

study was observed. This point was significantly improved in only two other pivotal studies. Little can be concluded from these data. The second endpoint, Episodic Secondary Memory, was identified as a key secondary endpoint for studies 3020, 3021 and 3022 (narcolepsy, OSAHS and SWSD studies, respectively). According to literature cited by the Sponsor this measures the ability to store, hold and retrieve information of an episodic nature (i.e. an event, a name, an object, a scene, an appointment). The Sponsor also notes that the **“the CDR system has been used in over 600 clinical studies worldwide and has been the subject of over 140 papers, chapters, published abstracts, and presentations.”** This endpoint indicated a statistically significant effect, as compared to placebo, in two of these studies (3020 and 3022) but not for the OSAHS study 3021. There was a statistically significant effect for study 3025, where this endpoint was not named to be a key secondary endpoint.

Moreover, and perhaps more importantly, the Sponsor has not provided evidence that this improvement is not related to armodafinil’s capacity in improving in wakefulness.

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## INTEGRATED REVIEW OF SAFETY

### 1.18 Methods and Findings

The integrated summary of safety provided by the Sponsor consisted of an analysis of the phase 3 development program. The Sponsor was asked to provide a listing for deaths, serious adverse events and discontinuations for the phase 1 and 2 studies. This was sent on 2/10/06 and added very few additional cases. Individual cases of significance that were believed to be potentially significant are discussed in this reviewer presentation of deaths, serious adverse events and discontinuations below.

#### 1.18.1 Deaths

**No deaths were observed “any study with armodafinil” in the original NDA application.**

#### 1.18.2 Other Serious Adverse Events

There were a total of 8 adverse events classified as serious in the double-blind placebo control studies. Six of these were reported in 645 patients on armodafinil and two in 445 patients on placebo. This brings the total number of serious adverse events for patients on armodafinil to a little less than 1% as compared to 0.4% for placebo. The table below lists these events by number (and percent) of patients, based upon the underlying sleep disorder. Five of the events on armodafinil were reported in OSAHS patients. All but one of the serious adverse events (colitis ulcerative) was reported in patients on the low dose of armodafinil (150 mg/day as opposed to 250 mg/day).

System organ class Preferred term	Number (%) of patients					
	Narcolepsy		OSAHS		SWSD	
	Armodafinil (N=131)	Placebo (N=63)	Armodafinil (N=391)	Placebo (N=269)	Armodafinil (N=123)	Placebo (N=123)
No. of patients with at least 1 SAE	1 (<1)	0	4 (1)	1 (<1)	1 (<1)	1 (<1)
<b>Gastrointestinal disorders</b>						
Colitis ulcerative	0	0	1 (<1)	0	0	0
Duodenal ulcer hemorrhage	0	0	1 (<1)	0	0	0
Gastroesophageal reflux disease	0	0	0	1 (<1)	0	0
<b>Infections and infestations</b>						
Meningitis viral	0	0	0	0	0	1 (<1)
<b>Nervous system disorders</b>						
Migraine	0	0	1 (<1)	0	0	0
<b>Psychiatric disorders</b>						
Affective disorder	0	0	1 (<1)	0	0	0
Depression suicidal	0	0	0	0	1 (<1)	0
Personality disorder	0	0	1 (<1)	0	0	0
<b>Skin and subcutaneous tissue disorders</b>						
Angioneurotic edema	1 (<1)	0	0	0	0	0

Most notable are the three adverse event reports labeled under “psychiatric disorders.” Two of these (“affective disorder” and “personality disorder”) are described in the same patient. Medication in both patients was discontinued and they were admitted to the hospital. Both cases are described below:

- Patient #0261497 is a 35 year old patient with **OSAHS and a history of “mood disorder, axis II” personality disorder.** Other significant medical history included acid reflux, joint pain, headaches, tingling (right side of face), hypertension, hypercholesterolemia, sinus headaches, allergies, dry mouth, gum sensitivity, and right frontal craniotomy. Concomitant medications included ibuprofen, amlodipine besylate plus benazepril hydrochloride, budesonide, famotidine, and paracetamol. He initially had drug discontinued on day 69 because of non-serious worsening of his preexisting mood disorder. Three days after discontinuation, however, the patient was admitted to the hospital because of serious worsening of his mood and personality disorder. Both adverse events were considered resolved on day 71 only to exacerbate again on day 72.

- **Patient #1349206 with “depression-suicidal”** was 44 year old women with a history of depression enrolled in the SWSD controlled trial. There is no mention of concomitant medications in the narrative. **This patient experienced “non serious” worsening of depression** on day 5 of treatment at which time study medication was discontinued. Six days latter the patient was hospitalized because of worsening of depression and 3ideation. At the time of hospitalization the patient noted depression 3 years ago because of martial difficulty. The depression reoccurred 6 months prior to hospitalization due to financial and gambling problems. The patient admitted to feeling suicidal 2 month prior to the study. The patient admitted to having walked into the dessert with suicidal intent on day 5 at the time of admission. In the hospital the patients was started on an SSRIs and hypnotic treatment (escitalopram oxalate and zolpidem tartrate). There was no mention of insomnia. These treatment was discontinued on day 20 and the patient was withdrawn from the study on day 20.

Another noteworthy finding is the single case of angioneurotic edema. This will be further discussed in the section on discontinuations below. Other serious adverse events do not appear to suggest any pattern that indicates obvious drug causality.

Sixteen patients out of a total of 1169 studied receiving armodafinil in the complete phase 3 database (open label and double-blind studies) experienced serious adverse events. These are summarized as number (and percent) in the table below. The general rate of serious adverse events was slightly lower in Narcolepsy as compared to SWSD and OSAHS. No additional patients outside of the controlled study database experiencing serious psychiatric and skin adverse events are identified in this larger database.

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System organ class Preferred term	Number (%) of patients			
	Narcolepsy (N=205)	OSAHS (N=716)	SWSD (N=248)	All patients (N=1169)
No. of patients with at least 1 SAE	1 (<1)	11 (2)	4 (2)	16 (1)
<b>Cardiac disorders</b>				
Myocardial infarction	0	2 (<1)	0	2 (<1)
Atrial fibrillation	0	1 (<1)	0	1 (<1)
Supraventricular tachycardia	0	1 (<1)	0	1 (<1)
<b>Gastrointestinal disorders</b>				
Abdominal hematoma	0	1 (<1)	0	1 (<1)
Colitis ulcerative	0	1 (<1)	0	1 (<1)
Duodenal ulcer hemorrhage	0	1 (<1)	0	1 (<1)
<b>General disorders and administration site conditions</b>				
Chest pain	0	2 (<1)	1 (<1)	3 (<1)
<b>Injury, poisoning and procedural complications</b>				
Tendon rupture	0	1 (<1)	0	1 (<1)
<b>Investigations</b>				
Nuclear magnetic resonance imaging brain abnormal	0	0	1 (<1)	1 (<1)
<b>Nervous system disorders</b>				
Migraine	0	1 (<1)	0	1 (<1)
<b>Psychiatric disorders</b>				
Affective disorder	0	1 (<1)	0	1 (<1)
Depression suicidal	0	0	1 (<1)	1 (<1)
Personality disorder	0	1 (<1)	0	1 (<1)
<b>Renal and urinary disorders</b>				
Nephrolithiasis	0	1 (<1)	1 (<1)	2 (<1)
<b>Respiratory, thoracic and mediastinal disorders</b>				
Chronic obstructive airways disease exacerbated	0	1 (<1)	0	1 (<1)
<b>Skin and subcutaneous tissue disorders</b>				
Angioneurotic edema	1 (<1)	0	0	1 (<1)
<b>Vascular disorders</b>				
Hematoma	0	1 (<1)	0	1 (<1)

What is notable is the number of patients with cardiac events or chest pain. Thus, there were two reports of MI in 2 separate patients, and 2 reports of rhythm disturbances (supraventricular tachycardia and one with atrial fibrillation) that originated from one of the patients with an MI. Both patients had OSAHS and an underlying risk factor for coronary artery disease (1 with diabetes and the other with hypertension, diabetes and a history of coronary artery disease and CABG). It is not completely clear whether the 3 cases of chest pain may be cardiac in origin. Thus, there is no mention in the narrative as to what constituted the complete evaluation for chest pain. It is not obvious from the narrations as to whether any of the 3 patients were admitted and evaluated for this problem. There is no mention of acute EKG changes that are consistent with this problem. No EKG results are noted after the event in one patient. Follow-up EKGs, weeks to month later, in the remaining two cases were either normal in one case or suggested changes

but that were not necessarily consistent with a prior MI. Two of the 3 patients with chest pain had a previous history of gastric reflux which may suggest another origin of this symptom. Of note, all patients with chest pain appeared to have risk factors for coronary artery disease including 2 with diabetes (the determination of one of these was made by the reviewer based upon concomitant medication, see below) and one with a previous history of an MI and CABG.

Patients who experienced chest pain are described below:

- A 57 year old male (#1404202) with SWSD and a history of gastric reflux hyperlipidemia, MI and S/P CABG experienced severe chest pain on day 73 of armodafinil at 250 mg/day of the study. At that time patients was additionally diagnosed with mild aortic valve sclerosis, moderate dilated left ventricle (MedDRA: cerebral ventricle dilatation), mild left atrial enlargement, mild mitral annular calcification, and mild trivial mitral regurgitation. Pain resolved and medication was presumably continued. An ECG performed on day 97 was noted to be **“more abnormal than those performed at screening and baseline” with “a left axis deviation, left atrial abnormality, and either acute anterior or an old process with persistent ST elevation.”**
- A 35 year old woman (#0261537) with OSAHS and a history of **“acid reflux”** and depression was admitted to an open label trial from double blind trial on 250 mg of armodafinil. Past medical history may have included diabetes as it was noted that the patient was or is presently on metformin (an oral hypoglycemic) and antidepressants. An EKG performed on day -2 (presumably on meds on this day as switching over from **double blind**) exhibited a **“possible inferior infarction.”** Patient experienced moderate intermittent chest pain on day 16 that continued till day 18 when it was resolved. As this was not thought to be related to medication armodafinil was continued. An EKG on day 96 was read as normal. The patient continued receiving medication at the time of the database cut-off.
- This was a 44 year old male (#2501927) with **OSAHS and a history of a “I/IV systolic murmur” and diet controlled DM (type 2)** who was initially enrolled in the double blind and continued in the open label study at a dose of 150 mg/day. On day 39 the patient experienced moderate chest pain that was classified as serious. Metoprolol was started **that day due to “hypertension.”** Chest pain resolved on day 42 **“without residual.”** The patient continued in the study.

The two cases of myocardial infarction are briefly described below:

- This patient is a 61 year old male (#1124107) with OSAHS and a history of type 2 diabetes mellitus (treated with pioglitazone) was reported to have a myocardial infarction for which he was admitted on day 91 of treatment with armodafinil at 200 mg/day. Armodafinil was discontinued that day. EKG changes observed at time of discharge (day 96) described aVF changes consistent with an inferior infarct. Baseline and day 28 EKGs were read as normal.

- This is a 57 year old male (#1021540) with a history of hypertension, coronary artery diseases (status post CABG), congestive heart disease, obesity, chronic bronchitis, left kidney cancer, left nephrectomy, arthritis, edema (legs), headaches, diabetes, rheumatic fever, anemia and hyperlipidemia. This patient first received placebo in double-blind trials. On day -2 an EKG was observed to have non-specific ST abnormality. EKG changes were observed on day 19 following initiation of armodafinil 250 mg/day. This included atrial fibrillation, supraventricular tachycardia and **“a non-q wave myocardial infarction.”** All events were later noted to be **“resolved with no residual effects”** on days 19 to 23. Non-serious cardiac changes were later reported on day 27 (non-specific ST-T abnormality) and day 83 (**“premature atrial systoles”** and **incomplete right bundle branch block**). The patient continues receiving medication at the time of database cut-off.

The serious reporting of atrial fibrillation and supraventricular tachycardia (one patient) is derived from the above patient (#1021540) that was also reported as a myocardial infarct.

Examination of non-phase 3 trials revealed one serious cardiovascular case. This case involved a cardiac rhythm disturbance described as **“tachycardia and ventricular extrasystoles.”** A Brief description of this case is included below:

- This report consists of a 26 year old healthy male (#001152) without a significant medical history or concomitant medications. The patient was enrolled in a bioequivalence study that compared two single dose forms of Nuvigil (separated by a 7 day washout period). Fifteen to 16 hours after the patient received a single dose of 150 mg the patient complained of chest pressure and palpitations. EKG was performed and sinus tachycardia and **“ventricular extrasystoles were** observed. Sinus tachycardia continued into the next day (90-97 BPM) and then resolved without residual. A holter was performed up to day 7 of the study and ventricular extrasystoles were noted (no mention of runs). They subsequently resolved. It would be difficult to attribute the ventricular extrasystoles to drug considering they continued for many days beyond treatment. The sinus tachycardia will have to be examined in the background of the larger control database, which will be presented in later sections.

In summary, two cases of myocardial infarction were described. These occurred in patients with risk factors. Because of this, and the fact that it was not in the control database, it is hard to attribute to drug. The 3 cases of chest pain do not contribute to causality as: 1) such events were not observed in the control database and included patients who possessed risk factors for cardiac disease<sup>5</sup>, 2) chest pain may have been confounded with other cases in one case (e.g. gastric reflux), 3) definitive diagnostic findings (cardiac enzymes or EKG during the event) were not

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<sup>5</sup> Patient #0261537, who experienced chest pain, did so on day -2 of an open label extension study. This may be considered part of prior double blind study. If viewed this way this way, it may be argued that one patient in receiving drug control studies and none in receiving placebo experienced chest pain. This is still a somewhat low value and case is not very definitive for being cardiac in origin.

described that will allow cardiac attribution. This does not mean that in attribution is not possible but only that the data are not adequate to make such a contention.

### 1.18.3 Dropouts and Other Significant Adverse Events

#### 1.18.3.1 Overall profile of dropouts

The table below presents the disposition, in terms of number (and percent), of patients who participated in all phase 3 double-blind studies. The most common cause for dropout in the combined drug group was the occurrence of adverse events (7% for combined dose). This was followed by consent withdraw (3%). There was suggestion of a dose/response relation with respect to withdrawal due to adverse events. Thus, withdrawal rate due to adverse events in the low dose was 50% greater than placebo; the rate in the high dose was twice that of placebo. Except for adverse events and one other exception, there was a less than approximately 1% difference between placebo and combined drug dose group for reasons for withdrawal. Three percent more patients withdrew in placebo group because of consent withdrawal than drug group.

Patient disposition	Number (%) of patients				
	Armodafinil			Placebo (N=454)	Total (N=1108)
	250 mg/day (N=198)	150 mg/day (N=456)	Combined (N=654)		
Randomized, not treated	0	9 (2)	9 (1)	9 (2)	18 (2)
Safety analysis set	198 (100)	447 (98)	645 (99)	445 (98)	1090 (98)
Completed study	166 (84)	371 (81)	537 (82)	382 (84)	919 (83)
Discontinued study	32 (16)	85 (19)	117 (18)	72 (16)	189 (17)
Adverse event	17 (9)	27 (6)	44 (7)	16 (4)	60 (5)
Lack of efficacy	2 (1)	1 (<1)	3 (<1)	2 (<1)	5 (<1)
Consent withdrawn	4 (2)	17 (4)	21 (3)	26 (6)	47 (4)
Protocol violation	2 (1)	4 (<1)	6 (<1)	3 (<1)	9 (<1)
Lost to follow-up	0	7 (2)	7 (1)	9 (2)	16 (1)
Noncompliance to study drug	2 (1)	0	2 (<1)	0	2 (<1)
Noncompliance to study procedures	2 (1)	9 (2)	11 (2)	3 (<1)	14 (1)
Other	3 (2)	20 (4)	23 (4)	13 (3)	36 (3)

Disposition of number (and percent) of patients in the complete phase 3 database are presented in the table below (open label and double-blind studies). The table also stratifies patients by sleep disorder. Values for all sleep disorders are similar to the double blind data presented above

except for a somewhat higher incidence of withdrawals from adverse events (compare 5% to 9%). The difference in rates is likely related to the increased exposure.

Patient disposition	Number (%) of patients			
	Narcolepsy (N=207)	OSAHS (N=723)	SWSD (N=253)	All patients (N=1183)
Randomized or enrolled, not treated	2 (<1)	7 (<1)	5 (2)	14 (1)
Safety analysis set	205 (>99)	716 (>99)	248 (98)	1169 (99)
Completed study	58 (28)	88 (12)	73 (29)	219 (19)
Ongoing in open-label studies	103 (50)	480 (66)	121 (48)	704 (60)
Discontinued study	46 (22)	155 (21)	59 (23)	260 (22)
Adverse event	14 (7)	77 (11)	12 (5)	103 (9)
Lack of efficacy	8 (4)	10 (1)	1 (<1)	19 (2)
Consent withdrawn	9 (4)	26 (4)	7 (3)	42 (4)
Protocol violation	0	7 (<1)	1 (<1)	8 (<1)
Lost to follow-up	2 (<1)	12 (2)	13 (5)	27 (2)
Noncompliance to study drug	2 (<1)	5 (<1)	0	7 (<1)
Noncompliance to study procedures	2 (<1)	7 (<1)	6 (2)	15 (1)
Other	9 (4)	10 (1)	19 (8)	38 (3)
Missing	0	1 (<1)	0	1 (<1)

### 1.18.3.2 Adverse events associated with dropouts

Adverse events, in terms of the number of patients (and rounded off percent), leading to dropouts in the double-blind trials are presented in the table below. The table categorizes these adverse by dose and organ class. One of the more obvious organs grouped system adverse events that appear drug related **are those included in "psychiatric disorders."** Thus, for the grouped data, less than 1% of placebo discontinuations occurred for this reason, whereas 3% to 4% of patients on drug discontinued as a result of adverse events. There was no obvious dose/response relation in the grouped data.

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Clinical Review  
 Norman Hershkowitz, MD, PhD  
 21,875 (000)  
 Nuvigil (armodafinil)

System organ class MedDRA preferred term, n (%)	CEP-10953 250 MG (N=198)	CEP-10953 150 MG (N=447)	CEP-10953 Combined (N=645)	Placebo (N=445)
<b>Number of patients with at least 1 AE causing discontinuation</b>	<b>17 (9)</b>	<b>27 (6)</b>	<b>44 (7)</b>	<b>16 (4)</b>
<b>CARDIAC DISORDERS</b>	<b>2 (1)</b>	<b>4 (&lt;1)</b>	<b>6 (&lt;1)</b>	<b>2 (&lt;1)</b>
PALPITATIONS	2 (1)	1 (<1)	3 (<1)	1 (<1)
CARDIAC FLUTTER	0	2 (<1)	2 (<1)	0
BUNDLE BRANCH BLOCK LEFT	0	1 (<1)	1 (<1)	0
PERICARDIAL EFFUSION	0	0	0	1 (<1)
PERICARDITIS	0	0	0	1 (<1)
<b>EAR AND LABYRINTH DISORDERS</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>1 (&lt;1)</b>
TINNITUS	0	0	0	1 (<1)
<b>EYE DISORDERS</b>	<b>2 (1)</b>	<b>1 (&lt;1)</b>	<b>3 (&lt;1)</b>	<b>0</b>
VISION BLURRED	1 (1)	0	2 (<1)	0
EYE REDNESS	0	1 (<1)	1 (<1)	0
<b>GASTROINTESTINAL DISORDERS</b>	<b>3 (2)</b>	<b>6 (1)</b>	<b>9 (1)</b>	<b>1 (&lt;1)</b>
NAUSEA	3 (2)	1 (<1)	4 (<1)	1 (<1)
DIARRHOEA	1 (<1)	2 (<1)	3 (<1)	1 (<1)
ABDOMINAL PAIN	1 (<1)	0	1 (<1)	0
ABDOMINAL PAIN UPPER	0	1 (<1)	1 (<1)	0
DUODENAL ULCER HAEMORRHAGE	0	1 (<1)	1 (<1)	0
DYSPHAGIA	1 (<1)	0	1 (<1)	0
FLATULENCE	0	1 (<1)	1 (<1)	0
<b>GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS</b>	<b>2 (1)</b>	<b>2 (&lt;1)</b>	<b>4 (&lt;1)</b>	<b>3 (&lt;1)</b>
CHEST PAIN	1 (<1)	1 (<1)	2 (<1)	1 (<1)
FATIGUE	0	1 (<1)	1 (<1)	0
LETHARGY	1 (<1)	0	1 (<1)	0
CHEST DISCOMFORT	0	0	0	1 (<1)
RAIN	0	0	0	1 (<1)
<b>INVESTIGATIONS</b>	<b>4 (2)</b>	<b>5 (1)</b>	<b>9 (1)</b>	<b>4 (&lt;1)</b>
ALANINE AMINOTRANSFERASE INCREASED	1 (<1)	2 (<1)	3 (<1)	1 (<1)
GAMMA-GLUTAMYLTRANSFERASE INCREASED	1 (<1)	2 (<1)	3 (<1)	0
ASPARTATE AMINOTRANSFERASE INCREASED	1 (<1)	1 (<1)	2 (<1)	1 (<1)
BLOOD PRESSURE INCREASED	0	1 (<1)	1 (<1)	1 (<1)
ELECTROCARDIOGRAM ST SEGMENT ABNORMAL	1 (<1)	0	1 (<1)	0
ELECTROCARDIOGRAM ST SEGMENT DEPRESSION	0	1 (<1)	1 (<1)	0
HEART RATE INCREASED	1 (<1)	0	1 (<1)	0
HEPATIC ENZYME INCREASED	1 (<1)	1 (<1)	2 (<1)	0
NEUTROPHIL COUNT DECREASED	1 (<1)	0	1 (<1)	0
PLATELET COUNT DECREASED	1 (<1)	0	1 (<1)	0
ELECTROCARDIOGRAM CHANGE	0	0	0	1 (<1)
LIVER FUNCTION TEST ABNORMAL	0	0	0	1 (<1)
<b>METABOLISM AND NUTRITION DISORDERS</b>	<b>1 (&lt;1)</b>	<b>0</b>	<b>1 (&lt;1)</b>	<b>0</b>
ANOREXIA	1 (<1)	0	1 (<1)	0
<b>MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS</b>	<b>2 (1)</b>	<b>0</b>	<b>2 (&lt;1)</b>	<b>4 (&lt;1)</b>
MUSCLE TIGHTNESS	1 (<1)	0	1 (<1)	0
MUSCULOSKELETAL CHEST PAIN	1 (<1)	0	1 (<1)	0
BACK PAIN	0	0	0	1 (<1)
JOINT STIFFNESS	0	0	0	1 (<1)
MUSCULOSKELETAL STIFFNESS	0	0	0	1 (<1)
MYALGIA	0	0	0	1 (<1)
<b>NERVOUS SYSTEM DISORDERS</b>	<b>6 (3)</b>	<b>6 (1)</b>	<b>12 (2)</b>	<b>3 (&lt;1)</b>
HEADACHE	5 (3)	3 (<1)	8 (1)	2 (<1)
DIZZINESS	2 (1)	0	2 (<1)	0
MIGRAINE	0	2 (<1)	2 (<1)	0
DISTURBANCE IN ATTENTION	1 (<1)	0	1 (<1)	0
SOMNOLENCE	0	1 (<1)	1 (<1)	1 (<1)
HYPOESTHESIA	0	0	0	1 (<1)
PARAESTHESIA	0	0	0	1 (<1)
<b>PSYCHIATRIC DISORDERS</b>	<b>7 (4)</b>	<b>12 (3)</b>	<b>19 (3)</b>	<b>3 (&lt;1)</b>
ANXIETY	2 (1)	2 (<1)	4 (<1)	2 (<1)
DEPRESSION	1 (<1)	3 (<1)	4 (<1)	1 (<1)
AGITATION	2 (1)	1 (<1)	3 (<1)	0
INSOMNIA	1 (<1)	2 (<1)	3 (<1)	0
NERVOUSNESS	1 (<1)	1 (<1)	2 (<1)	0
SLUMP DISORDER	1 (<1)	1 (<1)	2 (<1)	0
ABNORMAL BEHAVIOUR	1 (<1)	0	1 (<1)	0
AFFECTIVE DISORDER	0	1 (<1)	1 (<1)	0
DISORIENTATION	0	1 (<1)	1 (<1)	0
DYSPHORIA	0	1 (<1)	1 (<1)	0
MANIA	0	1 (<1)	1 (<1)	0
PERSONALITY DISORDER	0	1 (<1)	1 (<1)	0
<b>RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS</b>	<b>1 (&lt;1)</b>	<b>1 (&lt;1)</b>	<b>2 (&lt;1)</b>	<b>2 (&lt;1)</b>
DYSNOEIA	1 (<1)	1 (<1)	2 (<1)	1 (<1)
EPISTAXIS	0	0	0	1 (<1)
<b>SKIN AND SUBCUTANEOUS TISSUE DISORDERS</b>	<b>1 (&lt;1)</b>	<b>5 (1)</b>	<b>6 (&lt;1)</b>	<b>4 (&lt;1)</b>
RASH	0	2 (<1)	2 (<1)	0
ALLERGIC REACTION	0	1 (<1)	1 (<1)	0
HYPERHIDROSIS	0	1 (<1)	1 (<1)	0
RASH PAPULAR	0	1 (<1)	1 (<1)	0
URTICARIA	1 (<1)	0	1 (<1)	2 (<1)
RASH MACULAR	0	0	0	1 (<1)
SKIN ODOUR ABNORMAL	0	0	0	1 (<1)
<b>VASCULAR DISORDERS</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>2 (&lt;1)</b>
HYPERTENSION	0	0	0	2 (<1)

The number (and rounded off percent) of adverse events leading to dropouts, broken-down by organ system, in all phase 3 trials (double-blind and open label study) are presented in the two tables below.

