/day group compared to placebo group (20.7 versus 1.0, respectively, p = 0.0062), and the armodafinil 250 mg/day group compared to placebo group (16.5 versus 1.0, respectively, p = 0.0168).
- Mean sleep latency from the MWT (average of 4 tests at 0900, 1100, 1300, and 1500 h), change from baseline to Week 4 (2.1 versus -1.1 minutes, p = 0.0054), Week 8 (1.7 versus -1.2 minutes, p = 0.0481), and Week 12 (1.8 versus -1.7 minutes , p = 0.0264);
- Mean sleep latency from the MWT for later time points (average of 3 tests at 1500, 1700, and 1900 h), change from baseline at endpoint (1.5 versus -1.2 minutes, p=0.0286);
- Proportion of patients with at least minimal improvement in the CGI-C ratings at Week 4 (73% versus 39%, p <0.0001), Week 8 (69% versus 38%, p = 0.0001), and Week 12 (72% versus 30%, p <0.0001);
- Mean power of attention (average of 4 tests at 0930, 1130, 1330, and 1530), change from baseline to endpoint (-41.5 versus 158.0 msec, p = 0.0498);
- Mean power of attention for the later time points (average of 3 tests at 1530, 1730, and 1930), change from baseline to Week 12 (-9.8 versus 173.9 msec, p = 0.0219), and endpoint (3.5 versus 32.2 msec, p = 0.0413);
- Mean speed of memory (average of 4 tests at 0930, 1130, 1330, and 1530), change from baseline to Week 4 (-144.8 versus 1.8 msec, p=0.0141), Week 12 (-190.7 versus 92.7 msec, p=0.0360), and endpoint (-199.7 versus -6.3 msec, p=0.0178);
- Mean quality of episodic secondary memory (average of 4 tests at 0930, 1130, 1330, and 1530 h), change from baseline to Week 4 (14.2 versus -2.2, p = 0.0071), Week 8 (19.4 versus -1.3, p = 0.0005) and Week 12 (18.1 versus 2.9, p = 0.0362);
- Mean quality of episodic secondary memory for the later time points (average of 3 tests at 1530, 1730, and 1930), mean change from baseline at Week 12 (7.4 versus -8.8, p = 0.0344) and endpoint (8.5 versus -4.4 msec, p = 0.0256);
- Mean change in total ESS score at week 4 (-3.3 versus -2.2, p = 0.0282), Week 8 (-3.2 versus -1.4, p = 0.0014), Week 12 (-4.1 versus -1.4, p = 0.0002), and endpoint (-3.9 versus -1.9, p = 0.0006);
- Mean change in worst fatigue score from the BFI scale from baseline to Week 12 (-0.9 versus -0.1, p=0.0179);
- Mean change in average fatigue score from the BFI scale from baseline to week 4 (-1.4 versus-0.2, p <0.0001), week 8 (-1.5 versus -0.6, p = 0.0058), week 12 (-1.5 versus -0.1, p <0.0001), and endpoint (-1.4 versus -0.3, p = 0.0002).

*SWSD*

**Primary**

- The objective primary efficacy endpoint was the mean change from baseline to endpoint in mean sleep latency from a 20 minute MSLT (average of 4 naps at 0200,

0400, 0600 and 0800 h). The comparison between the treatment groups was tested in the FAS using an ANOVA with treatment and country as factors. The mean ± SD baseline sleep latency from the MSLT was 2.3 ± 1.59 minutes in the armodafinil 150 mg/day group (n = 112) and 2.4 ± 1.60 minutes in the placebo group (n = 104). The mean ± SD change in sleep latency from the MSLT from baseline to endpoint was 3.1 ± 4.46 minutes in the armodafinil 150 mg group and 0.4 ± 2.87 minutes in the placebo group, with the 2.7 minutes difference between the two groups being statistically significantly in favour of armodafinil (p <0.0001). In addition, the difference of 2.7 minutes is considered to be clinically meaningful.