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System organ class MedDRA preferred term, n (%)	Harcolopay (N=205)	OSAR5 (N=716)	SMED (N=248)	All Patients (N=1169)
Number of patients with at least 1 AE causing discontinuation	14 (7)	74 (10)	13 (5)	101 (9)
<b>BLOOD AND LYMPHATIC SYSTEM DISORDERS</b>				
ANEMIA	0	1 (<1)	0	1 (<1)
THROMBOCYTOPENIA	0	1 (<1)	0	1 (<1)
<b>CARDIAC DISORDERS</b>				
PALPITATIONS	0	8 (1)	3 (1)	11 (<1)
CARDIAC FLUTTER	0	6 (<1)	1 (<1)	7 (<1)
BRITTE BRANCH BLOCK LEFT	0	1 (<1)	1 (<1)	2 (<1)
MYOCARDIAL INFARCTION	0	0	1 (<1)	1 (<1)
MYOCARDIAL INFARCTION	0	1 (<1)	0	1 (<1)
<b>EAR AND LABYRINTH DISORDERS</b>				
TINNITUS	1 (<1)	0	0	1 (<1)
TINNITUS	1 (<1)	0	0	1 (<1)
<b>EYE DISORDERS</b>				
VISION BLURRED	1 (<1)	4 (<1)	1 (<1)	6 (<1)
VISION BLURRED	1 (<1)	2 (<1)	0	3 (<1)
ASTHENOPIC	0	1 (<1)	0	1 (<1)
EYE HAEMORRHAGE	0	0	1 (<1)	1 (<1)
EYE REDNESS	0	1 (<1)	0	1 (<1)
<b>GASTROINTESTINAL DISORDERS</b>				
Nausea	2 (<1)	19 (3)	3 (1)	24 (2)
DIARRHOEA	1 (<1)	10 (1)	2 (<1)	13 (1)
DIARRHOEA	1 (<1)	5 (<1)	0	6 (<1)
ABDOMINAL PAIN	0	2 (<1)	0	2 (<1)
ABDOMINAL PAIN UPPER	0	1 (<1)	1 (<1)	2 (<1)
DYSPEPSIA	0	2 (<1)	0	2 (<1)
CONSTIPATION	0	1 (<1)	0	1 (<1)
DRY MOUTH	0	1 (<1)	0	1 (<1)
DUODENAL ULCER HAEMORRHAGE	0	1 (<1)	0	1 (<1)
DYSPEPSIA	0	1 (<1)	0	1 (<1)
FLATULENCE	0	1 (<1)	0	1 (<1)
GASTRITIS	1 (<1)	0	0	1 (<1)
<b>GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS</b>				
ASTHENIA	1 (<1)	8 (1)	0	9 (<1)
CHEST PAIN	1 (<1)	1 (<1)	0	2 (<1)
CHEST PAIN	0	2 (<1)	0	2 (<1)
FEELING JITTERY	1 (<1)	1 (<1)	0	2 (<1)
CHEST DISCOMFORT	0	1 (<1)	0	1 (<1)
FATIGUE	0	1 (<1)	0	1 (<1)
FEELING ABNORMAL	0	1 (<1)	0	1 (<1)
LETHARGY	0	1 (<1)	0	1 (<1)
<b>IMMUNE SYSTEM DISORDERS</b>				
HYPERSENSITIVITY	0	1 (<1)	0	1 (<1)
HYPERSENSITIVITY	0	1 (<1)	0	1 (<1)
<b>INFECTIONS AND INFESTATIONS</b>				
VIRAL INFECTION	0	1 (<1)	0	1 (<1)
VIRAL INFECTION	0	1 (<1)	0	1 (<1)
<b>INJURY, POISONING AND PROCEDURAL COMPLICATIONS</b>				
CONTUSION	1 (<1)	0	0	1 (<1)
CONTUSION	1 (<1)	0	0	1 (<1)
<b>INVESTIGATIONS</b>				
ALANINE AMINOTRANSFERASE INCREASED	1 (<1)	10 (1)	4 (2)	15 (1)
ALANINE AMINOTRANSFERASE INCREASED	0	3 (<1)	1 (<1)	4 (<1)
GAMMA-GUTAMYLTRANSFERASE INCREASED	0	3 (<1)	1 (<1)	4 (<1)
ASPARTATE AMINOTRANSFERASE INCREASED	0	2 (<1)	0	2 (<1)
BLOOD PRESSURE INCREASED	0	1 (<1)	1 (<1)	2 (<1)
HEART RATE INCREASED	1 (<1)	1 (<1)	0	2 (<1)
ELECTROCARDIOGRAM QT CORRECTED INTERVAL PROLONGED	0	1 (<1)	0	1 (<1)
ELECTROCARDIOGRAM ST SEGMENT ABNORMAL	0	1 (<1)	0	1 (<1)
ELECTROCARDIOGRAM ST SEGMENT DEPRESSION	0	0	1 (<1)	1 (<1)
HEPATIC KETOYE INCREASED	0	1 (<1)	0	1 (<1)
NEUTROPHIL COUNT DECREASED	0	1 (<1)	0	1 (<1)
NUCLEAR MAGNETIC RESONANCE IMAGING BRAIN ABNORMAL	0	0	1 (<1)	1 (<1)
PLATELET COUNT DECREASED	0	1 (<1)	0	1 (<1)
WEIGHT DECREASED	0	1 (<1)	0	1 (<1)
<b>METABOLISM AND NUTRITION DISORDERS</b>				
ANOREXIA	0	5 (<1)	0	5 (<1)
ANOREXIA	0	3 (<1)	0	3 (<1)
DIABETES MELLITUS NON-INSULIN-DEPENDENT	0	1 (<1)	0	1 (<1)

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System organ class MedDRA preferred term, n (%)	Marolepsy (N=205)	OSAHs (N=716)	SNED (N=249)	All Patients (N=1169)
HYPERCHOLESTEROLAEMIA	0	1 (<1)	0	1 (<1)
HYPERGLYCAEMIA	0	1 (<1)	0	1 (<1)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (<1)	4 (<1)	0	5 (<1)
ARTHRALGIA	1 (<1)	0	0	1 (<1)
BACK PAIN	0	1 (<1)	0	1 (<1)
MUSCLE TIGHTNESS	0	1 (<1)	0	1 (<1)
MUSCULOSKELETAL CHEST PAIN	0	1 (<1)	0	1 (<1)
MYALGIA	0	1 (<1)	0	1 (<1)
PAIN IN EXTREMITY	1 (<1)	0	0	1 (<1)
NERVOUS SYSTEM DISORDERS	6 (3)	19 (3)	3 (1)	28 (2)
HEADACHE	4 (2)	10 (3)	2 (<1)	16 (1)
DIZZINESS	1 (<1)	4 (<1)	2 (<1)	7 (<1)
DISTURBANCE IN ATTENTION	1 (<1)	1 (<1)	0	2 (<1)
MIGRAINE	0	2 (<1)	0	2 (<1)
PSYCHOMOTOR HYPERACTIVITY	0	2 (<1)	0	2 (<1)
PARESTHESIA	0	1 (<1)	0	1 (<1)
SCHWOLENCE	0	1 (<1)	0	1 (<1)
PSYCHIATRIC DISORDERS	7 (3)	30 (4)	5 (2)	42 (4)
ANXIETY	2 (<1)	8 (1)	1 (<1)	11 (<1)
DEPRESSION	2 (<1)	5 (<1)	1 (<1)	8 (<1)
DEPRESSION	1 (<1)	3 (<1)	1 (<1)	5 (<1)
AGITATION	0	4 (<1)	0	4 (<1)
IRRITABILITY	0	3 (<1)	1 (<1)	4 (<1)
NERVOUSNESS	0	3 (<1)	0	3 (<1)
SLEEP DISORDER	1 (<1)	2 (<1)	0	3 (<1)
ECSTASY	0	1 (<1)	1 (<1)	2 (<1)
ABNORMAL BEHAVIOUR	1 (<1)	0	0	1 (<1)
AFFECTIVE DISORDER	0	1 (<1)	0	1 (<1)
COMPULSIONS	0	1 (<1)	0	1 (<1)
CONFUSIONAL STATE	0	1 (<1)	0	1 (<1)
DISORIENTATION	1 (<1)	0	0	1 (<1)
DYSPHORIA	0	1 (<1)	0	1 (<1)
INITIAL DEPRESSION	1 (<1)	0	0	1 (<1)
MANIA	0	1 (<1)	0	1 (<1)
PERSONALITY DISORDER	0	1 (<1)	0	1 (<1)
THINKING ABNORMAL	0	1 (<1)	0	1 (<1)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0	2 (<1)	0	2 (<1)
INFERTILE DYSFUNCTION	0	2 (<1)	0	2 (<1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (<1)	5 (<1)	0	6 (<1)
DYSPOEIA	0	2 (<1)	0	2 (<1)
BRONCHOSPASM	0	1 (<1)	0	1 (<1)
DYSPOEIA EXERCITIONAL	0	1 (<1)	0	1 (<1)
RHINITIS	1 (<1)	0	0	1 (<1)
SINUS CONGESTION	0	1 (<1)	0	1 (<1)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	3 (1)	3 (<1)	1 (<1)	7 (<1)
RASH	0	1 (<1)	1 (<1)	2 (<1)
ANGIOEDEMATOUS OEDEMA	1 (<1)	0	0	1 (<1)
HYPERHIDROSIS	0	1 (<1)	0	1 (<1)
PEORIASIS	1 (<1)	0	0	1 (<1)
RASH PAPULAR	0	1 (<1)	0	1 (<1)
URTICARIA	1 (<1)	0	0	1 (<1)
VASCULAR DISORDERS	0	2 (<1)	0	2 (<1)
FLASHING	0	1 (<1)	0	1 (<1)
THROMBOSIS	0	1 (<1)	0	1 (<1)

The most common reported system organ class reason for discontinuation, in both placebo-control and all phase 3 studies, was that related to psychiatric disorders. Thus, in placebo control studies 19 of 645 patients (2.9 %) of patients on drug discontinued from medication for psychiatric reasons. This compares to 3 of 445 (0.7%) patients on placebo. 42 out of 1,169 (3.6%) of patients in all phase 3 studies discontinued treatment because of psychiatric adverse events. Although, while this general category of adverse event appeared to be linked to drug use, as it was significantly more commonly seen with drug than placebo, it was not obviously dose dependent. It appeared somewhat more common in OSAHS than in the other disorders, but not markedly so.

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Anxiety was the most common psychiatric adverse event leading to discontinuation with 0.9% patients in drug and 0.4 % in placebo reporting this event. A similar percent of patients discontinued in open label studies as that reported for drug groups. Off interest, in a small number of cases in the complete phase 3 data base (3 of 11) insomnia was associated with anxiety. This number may be too small to assume causality between these two events, but it may raise some suspicion. Other psychiatric disorders, similar to anxiety reported a number of cases of irritability, agitation and nervousness at a lower rate. This reviewer feels that, as such reported adverse events are similar in nature, these events may be combined in a single group. This information is included in the table below for both double-blind and all phase 3 studies (total number and percent of patients). It is noteworthy that one case in the double-blind study reported both MedDRA terms of anxiety and nervousness for the same patient: this dual representation for this patient is corrected in the total calculation. Examination of this table reveals that few patients in placebo would discontinue because of this group of adverse events but 1.4% in the control trials and 1.9% in the complete phase 3 data base on drug discontinued. In general, while prior psychiatric history was noted in some of the patients with the above it was not always observed. The vast majority of the psychiatric events described in the table below (anxiety, agitation, nervousness and irritability) were of mild severity. Four cases of anxiety were severe (but not labeled as serious) in nature. Examination of the narration revealed little specific descriptions as to what specific behavior led to this label. All such adverse events were noted to resolve upon drug discontinuation. It should be noted that two additional events coded as mania and disorientation behavior might be added to the present group of anxiety like adverse event. Thus, the reported event of “mania” and “dysphoria” occurred in one patient who was described in the narration as experiencing severe (but not serious) “feeling of manic” and dysphoria (no specific mention of symptoms that would suggest this represented true mania such as delusions were noted). The single case of disorientation was described as a moderately severe event that included “inability to think clearly,” “driving on the wrong side of the road,” and “buzzed (alert).” This event resolved with drug discontinuation.

	Pivotal Double-Blind placebo Control Studies		All Phase 3
	Combined Drug (N=645)	Placebo (N=445)	Drug (N=1169)
anxiety	4 (0.6 %)	2 (0.3 %)	11 (0.9 %)
agitation	3 (0.5 %)	0 (%)	4 (0.3 %)
nervousness	2 (0.3 %)	0 (%)	3 (0.3 %)
irritability	0 (0.0 %)	0 (%)	4 (0.3 %)
Total	8(1.2 %)	2 (0.3 %)	22 (1.9 %)

Following anxiety, insomnia and depression were the most common psychiatric adverse events. Thus, medication was discontinued for reasons of depression occurring in 4 of 645 (0.6%) of patients on drug and 1 of 445 (0.2 %) of patients on placebo in the double-blind control studies. The incidence of discontinuation for this reason was similar for all phase 3 trials (5 of 1169 or 0.4% of patients). Examining the narrations reveals that all but one patient on drug had a previous history of a behavioral disorder (anxiety with hypothyroidism in one and depression in

3). Depression resolved in all but one case on drug and one on placebo following discontinuation. Some patients were started on treatment with antidepressants and other agents. Depression was graded as mild to severe. No suicidal ideation or intent is noted in the narratives except for one patient that has already been described in the section on serious events. The single case of depression in the placebo patient appeared similar to the drug associated cases. That is, severe depression occurred in this patient who had a history of depression: medication was discontinued and antidepressants started without resolution of symptoms.

Insomnia was not a reason for discontinuation in any placebo patient but was in 3 ((0.5%) of patients receiving drug in placebo control studies. In general most patients reporting insomnia in the complete phase 3 database were described as having mild or moderate insomnia. Two patients had severe insomnia. Except in one case, the insomnia resolved with drug discontinuation. In two cases insomnia and anxiety were listed in the same patients as reasons **for withdrawal. "Sleep disorder," as a reason** for discontinuation, was observed in 2 additional patients in the controlled trials. These two cases were associated with an additional behavioral **reason for discontinuation: i.e. "abnormal behavior" (poorly described) and "agitation."** Examination of the narrative did not clarify what this was meant by sleep disorder, however, **combining "insomnia" and "sleep disorder" results in 0.8 % of patients discontinuing in the controlled studies because sleep related problems while none were observed in placebo. Similar rates of patients were discontinued because of some form of sleep disorder (mild to moderate intensity) in the complete phase 3 data base (0.9%).**

In summary, anxiety related disorders, depression and sleep related disorders (e.g. insomnia) appear as true signals as reasons for discontinuation.

Of system organ class reasons for discontinuation, nervous system adverse events was the second most common cause of discontinuation with 2.6% of patients on drug and 0.7 on placebo in double-blind studies discontinuing for these reasons. A similar percent of patients receiving drug in all phase 3 trials discontinued (2.4%) as did in the drug group from the placebo controlled studies. Within these groups headaches overwhelmingly makes up the predominant reason for discontinuation. This adverse event is the most common reason for discontinuation in all phase 3 trials. The table below presents a summary of the incidence (total number and percent of patients) of headache, migraine and combined incidences in the placebo-control studies and all phase 3 studies. In pivotal studies, 2.2 % of patient in total was classified as discontinuing for reasons of headache. This was greater than those in the placebo group and slightly larger than the percent who discontinues in the full phase 3 database. Discontinuation from headache was more common at higher doses (2.5% for 250 mg/day and 0.6% at 150 mg/day in placebo-control studies). Over 70% of headaches in this group of patients in occurred within the first 2 weeks of treatment with many within the first few days. They almost universally resolved with treatment discontinuation. The narcolepsy population experienced only a slightly greater incidence (2 of 205 patients) than the OSAHS (7 of 716 patients) and SWSD (2 of 240 patients) in all phase 3 studies. Headaches in the population who discontinued were frequently associated with other symptoms that were also noted as reasons for discontinuations. The single most common other MedDRA term associated with these cases were **"dizziness. The narratives were not adequately detailed to determine whether this dizziness**

was vestibular or vascular in nature, although in a few cases the term dizziness was derived from the investigator term of “light headedness.” This symptom occurred in 5 patients whose reason for discontinuing included headache in the complete phase 3 database. Nausea was occasionally associated with headache (n=3) as was nervousness/anxiety/agitation (n=3).

	Pivotal Double-Blind placebo Control Studies		Phase 3 Trials
	Combined Drug (N=645)	Placebo (N=445)	Drug (N-1169)
Headache	12 (1.9 %)	3 (0.6 %)	16 (1.3 %)
Migraine	2 (0.3 %)	0 (0.0 %)	2 (0.2 %)
Total	14 (2.2 %)	3 (0.6 %)	18 (1.5 %)

Two cases of headaches were also associated with other symptoms that merit attention:

- Patient # 0024224 was a 46 year old female who suffered two episodes of headaches during treatment with 100 mg/day of armodafinil. On day 41, the patient experienced a second moderate headache (MedDRA: headache) in addition to mild dizziness (MedDRA: dizziness) and moderate increased blood pressure (MedDRA: blood pressure increased). The next day (day 42), the patient experienced mild nausea, and on day 53, she was diagnosed with a ruptured blood vessel in her right eye (MedDRA: eye hemorrhage) that was moderate in intensity. Pressures in the narration and CRF were, however, no greater than 140/90. The ruptured blood vessel was reported as resolved; however, unspecified residual effects were noted, and the resolution date was not reported. The dizziness, headache, and increased blood pressure were continuing at the time of this report.
- Patient 0981567 was a 45-year-old woman with OSAHS, began treatment with 150 mg/day. Significant medical history included frequent headaches, hypertension, constipation, gastroesophageal reflux disease, nervous and stomach, hysterectomy, **arthritis, Bell’s palsy.** Prior and concomitant medications taken by the patient, all of which she continued during the study included ranitidine hydrochloride, linseed oil, amlodipine besilate, cyanocobalamin, multivitamins, glucosamine, chromium picolinate, camphorated phenol, bismuth subsalicylate, verapamil, and pantoprazole. and loratadine. Prior to starting study drug, the patient experienced nonserious events of seasonal allergies (MedDRA: seasonal allergy) and sinus headache (MedDRA: sinus headache). The sinus headache resolved on day 8; however, on day 19, the patient experienced a moderate migraine headache (MedDRA: migraine) that was considered a serious adverse event. The migraine resolved with no residual effect on day 21; however, the next day (day 22), the patient experienced additional non-serious events of twisted lip (muscle constriction [MedDRA: muscle contracture]), shooting pain in the right eye (MedDRA: eye pain), and sensation of pressure in the right eye (MedDRA: abnormal sensation in eye). The twisted lip, right eye pain, and right eye pressure resolved with no

residual effect on days 23, 24, and 25, respectively. Study drug was discontinued on day 25; the migraine headache was reported as the reason for discontinuation of study drug. This is a rather confusing case because of the associated facial symptoms and perhaps the eye pain. Perhaps the facial symptoms are related to the previous history of Bells palsy (e.g. hemifacial spasms). The association with migraine and eye pain may suggest a possible complicated migraine or a vascular event.

Both the latter two cases represent headaches with associated symptoms that may represent a more worrisome process, but because these cases are isolated and cannot be definitively linked to such a process no definitive conclusions can be reached.

Dizziness was the second most common reason for discontinuation in the nervous system organ class with 1.2% of patient on drug and 0.0% of patients on placebo in the pivotal double blind withdrawing for this reason. Only 0.6% of patients in the complete phase 3 baseline studies withdrew for this reason. As noted previously **dizziness was sometimes characterized as “light headiness”, but was not specified other times.** As noted above dizziness was sometimes associated with headache. In one case it was associated with palpitations. Dizziness was more common at high doses (1% at 250 mg/day and 0 at 150 mg/day in placebo control studies), but the general incidence is probably too small to conclude a dose response. Dizziness would resolve upon the discontinuation of the drug.

Gastrointestinal disorders was the next most common organ system reason for withdrawal from the study with approximately 1% and 2% of patients discontinuing for this reason in the double blind and open label database, respectively. Nausea was the most common adverse event and appeared to have a slightly higher rate in the drug as compared to the placebo group in the double blind studies with a rate of 0.86% in drug and 0.22% in placebo. Nausea would almost always resolve upon drug discontinuation. It was frequently associated with other symptoms that varied greatly between patients, e.g. it could be associated with dizziness, psychiatric complaints (e.g. anxiety), headaches etc. No specific pattern could be discerned. Diarrhea was the second most common GI complaint. Control studies show only a slight preponderance in drug treated patients over those given placebo (e.g. compare 0.62% in drug treated group versus 0.225 in placebo treated group). It was occasionally accompanied by abdominal pain and would resolve upon drug discontinuation.

Cardiac disorders are the next most common adverse events categorized by organ class<sup>6</sup> that results in withdrawal with 0.93% of patients in the drug group and 0.45 in the placebo group withdrawing in placebo-controlled studies because of this class of adverse event. The incidence is nearly identical in the complete phase 3 database. Cardiac palpitations make up the predominate reason for withdrawal with 0.47% patients experiencing this adverse event in the drug treated group and 0.22% in the placebo group in the placebo-controlled trials. Cardiac flutter was the second most common adverse event. Examinations of the narrations reveal that cardiac flutter is derived from the **investigator classification of “heart flutter.” As this represents**

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<sup>6</sup> “Investigations” are more common, but does not refer to an individual organ class and will be discussed in the section on laboratories.

a symptom of cardiac awareness this reviewer believes that this value can simply be added to palpitations. In such case 0.78% (5 of 645 patients) of patients in drug group experiences some form of cardiac awareness in the drug-treated group whereas 0.22% (2 of 445) did so in the placebo group of the controlled trials. This may be a significant difference. Where described these events resolved upon drug discontinuation. Palpitations may be caused by a number of factors including rhythm or conduction disturbances or anxiety. Examination of the narrations did not describe EKGs during the episodes. There is no mention of significantly abnormal EKGs in the narrations during drug treatment or after medication was discontinued in the narration. Anxiety was associated with cardiac awareness and also listed as a reason for discontinuation in 3 cases as was headache in another in another 2 cases. Cardiac awareness was associated with chest pain in one case and light headiness in another case. The only rhythm/conduction disturbance noted as a reason for discontinuation was one case of bundle branch block. This occurred in a 35 year old male without a history of cardiac risk factors but with an abnormal EKG at baseline that mitigates the present finding. **The baseline EKG demonstrated “minor right intraventricular conduction defect and abnormalities consistent with a left anterior hemiblock.”** These data would suggest that there is no compelling data to indicate that the cardiac awareness is associated with rhythm disturbance.

The table below lists (number of patients and percent) various potential cardiological reasons for drug discontinuation. These were derived from various organ systems headings. Only one case of myocardial infarction related events causing discontinuation are noted in the phase 3 open label trials. None were observed in the placebo control trials. This reviewer identified a case labeled as “myocardial ischemia” in the open label phase 3 trials in the narrations that were not included in the Sponsor’s table. The table also lists cases of discomfort or pain that is referable to the chest that were included under organ systems of “General Disorders...” and “Musculoskeletal and Connective Tissue Disorders” as well as changes in electrocardiogram changes that may be consistent with cardiac ischemia.

	Phase 3 Double-Blind Placebo-Control		All Phase 3 Trials
	Combined Drug (%) N=645	Placebo (%) N=445	Drug (%) N=1169
Myocardial Infarction	0	0	1 (0.1%)
Myocardial Ischemia	0	0	1 (0.1%)
Chest Pain	2 (0.3%)	1 (0.2%)	2 (0.2%)
Chest Discomfort	0	1 (0.2%)	1 (0.1%)
Musculoskeletal Chest Pain	1 (0.2%)	0	1 (0.1%)
Electrocardiogram ST segment abnormal or ST depression	2 (0.3%)		2 (0.2%)
Electrocardiogram change (ischemic changes more marked than baseline)		1 (0.2%)	0

Brief descriptions of the drug related cases in double blind studies are presented as follows:

- **Chest Pain:** This occurred in 36-year-old black woman (#0281696) with OSAHS, began treatment with armodafinil 250 mg/day. Significant medical history included asthma, back problems from accident and diet controlled diabetes. Concomitant medications included naproxen sodium and salbutamol. At screening (day -43), ECG abnormalities including sinus tachycardia (ventricular rate over 100 bpm), ST-T depression, and a non-specific ST-T abnormality were noted; however, ECG findings at baseline (day -1) were normal. On day 13, the patient experienced severe difficulty swallowing (MedDRA: dysphagia) and breathing (MedDRA: dyspnea). Both events resolved without residual effect on day 17; however, the patient experienced nonserious adverse events of severe heart palpitation (MedDRA: palpitations), severe chest pain (MedDRA: chest pain), and moderate nausea (MedDRA: nausea) that same day. Study drug was discontinued on day 17 due to all 5 adverse events. The chest pain was treated with acetylsalicylic acid (study day 17), glyceryl trinitrate (days 17 and 18), and ketorolac tromethamine (days 17 and 18). The chest pain, heart palpitation, and nausea all resolved without residual effect on day 18, and the patient was withdrawn from the study on day 23; ECG findings were normal on day 23. The chest pain is suspicious for being of cardiac in origin because of the use of nitrates, symptomatic palpitations, and association with nausea, perhaps representing an autonomic response. No mention of EKG is made which would be helpful. This occurred in a patient with some risk factors for cardiac disease that included a history of diabetes and a prior abnormal EKG. With the added symptoms of dysphagia one may speculate as to whether this represents angioedema (see below).
- **Chest Pain and electrocardiogram ST segment abnormal:** This patient (3223435) is a 61 year-old women with OSAHS who began treatment with 250 mg/day of armodafinil. Significant medical history included hypertension, hyperlipidemia, chest pain, obesity, chronic obstructive pulmonary disease, asthma (stable), hiatal hernia, gastroesophageal reflux disease, occasional aches (back and hip), depression, and obesity. Concomitant medications included omeprazole magnesium (Prilosec), fluticasone propionate (Flonase), hydrochlorothiazide, ascorbic acid, acetylsalicylic acid, tocopherol, formoterol fumarate (for asthma), losartan potassium (an angiotensin antagonist), and phenazopyridine. Five days prior to starting medication the patient experienced elevation of blood pressure and intermittent chest pain light headedness and shortness of breath. The chest pain and increased blood pressure resolved 1 day before medication was started. Dizziness and dyspnea resolved on day 20 of treatment. Although screening and baseline ECG findings were normal an ECG performed on day 28 showed abnormalities **“including ST depression with slightly upsloping V4, V5, and V6.”** The medication was discontinued on day 32 for what was described as a recurrence of chest pain, elevation in blood pressure and EKG abnormalities day 28 and medication was discontinued on day 32. Metoprolol was later initiated for the increase in blood pressure. All symptoms along with EKG abnormalities resolved. Examination of the blood pressure information in the narration was somewhat confusing in that the screening (day -35) blood pressure was 145/85 and all subsequent blood pressures were (138-150/ 78-84). The associated chest pain and associated EKG changes following treatment is suspect for potential

ischemia. The fact that this patient may have had a similar event just prior to treatment and the risk factors partially confound the links to armodafinil.

- **Musculoskeletal Chest Pain:** This occurred in a 41 year-old Indian man placed on 250 mg/day of armodafinil with OSAHS and a significant medical history of diabetes **mellitus, hypercholesterolemia, and exercise induced asthma. Patient's concomitant medications** were metformin, salbutamol, acetylsalicylic acid, seretide mite, and atorvastatin. On day 33, the patient was noted **to experience a "nonserious adverse event of mild musculoskeletal pain, left of his sternum (MedDRA: musculoskeletal chest pain).** The study drug was discontinued on the same day **due to the pain. "The musculoskeletal"** pain resolved with no residual effect on day 37. Other adverse events were noted prior to this report of chest pain. These included nausea, excitability dry mouth pyrexia and generally resolved before chest pain was noted. For this case there is no definitive reason to believe that this is cardiac in origin. However there is inadequate information for this reviewer to classify as musculoskeletal.
- **ST Depression:** This occurred in a 34-year-old black man (2289176) with chronic SWSD. Significant medical history included right knee pain after running long distances. Concomitant medication included only ibuprofen. ECG results at screening were normal; however, an ECG performed at baseline (day -16) showed a minor right intraventricular conduction defect and abnormalities consistent with a left anterior hemiblock. On day 37, the patient had 2, nonserious, mild adverse events: left anterior hemiblock (MedDRA: bundle branch block left) and ST depression (MedDRA: electrocardiogram ST segment depression). An ECG performed the following day (day 38) supported baseline ECG findings, showing abnormalities consistent with a left anterior hemiblock, non-specific T wave abnormalities, and probable ischemia. An ECG performed at discharge was also abnormal, and the adverse events of left anterior hemiblock and ST depression were unresolved at the time of withdrawal. No additional adverse events or medications were reported. EKGs in this study suggest the potential of cardiac ischemia. While there are no risk factors in this patient, the presence of an abnormal baseline EKG is suspicious for some underlying cardiovascular disorder.

Brief descriptions of the drug related cases in open label studies are presented as follows:

- **Myocardial Ischemia:** Patient 0841401, a 61-year-old white man with OSAHS, received 250 mg of armodafinil per day in double-blind study and began treatment with open-label armodafinil on 16 May 2004. Significant medical history included hypertension, hyperlipidemia, and diabetes mellitus. Concomitant medications taken by the patient included quinapril, acetylsalicylic acid, diltiazem, furosemide, insulin, atorvastatin, and multivitamins. At the final visit for the double-blind study (day -2 relative to open-label dosing), ECG findings included an anterior, incomplete right bundle branch block in addition to a possible ST abnormality or ischemia and a deeply negative T-wave, and a nonserious adverse event of moderate cardiac ischemia (MedDRA: myocardial ischemia) was subsequently diagnosed that same day. Findings from an ECG performed on day 5 were also abnormal (ie, sinus rhythm, short PR interval accelerated, P terminally

negative V1 left atrial abnormality, abnormal left axis deviation, and ST depression), and a nonserious adverse event of mild elevated blood pressure (MedDRA: blood pressure increased) was noted (blood pressure of 158/84 mm Hg) that same day. The patient discontinued the study on day 5 due to the cardiac ischemia. The cardiac ischemia and elevated blood pressure were both unresolved at the time of study withdrawal. The investigator considered both adverse events to be possibly related to study drug. Presumably this case is classified as ischemia because of negative t-wave and possibly for reasons of ST abnormality.

- Myocardial infarction: This occurred in a 61 year old patient (#1124107) treated with 200 mg/day of armodafinil and is described in the section on serious adverse events.
- Chest Discomfort: This is a 52-year-old white man with OSAHS, received 150 mg/day in study double blind study and continued on 200 mg/day in an open-label study. Significant medical history included hypertension, hypercholesterolemia, gastroesophageal reflux disease, nephrectomy (right kidney), splenectomy, shooting accident resulting in abdominal surgery, hip surgery for right hip fracture, multiple abdominal scars, penicillin allergy, slight nervousness, tonsillectomy, and adenoidectomy. Concomitant medications included acetylsalicylic acid, hydrochlorothiazide, amlodipine besylate plus benazepril hydrochloride (LOTREL®, Novartis Pharmaceuticals), metoprolol, fluoxetine, ranitidine, and simvastatin. On day 9, the patient experienced a nonserious adverse event of moderate tightness in his chest (MedDRA: chest discomfort). Study drug was discontinued on day 63 due to the chest discomfort, which resolved with no residual effect on day 67. The investigator considered the chest tightness to be probably related to study drug. The patient was withdrawn from the study on day 69. No additional adverse events or medications were reported. There is insufficient information as to whether this may be cardiac or other in origin (e.g. patients with history of reflux).

Brief descriptions of the placebo related cases in open label studies are presented as follows:

- Chest Discomfort: This was a 52-year-old white man (3043416) with OSAHS. Significant medical history included erectile dysfunction, prostate enlargement, chronic lower back pain and left leg pain due to herniated disc, back surgery, surgical scar on left leg, depression, minor myocardial infarctions (bypass 15 years ago), angioplasty, stent insertion, and hypercholesterolemia (controlled with medication). Concomitant medications included tocopherol, acetylsalicylic acid, rosuvastatin calcium, clopidogrel sulfate, folic acid, diltiazem, cholestyramine, candesartan cilexetil, cortisone, ezetimibe, methocarbamol plus paracetamol (ROBAXISAL COMPUESTO®, Whitehall-Robins), oxycocet, yohimbine, bupropion hydrochloride, gabapentin, and ciprofloxacin (started day -2 and stopped day 6). On day 22, the patient experienced mild, nonserious adverse events of chest tightness (MedDRA: chest discomfort), anxiety (MedDRA: anxiety), heart palpitations (MedDRA: palpitations), shortness of breath (MedDRA: dyspnea), and anxiety attacks (MedDRA: anxiety). Study drug was discontinued on day 35 due to all 5

of these adverse events. The chest tightness resolved on day 22, and the anxiety, heart palpitations, and shortness of breath all resolved on day 43. With the exception of the dyspnea, all of these adverse events resolved with no residual effects; however, unspecified residual effects were reported for the dyspnea. The investigator considered all 5 of the adverse events to be not related to study drug. Abnormal ECG findings noted at screening included a broad QRS complex; anterior, incomplete bundle branch block; and AVF consistent with inferior infarction. No significant changes were noted in subsequent ECGs performed during the study. There is insufficient information to indicate as to whether the pain may be cardiac in origin (was an EKG performed during the episode- ask Sponsor). Thus, heart palpitations and dypnea may suggest cardiac origin whereas anxiety may suggest another cause.

- Chest Pain: Patient is a 34-year-old white woman (#0261421) with OSAHS. Significant medical history included gastroesophageal reflux disease, diabetes, increased blood pressure, and hyperthyroidism. Concomitant medications included lansoprazole, multivitamins, acetylsalicylic acid, and metformin hydrochloride. On day 27, she experienced a nonserious adverse event of mild, intermittent chest pain (MedDRA: chest pain). On day 37, the patient developed moderate, constant chest pain (MedDRA: chest pain) and mild shoulder tightness (MedDRA: joint stiffness). Study drug was discontinued on day 36 due to all 3 adverse events. **The outcome of the patient's chest pain was unknown, and the shoulder tightness was continuing at the time of withdrawal. There is inadequate information available to indicate whether this is cardiac in origin.**
- Electrocardiogram change: Patient is a 44-year-old male (1601903) with OSAHS who began treatment with placebo. The patient had abnormal ECG findings at screening and baseline that included sinus bradycardia and a non-specific ST-T abnormality. On day 27, mild ECG changes (ischemic changes more marked than the baseline abnormalities) were noted as a nonserious adverse event, and study drug was discontinued on day 32. This may be suspicious for an ischemic change.

An Initial examination of these cases indicates that all but one case of patient reported with a potential coronary ischemic like symptom occurred in patents being treated for OSAHS. These patients all had at least one, and frequently multiple, risk factors for vascular disease. The single exception was a patient with SWSD who was being treated for SWSD who experienced ST depression and other EKG changes that may have been linked to ischemia. While this patient did not have risk factors for ischemia, EKG changes observed at baseline might suggest some underlying risk factor. Examination of the placebo-control database indicates the 4 of 645 patients on armodafinil (0.62%) withdrew for adverse events that were potentially related to coronary ischemia in the drug treatment group. Three of 445 (0.67%) such cases were identified in the placebo group. This difference is not remarkable and both values may represent the background rates in this at risk population. The caveat, however, is that this reviewer rated the adverse events in the drug treatment groups as more suspicious of coronary ischemia then those in the placebo group. Examination of the complete phase 3 database reveals that 7 of 1169 patients (0.6%) were discontinued for adverse events that potentially represent coronary ischemic

symptoms. This rate is very similar to that identified in the double-blind database and adds little additional information to help interpret such changes.

Two ways a drug may provoke cardiac ischemia is to increase thrombosis (e.g. clotting or atherosclerosis) or alter autonomic function (e.g. increased heart rate or load). Alterations of autonomic function has been proposed as a potential mechanism of this effect by some stimulants. This reviewer however examined adverse event narratives to determine if there was any thrombosis signal. One 57 year-old patient (1384040) with OSHAS in an open label study was noted to discontinue for reasons of thrombosis. In reading the narrative it was determined that this patient had what appeared to be a deep venous thrombosis that required treatment, with a history of hypertension, exploratory surgery for abdominal pain (**right quadrant**), **“ongoing laser right quadrant abdominal pain,”** cystocele, prolapsed uterus, hysterectomy and high cholesterol. This one case in the open label database is not significant to indicate a signal.

In conclusions placebo control these data did not indicate an obvious signal for coronary ischemia. The open label experience revealed similar cases but this did not contribute to causality determination as the background rate in the study population is unknown.

A number of patients discontinued medication or placebo for skin reactions. Thus, in controlled trials 4 of the 645 patients (0.62%) discontinued because of a potential skin reaction (rash or urticaria)<sup>7</sup>. This compares to 3 of 445 (0.67%) patients discontinuing from placebo because of the same. One of the 3 cases (urticaria) in the placebo group, however, began prior to placebo treatment and really should not be considered an adverse event attributed to such treatment. This results in a true placebo rate of 0.45%, indicting slightly higher rates in the drug group. Examination of the narration did not indicate that these cases may represent TEN, Stevens-Johnson or erythema multiforme. Except for the single case of angioneurotic edema these skin reactions were not classified as serious and generally treated with antihistamines. The single case of angioneurotic edema, reported in a double blind study in narcolepsy, was noted to be serious. There was no mention in the narration as to whether the patient suffered respiratory distress. This was consequently treated with antihistamines and steroids and resolved. In reading the narrations, this reviewer identified another case that may represent angioneurtic edema although not labeled as such. This case was classified as a withdrawal due to **“hypersensitivity, dysphagia and broncospasm.”** It occurred in a 50 year old female (#1884236) being treated with 200 mg/day of armodafinil in an open label study. Of note, the patient had a prior history of sensitivity to penicillin, sulfa, meperidine hydrochloride, fluoxetine hydrochloride, and bupropion hydrochloride. On day 11, the patient experienced a moderate allergic reaction (MedDRA: hypersensitivity) and mild dysphagia (MedDRA: dysphagia), and on day 12, she experienced a moderate bronchospasm (MedDRA: **bronchospasm**). A **“mild” rash was noted on this day** but not listed as a reason or discontinuation. Treatment with diphenhydramine hydrochloride and prednisone was initiated for the allergic reaction (hypersensitivity), and treatment with methyl prednisolone sodium succinate was initiated for the bronchospasm on day 12; the allergic reaction, dysphagia, and bronchospasm all resolved with no residual effect that same day. Another case, described in the discussion on chest pain, may be suspicious for

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<sup>7</sup> The case of angioneurotic edema was also experienced urticaria. This, therefore, counts as one patient.

angioedema. This was a 36 year women (0281696) with dysphagia, dyspnea, palpitations, chest pain and nausea. Because of the potential of two cases of angioedema and the recent identification of a high number of serious allergic skin reactions identified in the pediatric database this reviewer performed a AERS DataMart search for modifainil and angioedema, the racemic formulation presently available. A total of 21 cases were observed. Many of these cases were poorly described, however, it was the general impression of this reviewer that many cases that included narration were non-confounded. No attempt was made to eliminate duplicates. While some cases apparently only involved urticaria some cases required hospitalization and treatment with steroids and a few cases were considered life threatening. Off note, angioedema is listed in the adverse events section the present labeling for Provigil.

#### 1.18.3.3 Other significant adverse events

See above.

#### 1.18.4 Other Search Strategies

This information is included in sections described above.

#### 1.18.5 Common Adverse Events

##### 1.18.5.1 Eliciting adverse events data in the development program

Information on adverse events was generally elicited at times of scheduled clinic visits. The reader should refer to a description of the original protocols in the appendix. This would occur on a schedule of every 2 weeks to **3 months in the double-blind** placebo controls studies and every 1 to 3 months in the open labeled extension studies.

##### 1.18.5.2 Appropriateness of adverse event categorization and preferred terms

All adverse events were coded with the use of the MedDRA which is generally considered an appropriate dictionary.

1.18.5.3 Incidence of common adverse events

The Sponsor has tabulated adverse event rates in the double-blind placebo-controlled studies by dose. The following table presents this information by organ system and preferred terms for adverse events occurring more commonly in drug than placebo groups and where it is observed in  $\geq 2\%$  of patients in any individual group. Number of patients (and percent) is presented. As apparent from this table the most common adverse event, which occur at a greater frequency in drug than placebo group, is headache with as much as 23% of patients in the high dose group experiencing such. This is followed in descending order by nausea, dizziness, insomnia, anxiety, diarrhea and dry mouth. Headache, nausea, dry mouth and rash show some indication of potential dose dependence. This table, perhaps, gives the best listing for potential drug dependent adverse events. Supporting this drug causality is the fact that most of these events also demonstrate dose dependency.

System organ class Preferred term	Number (%) of patients			
	250 mg (N=190)	150 mg (N=167)	All (N=445)	Placebo (N=46)
No. of patients with at least 1 AE	137 (69)	170 (60)	407 (65)	213 (48)
<b>Cardiac disorders</b>				
Palpitations	6 (3)	7 (2)	13 (2)	5 (1)
<b>Gastrointestinal disorders</b>				
Nausea	18 (9)	37 (6)	45 (7)	14 (3)
Diarrhea	7 (4)	19 (4)	26 (4)	8 (2)
Dry mouth	13 (7)	11 (2)	24 (4)	3 (<1)
Dyspepsia	2 (1)	14 (3)	16 (2)	2 (<1)
Constipation	4 (2)	4 (<1)	8 (1)	2 (<1)
<b>General disorders and administration site conditions</b>				
Chest pain	5 (3)	7 (2)	12 (2)	9 (2)
Fatigue	2 (1)	10 (2)	12 (2)	6 (1)
Thirst	5 (3)	1 (<1)	6 (<1)	1 (<1)
Pyrexia	4 (2)	0	4 (<1)	1 (<1)
<b>Investigations</b>				
Alanine aminotransferase increased	4 (2)	5 (1)	9 (1)	5 (1)
Aspartate aminotransferase increased	4 (2)	4 (<1)	8 (1)	4 (<1)
<b>Metabolism and nutrition disorders</b>				
Anorexia	6 (3)	3 (<1)	9 (1)	0
Decreased appetite	6 (3)	3 (<1)	9 (1)	0
<b>Musculoskeletal and connective tissue disorders</b>				
Back pain	4 (2)	11 (2)	15 (2)	8 (2)
<b>Nervous system disorders</b>				
Headache	46 (23)	63 (14)	109 (17)	39 (9)
Dizziness	10 (5)	20 (4)	30 (5)	8 (2)
Tremor	4 (2)	1 (<1)	5 (<1)	0
<b>Psychiatric disorders</b>				
Insomnia	12 (6)	18 (4)	30 (5)	5 (1)
Anxiety	10 (5)	18 (4)	28 (4)	4 (<1)
Depression	6 (3)	6 (1)	12 (2)	1 (<1)
<b>Respiratory, thoracic and mediastinal disorders</b>				
Cough	4 (2)	5 (1)	9 (1)	7 (2)
Pharyngolaryngeal pain	4 (2)	3 (<1)	7 (1)	3 (<1)
<b>Skin and subcutaneous tissue disorders</b>				
Rash	7 (4)	6 (1)	13 (2)	1 (<1)

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The Sponsor tabulated common adverse events derived from double-blind placebo-control study populations by specific sleep disorders. These tables are presented below. Numbers (and percent) of patients experiencing these adverse events are presented. The tables presents adverse events by organ system and preferred terms for adverse events occurring more commonly in drug then placebo groups and where it is observed in  $\geq 2\%$  of patients. Except for some minor exceptions there was not an obvious difference between incidences of these common adverse events amongst the different disorders. Exceptions included a lower predilection for headache in SWSD then narcolepsy and OSAHS, a greater incidence of decreased appetite, anorexia and nausea in narcolepsy then OSAHS and SWSD. It is unclear if this simply represents sampling error or real difference.

System organ class Preferred term	Number (%) of patients					
	Narcolepsy		OSAHS		SWSD	
	Armodafinil (N=131)	Placebo (N=63)	Armodafinil (N=391)	Placebo (N=260)	Armodafinil (N=123)	Placebo (N=122)
No. of patients with any adverse event	90 (69)	29 (46)	251 (64)	135 (52)	66 (54)	49 (40)
<b>Cardiac disorders</b>						
Palpitations	2 (2)	0	9 (2)	3 (1)	2 (2)	2 (2)
<b>Gastrointestinal disorders</b>						
Nausea	14 (11)	0	22 (6)	10 (4)	9 (7)	4 (3)
Diarrhea	5 (4)	1 (2)	17 (4)	6 (2)	4 (3)	1 (<1)
Dry mouth	4 (3)	2 (3)	15 (4)	0	5 (4)	1 (<1)
Dyspepsia	3 (2)	1 (2)	10 (3)	1 (<1)	3 (2)	0
Constipation	1 (<1)	0	7 (2)	2 (<1)	0	0
Abdominal pain upper	3 (2)	1 (2)	6 (2)	1 (<1)	2 (2)	1 (<1)
Vomiting	2 (2)	0	5 (1)	2 (<1)	0	0
<b>General disorders and administration site conditions</b>						
Chest pain	5 (4)	0	6 (2)	6 (2)	1 (<1)	3 (2)
Pyrexia	3 (2)	0	1 (<1)	1 (<1)	0	0
Fatigue	3 (2)	0	8 (2)	6 (2)	1 (<1)	0
Influenza-like illness	2 (2)	0	3 (<1)	0	0	0
Pain	0	0	2 (<1)	0	2 (2)	1 (<1)
<b>Infections and infestations</b>						
Bronchitis	2 (2)	0	3 (<1)	2 (<1)	1 (<1)	1 (<1)
Nasopharyngitis	5 (4)	5 (8)	8 (2)	10 (4)	7 (6)	4 (3)
Upper respiratory tract infection	1 (<1)	0	9 (2)	11 (4)	2 (2)	1 (<1)
<b>Injury, poisoning and procedural complications</b>						
Joint sprain	0	0	1 (<1)	1 (<1)	2 (2)	1 (<1)
<b>Investigations</b>						
Aspartate aminotransferase increased	1 (<1)	0	4 (1)	3 (1)	3 (2)	1 (<1)
Blood uric acid increased	0	1 (2)	1 (<1)	2 (<1)	2 (2)	0
Gamma-glutamyl transpeptidase increased	1 (<1)	0	6 (2)	1 (<1)	2 (2)	0
Neutrophil count decreased	1 (<1)	0	1 (<1)	0	2 (2)	1 (<1)

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System organ class Preferred term	Number (%) of patients					
	Narcolepsy		OSAS		SWSD	
	Armodafinil (N=131)	Placebo (N=63)	Armodafinil (N=301)	Placebo (N=269)	Armodafinil (N=123)	Placebo (N=122)
<b>Metabolic and nutrition disorders</b>						
Decreased appetite	6 (5)	0	3 (<1)	0	0	0
Anorexia	4 (3)	0	5 (1)	0	0	0
<b>Musculoskeletal and connective tissue disorders</b>						
Back pain	4 (3)	2 (3)	9 (2)	6 (2)	2 (2)	0
<b>Nervous system disorders</b>						
Headache	29 (22)	7 (11)	65 (17)	20 (8)	15 (12)	12 (10)
Dizziness	7 (5)	0	19 (5)	4 (2)	4 (3)	4 (3)
<b>Psychiatric disorders</b>						
Insomnia	5 (4)	0	22 (6)	3 (1)	3 (2)	2 (2)
Anxiety	2 (2)	0	20 (5)	2 (<1)	6 (5)	2 (2)
Agitation	0	0	7 (2)	0	0	0
Depression	4 (3)	0	6 (2)	1 (<1)	2 (2)	0
<b>Renal and urinary disorders</b>						
Polyuria	0	0	3 (<1)	1 (<1)	3 (2)	0
<b>Reproductive system and breast disorders</b>						
Dysmenorrhea	0	0	1 (<1)	0	2 (2)	0
<b>Respiratory, thoracic and mediastinal disorders</b>						
Cough	4 (3)	1 (2)	3 (<1)	6 (2)	2 (2)	0
Dyspnea	2 (2)	0	6 (2)	2 (<1)	0	0
Epistaxis	2 (2)	0	1 (<1)	1 (<1)	0	1 (<1)
Nasal congestion	2 (2)	0	3 (<1)	3 (1)	1 (<1)	1 (<1)
<b>Skin and subcutaneous disorders</b>						
Dermatitis contact	1 (<1)	0	6 (2)	2 (<1)	0	0
Rash	5 (4)	0	6 (2)	1 (<1)	2 (2)	0

The table below presents adverse events occurring in  $\geq 2\%$  of patients by organ system and preferred terms for all patients enrolled in the development program (in phase 3). The relative incidences between adverse events and amongst different disease conditions are similar to that described in the placebo—controlled data base.