- The subjective primary efficacy endpoint was the proportion of patients with at least minimal improvement in the CGI-C from baseline to endpoint. The comparison between treatments was tested in the FAS using a CMH chi-square test adjusted for country. The proportion of subjects with at least minimal improvement in the CGI-rating at endpoint was 79% (89/112) in the armodafinil 150 mg/day group and 59% (61/104) in the placebo group, with the difference between the two groups statistically significantly favoring armodafinil (p = 0.0010). The placebo response rate was unexpectedly high, resulting in the treatment difference between armodafinil 150 mg/day and placebo being of doubtful clinical significance.
- No statistical adjustment was made for multiplicity of the two primary efficacy variables, with a separate $\alpha$ of 0.05 being tested for each pairwise comparison. Therefore, in order to be deemed "positive" it is considered that the both primary endpoints should be significant at an $\alpha$ of 0.025 (two tailed test), based on the Bonferroni correction for multiplicity. As can be seen above, the p-values of both pairwise comparisons were ≤ 0.025.

**Secondary**

- The key secondary efficacy endpoint was the mean change from baseline to endpoint in the mean quality of episodic secondary memory from the tests of memory from the CDR system (average of 4 tests at 0230, 0430, 0630 and 0830 h). The mean change from baseline to endpoint for this variable statistically significantly favoured the armodafinil 150 mg/day group compared to the placebo group (18.4 versus -3.3, respectively, p <0.0001). The difference between the two treatments was 21.7 units, which is notably higher than the 14 unit difference used in the power calculation. This suggests that the difference between the two treatments in the quality of episodic memory favouring armodafinil 150 mg/day can be considered to be clinically meaningful.
- Other secondary efficacy endpoints of note which statistically significantly favoured armodafinil 150 mg/day compared to placebo group (p ≤0.05) were:
  - mean sleep latency from the MSLT (average of 4 naps at 0200, 0400, 0600, and 0800) from baseline to Weeks 4, 8 and 12;
  - proportion of patients with at least minimal improvement in CGI-C ratings from baseline to Weeks 4, 8 and 12;
  - mean quality of episodic secondary memory (average of 4 tests at 0230, 0430, 0630, and 0830) from the CDR system from baseline to Weeks 4, 8 and 12 ;
  - mean change in speed of memory (average of 4 tests at 0230, 0430, 0630, and 0830) from the CDR system from baseline to Weeks 8 and 12;
  - mean change in power of attention (average of 4 tests at 0230, 0430, 0630, and 0830) from the CDR system from baseline to Weeks 4, 8 and 12; and
  - mean change in KSS score (average of the 4 tests associated with the MSLT tests at 0200, 0400, 0600, and 0800) from baseline to Weeks 4, 8 and 12.

- Other secondary efficacy outcomes compared descriptively and favouring armodafinil 150 mg/day compared to placebo from baseline to post baseline were:
  - unintended sleep episodes during the night shift, and mean number of night naps during the night shift recorded by patient diaries; and
  - sleepiness during the night shift based on KSS scores from patient diaries.

***Long term (>12 months) studies***

The submission included long term, open label efficacy data relating to the use of flexible armodafinil dosage regimens (100 to 250 mg/day) for the treatment of excessive sleepiness in patients with narcolepsy, OSAHS or SWSD (Studies 3023, 3024 and 3046). The results from the two studies with long term data suggest that armodafinil (100 to 250 mg/day) can maintain satisfactory efficacy in the three patient groups. However, the conclusions from the studies should be interpreted cautiously due to the lack of a control group. There were no controlled data in the submission assessing the effect of armodafinil treatment for longer than 12 weeks.

**Safety**

Regarding overall conclusions on safety, the clinical evaluator stated that the key clinical trial safety data relating to the use of the armodafinil for treatment of the proposed indications are provided by the 4, pivotal Phase III double blind, placebo controlled studies of 12 weeks duration for the three sleep disorders of interest (studies 3020, 3021, 3022, 3025). The combined key safety data from the above indicated that:

- At least one AE was reported in 63% and 48% respectively of the armodafinil and placebo groups. The greatest difference (Δ) between armodafinil and placebo in the incidence of patients with at least one AE was observed in narcolepsy patients (69% versus 46%, Δ = 23%), followed by SWSD patients (54% versus 40%, Δ = 14%) and OSAHS patients (64% versus 52%, Δ = 12%).
- Treatment related AEs were reported in 38% of armodafinil treated patients compared to 21% of placebo treated patients. Treatment related AEs reported in ≥ 2% of patients in the combined armodafinil group (versus combined placebo group) were headache (14% versus 7%), nausea (6% versus 2%), insomnia (4% versus < 1%), dry mouth (4% versus < 1%), anxiety (3% versus < 1%), dizziness (3% versus < 1%), diarrhoea (2% versus < 1%), dyspepsia (2% versus < 1%), flatulence (2% versus 2%), and palpitations (2% versus < 1%). In all 7 clinical studies combined, treatment-related AEs reported in ≥ 2% of armodafinil treated patients were headache (19%), insomnia (10%), nausea (7%), anxiety (6%), dizziness (5%), dry mouth (5%), palpitations (3%), diarrhoea (3%), hypertension (3%), somnolence (2%), dyspepsia (2%), flatulence (2%), feeling jittery (2%), fatigue (2%), GGT increased (2%), heart rate increased (2%), decreased appetite (2%), nervousness (2%), irritability (2%), and tremor (2%).
- AEs were reported more commonly in patients treated with 250 mg/day compared to patients treated with 150 mg/day (69% versus 60%), and more commonly in both dose groups compared to placebo (48% for each of the comparisons). AEs reported in ≥ 2% more patients in the 250 mg/day dose group compared to the 150 mg/day dose group were headache (23% versus 14%, Δ = 9%), dry mouth (7% versus 2%, Δ = 5%), nausea (9% versus 6%, Δ = 3%), rash (4% versus 1%, Δ = 3%), insomnia (6% versus 4%, Δ = 2%), depression (3% versus 1%, Δ = 2%), anorexia (3% versus < 1%, Δ = 2%), decreased appetite (3% versus < 1%, Δ = 2%), and pyrexia (2% versus 0%, Δ = 2%). The only AE reported in ≥ 2% more patients in the 150 mg/dose group compared to the 250 mg/day dose group was dyspepsia (3% versus 1%, Δ = 2%). The results

demonstrate a dose response relationship between armodafinil and the incidence of commonly reported AEs.

- There were 6 (1%) armodafinil treated patients with SAEs compared to 2 (0.5%) placebo treated patients. In the narcolepsy population, SAEs were reported in 1 (0.8%) patient in the armodafinil group (angioneurotic oedema) and no patients in the placebo group. In the OSAHS population, SAEs were reported in 4 (1%) patients in the armodafinil group (1 x ulcerative colitis, 1 x duodenal haemorrhage, 1 x migraine, 1 x affective disorder, 1 x personality disorder) and 1 (0.4%) patient in the placebo group (1 x GORD). In the SWSD population, SAES were reported in 1 (0.8%) patient in the armodafinil group (1 x suicidal depression) and 1 (0.8%) patient in the placebo group (1 x viral meningitis). Of the reported SAEs, suicidal depression was considered to be related to treatment with armodafinil.
- AEs leading to discontinuation were reported in 7% (44/645) of armodafinil treated and 4% (16/445) of placebo treated patients. In armodafinil treated patients, AEs reported in more than 2 patients leading to discontinuation were: headache (8 patients [1%]); nausea, anxiety, and depression (4 patients each [0.6%]); and palpitations, diarrhea, ALT increased, GGT increased, agitation, and insomnia (3 patients each [0.5%]). No AEs leading to discontinuation were reported in more than 2 patients in the combined placebo group. AEs leading to discontinuation (armodafinil versus placebo) were reported in 5% versus 2% of patients, respectively, in the narcolepsy group, 8% versus 4% of patients, respectively, in the OSAHS group, and 6% versus 3% of patients, respectively, in the SWSD group. In general, the types of AEs leading to discontinuation were similar for the 3 sleep disorder populations.
- No clinically meaningful differences in clinical chemistry variables, haematological variables, or urinalysis results were observed between armodafinil and placebo. In particular, there was no evidence indicating that armodafinil is associated with haematological, hepatic or renal toxicity.
- Based on pre-specified criteria clinically significant elevated systolic and diastolic blood pressure were observed more frequently in patients treated with armodafinil (26% and 21%, respectively) compared to placebo (14% and 16%, respectively).