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System organ class Preferred term	Number (n) of patients			
	Narcolepsy (N=288)	OSAS (N=716)	SWSD (N=248)	All patients (N=1252)
No. of patients with at least 1 AE	129 (63)	470 (66)	126 (51)	725 (62)
<b>Cardiac disorders</b>				
Palpitations	2 (-1)	22 (3)	4 (2)	28 (2)
<b>Gastrointestinal disorders</b>				
Nausea	17 (8)	48 (7)	18 (9)	81 (7)
Diarrhea	6 (3)	29 (4)	6 (2)	41 (4)
Dry mouth	4 (2)	24 (3)	10 (4)	38 (3)
Dyspepsia	5 (2)	14 (2)	5 (2)	24 (2)
Flatulence	2 (-1)	14 (2)	5 (2)	21 (2)
Abdominal pain upper	3 (1)	12 (2)	3 (1)	18 (2)
<b>General disorders and administration site conditions</b>				
Fatigue	5 (2)	18 (3)	1 (-1)	24 (2)
Feeling jittery	1 (-1)	15 (2)	2 (-1)	18 (2)
<b>Infections and infestations</b>				
Nasopharyngitis	9 (4)	25 (3)	8 (3)	42 (4)
Upper respiratory tract infection	3 (1)	20 (3)	7 (3)	30 (3)
Sinusitis	4 (2)	20 (3)	2 (-1)	26 (2)
<b>Metabolism and nutrition disorders</b>				
Decreased appetite	10 (5)	7 (-1)	1 (-1)	18 (2)
<b>Musculoskeletal and connective tissue disorders</b>				
Arthralgia	5 (2)	17 (2)	3 (1)	25 (2)
Back pain	4 (2)	17 (2)	2 (-1)	23 (2)
<b>Nervous system disorders</b>				
Headache	44 (21)	121 (17)	29 (12)	194 (17)
Dizziness	10 (5)	37 (5)	8 (3)	55 (5)
<b>Psychiatric disorders</b>				
Insomnia	9 (4)	60 (8)	13 (5)	82 (7)
Anxiety	7 (3)	41 (6)	8 (3)	56 (5)
Depression	5 (2)	10 (1)	3 (1)	18 (2)
Nervousness	1 (-1)	15 (2)	2 (-1)	18 (2)
<b>Skin and subcutaneous tissue disorders</b>				
Rash	6 (3)	11 (2)	3 (1)	20 (2)

Most adverse events were of mild to moderate severity. Approximately 6% of adverse events in the double-blind placebo-controlled and open label studies were considered severe. Adverse events that were rated as severe in more than one patient included: headache, nausea and diarrhea observed in 4 patients; back pain observed in 3 patients; abdominal pain, chest pain and insomnia observed in 2 patients.

Sixty-five percent of all adverse events were reported within the first 2 weeks and 98% were reported within the first 3 months. Cumulative incidences of the common adverse event reporting showed a small increase from 2 weeks to 3 months (e.g. for headache 12% to 16 %, for nausea for 5 to 7% and for insomnia 5 to 7%).

#### 1.18.5.4 Common adverse event tables

See above.

#### 1.18.5.5 Identifying common and drug-related adverse events

Perhaps the best indicator of potential drug related events can be found in the table presented above that describes adverse events occurring more commonly in drug than placebo groups and

where it is observed in  $\geq 2\%$  of patients in any individual group. Such an analysis is only tentative, as the study was not powered for such a determination. Most of these events also demonstrate dose dependency (see above). More certainty might be drawn from adverse events that exhibit the largest differences ( $>3\%$ ) between placebo and drug groups such as nausea, dry mouth, headache, dizziness, insomnia and anxiety. All of these events demonstrate dose dependency.

#### 1.18.5.6 Additional analyses and explorations

The Sponsor performs a cumulative analysis for all patients in phase 3 studies of time dependency of some of the most common adverse events and those of special interest in the safety update. Because this information could not be found in the original NDA submission this cumulative analysis is presented in this section. Note the total number of patients studied in the safety update was 1271. The reader is also referred to the safety update section.

Of the 277 patients reporting headache, 50% occurred in the first 10 days, 75% occurred in the first 30 days, and 90% occurred in the first 75 days. For 50% of the reported adverse events of headache, the longest duration was 7 days; 75% of the headaches resolved within 19 days; and 90% of the headaches resolved within 44 days. A total of 42 events were continuing at last report; of those that resolved, 96% resolved with no residual effect.

Of the 156 patients reporting insomnia, 50% occurred in the first 19 days, 75% occurred in the first 61 days, and 90% occurred in the first 147 days. For 50% of the reported adverse events of insomnia, the longest duration was 14 days; 75% of the insomnia adverse events resolved within 26 days; and 90% of the insomnia adverse events resolved within 49 days. A total of 29 events were continuing at last report; of those that resolved, 99% resolved with no residual effect.

Of the 105 patients reporting nausea, 50% occurred in the first 9 days, 75% occurred in the first 30 days, and 90% occurred in the first 57 days. For 50% of the reported adverse events of nausea, the longest duration was 9 days; 75% of the adverse events of nausea resolved within 19 days; and 90% of the adverse events of nausea resolved within 40 days. A total of 12 events were continuing at last report; of those that resolved, 98% resolved with no residual effect.

Of the 89 patients reporting dizziness, 50% occurred in the first 20 days, 75% occurred in the first 47 days, and 90% occurred in the first 95 days. For 50% of the reported adverse events of dizziness, the longest duration was 5 days; 75% of the adverse events of dizziness resolved within 11 days; and 90% of the adverse events of dizziness resolved within 17 days. A total of 13 events were continuing at last report; of those that resolved, 96% resolved with no residual effect.

In summary, with regard to the above common adverse events (headache, dizziness and nausea), a majority occurred within the first month and greater than 75% occurred within the first 2 months. Seventy five percent of these common events lasted no longer than 2 weeks.

Of the 37 patients reporting rash of any kind, 50% occurred in the first 57 days, 75% occurred in the first 110 days, and 90% occurred in the first 227 days. For 50% of the reported adverse events of rash, the longest duration was 8 days; 75% of the adverse events of rash resolved within 20 days; and 90% of the adverse events of rash resolved within 59 days. A total of 9 events were continuing at last report; of those that resolved, 96% resolved with no residual effect.

Of the 12 patients reporting tachycardia (including supraventricular tachycardia), 50% occurred in the first 19 days, 75% occurred in the first 67 days, and 90% occurred in the first 168 days. For 50% of the reported adverse events of tachycardia, the longest duration was 6 days; 75% of the tachycardia adverse events resolved within 28 days; and 90% of the tachycardia adverse events resolved within 70 days. All events (100%) resolved with no residual effect.

Of the 25 patients reporting increased blood pressure (including blood pressure fluctuations, systolic blood pressure increase), 50% occurred in the first 44 days, 75% occurred in the first 89 days, and 90% occurred in the first 187 days. For 50% of the reported adverse events of increased blood pressure, the longest duration was 15 days; 75% of the adverse events of increased blood pressure resolved within 39 days; and 90% of the adverse events of increased blood pressure resolved within 87 days. A total of 7 events were continuing at last report; of those that resolved, 89% resolved with no residual effect.

Of the 44 patients reporting hypertension (including systolic hypertension), 50% occurred in the first 71 days, 75% occurred in the first 154 days, and 90% occurred in the first 224 days. For 50% of the reported adverse events of hypertension, the longest duration was 12 days; 75% of the adverse events of hypertension resolved within 23 days; and 90% of the adverse events of hypertension resolved within 63 days. A total of 14 events were continuing at last report; of those that resolved, 83% resolved with no residual effect.

Of the 39 patients reporting of chest pain (including chest discomfort), 50% occurred in the first 28 days, 75% occurred in the first 73 days, and 90% occurred in the first 129 days. For 50% of the reported adverse events of chest pain, the longest duration was 3 days; 75% of the adverse events of chest pain resolved within 19 days; and 90% of the adverse events of chest pain resolved within 55 days. A total of 5 events were continuing at last report; of those that resolved, 98% resolved with no residual effect.

Of the 40 patients reporting palpitations, 50% occurred in the first 18 days, 75% occurred in the first 47 days, and 90% occurred in the first 74 days. For 50% of the reported adverse events of palpitations, the longest duration was 6 days; 75% of the adverse events of palpitations resolved within 12 days; and 90% of the adverse events of palpitations resolved within 23 days. A total of 3 events were continuing at last report; of those that resolved, all (100%) resolved with no residual effect.

### 1.18.6 Less Common Adverse Events

The reader is referred to the above sections for such adverse events.

### 1.18.7 Laboratory Findings

#### 1.18.7.1 Overview of laboratory testing in the development program

Routine blood chemistries, a complete blood count and urinalysis were obtained during various visits in all phase 3 studies. Laboratories were monitored monthly in the double-blind placebo-control studies. The schedule of laboratory testing was less frequent in the open label studies and varied from monthly to every 6 months with urinalysis tested less frequently than other labs.

#### 1.18.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

As in the adverse event analysis, two analyses population were selected by the Sponsor. These included patients in pivotal phase 3 double-blind placebo-control studies and those in all phase 3 studies. The ISS only included analyses of blood chemistries and hematology, but not urinalysis. Moreover, data from phase 1 and 2 studies were not included. This missing information was requested in two telephone calls made to the Sponsor on 2/28/06 and 3/1/06. According to **Cephalon's Regulatory contact**, Coleen D. Murray, the missing phase 3 information was not included because it was normal. The urinalysis data was not received till 4/6/05. This did not leave adequate time for a complete review of this information.

#### 1.18.7.3 Standard analyses and explorations of laboratory data

##### *1.18.7.3.1 Analyses focused on measures of central tendency*

###### 1.18.7.3.1.1 Serum Chemistry

The table below presents mean ( $\pm$  SD) of laboratory values at baseline and change from baseline at the last endpoint examination for the OSAHS pivotal placebo-control double-blinded studies. The only potential changes that can be appreciated are in slight reduction in uric acid and an

increase in GGT. The small reduction on uric acid is likely not clinically significant. The GGT underwent a moderate increase over placebo following treatment by 7.2 U/L. This was found to be somewhat dose dependent with a mean increase of 9.4 and 7.0 U/L in the 250 and 150 mg/kg dose, respectively. The fact that this is not associated with changes in SGPT, SGOT or bilirubin suggests this is not a result of liver toxicity. A very small increase in Alkaline Phosphatase may suggest that this may represent a biliary stasis like effect but because this is rather small increase (4.4 U/L over placebo) such a conclusion is premature. The outlier data should be examined to further explore this effect (see below). Data from the SWSD and narcolepsy controlled pivotal studies were provided for only selected laboratories in the ISS, but all where examined in the original study reports by this reviewer. Some of these are provided in Appendix D. The data were similar to that observed in the OSAHS studies with small increases in GGT and alkaline phosphates, but no other consistent liver function enzyme increase. Small, but consistent, reductions were also observed in uric acid in these other studies. Thus, approximately 8 to 14 umol/L reductions in uric acid over placebo were observed against a background baseline of approximately 320 umol/L. This isolated finding probably indicates a mild uricosuric effect of this agents. The clinical significance of this effect on uric acid is undetermined but it is noteworthy that low uric acid does not in itself cause symptoms or pathology.

	Armodafinil (n=391)		Placebo (n=260)	
	Mean Baseline (± SD)	Endpoint change from Baseline (± SD)	Baseline (± SD)	Endpoint Change from Baseline (± SD)
Sodium (mmol/L)	140.8 ± 2.12	0.2 ± 2.31	140.9 ± 2.11	-0.3 ± 2.32
Potassium (mmol/L)	4.2 ± 0.32	0.0 ± 0.33	4.2 ± .34	0.0 ± 0.36
Chloride (mmol/L)	103.9 ± 2.43	-0.1 ± 2.53	103.7± 2.68	-0.1± 2.64
Bicarbonate (mmol/L)	26 ± 3.03	0.3 ± 2.96	25.8 ± 2.83	-0.2 ± 3.04
Glucose (mmol/L)	6.3 ± 1.98	-0.2 ± 1.41	6.2 ± 1.62	0.0 ± 1.34
BUN (mmol/L)	6.1 ± 1.66	-0.1 ± 1.30	6.2 ± 1.66	0.0 ± 1.24
Creatinine (umol/L)	79.1 ± 18.00	-1.6 ± 9.33	79.0 ± 18.84	0.9 ± 10.26
Calcium (mmol/L)	2.4 ± 0.10	0.0 ± 0.10	2.4 ± 0.09	0.0 ± 0.09
Phosphorus (mmol/L)	1.2 ± 0.19	0.0 ± 0.20	1.2 ± 0.21	0.0 ± 0.20
Total Protein (g/L)	71.2 ± 3.73	0.3 ± 3.80	71.5 ± 4.24	-0.2 ± 3.77
Albumen (g/L)	40.9 ± 3.18	0.2 ± 2.57	41.1 ± 2.91	-0.3 ± 2.48

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Uric Acid (umol/L)	390.1 ± 83.61	-11.0 ± 48.26	293.3 ± 62.61	-3.5 ± 52.73
SGOT (U/L)	24.2 ± 10.66	0.2 ± 7.73	24.9 ± 11.45	0.8 ± 7.70
SGPT (U/L)	31.1 ± 17.00	-0.4 ± 12.24	31.8 ± 16.57	0.6 ± 12.35
Alk Pos (U/L)	78.1 ± 20.99	3.3 ± 10.63	81.1 ± 23.42	-1.1 ± 10.25
GGT (U/L)	34.3 ± 23.81	7.8 ± 20.94	39.0 ± 37.32	0.6 ± 15.77
Total Bilirubin (umol/L)	7.8 ± 3.90	-0.8 ± 3.23	8.0 ± 4.11	-0.2 ± 3.06
Cholesterol (mmol/L)	5.0 ± 0.97	0.1 ± 0.72	5.1 ± 1.06	-0.1 ± 0.71

Data for all phase 3 pivotal trials are presented in the table below. Included is the baseline and final changes from endpoint. These data are similar to that observed in the control database above. The Sponsor identified a tendency for increasing alkaline phosphatase and GGT over time. A table demonstrating this is presented in below. The reduction in values at the 6 month time point indicates a reversal of this trend. The interpretation of these data is unfortunately confounded by the loss of patients over time. According to discontinuations noted above, 4 patients were discontinued for reasons of GGT elevations and one **for an increase in "hepatic enzymes."** It is difficult to imagine that these cases would influence the values. These cases will be discussed further in the section below. The meaning of these changes is difficult to determine.

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	Mean Baseline (± SD)	Final change from Baseline (± SD: n=1169)
Sodium (mmol/L)	140.7 ± 2.22	-0.1 ± 2.57
Potassium (mmol/L)	4.2 ± 0.35	0.0 ± 0.39
Chloride (mmol/L)	104.0 ± 2.49	-0.7 ± 2.60
Bicarbonate (mmol/L)	25.6 ± 2.89	-0.2 ± 2.95
Glucose (mmol/L)	5.9 ± 1.79	-0.1 ± 1.66
BUN (mmol/L)	5.7 ± 1.63	-0.1 ± 1.27
Creatinine (umol/L)	77.4 ± 18.06	-1.4 ± 11.36
Calcium (mmol/L)	2.2 ± 0.10	0.0 ± 0.10
Phosphorus (mmol/L)	1.2 ± 0.19	0.0 ± 0.23
Total Protein (g/L)	71.9 ± 4.09	0.9 ± 3.81
Albumen (g/L)	41.4 ± 3.23	0.3 ± 2.60
Uric Acid (umol/L)	368.8 ± 91.92	-18.1 ± 51.28
SGOT (U/L)	24.2 ± 11.70	0.5 ± 18.0
SGPT (U/L)	29.4 ± 17.98	1.2 ± 38.73
Alk Pos (U/L)	78.2 ± 22.8	3.4 ± 10.47
GGT (U/L)	32.3 ± 27.79	7.1 ± 19.19
Total Bilirubin (umol/L)	8.0 ± 4.23	-0.9 ± 3.34
Cholesterol (mmol/L)	5.1 ± 1.0	0.1 ± 0.69

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Variable	Time point				
	Baseline	Month 1	Month 3	Month 4	Month 6
<b>Alkaline phosphatase (U/L)</b>					
n	1141	1005	830	253	213
Mean (SD)	78.2 (22.18)	80.2 (22.81)	81.1 (22.93)	84.8 (23.61)	81.0 (22.66)
Mean change (SD)	—	1.9 (11.10)	3.0 (10.05)	6.0 (10.63)	2.6 (9.36)
<b>GGT (U/L)</b>					
n	1141	1005	829	253	213
Mean (SD)	32.3 (27.79)	36.5 (44.40)	37.9 (34.12)	39.0 (25.37)	34.2 (17.09)
Mean change (SD)	—	4.3 (34.71)	6.8 (20.27)	8.1 (17.24)	5.2 (9.70)

1.18.7.3.1.1.2 Hematology

The following table was provided in the ISS for hematological changes from baseline to the final endpoint in the phase 3 controlled trials. No clinically significant mean change in CBC indices (e.g. HCT, WBC, neutrophils, eosinophils and platelets) at the final evaluation on drug measure from baseline is apparent from this table. Not included in the ISS were results on monocytes and lymphocytes. Examination of the source study reports failed to indicate any clinically significant changes in these cellular elements from baseline at the final on drug examination in all of the pivotal studies.

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Hematology variable*	Time point Statistic	Narcolepsy		OSAS		SWSD	
		Armodafinil (N=131)	Placebo (N=63)	Armodafinil (N=391)	Placebo (N=260)	Armodafinil (N=123)	Placebo (N=122)
Hematocrit, l/l	Baseline						
	n	130	61	391	260	123	122
	Mean	0.4	0.4	0.4	0.4	0.4	0.4
	SD	0.04	0.04	0.04	0.04	0.04	0.04
	Median	0.4	0.4	0.4	0.4	0.4	0.4
	Min, max	0.3, 0.5	0.3, 0.5	0.3, 0.6	0.3, 0.5	0.3, 0.5	0.3, 0.6
	Change from baseline						
	n	124	59	379	257	118	112
	Mean	-0.0	-0.0	-0.0	-0.0	0.0	0.0
	SD	0.03	0.02	0.03	0.03	0.03	0.03
Hemoglobin, g/L	Baseline						
	n	130	62	391	260	123	122
	Mean	141.0	141.9	143.8	143.2	141.6	142.7
	SD	13.57	15.79	13.09	13.34	15.22	15.22
	Median	140.0	143.0	146.0	144.0	144.0	141.5
	Min, max	107.0, 184.0	107.0, 173.0	93.0, 174.0	92.0, 174.0	105.0, 174.0	103.0, 188.0
	Change from baseline						
	n	124	60	379	257	120	113
	Mean	-1.3	-0.3	-0.8	-1.2	0.8	-0.3
	SD	7.77	7.13	7.51	7.32	8.40	8.30
White blood cell (WBC) counts, x 10 <sup>9</sup> /L	Baseline						
	n	130	62	391	260	123	122
	Mean	6.9	6.7	6.9	7.0	6.6	6.6
	SD	2.29	1.67	1.85	1.65	1.74	1.91
	Median	6.4	6.5	6.6	6.8	6.6	6.4
	Min, max	3.6, 16.4	3.0, 11.7	2.5, 16.2	3.8, 14.2	2.9, 11.1	2.4, 12.8
	Change from baseline						
	n	124	60	379	257	120	113
	Mean	0.1	0.1	0.1	-0.1	-0.0	-0.1
	SD	2.09	1.45	1.33	1.07	1.60	1.25
Eosinophils, %	Baseline						
	n	130	62	391	260	123	122
	Mean	2.2	2.3	2.2	2.1	2.0	2.0
	SD	1.50	1.52	1.39	1.16	1.10	1.24
	Median	1.9	2.0	1.8	2.0	1.8	1.7
	Min, max	0.0, 11.3	0.3, 9.0	0.0, 10.0	0.0, 6.7	0.0, 5.9	0.3, 7.9
	Change from baseline						
	n	124	60	379	257	120	113
	Mean	0.1	-0.1	-0.0	0.1	0.3	0.5
	SD	1.41	1.05	1.35	1.30	1.43	1.28
Absolute neutrophil count (ANC), x 10 <sup>9</sup> /L	Baseline						
	n	130	62	391	260	123	122
	Mean	3.9	3.7	4.0	4.1	3.9	3.9
	SD	1.86	1.20	1.48	1.31	1.47	1.44
	Median	3.3	3.6	3.7	3.9	3.7	3.8
	Min, max	0.7, 11.0	1.4, 7.9	1.0, 14.9	1.1, 9.1	1.3, 8.6	1.0, 9.3
	Change from baseline						
	n	124	60	379	257	120	112
	Mean	0.2	0.1	0.1	-0.1	-0.1	-0.2
	SD	1.79	1.22	1.21	0.85	1.44	1.03
Platelet count, 10 <sup>9</sup> /L	Baseline						
	n	130	62	389	258	122	122
	Mean	270.7	248.4	249.3	250.3	267.3	256.3
	SD	63.68	61.60	61.58	61.70	53.86	65.46
	Median	263.5	239.5	242.0	240.5	266.0	245.5
	Min, max	164.0, 518.0	133.0, 439.0	110.0, 503.0	110.0, 546.0	140.0, 417.0	27.0, 451.0
	Change from baseline						
	n	124	60	375	255	119	111
	Mean	5.4	2.1	6.0	-3.1	6.3	0.8
	SD	40.70	38.82	34.96	37.70	40.73	34.07

Mean changes in hematology indices were similar in the complete armodafinil phase 3 database as that observed in for armodafinil treated patients in the control phase 3 studies.

This section should focus on patients whose laboratory values deviate substantially from the reference range. The criteria used to identify outliers should be described.

*1.18.7.3.2 Analyses focused on outliers or shifts from normal to abnormal*

1.18.7.3.2.1.1 Serum Chemistry

Shift tables provided by the Sponsor for OSAHS placebo control phase 3 studies are presented in Appendix C. Criteria for shift determinations were based upon laboratory established criteria normal range. In general no obvious differences in shifts from normal to high or low laboratory values were appreciated in OSAHS upon the examination of this table. This reviewer examined the shift tables for the remaining two controlled phase 3 studies on SWSD and narcolepsy and could not discern obvious differences between drug and placebo groups. Because of suggestions of GGT and Alkaline phosphatase elevations noted above these issues were more carefully examined for liver function related testing. The table below presents this data as the number and percent of patients who started out as normal and shifted to higher than normal following drug (all doses) or placebo in all placebo-control phase 3 studies. Although there was a minimal trend for normal values to shift to above normal in the drug group for all labs at the final treatment reading, the difference between drug and placebo treatment, except perhaps for GGT, was minimal. These data therefore indicates a small and but probably clinically non-significant shift. The slight preponderance in the GGT is consistent with the central tendency findings. Similar shifts in these liver function related tests occurred at a similar percent in the complete phase 3 database (data not shown).

	Cases of Shift from Normal at Baseline to above Normal at Final Endpoint for all control phase 3 patients <sup>1</sup> (%)	
	Armodafinil	Placebo
SGOT (AST)	571/17 (3.0%)	395/11 (2.7%)
SGPT (ALT)	533/42 (7.9%)	356/20 (5.6%)
Alkaline Phosphatase	498/8 (1.6%)	412/5 (1.2%)
SGGT	541/16 (3.0%)	373/89 (2.1%)
Bilirubin	553/6 (1.1%)	390/4 (1.0%)

<sup>1</sup> # patients normal at baseline/# normal at baseline shift to above normal at endpoint

1.18.7.3.2.1.2 Hematology

Shift tables for the two placebo-controlled OSAHS studies were presented in the ISS and are provided in Appendix E. Examination of these data along with data contained in the controlled pivotal studies on SWSD and narcolepsy revealed to obvious difference between drug and placebo groups. These data were collated by the reviewer in the table below that shows the percent of patients who were normal at baseline and either increased to below or above normal at the final endpoint evaluation. Examination of this table indicates almost no difference from placebo and drug treatment groups except for a very small preponderance of increase in WBC and absolute lymphocyte count in drug over placebo at the final endpoint measure. This change is adequately small to very unlikely be clinically significant.

	Armodafinil		Placebo	
	Decrease from normal (%)	Increase form normal (%)	Decrease from normal (%)	Increase from normal (%)
WBC	0.7 %	2.1 %	1.0 %	1.0 %
Absolute Neutrophils	2.4 %	2.4 %	2.2 %	1.7 %
Absolute lymphocytes	0.3 %	1.7 %	0.5 %	0.7 %
Absolute monocytes	0.5 %	0.5 %	0.7 %	0.2 %
Platelets	0.5 %	1.2 %	1.4 %	0.7 %
Hematocrit	1.3 %	0.8 %	0.7 %	1.0 %

*1.18.7.3.3 Marked outliers and dropouts for laboratory abnormalities*

1.18.7.3.3.1.1 Serum Chemistry

Criteria for clinically significant abnormalities in selected laboratories are presented in Appendix H.

The table below presents the number (and percent) of cases identified with clinically significant abnormalities in the pivotal double blind control phase 3 studies. This table suggests that the most common marked outlier laboratory is uric acid. Values in placebo exposed patients ranged as high as 880 umol/L and in drug exposed patients as high as 767 umol/L. Considering the similar range of values in both experimental groups and the fact that rates of such uric acid elevations were in fact more common, albeit not significantly so, in the placebo groups, these changes are unlikely to be drug related.

BUN was also likely not related to a drug effect. Thus, the incidences were similar between placebo and armodafinil groups. The maximal BUN level in patients receiving drug was 18.3 and in patients receiving placebo was 14.6.

Chemistry variable	Criteria	Number (%) of patients					
		Narcolepsy		OSAS		SWSD	
		Armodafinil (N=131)	Placebo (N=63)	Armodafinil (N=391)	Placebo (N=268)	Armodafinil (N=123)	Placebo (N=123)
BUN	≥10.71 mmol/L	0	0	8 (2)	7 (3)	1 (<1)	0
Creatinine	≥177 μmol/L	0	0	0	1 (<1)	0	0
Uric acid	M: ≤625 μmol/L F: ≥506 μmol/L	2 (2)	2 (3)	6 (2)	9 (3)	1 (<1)	1 (<1)
AST	≥3 x ULN	1 (<1)	0	3 (<1)	2 (<1)	0	1 (<1)
ALT	≥3 x ULN	0	0	4 (1)	3 (1)	1 (<1)	1 (<1)
GGT	≥3 x ULN	2 (2)	1 (2)	11 (3)	4 (2)	1 (<1)	1 (<1)
Total bilirubin	≥34.2 μmol/L	1 (<1)	0	0	0	1 (<1)	0

Examination of the significant liver function related tests support observations made in the central tendency. The table below presents the incidence of these different tests in the controlled pivotal trials. Thus, clinically significant ALT and AST were equally common in both placebo and drug treated groups. Clinically significant elevations in GGT appear more common in the drug treated group. With one exception, clinically significant elevations in transaminases varied from 3 to 6 times the upper limit of normal. The exception involved one case where GGT rose to nearly 20 times the upper limit of normal (patients #0801571). None these increases were accompanied by elevations in bilirubin. The two noted cases of bilirubin elevations in drug groups were not accompanied by significant elevations in transaminase. One case (patient 0309194) was reported to have a bilirubin of 37.62 umol/L (about 3 times the upper limit of normal) during drug treatment, but this patient also exhibited an elevated pre-drug baseline bilirubin (37.62 and 35.91 uM/L). The second case exhibited a pre-drug baseline slightly above normal and subsequently exhibited a transient elevation in bilirubin such that it rose to 3 times the upper limit of normal at week four (34.2 umol/L) but declined with continued treatment to baseline values at week 8. Without liver function elevation both these cases may represent **Gilbert's syndrome** and not liver toxicity.

	Incidence of clinically significant liver function related tests (Percent)	
	Armodafinil (n=645)	Placebo (n=445)
GGT	2.2 %	1.3 %
AST	0.4 %	0.7 %
ALT	0.8 %	0.7 %
Bilirubin	0.3%	0

Additional cases of clinically significant laboratory abnormalities were observed in the complete phase 3 database. However, these were observed in the same labs and at the same rate as that observed for the phase 3 control database. One additional case of clinically significant elevated bilirubin (39.33 umol/L, patient# 0944271) was observed in the complete phase 3 database. This elevation was accompanied by clinically significant elevations in GOT (130 U/L) and GPT (238 U/L). This occurred in a patient who was HIV positive with clinically significant bilirubin (42.75 umol/L) and SGPT ((175 U/L) elevations during the pre-drug baseline period. Considering the preexistent abnormal transaminase and bilirubin elevations these results do not appear to be drug related.

No clinical chemistry results were labeled as a serious adverse event. A number, however, were resulted in treatment discontinuation. These data were tabulated in the tables in the section on discontinuations and are presented below in terms of absolute number (and percent). In total these reported cases represent 6 unique cases (patient numbers 080157, 0969058, 2069011, 2061547, 0981454 and 1941719): i.e. all cases reported multiple elevations in transaminases. The narrations were read by this reviewer. Of note, bilirubin is specifically noted to be within normal limits during the transaminase elevations in 3 cases (080157, 0969058 and 2069011). Bilirubin values are not described in the three remaining cases in the narration (2061547, 0981454 and 1941719). Examination of the CRF in these cases indicated no elevations in bilirubin. Drug was discontinued anywhere from day 1 to day 58. In all cases, except one, transaminase appeared to trend toward normalizing once drug was discontinued. The single exception involved a case with limited follow-up of only a few days.

	Discontinuations for high lab values in controlled phase 3 Studies Number of patients (percent)		Discontinuations for high lab values in all Phase 3 studies Number of patients (percent) n=1169
	Armodafinil n=645	Placebo n=445	
SGPT (ALT) Increased	3 (0.5%)	1 (0.2%)	4 (0.3%)
SGOT (AST) increased	2 (0.3%)	1 (0.2%)	2 (0.2%)
GGT increased	3 (0.5%)	0	4 (0.3%)
Hepatic Enzymes Increased	1 (0.2%)	0	1 (0.1%)

#### 1.18.7.3.3.1.2 Hematology

Clinically significant (marked outliers) abnormal hematology are presented for the placebo-controlled trials in the table below. The table presents number (and percent) of patients fulfilling the outlier criteria, which is also presented in the table. Outlier criteria can also be found in Appendix H.

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Hematology variable	Criteria	Number (%) of patients					
		Narcolepsy		OSAHS		SWSD	
		Armodafinil (N=131)	Placebo (N=63)	Armodafinil (N=391)	Placebo (N=260)	Armodafinil (N=123)	Placebo (N=122)
WBC	$\leq 3.0 \times 10^9/L$	0	0	1 (<1)	0	4 (3)	2 (2)
Hemoglobin	M: $\leq 115$ g/L	0	0	2 (<1)	2 (<1)	1 (<1)	1 (<1)
	F: $\leq 95$ g/L						
Hematocrit	M: $\leq 0.37$ l/l	0	0	1 (<1)	5 (2)	3 (2)	1 (<1)
	F: $\leq 0.32$ l/l						
ANC	$\leq 1.0 \times 10^9/L$	0	0	0	1 (<1)	1 (<1)	0
Eosinophils	$\geq 10.0$ %	2 (2)	0	1 (<1)	2 (<1)	1 (<1)	1 (<1)

To better compare rates in studies the number and percent of such instances are compared in the table below across placebo and drug groups in control studies and across all phase 3 studies. As apparent from this table the incidences of significant outliers were approximately similar in the controlled phase 3 database between the placebo and drug groups with two small exceptions. Thus, there was a slightly greater incidence of reduced WBCs observed in the drug group and a greater incidence of reduced hematocrit in the placebo group. The incidence of significant hematological abnormalities in drug treated patients was similar between the placebo-controlled and the complete phase 3 database. Because of the mild disparity across the WBC indices across experimental groups, values were more carefully examined. The lowest WBC value for placebo and drug group were similar with the lowest values reported as 2.1 and 2.6 reported for the placebo and drug groups, respectively.

	Controlled Phase 3 Studies Number of patients (percent)		All Phase 3 Studies Number of patients (percent) n=1169
	Armodafinil n=645	Placebo n=445	
Reduced WBCs	5 (0.8%)	2 (0.4%)	7 (0.6%)
Reduced Hemoglobin	3 (0.5%)	3 (0.7%)	10 (0.9%)
Reduced Hematocrit	4 (0.6%)	6 (1.3%)	11 (0.9%)
Reduced Neutrophils	1 (0.2%)	1 (0.2%)	1 (0.0%)
Increased Eosinophils	4 (0.6%)	3 (0.7%)	6 (0.5%)

Off note, there were no cases of serious events linked to hematological abnormalities. Two cases of hematological abnormalities resulted in drug discontinuations (see tabulations in the section on drug discontinuations). The first case in an open label drug trial (study 3023) described the **reason for discontinuation as “pancytopenia (Note: Lymphocytes, eosinophils, basophils, and neutrophils were normal.)” and occurred in a 51 year old male with OSAHS (patient # 1824002) on 150 mg/day of armodafinil. Patient’s significant medical history included hypertension, heartburn, type 2 diabetes, “hemosiderin pigmentation.” The patient was on multiple medications including antihypertensives, NSAD, multivitamins, insulin and oral hypoglycemics. A record of changes in indices is presented in the table below (negative days indicate pre-drug values). Drug was discontinued on day 37 because of abnormalities in all indices noted on day 35. Indices subsequently returned to normal. This case is somewhat confusing in that there was a strong**

suggestion of a reduction in WBC and absolute neutrophil count (ANC) prior to drug treatment. Decreases in RBC and Platelets were better linked to drug treatment. These data suggest a possible relationship to drug but the relation is somewhat confounded.

Day	RBC (4.5-6.4x10 <sup>12</sup> /L)	Hgb (12.7-18.1 g/dL)	HCT (39-54%)	Platelets (140-400x10 <sup>9</sup> /L)	WBC (3.8-10.7x10 <sup>9</sup> /L)	ANC (1.96-7.23x10 <sup>9</sup> /L)
-15	4.9	14.4	41	333	7.43	5.02
-1	4.6	13.8	40	285	5.73	3.17
35	3.6	10.7	31	108	3.01	1.67
51	4.6	13.8	40	267	7.19	5.47
69	4.6	13.7	40	332	7.96	4.87

The second case of drug discontinuation resulting from a change in hematological indices was that observed in a 35 year old male (#0981415) participating in a placebo-control trial (3021) with OSAHS with a history of a benign parotid cyst and no concomitant medications. The reason for withdrawal was "platelet count decreased, neutrophil count decreased, and absolute neutrophil count decreased." According to the narration the patient was withdrawn from medication on day 61 because of stated adverse events. Changes in these cellular elements are presented in the table below, copied from the narration. Small changes can be observed at day 56. These changes are probably too small, particularly when baseline day -2 are used for comparison, to attribute to a drug effect.

Study day	Absolute neutrophils (1.96-7.23 x 10 <sup>9</sup> /L)	Neutrophils (40.5 - 75.0%)	Platelets (140 - 400 x 10 <sup>9</sup> /L)
-28 (screening)	2.97	57.0	228
-2 (baseline)	1.79	44.7	159
27	1.63	41.4	156
56	1.61	41.2	124
66	2.07	39.3	179
73	2.07	45.1	159

#### 1.18.7.4 Additional analyses and explorations

No further analyses were carried out.

#### 1.18.7.5 Special assessments

All special assessments are described above.

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## 1.18.8 Vital Signs

### 1.18.8.1 Overview of vital signs testing in the development program

Vital signs, including a sitting blood pressure and pulse, were monitored at each patient visit in all studies. In phase 3 trials vital signs included those monitored at approximately 2 to 3 hours following drug/placebo administration, this represents an approximate Tmax. Latter day vital signs were also accessed at some visits.

### 1.18.8.2 Selection of studies and analyses for overall drug-control comparisons

Phase 3 trials data were used for the analysis of vital signs.

### 1.18.8.3 Standard analyses and explorations of vital signs data

#### *1.18.8.3.1 Analyses focused on measures of central tendencies*

The table below presents central analysis for changes in morning blood pressure in phase 3 placebo-control studies measured at the last endpoint evaluation clinic visit. Different underlying treated disorders are analyzed separately. Mean baseline pulse values were relatively similar across all groups. There was a very small, but consistent, mean increase in pulse rate with drug when compared to placebo. This ranged from a mean of 0.9 to 3.5 BPM. Mean baseline systolic blood pressure appeared somewhat greater in the OSAHS group than those being treated for other disorders, being approximately 8 mmHg greater than other groups. This would be consistent with the association of elevated blood pressure with OSAHS and the demography of this patient population, i.e. greater age. As with pulse small mean increases in systolic blood pressure, ranging from 1.2 to 4.3 mm Hg, were observed in the armodafinil group when compared to placebo. The effect in OSAHS was the smallest (1.2 mm Hg). Mean baseline diastolic blood pressures were similar across groups except for a slightly higher value in OSAHS patients (3-4 mm Hg). Again, there was a small but consistent increase in diastolic blood pressure in the armodafinil group over the placebo group (1.3 to 3.1 mm Hg).

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Vital signs parameter*	Time point Statistic	Narcolepsy		OSAHS		SWSD	
		Armodafinil (N=131)	Placebo (N=63)	Armodafinil (N=391)	Placebo (N=260)	Armodafinil (N=123)	Placebo (N=122)
Pulse, bpm	Baseline						
	n	131	63	391	260	123	121
	Mean	68.1	69.0	67.9	67.5	66.8	68.2
	SD	11.49	11.32	9.56	9.87	9.44	9.69
	Median	66.0	68.0	68.0	67.0	66.0	68.0
	Min, max	46.0, 109.0	45.0, 96.0	45.0, 93.0	47.0, 93.0	42.0, 93.0	43.0, 91.0
	Change from baseline						
	n	126	61	379	259	119	111
	Mean	4.3	0.8	2.3	1.4	4.1	0.9
	SD	10.80	10.08	9.60	9.63	11.04	8.41
	Median	4.0	0.0	2.0	1.0	4.0	1.0
	Min, max	-20.0, 40.0	-28.0, 30.0	-29.0, 36.0	-29.0, 29.0	-30.0, 39.0	-28.0, 22.0
	Systolic blood pressure, mm Hg	Baseline					
n		131	63	391	260	123	120
Mean		118.3	118.6	127.4	128.4	120.7	122.7
SD		12.69	16.64	14.46	14.06	14.33	14.81
Median		118.0	116.0	126.0	128.0	120.0	120.0
Min, max		90.0, 150.0	96.0, 161.0	95.0, 180.0	96.0, 164.0	90.0, 162.0	94.0, 192.0
Change from baseline							
n		126	61	379	259	119	110
Mean		2.7	0.9	0.2	-1.0	3.7	-0.6
SD		12.20	14.78	14.16	14.60	14.04	14.14
Median		1.5	0.0	0.0	0.0	2.0	-1.5
Min, max		-28.0, 40.0	-26.0, 77.0	-78.0, 38.0	-38.0, 40.0	-44.0, 37.0	-63.0, 33.0
Diastolic blood pressure, mm Hg		Baseline					
	n	131	63	391	260	123	120
	Mean	74.1	74.6	78.0	78.8	74.8	76.7
	SD	9.51	10.64	9.13	9.37	9.62	9.93
	Median	74.0	74.0	78.0	79.0	74.0	76.0
	Min, max	53.0, 96.0	54.0, 98.0	56.0, 110.0	56.0, 115.0	46.0, 98.0	40.0, 102.0
	Change from baseline						
	n	126	61	379	259	119	110
	Mean	1.6	-0.7	0.3	-1.0	2.3	-0.9
	SD	10.29	8.87	9.29	9.96	11.57	9.72
	Median	1.0	-2.0	0.0	0.0	0.0	-1.0
	Min, max	-22.0, 38.0	-20.0, 20.0	-32.0, 31.0	-41.0, 33.0	-23.0, 45.0	-40.0, 27.0

SOURCE: Summary 6.1.2; study 3020 and study 3022 clinical study reports.

\* Vital signs were obtained approximately 2-3 hours after study drug administration.

min=minimum; max=maximum; SD=standard deviation; bpm=beats per minute; OSAHS=obstructive sleep apnea/hypopnea syndrome; SWSD=shift work sleep disorder.

Two doses (150 and 250 mg/day) were examined in two disorders (SWSD and OSAHS). Comparison of these studies for a dose dependent effect did not reveal an obvious effect on pulse or diastolic blood pressure. There was a slightly greater tendency of the high dose in increasing systolic blood pressure: i.e. there was a 1.2 to 3.1 mm Hg greater increase with the 250 mg/day as compared to 150 mg/day dose in both disorders.

Mean changes for vital signs from baseline for the complete phase 3 database over time is presented in the table below. Increases of similar magnitudes of controlled studies in pulse, systolic and diastolic blood pressures are apparent over time. No obvious change over time.

Variable Statistic	Time point				
	Baseline	Month 1	Month 3	Month 4	Month 6
<b>Pulse, bpm</b>					
n	1137	1011	809	250	165
Mean (SD)	69.0 (10.17)	70.5 (10.15)	71.6 (10.27)	73.3 (9.64)	72.3 (9.65)
Mean change (SD)	—	1.7 (9.52)	2.6 (9.96)	5.9 (11.22)	2.6 (10.39)
<b>Systolic blood pressure, mm Hg</b>					
n	1137	1010	807	250	166
Mean (SD)	125.1 (14.50)	125.7 (14.70)	126.1 (14.23)	126.8 (15.25)	126.6 (13.84)
Mean change (SD)	—	0.5 (13.33)	1.3 (13.76)	2.2 (15.09)	2.3 (14.83)
<b>Diastolic blood pressure, mm Hg</b>					
n	1137	1010	807	250	166
Mean (SD)	77.4 (9.25)	78.0 (9.11)	77.8 (9.52)	78.1 (9.40)	78.8 (8.62)
Mean change (SD)	—	0.6 (9.41)	0.4 (9.81)	1.7 (9.56)	1.0 (9.35)

*1.18.8.3.2 Analyses focused on outliers or shifts from normal to abnormal*

A shift table presenting increases in blood pressures from >10 to >30 mm Hg in the control database is presented in the table below. Numbers (and percent) of patients fitting into each criteria are presented in this table. There was a slight preponderance of patients with >20 mm Hg increase in blood pressure over baseline in patients with narcolepsy and perhaps SWSD. This was not true for patients with OSAHS who where placebo patients appeared to have more frequent increases in systolic pressures. The data are difficult to definitively interpret.

Variable, criteria	Number (%) of patients					
	Narcolepsy		OSAHS		SWSD	
	Armodafinil (N=131)	Placebo (N=63)	Armodafinil (N=391)	Placebo (N=260)	Armodafinil (N=123)	Placebo (N=122)
<b>SBP, mm Hg</b>						
>10 to ≤20	38 (29)	15 (24)	140 (36)	74 (28)	45 (37)	31 (25)
>20 to ≤30	33 (25)	7 (11)	60 (15)	48 (18)	16 (13)	23 (19)
>30	5 (4)	5 (8)	36 (9)	32 (12)	14 (11)	4 (3)
<b>DBP, mm Hg</b>						
>10 to ≤20	39 (30)	15 (24)	115 (29)	81 (31)	45 (37)	33 (27)
>20 to ≤30	11 (8)	1 (2)	29 (7)	15 (6)	13 (11)	8 (7)
>30	3 (2)	2 (3)	5 (1)	2 (<1)	4 (3)	2 (2)

The table below was derived by combining data from the above table for all disorders for patients who experience at least a >20 mmHg increase in blood pressure. When examined as a group, the differences between placebo and drug are smaller. The question may be raised if effects are small or if the drug influence on patients with OSAHS is more resistant to alterations

in blood pressure. These studies cannot answer this question. But, I do indicate a potential small increase in blood pressure.

	Armodafinil Percent Patients >20 mmHg	Placebo Percent Patients >20 mmHg
Systolic Blood Pressure	25.4%	26.7%
Diastolic Blood Pressure	10.1 %	6.7%

*1.18.8.3.3 Marked outliers and dropouts for vital sign abnormalities*

The Sponsor tabulated significant increases in blood pressure using the WHO definition of hypertension for patients in the phase 3 control trials. The tabulation and criteria are presented in the table below. Like the shift tables described above little change can be appreciated in the OSAHS patients. There is, however, a subtle suggestion of greater hypertensive shifts in the Narcolepsy and less so in the SWSD patients. No obvious changes in pulse rate can be appreciated.

Variable, criteria <sup>a</sup>	Number (%) of patients					
	Narcolepsy		OSAHS		SWSD	
	Armodafinil (N=131)	Placebo (N=63)	Armodafinil (N=391)	Placebo (N=260)	Armodafinil (N=123)	Placebo (N=122)
Pulse (bpm), ≥120 and increase ≥15	0	0	0	0	0	0
Systolic BP (mm Hg), ≥140 and increase of ≥10%	34 (26)	9 (14)	125 (32)	89 (34)	28 (23)	17 (14)
Diastolic BP (mm Hg), ≥90 and increase of ≥10%	27 (21)	10 (16)	90 (23)	68 (26)	23 (19)	25 (20)

More severe outlier criteria for blood pressure changes, presented in the table below, failed to indicate an obvious difference between placebo and armodafinil groups.

Variable, criteria <sup>a</sup>	Number (%) of patients					
	Narcolepsy		OSAHS		SWSD	
	Armodafinil (N=131)	Placebo (N=63)	Armodafinil (N=391)	Placebo (N=260)	Armodafinil (N=123)	Placebo (N=122)
Systolic BP (mm Hg), ≥180 and increase of ≥20	1 (<1)	0	6 (1)	6 (2)	3 (2)	2 (2)
Diastolic BP (mm Hg), ≥105 and increase of ≥15	3 (2)	1 (2)	9 (2)	9 (3)	5 (4)	1 (<1)

Shifts for the complete database using the WHO criteria tended to reveal a lower incidence of outliers (data not shown).

No alterations in blood pressure or pulse were categorized as a serious event. One case of “blood pressure increased” and one of “heart rate increased” was categorized as a reason for discontinuation on drug in controlled phase 3 trials. There was one case of “blood pressure increased” in the placebo group. One additional case was of blood “pressure increased” and one of increased pulse was observed in the complete phase 3 database.

#### 1.18.8.4 Additional analyses and explorations

Because of the confounding effect of treatment with antihypertensives, this division had requested an examination of the pattern of use of antihypertensive medication use during the treatment period. It was thought that an increase in antihypertensive medication would offset the magnitude of any blood pressure differences between control and placebo groups. To respond to this, the Sponsor classified patients as “newly diagnosed hypertension” if they were started anew on antihypertensive medication during the treatment period or, “worsening hypertension” if they were receiving antihypertensive medication during baseline but required an increase in the dose or the addition of a new medication during. These data are tabulated below as the number (and percent) of patients fulfilling the different criteria. What is apparent is a slightly greater incidence in both parameters in the armodafinil drug group when compared to placebo, perhaps suggesting a subtle and small hypertensive effect.

	Armodafinil (n=645)	Placebo (n=445)
Newly Diagnose	4 (0.6 %)	1 (0.2%)
Worsening Hypertension	15 (2.3%)	7 (1.6%)
Combined	19 (2.9%)	8 (1.8%)

Analysis of these parameters for the OSAHS placebo-control database was similar to the analysis of the full placebo control. Thus, there were 3.6% of cases in the armodafinil group and 2.3% of cases in the placebo group that required additional hypertension therapy (newly diagnosed + worsening hypertension). There was no obvious dose response relationship in this phenomenon.

In conclusion armodafinil may cause small increases in blood pressure. This is suggested by small, but consistent increases in blood pressure in the central tendency analysis and a suggestion for a slight increase in the incidence of increased antihypertensive use in the armodafinil as compared to placebo group. Outlier analysis, however, was not as clear.

#### 1.18.9 Electrocardiograms (ECGs)

#### 1.18.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

EKGs were performed at every visit in the placebo-control studies at the approximate T<sub>max</sub> for the drug (3 hours post dose). EKGs were read by an outside expert central reader. There were no adequate placebo/and positive control phase 1 QT interval studies.

#### 1.18.9.2 Selection of studies and analyses for overall drug-control comparisons

Quantitative analysis was performed on the phase 3 trials.

#### 1.18.9.3 Standard analyses and explorations of ECG data

##### *1.18.9.3.1 Analyses focused on measures of central tendency*

Minimal mean changes from placebo were observed at the final endpoint measure for ventricular rate (0-3 BPM), PR interval (-2.6 to -5 msec) and QRS (-0.3 to 0.8 msec) segment for the different disorders studies. These are presented in Appendix F.

The table below presents mean changes in QT, QTcB and QTcF in the phase 3 control trials for the various studied disorders. Values represent change from baseline to the final on-drug endpoint visit. No mean QT, QTcF or QTcB prolongations were equal or greater than 5 msec. Indeed most prolongations were substantially less than 5 msec.

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Variable	Time point Statistic	Narcolepsy		OSAS		SWSD		
		Armodafinil (N=131)	Placebo (N=63)	Armodafinil (N=391)	Placebo (N=260)	Armodafinil (N=123)	Placebo (N=122)	
QTc interval Bazett, msec	Baseline							
	n	131	62	391	260	123	122	
	Mean	403.9	404.9	407.6	406.6	405.4	405.5	
	SD	23.78	22.09	26.14	24.64	26.03	25.15	
	Median	400.0	401.5	407.0	405.0	409.0	408.0	
	Min, max	345, 475	358, 449	341, 530	344, 547	341, 456	344, 483	
	Change from baseline							
	n	125	59	378	258	119	114	
	Mean	4.3	0.8	0.2	-0.5	-2.8	2.6	
	SD	20.51	19.41	20.90	21.51	22.07	21.92	
	Median	4.0	0.0	0.0	-0.5	-3.0	3.0	
	Min, max	-49, 65	-44, 36	-69, 68	-99.0, 96.0	-69, 72	-50, 49	
	QTc interval Fridericia, msec	Baseline						
		n	131	62	391	260	123	122
Mean		399.9	401.2	403.3	402.5	401.8	400.8	
SD		22.01	18.49	22.08	22.35	22.85	20.73	
Median		397.0	399.5	402.0	401.0	404.0	402.0	
Min, max		349, 466	360, 442	336, 508	340, 531	346, 469	353, 466	
Change from baseline								
n		125	59	378	258	119	114	
Mean		0.2	-0.7	-2.5	-1.6	-5.6	1.0	
SD		17.50	17.45	18.31	18.81	20.75	18.77	
Median		1.0	-2.0	-2.0	-1.0	-6.0	2.0	
Min, max		-50, 50	-47, 44	-70, 53	-95, 101	-74, 59	-34, 62	
QT interval, msec		Baseline						
		n	131	62	391	260	123	122
	Mean	392.9	394.9	395.8	395.3	395.4	392.4	
	SD	31.04	26.78	28.48	29.98	27.70	26.71	
	Median	390.0	393.0	395.0	392.0	395.0	390.5	
	Min, max	315, 471	326, 454	302, 505	329, 499	333, 503	327, 487	
	Change from baseline							
	n	125	59	378	258	119	114	
	Mean	-7.5	-3.6	-8.0	-3.6	-10.9	-2.1	
	SD	24.97	21.98	23.26	22.07	28.05	23.68	
	Median	-9.0	-2.0	-7.0	-2.5	-9.0	-5.0	
	Min, max	-70, 82	-64, 64	-98, 70	-87, 113	-112, 78	-70, 90	

The changes in mean QT, QTcF and QTcB for all patients in the total phase 3 data base was calculated for various times after treatment was started (1, 3, 4 and 6 months post treatment). Mean absolute change from baseline QTcF change from baseline varied over the time points from -3.2 to 0.1 msec.