Composite safety conclusions were also drawn by the CE from the safety data outcome of the three supporting long term studies (3023, 3024, and 3046) and the safety outcome already mentioned above, for the four pivotal studies (3020, 3021, 3022 and 3025). The clinical evaluator commented that in all 7 clinical studies (n = 1516) taken together:

- AEs reported in ≥ 5% of armodafinil treated patients were headache (24%), insomnia and nasopharyngitis (12% each), nausea (11%), upper respiratory tract infection (9%), anxiety (8%), dizziness and sinusitis (7% each), diarrhoea and dry mouth (6% each), and influenza, back pain, arthralgia, and hypertension (5% each).
- Cumulative AE data from month 0 through month 24 showed that the majority of AEs were reported in first 3 months of treatment with armodafinil. Of the 1516 armodafinil treated patients, 47% reported at least one AE during the first 2 weeks of treatment, 72% reported at least one AE during the first 3 months of treatment, and 85% reported at least one AE during the first 24 months of treatment
- There was 1 death (0.1%) due to atherosclerotic cardiovascular disease considered by the investigator to be unrelated to treatment with armodafinil
- SAEs were reported in 80 (5%) armodafinil treated patients, including 8 (2%) patients with narcolepsy, 62 (7%) patients with OSAHS, and 10 (4%) patients with SWSD. The following SAEs were considered by investigators to be related to treatment with armodafinil: pulmonary embolism (2x), chest pain (2x) and 1x each for myocardial infarction, ventricular tachycardia, headache, transient ischemic attack, depression,

suicidal depression, asthma, hypertension, and thrombosis. All other SAEs were considered to be either not related or unlikely to be related to treatment with armodafinil.

- At least one AE leading to withdrawal in armodafinil treated patients was reported in 12% of patients with narcolepsy, 18% of patients with OSAHS, and 9% of patients with SWSD. The most frequently reported AEs leading to discontinuation (≥ 1% of patients) in armodafinil treated patients were headache (2%), anxiety (1%), and nausea (1%).
- There was no evidence that armodafinil detrimentally affected the ECG (including QTc prolongation) or the PSG.

On post marketing experience, the CE stated that:

- The submission also included important post marketing safety data from 987 adverse drug reaction reports collected by the sponsor from the date of first approval of armodafinil in June 2009 through 31 October 2013 (926 spontaneous reports, 61 solicited reports). Based on US sales data from approval date through 31 October 2013, the estimated total patient treatment days for armodafinil is 130,213,842 and the estimated total patient treatment years of treatment is 356,750.
- The post marketing data raise concerns relating to the association between armodafinil treatment and serious and potentially fatal skin conditions including SJS and DRESS syndrome. Both of these conditions have each been associated with at least one death in armodafinil treated patients. Other serious skin conditions reported in association with armodafinil treatment include dermatitis bullous, exfoliative rash, toxic epidermal necrolysis, and erythema multiforme. Other safety concerns related to armodafinil treatment arising from the post marketing data include psychiatric disorders, in particular, suicidal ideation, depression and mania, and immune system disorders, in particular, hypersensitivity disorders, anaphylactic reactions, and anaphylactic shock.

### Risk management plan

All the evaluators have raised no objection to the registration of armodafinil (Nuvigil), a new racemate [R-enantiomer] of the previously approved and registered active ingredient {modafinil}, for the proposed indications which are identical to those of modafinil (Modavigil):

- To improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy.
- To treat excessive sleepiness associated with moderate to severe chronic shift work sleep disorder where non pharmacological interventions are unsuccessful or inappropriate.
- As an adjunct to CPAP in OSAHS in order to improve wakefulness.

There are no major concerns in terms of safety and the benefit-risk balance is regarded as favourite for the proposed indications.

The PI requires modifications as raised in the clinical, toxicological and RMP evaluation reports before finalisation of the application.

## Risk-benefit analysis

### Proposed action

Based on the evidence arising from the submitted data evaluation, the Delegate is inclined at this stage to favour the approval of the application subject to resolving issues, which may arise from the deliberations of the Advisory Committee on Prescription Medicines (ACPM) and finalisation of matters pertaining to the draft PI and RMP to the satisfaction of the TGA.

### Request for ACPM advice

- Acceptability or otherwise of this application in terms of the submitted and evaluated data.

### Response from sponsor

#### *Summary of issues*

The applicant welcomes the Delegate's summary acknowledging that, based on the evaluation outcomes, all the evaluators believe that the data are sufficiently supportive to register Nuvigil (armodafinil) 50 mg, 150 mg and 250 mg tablets on quality, toxicology, efficacy and safety grounds for the proposed indications, namely:

- To improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy
- To treat excessive sleepiness associated with moderate to severe chronic shift work sleep disorder where non pharmacological interventions are unsuccessful or inappropriate
- As an adjunct to CPAP in OSAHS in order to improve wakefulness.