#### 1.18.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

See the next section.

#### 1.18.9.3.3 Marked outliers and dropouts for ECG abnormalities

Categorical absolute and change from baseline significant QTcF incidences from placebo-control phase 3 studies are presented in the table below. Number of patients (and percent) to fit criteria are presented. Although there was a slight preponderance of significant change from baseline categorical changes in the drug versus placebo grouping the narcolepsy studies this was not

observed in any of the other studies. Considering that these studies were not designed according to strict QT design recommendation, the significance of this finding is questionable. Data in general from other studies (OSAHs and SWSD) as well as central tendencies do not indicate a significant QT effect.

QTc interval (Fridericia)	Number (%) of patients*					
	Narcolepsy		OSAHs		SWSD	
	Armodafinil (N=131)	Placebo (N=63)	Armodafinil (N=391)	Placebo (N=260)	Armodafinil (N=123)	Placebo (N=122)
<b>Absolute value, msec</b>						
>450	3 (2)	1 (2)	13 (3)	7 (3)	2 (2)	2 (2)
>480	0	0	2 (<1)	1 (<1)	0	0
>500	0	0	1 (<1)	0	0	0
<b>Change from baseline, msec</b>						
<30	94 (72)	52 (83)	305 (78)	206 (79)	95 (77)	90 (74)
30-60	29 (22)	7 (11)	64 (16)	48 (18)	22 (18)	22 (18)
>60	2 (2)	0	9 (2)	4 (2)	2 (2)	2 (2)

Two serious adverse events, atrial fibrillation and supraventricular tachycardia, were associated with EKG abnormalities. These occurred in the same patient (#021540 EKG) who had evidence of ischemic changes and substantial risk factors and preexisting heart disease: i.e. patient with a history of hypertension, coronary artery diseases (status post CABG), congestive heart disease, obesity, diabetes, rheumatic fever, anemia and hyperlipidemia. This patient has been discussed in previous sections. The EKG changes likely result from the preexisting cardiac disease.

Two EKG related adverse events, unrelated to ischemia, were also reported as reasons for discontinuations. This included a case already discussed (patient #2289176) of bundle branch block and ST depression. This patient, however, showed a minor right intraventricular conduction defect consistent with a left anterior hemiblock on one of the screening EKGs. This change can, therefore, not be directly linked to a drug effect. The second case (patient # 0841423) involves a 56 year old woman with palpitations associated with prolongation of the QT interval. According to the CRF the QTc (B or F????) duration increased from 450 to 506 and resolved with drug discontinuation. This patient is included in the above analyses.

#### 1.18.10 Immunogenicity

No through analysis of this was performed by the Sponsor. The reporting rates for the organ class **"infections and infestations" of adverse events** did not significantly differ between drug (12%) and placebo (15%). This may suggest no immunosuppressant activity.

#### 1.18.11 Human Carcinogenicity

No relevant clinical studies were performed that explored carcinogenicity.

## 1.18.12 Special Safety Studies

### 1.18.12.1 Effects on Scheduled sleep

Effects of armodafinil on scheduled nighttime (SWSD and OSAHS) and daytime (SWSD) was examined through polysomnography and sleep diaries in the placebo-control phase 3 studies.

#### *1.18.12.1.1 Polysomnography*

The various polysomnography sleep parameters from the controlled phase 3 trials are presented in the table below. These include latency to persistent sleep, number of arousals, number of awakenings, sleep efficiency and wake after sleep onset. Changes are of small magnitude and of varied sign across indications, sometimes indicating a very slight improvement or very slight worsening from baseline of the armodafinil group over the placebo group. These data would suggest no clinically significant effect. A negative value in the mean change in this table refers to a reduction in the value at the final endpoint over baseline.

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Variable	Time point Statistic	Narcolepsy		OSAS		SWS	
		Armodafinil (N=131)	Placebo (N=63)	Armodafinil (N=391)	Placebo (N=160)	Armodafinil (N=123)	Placebo (N=122)
Latency to persistent sleep (minutes)	Baseline						
	n	130	60	382	255	123	122
	Mean	16.3	15.1	22.3	21.3	10.8	10.4
	SD	17.57	14.89	26.86	23.97	12.89	14.04
	Median	9.8	11.8	14.5	14.0	6.5	7.0
	Min, max	0.0, 100.5	0.5, 70.0	0.00, 210.0	0.0, 153.0	0, 80	0, 123.5
	Change from baseline						
	n	107	54	327	232	102	91
	Mean	-0.6	7.2	-1.6	-0.3	3.1	1.1
	SD	20.09	31.02	26.84	26.09	15.25	12.54
	Median	0.0	1.0	0.0	0.0	1.5	0.5
	Min, max	-69.5, 66.0	-61.5, 118.5	-180.0, 163.0	-132.5, 96.5	-43, 62	-39.5, 45
Number of arousals	Baseline						
	n	130	60	382	255	123	122
	Mean	22.6	21.7	20.0	18.7	16.9	16.0
	SD	12.82	13.53	11.25	9.74	10.28	10.69
	Median	21.0	20.5	19.0	18.0	16.0	14.0
	Min, max	2.0, 63.0	0.0, 70.0	0.0, 78.0	1.0, 54.0	1, 52	2, 71
	Change from baseline						
	n	107	54	327	232	102	91
	Mean	-0.7	-1.5	-1.7	-0.4	-0.5	-0.1
	SD	12.52	9.35	9.13	9.80	8.77	8.06
	Median	0.0	0.0	-1.0	0.0	-2.0	0.0
	Min, max	-35.0, 36.0	-36.0, 15.0	-34.0, 32.0	-31.0, 31.0	-16, 34	-18, 23
Number of awakenings	Baseline						
	n	130	60	382	255	123	122
	Mean	9.9	10.7	8.8	8.7	7.8	7.6
	SD	6.37	6.32	4.71	5.05	4.68	4.02
	Median	10.0	10.0	9.0	8.0	8.0	7.0
	Min, max	0.0, 36.0	0.0, 26.0	0.0, 27.0	0.0, 33.0	0, 22	1, 19
	Change from baseline						
	n	107	54	327	232	102	91
	Mean	0.3	0.3	0.5	1.1	-0.2	0.0
	SD	4.97	5.63	5.17	5.80	4.71	4.40
	Median	1.0	1.0	1.0	1.0	-1.0	0.0
	Min, max	-14.0, 15.0	-21.0, 15.0	-14.0, 20.0	-16.0, 19.0	-13, 15	-12, 12
Sleep efficiency (%)	Baseline						
	n	130	60	382	255	123	122
	Mean	84.4	81.3	82.4	82.0	71.1	70.9
	SD	11.97	12.76	10.87	12.10	16.00	15.44
	Median	87.7	85.2	84.6	84.9	73.4	75.2
	Min, max	32.2, 99.1	51.5, 97.9	36.3, 98.8	26.5, 99.5	19.6, 99.1	15.7, 93.1
	Change from baseline						
	n	107	54	327	232	102	91
	Mean	-0.6	-0.9	-0.4	-0.7	-2.1	0.5
	SD	10.25	10.91	12.53	11.80	19.28	18.49
	Median	-0.7	0.9	-0.1	-0.8	-1.4	-0.6
	Min, max	-43.9, 27.9	-26.3, 24.6	-98.1, 48.1	-46.4, 38.4	-76.8, 49.0	-39.9, 82.3
Wake after sleep onset (minutes)	Baseline						
	n	130	60	382	255	123	122
	Mean	62.3	78.2	66.6	68.7	130.6	132.8
	SD	54.33	61.37	43.89	50.25	73.03	73.52
	Median	47.8	58.8	59.8	56.5	118.0	112.3
	Min, max	2.0, 323.0	2.5, 225.5	0.0, 270.5	2.5, 347.0	4.5, 375.0	24.5, 396.0
	Change from baseline						
	n	107	54	327	232	102	91
	Mean	3.5	-3.6	1.7	1.7	6.2	-4.7
	SD	43.18	43.06	47.57	48.93	90.96	87.20
	Median	4.0	-5.0	-1.0	2.3	6.3	7.0
	Min, max	-128.5, 177.0	-115.5, 104.0	-150.5, 239.5	-213.0, 131.0	-250.0, 351.5	-390.5, 191.0

Differences in staged sleep, percent of time spent in phases 1, 2/3/4 and REM, were evaluated in the polysomnogram for the various disorders (see Appendix G). The effects were generally small and inconsistent across disorders. Such effects are likely not clinically significant.

#### *1.18.12.1.2 Sleep diaries*

Changes in sleep efficiency and latency in the controlled phase 3 trials are presented in the table below. There were inconsistent and small changes observed in the sleep efficiency across disorders that are probably not clinically significant. There were no changes in sleep latency for patients with OSHAS but there was a mild prolongation in patients with narcolepsy and SWSD. The increases in latency on drug as compared to placebo with narcolepsy were contrary to those measured by polysomnography which showed a reduction in latency on drug. Although this increase in latency may not always be confirmed by the objective polysomnography testing it is likely related to the high degree of the complaint of insomnia for patients receiving armodafinil (5%) in these placebo-control trials.

#### 1.18.13 Withdrawal Phenomena and/or Abuse Potential

There were no specific studies to investigate the effect of armodafinil on abuse potential or withdrawal. The racemic product, Provigil, is a schedule IV product. A CSS consult is pending.

#### 1.18.14 Human Reproduction and Pregnancy Data

Use of this agent has not been studied in pregnant or lactating women.

#### 1.18.15 Assessment of Effect on Growth

These studies were performed in adults and therefore growth parameters have not been carefully examined.

#### 1.18.16 Overdose Experience

No information was collected in the present studies that were relevant to overdose.

#### 1.18.17 Postmarketing Experience

There is no postmarketing experience on this product. There is postmarketing experience on the racemate mixture, Provigil. The Sponsor has not presented this information, nor where they asked to, in the application.

## 1.19 Adequacy of Patient Exposure and Safety Assessments

### 1.19.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

#### 1.19.1.1 Study type and design/patient enumeration

The data base includes 1169 unique patients with one of the three studied sleep disorders who have received armodafinil in a total of 6 phase 3 studies. Data cut-off for the presentation in the initial NDA submission was 12/15/04. Of the 6 phase 3 studies, 4 were pivotal double-blind placebo-control studies. Two of the placebo-control studies were performed in patients with OSAHS and one in patients with narcolepsy and another in patients with SWSD. The table below presents summary information on the double-blind placebo-controlled studies.

Disorder	Study number	Duration	Number of patients treated				
			Armodafinil (mg/day)			Placebo	Total
			250	150	Total		
OSAHS							
	Study 3021	12 weeks	131	131	262	130	392
	Study 3025	12 weeks	—	129	129	130	259
SWSD							
	Study 3022	12 weeks	—	123	123	122	245
Narcolepsy							
	Study 3020	12 weeks	67	64	131	63	194
<b>Total</b>			<b>198</b>	<b>447</b>	<b>645</b>	<b>445</b>	<b>1090</b>

The remainder of the phase 3 studies included 2 ongoing long term open label studies. These are summarized in the table below. Dosages used in these studies were 100 to 250 mg/day. As apparent patients in these studies suffered any of the three sleep disorder. Patients in study 3024 were required to have participated in previous phase 3 double-blind placebo controlled studies. Patients in 3023 were not derived from prior double-blind studies.

Study number	Number of patients treated by sleep disorder			Total
	OSAHS	SWSD	Narcolepsy	
Study 3023 <sup>a</sup>	164	107	48	319
Study 3024 <sup>b</sup>	407	42	72	521
<b>Total</b>	<b>571</b>	<b>149</b>	<b>120</b>	<b>840</b>

An additional 245 healthy subjects received armodafinil in a variety of PK, bioequivalence and PD studies. These are briefly summarized in the table below.

Study number	Study design	Duration of treatment	Armodafinil dose	N <sup>a</sup>
Study 1023	Open-label, 2-way crossover, bioequivalence	Single dose (x2)	250 mg	30
Study 101	Double-blind, placebo-controlled, pharmacokinetics	Single dose <sup>c</sup>	50–400 mg	30
Study 102	Double-blind, placebo-controlled, pharmacokinetics	14 days	50–400 mg	37
Study 103 <sup>b</sup>	Double-blind, placebo- and active-controlled, pharmacodynamics	Single dose	100–300 mg	71
Study 1021	Open-label, 2-way crossover, drug interaction	Single dose	400 mg	24
Study 1022	Open-label, drug interaction	31 days	250 mg	24
Study 1025	Open-label, drug interaction	29 days	250 mg	29
<b>Total</b>				<b>245</b>

The Sponsor has presented only patient and not health subject data in their integrated summary of safety. The safety analysis set included all patients randomized who received 1 or more doses of the study medication.

#### 1.19.1.2 Demographics

The patient population demographic variables for all patients, divided by disorder, are presented in the table below. There was a moderate preponderance of males to females that resulted from OSAHS studies and were likely a result of the preponderance of males in this disorder. Approximately 29% of the patients were classified as “non-white.” **More than 80% of patients** originated from studies carried out in the United States.

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Demographic variable	Number (%) of patients			
	Narcolepsy (N=205)	OSAHS (N=716)	SWSD (N=248)	All patients (N=1169)
<b>Age, years</b>				
Mean	39.4	49.7	39.2	45.7
SD	13.29	8.93	10.59	11.35
Median	38.0	51.0	39.0	47.0
Min, max	18.0, 70.0	25.0, 69.0	18.0, 63.0	18.0, 70.0
<b>Age group (years), n (%)</b>				
18-29	65 (32)	13 (2)	60 (24)	138 (12)
30-40	46 (22)	112 (16)	70 (28)	228 (20)
41-55	66 (32)	375 (52)	105 (42)	546 (47)
>55	28 (14)	216 (30)	13 (5)	257 (22)
<b>Sex, n (%)</b>				
Male	90 (44)	516 (72)	146 (59)	752 (64)
Female	115 (56)	200 (28)	102 (41)	417 (36)
<b>Race group, n (%)</b>				
White	149 (73)	614 (86)	172 (69)	935 (80)
Non-white	50 (24)	102 (14)	76 (31)	228 (20)
Missing	6 (3)	0	0	6 (<1)
<b>BMI, kg/m<sup>2</sup></b>				
Mean	28.8	36.4	29.8	33.7
SD	6.45	7.86	6.47	8.12
Median	28.0	34.9	28.8	32.4
Min, max	15.4, 59.2	19.6, 80.7	13.3, 51.4	13.3, 80.7
<b>CGI-S group, n (%)</b>				
Moderately ill	75 (37)	401 (56)	148 (60)	624 (53)
Markedly, severely, or extremely ill	124 (60)	298 (42)	95 (38)	517 (44)
Missing	6 (3)	17 (2)	5 (2)	28 (2)
<b>Country, n (%)</b>				
United States	139 (68)	607 (85)	210 (85)	956 (82)
Canada	30 (15)	40 (6)	11 (4)	81 (7)
France	7 (3)	0	0	7 (<1)
Germany	11 (5)	3 (<1)	0	14 (1)
Australia	9 (4)	21 (3)	0	30 (3)
Russia	9 (4)	45 (6)	27 (11)	81 (7)

1.19.1.3 Extent of exposure (dose/duration)

One thousand and sixty-nine patients received at least one dose of armodafinil for a total of 401.16 patient-year exposure. The table below includes information on exposure duration for patients with the various diagnoses studied in this NDA. As apparent 59% (684 patients) received treatment of 3 months or greater. The largest group of patients studied was those with OSAHS. No patients were exposed for 1 year or greater.

<b>Study drug exposure</b>	<b>Narcolepsy (N=205)</b>	<b>OSAHS (N=716)</b>	<b>SWSD (N=248)</b>	<b>All (N=1169)</b>
<b>Duration range, n (%)</b>				
<2 weeks	4 (2)	22 (3)	5 (2)	31 (3)
≥2 weeks and <1 month	17 (8)	43 (6)	10 (4)	70 (6)
≥1 month and <2 months	16 (8)	76 (11)	23 (9)	115 (10)
≥2 months and <3 months	68 (33)	129 (18)	72 (29)	269 (23)
≥3 months and <6 months	60 (29)	274 (38)	93 (38)	427 (37)
≥6 months and <9 months	34 (17)	164 (23)	39 (16)	237 (20)
≥9 months and <12 months	6 (3)	8 (1)	6 (2)	20 (2)
At least 12 months	0	0	0	0
<b>Patient-years</b>	<b>65.78</b>	<b>251.46</b>	<b>83.92</b>	<b>401.16</b>

Tabulation for exposure by dose is presented in the table below. Most patients were exposed to a dose of 150 mg and above with most of these exposures being greater than 3 months.

<b>Study drug exposure</b>	<b>≤100 mg (N=110)</b>	<b>150 mg (N=584)</b>	<b>200 mg (N=91)</b>	<b>250 mg (N=384)</b>	<b>All (N=1169)</b>
<b>Duration range, n (%)</b>					
<2 weeks	7 (6)	14 (2)	5 (5)	5 (1)	31 (3)
≥2 weeks and <1 month	13 (12)	23 (4)	5 (5)	29 (8)	70 (6)
≥1 month and <2 months	30 (27)	50 (9)	8 (9)	27 (7)	115 (10)
≥2 months and <3 months	7 (6)	175 (30)	8 (9)	79 (21)	269 (23)
≥3 months and <6 months	31 (28)	219 (38)	44 (48)	133 (35)	427 (37)
≥6 months and <9 months	18 (16)	98 (17)	19 (21)	102 (27)	237 (20)
≥9 months and <12 months	4 (4)	5 (<1)	2 (2)	9 (2)	20 (2)
At least 12 months	0	0	0	0	0
<b>Patient-years</b>	<b>32.78</b>	<b>192.29</b>	<b>35.43</b>	<b>140.66</b>	<b>401.16</b>

## 1.19.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

### 1.19.2.1 Other studies

There is extensive experience for adult exposure of the racemic mixture of armodafinil, Provigil, in open-label and placebo-control studies that have been used for the approval of this agent in the treatment of narcolepsy, OSAHS and SWSD.

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### 1.19.2.2 Postmarketing experience

There is no postmarketing experience for this product. A review of the postmarketing experience for the racemic mixture, Provigil, is extensive but was not included in the submission and is beyond the scope of the present review.

### 1.19.2.3 Literature

There is no pertinent literature on armodafinil.

## 1.19.3 Adequacy of Overall Clinical Experience

Studies were of conventional design, placebo-control and open label extensions that should allow the examination of routine adverse event profile.

While the exposures for the additional NDA do not reach ICH guideline recommended values (insufficient 1 year exposures). The problem is resolved because: 1) there has already been more than adequate exposure with the racemic mixture, Provigil, and 2) the ICH guidelines are met with the additional safety update submission (see below). The predominate doses of exposure were at intended therapeutic values.

While a formal QT study has not been performed, no problem has been identified with the racemic mixture. Moreover, an evaluation of QT intervals in placebo-control data and adverse event reporting for armodafinil do not suggest an effect on the QT interval.

#### 1.19.4 Adequacy of Special Animal and/or In Vitro Testing

The reader is referred to the pharm/tox review.

#### 1.19.5 Adequacy of Routine Clinical Testing

Monitoring for adverse events were generally adequate.

#### 1.19.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The reader is referred to the clinical pharmacology review.

#### 1.19.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The adverse events that may be most worrisome with this class of agents include sleep disturbances, alterations in blood pressure and psychiatric effects. Generally these adverse events were well monitored and completely analyzed. Narrations, however, sometimes were not comprehensive and required the examination of CRF or discussions with the Sponsor. Also this reviewer at times had to perform additional analyses that better integrated certain adverse events so as to obtain a better understanding of potential adverse event profile. For example, this reviewer reclassified events that may potentially be related to cardiac ischemia and combined psychiatric adverse events so that a determination for drug causality and risk can be made.

#### 1.19.8 Assessment of Quality and Completeness of Data

Generally the quality of data was adequate. As noted above, however, the narrations were somewhat lacking.

#### 1.19.9 Additional Submissions, Including Safety Update

##### 1.19.9.1 Safety Update

A 6 month safety update was provided on 9/29/05. This update provided additional information on 102 new patients (28 with narcolepsy, 35 with OSAHS and 39 with SWSD) participating in the open label studies. Moreover, with this safety update resulted in a greater accumulated

number of patients exposed to armodafinil for longer periods of time: i.e. a total of 781 patients were now exposed for 6 months and 335 for a period of one year. New safety exposure data is presented in the table below.

Study drug exposure	Narcolepsy (N=233)	OSAHS (N=751)	SWSD (N=287)	All patients (N=1271)
<b>Duration range, n (%)</b>				
<2 weeks	5 (2)	22 (3)	8 (3)	35 (3)
≥2 weeks and <1 month	18 (8)	57 (8)	12 (4)	87 (7)
≥1 month and <2 months	12 (5)	41 (5)	20 (7)	73 (6)
≥2 months and <3 months	19 (8)	67 (9)	48 (17)	134 (11)
≥3 months and <6 months	27 (12)	93 (12)	41 (14)	161 (13)
≥6 months and <9 months	32 (14)	34 (5)	45 (16)	111 (9)
≥9 months and <12 months	75 (32)	190 (25)	70 (24)	335 (26)
At least 12 months	45 (19)	247 (33)	43 (15)	335 (26)
<b>Patient-years</b>	<b>152.28</b>	<b>526.51</b>	<b>167.13</b>	<b>845.91</b>

Dose dependent exposure (see table below) in this safety update reveals that most of the prolonged exposures (≥ 6 months and ≥ 12 months) were in patients in the therapeutic dose range (150 to 250 mg/day).

Study drug exposure	≤100 mg (N=118)	150 mg (N=484)	200 mg (N=115)	250 mg (N=454)	All (N=1271)
<b>Duration range, n (%)</b>					
<2 weeks	12 (10)	15 (3)	3 (3)	5 (<1)	35 (3)
≥2 weeks and <1 month	22 (19)	25 (5)	5 (4)	35 (6)	87 (7)
≥1 month and <2 months	9 (8)	33 (7)	4 (3)	27 (5)	73 (6)
≥2 months and <3 months	5 (4)	90 (19)	3 (3)	36 (6)	134 (11)
≥3 months and <6 months	9 (8)	83 (17)	9 (8)	60 (11)	161 (13)
≥6 months and <9 months	10 (8)	28 (6)	17 (15)	56 (10)	111 (9)
≥9 months and <12 months	32 (27)	94 (19)	37 (32)	172 (31)	335 (26)
At least 12 months	19 (16)	116 (24)	37 (32)	163 (29)	335 (26)
<b>Patient-years</b>	<b>62.92</b>	<b>283.05</b>	<b>89.64</b>	<b>410.30</b>	<b>845.91</b>

The present review will concentrate on significant adverse events reported as deaths, serious adverse events or discontinuations. All new reporting is restricted to open label studies.

#### 1.19.9.1.1 Deaths

One patient was noted to have died during the interim period, bringing a total number of deaths for the complete application to 1. The death occurred in a 59 year old male with OSAHS with a history of arthritis who received placebo in the double-blind study but continued in the open label study on 250 mg/day of armodafinil. Concomitant medications included NSAID including a COX-2 inhibitor (rofecoxib). Approximately 6 months after starting armodafinil the patient was seen for a "borderline pneumonia." Three to 4 days later he was found dead in bed. The

**patient's death certificate listed the death as caused by atherosclerotic cardiovascular disease (MedDRA: atherosclerosis).** No other information is provided in the narrative. Examination of the CRF adds little additional significant information. Although there are no noted risk factors for atherosclerotic disease noted, it is noteworthy that the patient is on a COX-2 inhibitor, the class of agents that has been linked to such atherosclerotic disease.

*1.19.9.1.2 Other Serious Adverse Events*

There were a sizable number of additional adverse events listed as serious events in this extended database. Thus an additional 30 patients were observed to suffer adverse events that were classified as serious to make a total of 46 patients experiencing serious adverse events in the complete phase 3 database. The tables below present the compiled serious adverse event reporting for the complete phase 3 database that includes data reported in the original NDA submission.