Within the summary of issues section, reference is also made to modifications to the draft PI that have been raised by the clinical, toxicological and RMP evaluators before the finalisation of the application. We take this opportunity to clarify that these amendments have been addressed previously, our company responses of 18 May 2015 refers. For ease of reference and for the purposes of consistency the requested amendments and the applicant's response are reproduced in full below.

- *Interactions with other medicines: The PI should include a statement on the potential of armodafinil to induce CYP2B6 activity, unless it can be satisfactorily determined from the in vitro data that a clinically significant interaction is unlikely.*

*Sponsor response*

Teva has advised that in accordance with clinical evaluation report, they have proposed a statement based on in vitro human hepatocyte information, since the extrapolation of CYP enzyme induction potential from animal studies to humans is more ambiguous. The addition of in vitro data based on studies conducted with racemic modafinil is more relevant to NUVIGIL for prescribers. Therefore, statement related to dogs was not added. The proposed information is located under the INTERACTIONS WITH OTHER MEDICINES section of the annotated PI.

- *Interactions with other medicines: The PI should include a summary of the results of the interaction between armodafinil (CYP3A4 substrate and inducer) and carbamazepine*

*(CYP3A4 substrate and inducer) published in the clinical paper referred to in Pharmacokinetics Q9.*[33]

*Sponsor response*

Teva has included this information in the INTERACTIONS WITH OTHER MEDICINES under the Drugs Metabolised by CYP3A4/5 section of the annotated PI.

- *Interactions with other medicines (interaction with P-glycoprotein): The following sentence should be added to this section:*
  - The clinical impact of inhibition of Pglycoprotein on the bioavailability of armodafinil is not known.

*Sponsor response*

Teva has included this information in the INTERACTIONS WITH OTHER MEDICINES under the Interaction with P-glycoprotein section of the annotated PI.

- *Dosage and Administration: This section of the PI includes no information on whether armodafinil can be taken with or without food. It would be reasonable to include a statement indicating that while armodafinil can be taken with or without food, administration with food may delay the onset of action and prolong the effect of the drug (cross referenced to the Precautions section).*

*Sponsor response*

Teva has included this information in the DOSAGE AND ADMINISTRATION section of the annotated PI.

- *Dosage and Administration (Dosing in Special Populations): It is considered that the Precautions and the Dosage and Administration sections of the PI should recommend that the dose of armodafinil be reduced by half in patients with severe hepatic impairment. Based on the submitted PK data for armodafinil and racemic modafinil it is considered that the dosage recommendations for Nuvigil for patients with severe hepatic impairment should be the same as those approved for Modavigil (that is, reduce the dose by half).*

*Sponsor response*

The sponsor has advised that the change is not justified because the available strengths of Nuvigil submitted for registration are 50 mg, 150 mg, and 250 mg. Therefore, it is not possible to reduce the dose by half, which is applicable to Modavigil (modafinil).

***RMP***

The Delegate's report details outstanding issues in relation to the RMP that have been raised by the RMP evaluator. It should be noted that the requested revisions have previously been incorporated in the Australian RMP version 1.2, submitted to TGA on 28 May 2015. For ease of reference and for consistency the matters raised, the sponsor's responses are outlined below.

- With regard to off-label, the sponsor should provide an explanation for the discrepancy in the response given by the sponsor and provide information on the extra cases of off label use.

*Sponsor's response*

Summary table of the extra cases on off-label use, of modafinil in Australia has been corrected and included in the updated RMP. Information on two additional cases of off-

[33] Darwish M, et al. Evaluation of the potential for pharmacokinetic drug-drug interaction between armodafinil and carbamazepine in healthy adults. *Clin Ther.* 37: 325-337 (2015).

label use of modafinil in Australia have been added, including one case of narcolepsy in a paediatric patient and one case of unknown indication, and therefore the total number of cases is 13 (added cases highlighted in yellow; Table 27).

**Table 27: Summary of Off-label use indications in patients on Modafinil in Australia.**

| SOC | PT | No. of cases |
|---|---|---|
| General disorders and administration site conditions | Fatigue (Of which 1 included both fatigue and depression) | 2 |
| | Chronic fatigue syndrome | 1 |
| | Loss of Energy | 1 |
| Nervous system disorder | Hypersomnia | 4 |
| | MS | 1 |
| | Narcolepsy (pediatric patient) | 1 |
| Psychiatric disorders | ADHD | 1 |
| Nervous system disorder | Stroke | 1 |
| Unknown | | 1 |
| | **Total** | 13 |

- The nonclinical section of the RMP should be updated to reflect the nonclinical findings with regard to toxicity in bone marrow, kidney and urinary bladder.

*Sponsor's response*

The nonclinical section of the RMP has been updated to reflect the non-clinical findings with regard to toxicity in bone marrow, kidney and urinary bladder.

- Based on the recommendation in the nonclinical evaluation report, 'Carcinogenicity' should be added as Missing Information (Reference: Round 2 recommendation).

*Sponsor response*

'Carcinogenicity' has been added to the RMP as Missing Information.

- With regard to Developmental Toxicity, the sponsor should make the changes to the RMP requested by the nonclinical evaluator, including the addition of 'Developmental toxicity' as Important Potential Risk. The nonclinical section of the RMP should be updated to reflect the nonclinical findings.

*Sponsor's response*

'Developmental Toxicity' has been added to the RMP as an Important Potential Risk. The nonclinical section of the RMP and other appropriate sections have been updated accordingly.

On the basis that a revised RMP has been submitted previously incorporating the requested revisions, we would respectfully suggest that suggested wording for the condition to registration be revised to; Implement Australian RMP Version 1.2 (dated 22 May 2015).

### *Conclusion*

On the basis of the information provided we believe that all matters raised in relation to this application to date have been addressed. We look forward to receipt of the ACPM minutes.

## Advisory Committee considerations

The ACPM resolved to recommend to the TGA Delegate of the Minister and Secretary that:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Nuvigil tablet containing 50 mg,150 mg and 250 mg of armodafinil to have an overall positive benefit-risk profile for the indications:

- To improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy.
- To treat excessive sleepiness associated with moderate to severe chronic shift work sleep disorder where nonpharmacological interventions are unsuccessful or inappropriate.
- As an adjunct to CPAP in OSAHS in order to improve wakefulness.

### *Proposed conditions of registration*

The ACPM agreed with the Delegate on the proposed conditions of registration.

### *Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments*

The ACPM agreed with the Delegate as to the proposed amendments to the PI and CMI and specifically advised on the inclusion of the following;

The need for a substantial editing and revision of the PI and CMI to better relate the text to this particular product, where there are available data.

Statements in the 'Dosage and Administration' section on renal and hepatic impairment to be more specific, as related to the level of impairment or suitable statements as to the lack of data. Statements in the relevant sections of the CMI should take into account such dosage instructions.

The strengthening of the statement in paediatric use such as:

*There is lack of either efficacy or safety data for use in paediatric populations.*

The PK section should specify absorption in the fasted and fed states, especially as it relates to $T_{max}$.

The 'Drug Interaction' section should list **all** drug interactions based on both known and probable or predictable interactive effects on the Cytochrome P450 isoenzymes including both PK and pharmacodynamic interactions.

### *Specific advice*

The ACPM advised the following in response to the Delegate's specific questions on this submission:

- Acceptability or otherwise of this application in terms of the submitted and evaluated data.

The ACPM agreed the efficacy results were acceptable to support the proposed indications in adults and the safety profile was satisfactory.

The ACPM was also of the view that submission of clinical trial data made the assessment of safety and efficacy in the case of a biosimilar much less challenging.

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

### Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Nuvigil (armodafinil) 50 mg, 150 mg and 250 mg tablet bottles and 150 mg and 250 mg tablet blister packs, indicated for:

- *To improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy.*
- *To treat excessive sleepiness associated with moderate to severe chronic shift work sleep disorder where nonpharmacological interventions are unsuccessful or inappropriate.*
- *As an adjunct to continuous positive airways pressure (CPAP) in obstructive sleep apnoea/hypopnoea syndrome in order to improve wakefulness.*

### Specific conditions of registration applying to these goods

- The armodafinil RMP, Version 1.1 (dated 5 March 2015, DLP 31 October 2013), and any subsequent revisions and further updates, as agreed with the TGA will be implemented in Australia.

# Attachment 1. Product Information

The PI approved for Nuvigil at the time this AusPAR was published is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

# Attachment 2. Extract from the Clinical Evaluation Report

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