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System organ class Preferred term	Number (%) of patients			
	Narcolepsy (N=233)	OSAHS (N=751)	SWSD (N=287)	All patients (N=1271)
<b>No. of patients with at least 1 SAE</b>	6 (3)	32 (4)	8 (3)	46 (4)
<b>Cardiac disorders</b>	1 (<1)	5 (<1)	0	6 (<1)
Myocardial infarction	0	2 (<1)	0	2 (<1)
Angina pectoris	1 (<1)	0	0	1 (<1)
Atrial fibrillation	0	1 (<1)	0	1 (<1)
Sinus bradycardia	0	1 (<1)	0	1 (<1)
Supraventricular tachycardia	0	1 (<1)	0	1 (<1)
Tachycardia	0	1 (<1)	0	1 (<1)
Tachycardia paroxysmal	0	1 (<1)	0	1 (<1)
<b>Gastrointestinal disorders</b>	2 (<1)	9 (1)	0	11 (<1)
Hemorrhoidal hemorrhage	1 (<1)	1 (<1)	0	2 (<1)
Abdominal adhesions	0	1 (<1)	0	1 (<1)
Abdominal hematoma	0	1 (<1)	0	1 (<1)
Abdominal pain	0	1 (<1)	0	1 (<1)
Colitis ulcerative	0	1 (<1)	0	1 (<1)
Diverticulitis	0	1 (<1)	0	1 (<1)
Duodenal ulcer hemorrhage	0	1 (<1)	0	1 (<1)
Gastric ulcer hemorrhage	1 (<1)	0	0	1 (<1)
Gastroesophageal reflux disease	0	1 (<1)	0	1 (<1)
Pancreatitis	0	1 (<1)	0	1 (<1)
<b>General disorders and administration site conditions</b>	0	4 (<1)	1 (<1)	5 (<1)
Chest pain	0	4 (<1)	1 (<1)	5 (<1)
<b>Hepatobiliary disorders</b>	0	2 (<1)	0	2 (<1)
Cholecystitis	0	1 (<1)	0	1 (<1)
Cholelithiasis	0	1 (<1)	0	1 (<1)
<b>Infections and infestations</b>	0	1 (<1)	1 (<1)	2 (<1)
Appendicitis	0	0	1 (<1)	1 (<1)
Cellulitis	0	1 (<1)	0	1 (<1)

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System organ class Preferred term	Number (%) of patients			
	Narcolepsy (N=233)	OSAHS (N=751)	SWSD (N=287)	All patients (N=1271)
<b>Injury, poisoning and procedural complications</b>	0	3 (<1)	1 (<1)	4 (<1)
Pelvic fracture	0	1 (<1)	0	1 (<1)
Rib fracture	0	0	1 (<1)	1 (<1)
Skin laceration	0	1 (<1)	0	1 (<1)
Tendon rupture	0	1 (<1)	0	1 (<1)
<b>Metabolism and nutrition disorders</b>	0	2 (<1)	0	2 (<1)
Diabetes mellitus	0	1 (<1)	0	1 (<1)
Hypokalemia	0	1 (<1)	0	1 (<1)
<b>Musculoskeletal and connective tissue disorders</b>	1 (<1)	0	0	1 (<1)
Intervertebral disc compression	1 (<1)	0	0	1 (<1)
<b>Neoplasms benign, malignant and unspecified (incl. cysts and polyps)</b>	0	3 (<1)	1 (<1)	4 (<1)
Chronic myeloid leukemia	0	1 (<1)	0	1 (<1)
Colon cancer	0	1 (<1)	0	1 (<1)
Parathyroid tumor benign	0	0	1 (<1)	1 (<1)
Prostate cancer	0	1 (<1)	0	1 (<1)
<b>Nervous system disorders</b>	0	2 (<1)	1 (<1)	3 (<1)
Dizziness	0	1 (<1)	0	1 (<1)
Migraine	0	1 (<1)	0	1 (<1)
Multiple sclerosis	0	0	1 (<1)	1 (<1)
<b>Psychiatric disorders</b>	0	2 (<1)	1 (<1)	3 (<1)
Affective disorder	0	1 (<1)	0	1 (<1)
Depression	0	1 (<1)	0	1 (<1)
Depression suicidal	0	0	1 (<1)	1 (<1)
Personality disorder	0	1 (<1)	0	1 (<1)

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System organ class Preferred term	Number (%) of patients			
	Narcolepsy (N=233)	OSAHS (N=751)	SWSD (N=287)	All patients (N=1271)
<b>Renal and urinary disorders</b>	0	2 (<1)	1 (<1)	3 (<1)
Nephrolithiasis	0	2 (<1)	1 (<1)	3 (<1)
<b>Reproductive system and breast disorders</b>	1 (<1)	0	1 (<1)	2 (<1)
Menometrorrhagia	0	0	1 (<1)	1 (<1)
Uterine polyp	1 (<1)	0	0	1 (<1)
<b>Respiratory, thoracic and mediastinal disorders</b>	0	4 (<1)	1 (<1)	5 (<1)
Atelectasis	0	1 (<1)	0	1 (<1)
Chronic obstructive airways disease exacerbated	0	1 (<1)	0	1 (<1)
Dyspnea	0	1 <sup>a</sup> (<1)	0	1 (<1)
Pneumothorax	0	0	1 (<1)	1 (<1)
Pulmonary embolism	0	1 (<1)	0	1 (<1)
<b>Skin and subcutaneous tissue disorders</b>	1 (<1)	0	0	1 (<1)
Angioneurotic edema	1 (<1)	0	0	1 (<1)
<b>Vascular disorders</b>	1 (<1)	2 (<1)	0	3 (<1)
Hypertension	1 (<1)	1 (<1)	0	2 (<1)
Hematoma	0	1 (<1)	0	1 (<1)

An additional 4 patients were noted to have serious adverse classified as “cardiac disorders” and 2 additional patients were noted to have “chest pain” that was under the “General Disorders” classification. One new serious adverse event of dyspnea was also noted. These cases are briefly described below:

- One case, a 51 year old male, was reported to have “angina pectoris and hypertension.” This patient was noted have a history of hyperlipidemia and hypertension and was on antiplatelet and antihypertensive treatment. On day 170 of treatment the patient was noted to experience angina and hypertension (BP increased from baseline from 146/77 to 208/105). Medication was stopped on day 182. Angiogram revealed triple vessel disease for which the patient was treated with a stent.
- The single case of “bradycardia” occurred in a 54 year old patient with a significant history of hypertension, hyperlipidemia, Prinzmetal’s angina and obesity. This patient developed symptomatic (“near syncope”) sinus bradycardia. Workup included an angiogram that revealed normal coronaries. A pacemaker was placed and drug was discontinued. The cause of this remains undetermined but it does not appear to be related to symptoms or signs of coronary artery disease.
- The single case of “tachycardia” was actually a “seven beat run of ventricular tachycardia” that was observed in a holter as part of a work up for “near syncope, vertigo and “feeling unwell” 172 to 181 days after treatment was initiated for OSAHS. The

patient was a 64 year old male with a history of mildly leaky mitral valve (untreated), borderline hypertension. Drug was discontinued in this case.

- **The case of “tachycardia paroxysmal” was observed** in a 60 year old male in a patient with a history of hypertension and diabetes on day 348 during a colonoscopy. The patient was being treated with 250 mg/day of armodafinil for OSAHS. The patient was **observed to have a “severe hyopkalemia”** secondary to a bowel preparation and was admitted to telemetry. The patient was observed to have supraventricular tachycardia (130 BPM) associated and a run of 6 beat ventricular tachycardia. Medication was not discontinued.
- One case of chest pain occurred in a patient whom serious events of hypertension and gastroesophageal reflux was reported as serious events. This occurred in a 53 year old male who was being treated for OSAHS (250mg/day). The patient's past medical history included granulomatous lung disease, mild gastroesophageal reflux and urine albumin. The patient was taking naprosyn during the study. On day 302 the patient experienced severe chest pain without other symptoms but with blood pressure elevation of 220/130 (from 112/72). The patient was initially treated with nitrates and aspirin. The patient was admitted to the hospital with a negative cardiac work up and a tentative diagnosis of pain related to an abdominal cause that was later diagnosed as chronic duodenitis and a hiatal hernia. The patient continued on armodafinil and a proton pump inhibitor was added.
- Left sided chest pain occurred 2 days following armodafinil discontinuation in a 40 year old patient with no significant cardiac history except mitral valve prolapse. Discontinuation occurred on day 20 due to lack of efficacy. The patient was admitted to the hospital for chest pain evaluation on that day. An EKG performed on day 27 indicated that an anteroseptal myocardial infarction (unknown date) could not be ruled out, and the patient was withdrawn from the study that same day. On 28 a technetium (99mTc) single photon emission computerized tomography (SPECT) rest/stress test and no significant cardiac ischemia was observed. The results of an echocardiogram showed normal left ventricular function, a normal left atrium with trace mitral regurgitation, and trace aortic and tricuspid insufficiency. The investigator assessed the chest pain as unrelated to study drug and determined it to be probably musculoskeletal in origin.
- Dyspnea occurred in a 46 year old man being treated for OSAHS (100 mg/day) with a history of hypertension, heart murmur hyperlipidemia and obesity. This patient initially developed right neck and shoulder pain about 1 year after treatment was initiated. This was followed by dyspnea and chest pain one week later: neck and shoulder pain was still present. The chest pain was not noted categorized as a serious adverse event. The patient was hospitalized. The patient received nitroglycerin, meperidine, and promethazine with relief of pain. His blood pressure was 155/87 mmHg, cardiac enzymes were normal, and an electrocardiogram (ECG) showed no evidence of ischemia. Armodafinil was discontinued and patient had a cardiac catheterization performed with only 20% stenosis identified. It was determined by the investigator that dyspnea was not cardiac in origin. No mention was made of chest pain, but in view of the negative cardiac work-up (particularly EKG that was presumably performed during pain) there is no reason to suspect a cardiac origin for this.

Of other new serious adverse events potentially related to cardiac function was one serious case of dizziness that was also associated with the serious adverse event of new onset diabetes. The former is likely related to the new onset diabetes and not to armodafinil. Other new cases that may be related to are 4 injuries that could be potentially associated with cardiac events: i.e. as a result of presyncope or syncope. All the cases of injury (pelvic fracture, rib fracture, skin laceration and tendon rupture) were examined by this reviewer and none appeared to be associated with such cardiac events.

Two new cases of hypertension were classified as serious. No cases of hypertension in the original NDA safety database were classified as serious. Both cases were discussed above. One case was associated with angina and the other case was associated with chest pain, not thought to be cardiac, in origin. Elevated pressures in both cases may have resulted from the pain.

In conclusion, the profile of new patients presenting with potential cardiovascular related disorders do not appear different from that observed in the original NDA database. Some of the cases of chest pain or discomfort could not be attributed to cardiac cases. Other cardiac related symptoms, including the death from atherosclerosis (see prior section), could not easily be attributed to drug as it could not be separated from the background rate. Many of these cases had other cardiac risk factors.

Two new cases were characterized under the hepatobiliary disorders organ system. These included one case of cholecystitis and one of cholelithiasis. Both cases are described as follows:

- Cholecystitis occurred in a 41 year old female without a previous hepatobiliary history. The report notes that the patient was admitted approximately 9 months after starting armodafinil (250 mg/day) for right upper quadrant pain. A CT scan was negative and a hepatominodiacetic acid scan showed a very low ejection fraction. The patient underwent a laparoscopic cholecystectomy for acalculous cholecystitis. The acalculous cholecystitis was considered by the investigator to be a serious adverse event of severe intensity. The cholecystitis resolved the following day (day 281) with no residual effect, and the investigator considered the event unlikely to be related to study drug. No laboratories are included with the narration but CRF indicted no increase in transaminase or bilirubin. It does not appear that medication was discontinued. Resolution without drug discontinuation makes it unlikely to be related to drug.
- The single case of cholelithiasis was also associated with the serious adverse event of pancreatitis and occurred in 54 year old women who presented abdominal pain and increased amylase. Imaging revealed numerous gallstones. The patient underwent stone extraction. Armodafinil was continued. There is no mention of LFTs or bilirubin in the narration. The CRF indicted no changes in bilirubin or transaminase. Amylase was not reported in the CRF. This does not appear to be related to drug treatment.

None of these adverse events appear to be related to medication as resolution occurred with medication continuation or a structural cause of the problem was identified.

One new psychiatric serious adverse event, depression, was classified as serious. This occurred in a patient who was on venlafaxine hydrochloride for a past medical history of depression. On day 198 the patient was noted to experience a severe exacerbation of his depression. As a result **of this the patient's psychiatrist readjusted the patient's antidepressant treatment by switching to escitalopram oxalate.** The narration indicates that the patients psychiatrist also change armoidafinil dose, first down and latter up. **The patient subsequently developed "suicidal ideation" and armodafinil was discontinued.** Later, the patient was referred for intensive outpatient counseling and prescribed lithium in addition to modafinil." This means a total of two patients (one from open label and one form control trials) in the complete database that were reported with worsening depression and suicide ideation. This should likely be noted in the label.

No serious skin reactions were reported. This profile does not alter the impression from the original NDA database: i.e. while potential allergic skin reactions were observed none appeared consistent with serious skin reactions (erythema multiforme, Stevens Johnson Syndrome and toxic epidermal necrolysis).

#### *1.19.9.1.3 Adverse Events Associated with withdrawal.*

An additional 31 patients, over the 101 patients from the original NDA, withdrew from the studies in this safety update. This raises the total percent of withdrawals from adverse events from 8.7% to 10.3% of all patients participating in phase 3 studies.

There was no new unexpected or significant number of additional adverse events leading to withdrawal attributed to the cardiovascular system. Thus, there was one case of angina pectoris. This occurred in 64 year old woman who was treated for narcolepsy and with a complex medical history that included significant history of smoking. Patient had two episodes of angina on day 113 of treatment that was successfully treated with nitrates. The drug was discontinued because of this adverse event. This patient also had previous adverse events of tachycardia and thrombocythemia. These were also noted as reasons for discontinuation.

There were two new reported withdrawals for hypertension but these only involved very small increases over baseline.

**One patient withdrew because of "mild thinking abnormal" (# 1221514). The narration poorly described what was meant by this term. The CRF did not clarify this. Other than this case and the case of depression noted above there were no new unexpected psychiatric cases reported as reasons for drug discontinuation.**

Except for one additional rash (not serious) and a case of alopecia areata, there were no new cases of adverse skin reactions associated with patient withdrawal.

There were no further cases of reduced white cell count or pancytopenia reported as a reason for discontinuation. No additional cases of low white cell count were observed in the outlier analysis. As noted above there was one case of a discontinuation that resulted from thrombocythemia. Information derived from the CRF revealed that platelets were actually high normal at baseline (391) and increased a small additional amount to 476. These changes are likely not clinically significant.

Examinations of discontinuations for reasons of laboratory abnormalities revealed a number of interim new reports. Thus, there were new reports of discontinuations because of increases in AST, ALT and GGT. These reports were from 2 patients. One exhibited an approximately 19 fold increase in AST and 7.8 fold increase in ALT without bilirubin changes. LFT values in this case values declined to 3-4 times baseline 3 days after discontinuation. The other report noted increases in ALT, AST and GGT by approximately 4, 2, and 2 fold, respectively. Examination of the CRF for this patient does not indicate an elevation in bilirubin.

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## **1.20 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions**

See above.

## **1.21 General Methodology**

### **1.21.1 Pooling Data Across Studies to Estimate and Compare Incidence**

#### **1.21.1.1 Pooled data vs. individual study data**

#### **1.21.1.2 Combining data**

As apparent from the above data pooling was based upon the disorder studied (SWSD, OSAHS and narcolepsy). At times the complete data, across indication, was pooled for analysis.

### 1.21.1.3 Explorations for Predictive Factors

### 1.21.1.4 Explorations for dose dependency for adverse findings

### 1.21.1.5 Explorations for time dependency for adverse findings

### 1.21.1.6 Explorations for drug-demographic interactions

In general adverse events were more commonly reported in women than men. The overall rate of adverse events in women and men receiving armodafinil in control phase 3 studies was 67% and 61%, respectively. The incidence of adverse events for women and men receiving placebo was 51% and 46%, respectively. This difference was most obvious for the adverse events of palpitations, nausea, dry mouth, diarrhea and rash, but was generally of small magnitude. This can be appreciated in the table below that presents incidence of adverse events, stratified by sex, in control phase 3 trials for those which occurred at a rate of  $\geq 2\%$ .

System organ class Preferred term	Number (%) of patients			
	Men		Women	
	Armodafinil (N=402)	Placebo (N=279)	Armodafinil (N=243)	Placebo (N=166)
No. of patients with at least 1 AE	244 (61)	128 (46)	163 (67)	85 (51)
<b>Cardiac disorders</b>				
Palpitations	6 (1)	4 (1)	7 (3)	1 (<1)
<b>Gastrointestinal disorders</b>				
Nausea	17 (4)	2 (<1)	28 (12)	12 (7)
Diarrhea	14 (3)	3 (1)	12 (5)	5 (3)
Dry mouth	13 (3)	2 (<1)	11 (5)	1 (<1)
Dyspepsia	8 (2)	1 (<1)	8 (3)	1 (<1)
<b>General disorders and administration site conditions</b>				
Fatigue	8 (2)	3 (1)	4 (2)	3 (2)
<b>Nervous system disorders</b>				
Headache	65 (16)	21 (8)	44 (18)	18 (11)
Dizziness	19 (5)	5 (2)	11 (5)	3 (2)
<b>Psychiatric disorders</b>				
Insomnia	18 (4)	3 (1)	12 (5)	2 (1)
Anxiety	18 (4)	3 (1)	10 (4)	1 (<1)
Depression	8 (2)	0	4 (2)	1 (<1)
<b>Skin and subcutaneous tissue disorders</b>				
Rash	6 (1)	1 (<1)	7 (3)	0

Although the incidence of adverse events in the non-white patients exceeded that in the white patients, there was a greater incidence of adverse events with drug when compared to placebo in the white population versus the non-white population. The overall rate of adverse events in nonwhite and white patients receiving armodafinil in control phase 3 studies was 66% and 62%, respectively. The incidence of adverse events for nonwhite and white patients receiving placebo

was 66% and 55%, respectively. When individual common adverse events were compared some adverse events were more common when compared to placebo in the white population (e.g. insomnia and anxiety) and others were more common in the non-white population (palpitations and dry mouth). The differences were generally small in magnitude.

The adverse event profile for common ( $\geq 2\%$ ) adverse events in various age groups are presented in the table below. Numbers of patients (and percent) are presented in this table. While absolute incidence of total adverse events were similar across age groups (61 to 67%) the absolute increase over placebo may have been greater in the young adult age (18-29%) group as compared to older patients (see table below). Headache, and perhaps nausea, appeared to exhibit their greatest preponderance in the armodafinil over the placebo group in the young.

System organ class Preferred term	Number (%) of patients							
	18-29 years		30-40 years		41-55 years		>55 years	
	Armodafinil (N=86)	Placebo (N=48)	Armodafinil (N=130)	Placebo (N=83)	Armodafinil (N=293)	Placebo (N=208)	Armodafinil (N=137)	Placebo (N=106)
No. of patients with at least 1 AE	57 (67)	21 (44)	83 (64)	42 (51)	183 (62)	93 (45)	84 (61)	57 (54)
<b>Cardiac disorders</b>								
Palpitations	1 (1)	1 (2)	3 (2)	0	5 (2)	2 (<1)	4 (3)	2 (2)
<b>Gastrointestinal disorders</b>								
Nausea	11 (13)	1 (2)	8 (6)	5 (6)	19 (6)	7 (3)	7 (5)	1 (<1)
Diarrhea	2 (2)	1 (2)	2 (2)	3 (4)	15 (5)	2 (<1)	7 (5)	2 (2)
Dry mouth	3 (4)	0	2 (2)	1 (1)	15 (5)	1 (<1)	4 (3)	1 (<1)
Dyspepsia	1 (1)	0	6 (5)	1 (1)	4 (1)	1 (<1)	5 (4)	0
<b>General disorders/ administration site conditions</b>								
Fatigue	0	0	0	0	9 (3)	3 (1)	3 (2)	3 (3)
<b>Nervous system disorders</b>								
Headache	21 (25)	5 (10)	21 (16)	10 (12)	47 (16)	14 (7)	20 (15)	10 (9)
Dizziness	5 (6)	1 (2)	6 (5)	4 (5)	13 (4)	2 (<1)	6 (4)	1 (<1)
<b>Psychiatric disorders</b>								
Insomnia	4 (5)	0	5 (4)	2 (2)	13 (4)	2 (<1)	8 (6)	1 (<1)
Anxiety	5 (6)	0	3 (2)	0	14 (5)	3 (1)	6 (4)	1 (<1)
Depression	3 (4)	0	3 (2)	1 (1)	4 (1)	0	2 (1)	0
<b>Skin and subcutaneous tissue disorders</b>								
Rash	2 (2)	0	1 (<1)	0	8 (3)	0	2 (1)	1 (<1)

In summary, while there were some demographic interactions these were scattered and small in magnitude.

#### 1.21.1.7 Explorations for drug-disease interactions

##### 1.21.1.7.1 Hypertension in patients with OSAHS

The Sponsor performed an analysis of differences in blood pressure alterations following treatment in OSAHS patients participating in phase 3 trials who present with/and without a history of hypertension. These data are presented in the table below in terms of number (and percent) of patients. This was important because of the proclivity of this particular group for developing hypertension. Mean changes in blood pressure were not significantly different between both groups. An outlier analysis, presented in the table below demonstrated a higher incidence of elevated pressures in patients with a history of hypertension. This result is

expected. Comparison within the hypertensive and non-hypertensive groups reveals little or no difference except a mild unexpected lower incidence in increased systolic pressures in the hypertensive armodafinil as compared to the placebo group. The reason for this is unclear. Perhaps it simply represents a sampling error.

Variable, criteria	Number (%) of patients			
	History of hypertension		No history of hypertension	
	Armodafinil (N=159)	Placebo (N=168)	Armodafinil (N=232)	Placebo (N=152)
Systolic BP (mm Hg), ≥140 and increase of ≥10%	59 (37)	50 (46)	66 (28)	39 (26)
Diastolic BP (mm Hg), ≥90 and increase of ≥10%	44 (28)	31 (29)	46 (20)	37 (24)

#### 1.21.1.7.2 CPAP usage in patients with OSAHS

CPAP usage was monitored in phase 3 studies for patients with OSAHS. CPAP usage not only impacts on interpretation of the efficacy results (any difference between experimental groups may obfuscate interpretation) but also on safety. The table presenting these data are presented below. Values are presented in terms of hours of evening CPAP use. Thus, symptomatic treatment of daytime sleepiness may reduce CPAP usage and expose patients to the ill effects long term effects of episodic nocturnal periods hypoxia (e.g. hypertension and coronary artery disease). CPAP usage in control clinical trials is presented in the table below. There was an approximately mean 12 minute reduction in CPAP usage in armodafinil group over placebo. This only represents 3% of full mean time that CPAP is used over the evening and is likely not clinically significant. This effect would bias against the detection of a treatment effect.

Time point Statistic	Armodafinil			Placebo (N=260)
	250 mg/day (N=131)	150 mg/day (N=260)	Combined (N=391)	
<b>Baseline</b>				
n	131	258	389	255
Mean	7.1	6.8	6.9	6.9
SD	1.01	1.23	1.16	0.99
Median	7.1	6.8	7.0	6.9
Min, max	3.4, 9.5	3.3, 10.6	3.3, 10.6	3.7, 9.2
<b>Postbaseline</b>				
n	125	246	371	252
Mean	6.7	6.6	6.6	6.8
SD	1.07	1.12	1.11	1.04
Median	6.7	6.5	6.6	6.8
Min, max	2.6, 8.8	3.5, 10.4	2.6, 10.4	3.7, 9.3
<b>Change from baseline</b>				
n	125	246	371	252
Mean	-0.4	-0.3	-0.3	-0.1
SD	0.65	0.66	0.66	0.60
Median	-0.4	-0.3	-0.3	-0.1
Min, max	-2.5, 2.3	-2.5, 2.6	-2.5, 2.6	-2.2, 2.0

Usage in all phase 3 OSAHS studies over time is presented in the table below. Values are in terms of hours of evening CPAP use. There is a small, but perhaps not insubstantial tendency for reduced use over time.

Statistic	OSAHS (N=716)					
	Baseline	Month 1	Month 2	Month 3	Month 4	Month 6 or after
Visit						
n	579	542	480	427	192	60
Mean (SD)	6.8 (1.13)	6.6 (1.17)	6.5 (1.26)	6.4 (1.23)	6.3 (1.41)	6.5 (1.10)
Change from baseline						
n	--	537	471	420	189	60
Mean (SD)	--	-0.2 (0.71)	-0.4 (0.92)	-0.5 (0.88)	-0.6 (1.10)	-0.7 (0.71)

These data underscores the need to stress the continued use of CPAP in OSAHS patients using armodafinil.

#### 1.21.1.8 Explorations for drug-drug interactions

The Sponsor argues that the existence of multiple pathways of metabolism and the fact that non-CYP pathways are the most rapid route of metabolism **suggests a “low probability of substantive effects on the overall pharmacokinetic profile of armodafinil due to CYP inhibition by concomitant medications.”** *In vitro* studies suggest a mild induction of CYP1A2 and possibly CYP3A and inhibition of CYP2C19. Studies in patients revealed the potential for this drug to induce CYP1A2, CYP3A4 and inhibit CYP219.

#### 1.21.2 Causality Determination

A number of common adverse events appeared to be directly related to drug use. The determination of causality was in part dependent on the temporality of the occurrence of adverse event, resolution with drug discontinuation, differences in rates between placebo and drug treated groups and dose dependency. These included, but are probably not limited to, psychiatric events such as anxiety, insomnia and potentially depression. Also included are nausea, diarrhea, headache, dizziness, cardiac palpitations/flutter and rash. Rash is of specific concern because the recent case of Stevens Johnson identified in the small trial database for the Provigil ADHD studies. As noted a small number of such cases were seen in the Provigil postmarketing reports as well. The skin reactions for Nuvigil, including two potential cases of angioedema, appeared allergic in nature and potentially drug related. As to whether Provigil, and therefore Nuvigil, is associated with serious skin reactions is still under investigation and require additional information from the Sponsor. Elevations in GGT, reductions in uric acid and elevations in alkaline phosphatase also appeared to be drug related. Transaminase elevations were observed, but could not easily be associated with drug treatment the rates of such events were similar between drug and placebo groups in the control database. Elevation in bilirubin was not observed in these cases. Two isolated cases of bilirubin elevation was observed but occurred in the absence of transaminase increase, but could not be related to drug because of preexisting

elevations, complex medical history and transient course. Small elevations in blood pressure and heart rate were also likely related to drug. Of specific concern was the large number of adverse events associated with cardiac ischemia, which included the only death observed in the phase 3 database. Careful examination of this issue could not identify significant differences of such events between placebo and drug treated patients in control trials. The incidence may have been associated with the high background incidence in the study population. One case of mild pancytopenia was observed that reversed upon drug withdrawal, it is difficult to determine if this is casually related to the drug as there was a small trend toward lowering of the cellular indices, nonetheless this information should be included in the label.

## **ADDITIONAL CLINICAL ISSUES**

### **1.22 Dosing Regimen and Administration**

Presently the Sponsor is recommending treatment at two doses, 150 and 250 mg/day, for two of the disorders, OSAHS and Narcolepsy. Recommended dose for SWSD is 150 mg/day. There is a suggestion, but no definitive proof, that the higher doses may produce a slightly greater therapeutic effect. Some of the common adverse events however appear to be dose related including headache, rash, depression, dry mouth, insomnia, nausea, anorexia/decreased appetite. For this reason this reviewer would imagine that the lowest dose 150 mg/day would be the most beneficial to most patients. Lower doses were not exhaustively studied and may also potentially be useful.

### **1.23 Drug-Drug Interactions**

Please see PK review.

### **1.24 Special Populations**

There were no specific studies in pregnant women. Armodafinil has been classified as pregnancy category C.

For geriatric population and those with renal and hepatic impairment, the reader is referred to the PK review.

### **1.25 Pediatrics**

Provigil in an ADHD pediatric population, at higher exposures than those observed for adult Provigil treatment of sleep disorders, suggest a potentially high risk for serious skin reactions. These studies also suggested a higher risk for psychiatric complications. Both, of these may be

related to the higher exposures. ~~\_\_\_\_\_~~

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Before pediatric labeling advice can be devised, the division is awaiting clarification of the risk for Stevens Johnson syndrome.

~~\_\_\_\_\_~~, the division should request narcolepsy studies. OSAHS studies I pediatrics should be waived as most pediatric patients with this condition can be treated with surgical management.

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### **1.26 Advisory Committee Meeting**

Does not apply

### **1.27 Literature Review**

There is no significant clinical literature the agent.

### **1.28 Postmarketing Risk Management Plan**

None are priestly recommended. This may change once the issue of serious skin reactions is clarified.

### **1.29 Other Relevant Materials**

Does not apply.

## **OVERALL ASSESSMENT**

### **1.30 Conclusions**

The present study has demonstrated that Nuvigil is effective in the recommended doses for the indications of SWSD, narcolepsy and OSAHS. Adverse events are similar to the racemate, Provigil. The worrisome adverse events of the serious skin reactions recently observed for Provigil require further evaluation before the final labeling can be recommended. The labeling will likely require a warning for such skin reactions. To better examine this issue, this reviewer would like to examine all previous Provigil narrations of skin reactions to determine if there were any that may have potentially represented a serious skin reactions but were not labeled as such. In the present Nuvigil database, no such reactions were apparent. Additional clarification will be requested on a recent Provigil post marketing report that indicates a potential multiorgan sensitivity reaction.

### **1.31 Recommendation on Regulatory Action**

Approvable, pending requested additional information.

### **1.32 Recommendation on Postmarketing Actions**

None are recommended at present. This may change pending analysis serious skin reactions.

#### **1.32.1 Risk Management Activity**

None are recommended at present. This may change pending analysis serious skin reactions.

#### **1.32.2 Required Phase 4 Commitments**

The Sponsor will be requested to perform studies in narcolepsy in children. Other disciplines have recommended additional studies.

#### **1.32.3 Other Phase 4 Requests**

No clinical requests are presently recommended.

### **1.33 Labeling Review**

Not the Following review includes the efforts of both this reviewer and all other clinical and non-clinical reviewing staff.

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38 Page(s) Withheld

       Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

       Draft Labeling (b5)

       Deliberative Process (b5)

Clinical Review  
Norman Hershkowitz, MD, PhD  
21,875 (000)  
Nuvigil (armodafinil)

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b(5)

b(4) b(5)

### 1.35 Comments to Applicant

- The division requires a full examination of serious skin reactions. This includes:

- Examinations being carried out by the psychiatry division at the FDA.
- Request the submission of all narrations (serious and discontinuations) that dealt with skin reactions from all clinical trials dating back to the original NDA submission.
- A recent Provigil postmarketing report was of some concern (Manufacturer # US016978). Thus, a death was observed in a 31 year old male that appeared to result from a multiorgan hypersensitivity reaction (pathologically proven hypersensitivity). The division would like more information to help determine causality in this case. This information should include, but not limited, information on when Provigil was discontinued and confirmation that the patient was on **Trileptal for "many years."** The Sponsor should examine their complete database (clinical trials and postmarketing) to determine if there are any similar cases. The examination should be exhaustive and will require a careful examination of a number of clinical signs and symptoms as this disorder may effect a number of organ systems.
- The integrated phase 3 urinalysis results that were provided late have not yet been reviewed.

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## **APPENDICES**

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## **1.36 Appendix A: Review of Individual Study Reports**

### **1.36.1 Studies in OSAHS (3021 and 3025)**

#### **1.36.1.1 Design**

Both studies were multi-center, 12-Week, Randomized, Double-Blind, Placebo-Controlled, and Parallel-Group Studies to evaluate the efficacy and short term safety of CEP-10953 as treatment for adults with residual excessive sleepiness associated with Obstructive Sleep Apnea/Hypopnea Syndrome (OSAHS). Study 3025 compared Nuvigil at a dose of 150 mg/day with placebo whereas study 3021 compared Nuvigil at a dose of 150 mg/day and 250 mg/day to placebo.

Two studies were performed in OSAHS these studies are similar in nature in will therefore be described under one heading. Unless otherwise specified it should be assumed that the elements described are shared both studies.

#### **1.36.1.2 Schedule**

The schedule of assessments for study 3025 is presented in the table below. As both OSAHS studies had identical assessment schedule this tabular presentation also applies to study 3021.

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Procedures and assessments	Screening		Baseline	Double-blind treatment period			
	Visit 1A	Visit 1B	Visit 2	Telephone contact (2 weeks)	Visit 3 Week 4	Visit 4 Week 8	Visit 5 Week 12*
Informed consent	X						
Inclusion and exclusion criteria	X		X				
Medical and psychiatric history	X						
Prior medication history	X						
Full physical examination	X <sup>b</sup>		X <sup>a</sup>				X
Clinical laboratory tests <sup>d</sup> (serum chemistry and hematology)	X		X		X	X	X
Urinalysis and urine drug screen (UDS)	X						X
Vital signs measurements <sup>e</sup>	X	X	X		X	X	X
Clinical Global Impression of Severity of Illness (CGI-S)	X						
Electrocardiography (12-lead)	X		X		X	X	X
Dispense/review/collect diary	X	X	X	X	X	X	X
Review nCPAP usage		X	X		X	X	X
Nocturnal polysomnography (PSG)		X					X
Adverse event inquiry		X	X	X	X	X	X
Concomitant medication inquiry		X	X	X	X	X	X
Cognitive Drug Research (CDR) system training		X					
Clinical Global Impression of Change (CGI-C)					X	X	X
Epworth Sleepiness Scale (ESS)	X				X	X	X
Brief Fatigue Inventory (BFI)			X		X	X	X
Maintenance of Wakefulness Test (MWT)			X		X	X	X
CDR system testing <sup>f</sup>			X		X	X	X
Blood samples for drug assay <sup>g</sup>			X		X	X	X
Administer/dispense/collect study drug			X		X	X	X

\* Endpoint or early termination.  
<sup>a</sup> Included body weight and height at the initial screening visit; only body weight at visit 5 (week 12 or early termination).  
<sup>b</sup> Brief physical examination, if more than 6 weeks from first screening visit.  
<sup>c</sup> Included serum chemistry and hematology. Beta human chorionic gonadotropin (βHCG) for all women was performed at all visits where clinical laboratory tests were designated.  
<sup>d</sup> Included blood pressure and pulse, and oral temperature at screening only.  
<sup>e</sup> Administered between MWT naps.  
<sup>f</sup> Blood samples (10 mL) for armodafinil trough plasma concentrations were collected at the baseline visit and before study drug administration at the week-4, week-8, and week-12 visits.  
 NOTE: There were to be at least 14 days between the preliminary screening visit (the first time a patient came to the clinic) and the baseline visit in order to assess nCPAP usage and to collect at least 7 days of diary data. A washout period from medications excluded by the protocol occurred before assessments were made. Nocturnal PSG started (ie, lights out) within 30 minutes before or after the patient's habitual bedtime (as determined by sleep history), but no earlier than 2130. Visits 1B, 2, 3, and 4 were 1-night visits; visit 5 was a 2-night visit.  
 nCPAP=nasal positive continuous airway pressure.

A washout period from medications excluded by the protocol occurred before any screening assessments were made. A Patient would first be seen at a preliminary screening session (1A) where initial screening procedures would be performed. If inclusion criteria was meet the patients underwent a 2-week nCPAP therapy assessment period where nCPAP therapy usage was evaluated using the nCPAP device provided ( \_\_\_\_\_ System) that monitored home use. The patient would then return for a second screening visit (1B) for additional assessments, including the ESS and nocturnal PSG, which recorded the apnea-hypopnea index (AHI) for the assessment of nCPAP effectiveness. Nocturnal PSG, which was conducted after other procedures/assessments were performed, started at lights out, within 30 minutes before or after the patient's habitual bedtime (as determined by sleep history), but no earlier than 2130.

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Patients who met the inclusion/exclusion and screening criteria returned to the clinic for the evening (visit 2), with baseline assessments commencing the next morning. Baseline outcome assessments included the MWT administered 6 times (naps at 0900, 1100, 1300, 1500, 1700, and 1900), CDR system testing administered between MWT naps, and the BFI assessed prior to the first MWT nap, with the patient discharged the following morning.

For each remaining clinic visit, patients arrived at the clinic in the evening, stayed overnight, and were administered study drug at 0700 ( $\pm 15$  minutes) the next day, about 30 minutes before breakfast. The MWT was administered 6 times (naps at 0900, 1100, 1300, 1500, 1700, and 1900) at weeks 4, 8, and 12. The CGI-C, the ESS, and the BFI were administered before the first MWT/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 daily diary entries on the effect on daytime sleepiness and nighttime sleep were reviewed at weeks 4, 8, and 12. For the purposes of assessing effect on nighttime sleep, the week-12 visit also included a nocturnal PSG conducted overnight, with an identical starting time as performed during baseline.

If withdrawal occurred after administration of the study drug but before all evaluations were completed, efforts were made to complete the evaluations and report the observations up to the time of withdrawal as thoroughly as possible. A complete final evaluation was performed at the **time of the patient's withdrawal.**

#### 1.36.1.3 Drug dose and Concomitant Medications

Patients were instructed in both studies to take drug (or placebo) once daily 30 minutes before breakfast about 30 minutes prior to breakfast. Placebo was compared to a dose of 150 mg/day of Nuvigil in study 3025 patients. Placebo was compared to a dose of 150 mg/day and 250 mg/day of Nuvigil in study 3021. In both studies the dose was titrated over several days with the patients started on 50 mg/day for the first day and subsequent increases in dose by 50 mg each day till the targeted maintenance dose was achieved. The dose selection was based upon PK studies that **indicated that "doses between 100 and 250 mg were shown to be well tolerated."**

**Any medication that would "make the patients sleepy" was not to be used during the study or within 7 days prior to initiating the study.** These were specifically listed and included melatonin, sodium oxybate, lithium, St. John's Wort, methylphenidate, amphetamines, pemoline, antipsychotic agents, benzodiazepines, zolpidem, monoamine oxidase (MAO) inhibitors, anticoagulants (e.g., warfarin sodium), anticonvulsants (unless used for other than seizure disorders), and barbiturates.

#### 1.36.1.4 Number of Patient Planned for Study

The Sponsor planned to enroll 240 patients (1:1; 150 mg/day: placebo) in study 3025 and 360 patients for study 3021 (1:1:1; 150 mg/day: 250 mg/day: placebo). Patient randomization was stratified by country.

#### 1.36.1.5 Endpoints

Primary and secondary efficacy endpoints are described in the integrates summary of efficacy. Along with routine adverse event monitoring (see schedule above), patients will be evaluated for effects on nighttime sleep by nighttime diaries and week 12 PSG (see integrated summary of safety). Blood samples were also collected for trough levels at weeks 4, 8 and 12 (see schedule above).

#### 1.36.1.6 Principal Inclusion Criteria

- The patient is a man or woman of 18 to 65 years of age (inclusive).
- The patient has a complaint of residual excessive sleepiness despite nCPAP therapy being effective and being a regular user of nCPAP therapy.
- The patient has a current diagnosis of OSAHS according to ICSD criteria.
- The patient must met the following nCPAP therapy requirements:
  - Adequate education and intervention efforts to encourage nCPAP therapy use were documented.
  - **A patient's nCPAP therapy regimen was stable for at least 4 weeks.**
  - nCPAP therapy was shown to be effective, with effectiveness defined as having an AHI of 10 or less during nocturnal PSG, and, in the opinion of the investigator, nCPAP was an effective therapy.
  - Evidence of regular nCPAP usage was shown during a 2-week evaluation period (i.e., nCPAP usage for at least 4 hours per night on at least 70% of the nights).
- The patient was in good health as determined by a medical and psychiatric history, physical examination, ECG, and serum chemistry and hematology.
- Women of child-bearing potential must be using a medically accepted method of birth control (hormonal birth control must be accompanied by a barrier method) and agree to continue use of this method for the duration of the study.
- The patient has a CGI-S rating of 4 or more and an ESS score of 10 or more.
- The patient did not have any medical or psychiatric disorders that could account for the excessive daytime sleepiness.
- The patient was able to complete self-rating scales and computer-based testing.

#### 1.36.1.7 Principal Exclusion Criteria

- The patient had any clinically significant, uncontrolled medical or psychiatric conditions (treated or untreated).
- The patient had a probable diagnosis of a current sleep disorder other than OSAHS.
- The patient consumed caffeine, including coffee, tea and/or other caffeine-containing beverages or food, averaging more than 600 mg of caffeine per day.
- The patient used any prescription drugs disallowed by the protocol or had clinically significant use of over-the-counter (OTC) drugs within 7 days before the second screening visit.
- The patient had a history of alcohol, narcotic, or any other drug abuse as defined by the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association, 4th Edition (DSM-IV) (American Psychiatric Association 1994). The patient had a positive urine drug screen (UDS).
- The patient had a known clinically significant drug sensitivity to stimulants or modafinil.
- The patient had a positive urine drug screen (UDS).
- The patient had a clinically significant deviation from normal in the physical examination.
- The patient was a pregnant or lactating woman. (Any woman becoming pregnant during the study was to be withdrawn from the study.)
- The patient had used an investigational drug within 1 month before the initial screening visit.
- The patient had any disorder that could interfere with drug absorption, distribution, metabolism, or excretion (including gastrointestinal surgery).

#### 1.36.1.8 Amendments

There was one identical amendment to both protocols (3/3/04) that was issued prior to any patient enrolment for study 3025 and 3 weeks following the first patient enrolment in study 3021. The amendment included a number of changes in study design but as the changes preceded any patient enrolment in study 3025 and were initiated soon after enrolment was started for 3021 these changes are incorporated in to the above protocol description the amendment is not discussed in detail.

#### 1.36.1.9 Disposition

##### *1.36.1.9.1 Protocol 3025*

The table below presents the patients disposition in study 3025. As can be seen of the 466 patients screened 263 were randomized. Of the patients randomized 236 received at least one dose of drug and had at least one post-baseline co-primary efficacy analysis (the “full analysis set”). A slightly greater number of patients withdrew from the Nuvigil treatment group as compared to placebo group. This was accounted for by a slightly greater number of patients withdrawing consent, with protocol violations and who were non-compliant. In absolute numbers, however, these differences are not great.

Patient disposition	Number (%) of patients		
	Armodafinil 150 mg (N=131)	Placebo (N=132)	Total (N=263)
Screened	—	—	466
Randomized	131 (100)	132 (100)	263 (100)
Randomized, not treated	2 (2)	2 (2)	4 (2)
Safety analysis set	129 (98)	130 (98)	259 (98)
Full analysis set	116 (89)	120 (91)	236 (90)
Completed	111 (85)	118 (89)	229 (87)
Discontinued	20 (15)	14 (11)	34 (13)
Adverse event	5 (4)	6 (5)	11 (4)
Lack of efficacy	1 (<1)	0	1 (<1)
Consent withdrawn	5 (4)	3 (2)	8 (3)
Protocol violation	2 (2) <sup>a</sup>	3 (2) <sup>a</sup>	5 (2)
Lost to follow-up	2 (2)	2 (2)	4 (2)
Noncompliance to study procedures	3 (2)	0	3 (1)
Other <sup>b</sup>	2 (2)	0	2 (<1)

SOURCE: Summary 15.1, Listing 2 and Listing 3.

<sup>a</sup> Includes patients 0581815 and 2481969 in the armodafinil group, and patients 8286813, 2361853, and 6047830 in the placebo group.

<sup>b</sup> Two patients were discontinued for reasons of “other.” 1 patient (patient 1601875) was discontinued due to the patient being unable to comply with overnight visits due to work schedule, and 1 patient (patient 2261961) was discontinued because the study ended prior to the patient completing the final visit.

NOTE: Patient 6047830 was not reported as a protocol violation (see section 10.3).

The Sponsor defined three sets of divergence from the protocol, which will be used all protocols described in this Appendix:

- A **protocol deviation** was defined as nonadherence to study procedures or schedules as specified by the protocol that did not involve inclusion criteria, exclusion criteria, or primary endpoint criteria. The significance of the deviation was based on the frequency of the deviation and/or the impact on the study objectives.
- A **protocol violation** was defined as nonadherence by the patient, investigator, or sponsor to inclusion criteria, exclusion criteria, primary endpoint criteria, and/or GCP guidelines. A violation occurred when the patient enrolled and/or continued in the study without prior approval from the sponsor. In this situation, the medical monitor or designee was notified immediately.

- A **protocol exception** was granted to an individual patient if that patient did not meet specific criteria for entering or continuing in the study as defined by the protocol, but in the opinion of the investigator and sponsor, the patient would possibly benefit from participation and entry of the patient into the study would not compromise the objective of the study. In this situation, it was required that the medical monitor or designee grant approval before the patient entered the study.

In a total 14 (6 in drug and 8 in placebo) patients with known minor infractions of protocol or inclusion/exclusion criteria were allowed to continue in the study and included in the full set analysis and described as a protocol exception. These patients included patients who did not fully meet CPAP requirements, age range, ESS and patients with positive drug urine screen when there was a medical reason for this abnormality. It is unlikely that these would affect the study outcome.

Twenty-six patients (12 in drug and 14 in placebo) were in violation of the protocol. A summary of the reasons for violation are presented in the table below. A vast majority of these includes issues related to inclusion/exclusion criteria. Four of the patients (2 drug and 2 placebo) with protocol violations were withdrawn from the study (patients 0581815, 2361853, 2481969 and 8286813). On the whole it is unlikely that these will affect the results of the study but as there are a large number of such events.

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<b>Treatment</b>	<b>Patient number</b>	<b>Event description</b>	<b>Outcome/Action</b>
<b>Armodafinil, 150 mg</b>			
	0581815	Inclusion criteria: missed ESS	Rejected/withdrawn
	0821868	GCP guidelines: study drug sent unsecured by mail to patient Primary endpoint criteria: study drug not given at visit 5; MWT sleep latency data not obtained at endpoint	Enrolled/continued
	1601952	Inclusion criteria: screening ESS performed prior to washout of prohibited medication	Enrolled/continued
	2181896	Inclusion criteria: patient randomized but did not meet nCPAP therapy requirements	See footnote <sup>a</sup>
	2301841	Inclusion criteria: patient randomized but visit-1B PSG was unreadable	Enrolled/continued
	2301843	Inclusion criteria: patient randomized but visit-1B PSG was unreadable	Enrolled/continued
	2481969	Exclusion criteria: patient enrolled in another clinical trial	Rejected/withdrawn
	2521909	Exclusion criteria: patient identified as a shift worker following visit 4 Primary endpoint criteria: visit 3/CGI-C not performed	Enrolled/continued
	2521964	Inclusion criteria: nCPAP usage less than 70%	Enrolled/continued
	6067829	Inclusion criteria: patient had less than 70% of nights 4-hour nCPAP usage	Enrolled/continued
	8326819	Inclusion criteria: nCPAP usage before randomization approximately 50%	Enrolled/continued
	2161804	Inclusion criteria: sleep latency greater than 10 minutes	Enrolled/continued
<b>Placebo</b>			
	2161803	Inclusion criteria: sleep latency 20 minutes Inclusion criteria: BI-PAP usage	Enrolled/continued
	0821838	Primary endpoint criteria: visit 2 MWT not performed	Enrolled/continued
	0821867	Inclusion criteria: baseline CGI-S performed prior to prohibited medication washout Inclusion criteria: baseline ESS performed prior to prohibited medication washout Primary endpoint criteria: visit 3 study drug given at 0900 hours on 18 July 2004 Primary endpoint criteria: visit 4 study drug given at 0800 hours on 15 August 2004	Enrolled/continued
	0821884	Primary endpoint criteria: study drug not given at visit 5	Enrolled/continued
	2121993	Inclusion criteria: CGI-S completed prior to washout Inclusion criteria: ESS completed prior to washout Inclusion criteria: patient signed informed consent after ESS administered	Enrolled/continued
	2181816	Inclusion criteria: screening ESS not performed	Enrolled/continued

Footnotes and abbreviations appear at the end of the table.

(continued)

Treatment		
Patient number	Event description	Outcome/ action
<b>Placebo</b>		
2361853	Inclusion criteria: patient should not have been randomized <sup>b</sup>	Rejected/withdrawn
6007807	Exclusion criteria: patient enrolled in another clinical trial	Enrolled/continued
6087821	Exclusion criteria: patient randomized despite having periodic limb movement	Enrolled/continued
6087832	Exclusion criteria: patient randomized despite having periodic limb movement	Enrolled/continued
8286813	Inclusion criteria: AHI greater than 10	Rejected/withdrawn
8326807	Inclusion criteria: nCPAP usage compliance before randomization was 67%.	Enrolled/continued
8326811	Inclusion criteria: nCPAP usage before randomization was approximately 60%.	Enrolled/continued
8326818	Inclusion criteria: nCPAP usage before randomization was 50%.	Enrolled/continued

Source: Listing 40.

<sup>a</sup> Patient 2181896 is reported in section 16.2, Listing 40 as being withdrawn from the study; however, this patient completed the study with MWT data collected through visit 5 (week 12).

<sup>b</sup> Patient 2361853 did not meet nCPAP therapy requirements for study entry (see Listing 4).

NOTE: ESS=Epworth Sleepiness Scale; PSG=polysomnography; CGI-S=Clinical Global Impression of Severity; nCPAP=nasal continuous positive airway pressure; AHI=apnea-hypopnea index; MWT=Maintenance of Wakefulness Test; BI-PAP=bilevel (biphasic) positive airway pressure.

### 1.36.1.9.2 Protocol 3021

The Table below presents the disposition for patients in study 3021. Of the 638 patients screened 395 were randomized. Of these a total of 365 patients received at least one dose of treatment and had at least one post-dose co-primary **endpoint valuation (the "full analysis set")**. The most common reason for withdrawal was that due to adverse events with a greater percent occurring in the drug treated groups. The second most common cause was the withdrawal of consent that occurred at similar rates in both the drug and placebo groups.

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Patient disposition	Number (%) of patients				Total (N=395)
	Armodafinil 250 mg/day (N=131)	Armodafinil 150 mg/day (N=133)	Armodafinil combined (N=264)	Placebo (N=131)	
Screened	—	—	—	—	638
Randomized	131 (100)	133 (100)	264 (100)	131 (100)	395 (100)
Randomized, not treated	0	2 (2)	2 (<1)	1 (<1)	3 (<1)
Safety analysis set	131 (100)	131 (98)	262 (>99)	130 (>99)	392 (>99)
Full analysis set	121 (92)	120 (90)	241 (91)	124 (95)	365 (92)
Completed	110 (84)	114 (86)	224 (85)	120 (92)	344 (87)
Discontinued	21 (16)	19 (14)	40 (15)	11 (8)	51 (13)
Adverse event	15 (11)	10 (8)	25 (9)	5 (4)	30 (8)
Lack of efficacy	0	0	0	0	0
Consent withdrawn	1 (<1)	5 (4)	6 (2)	3 (2)	9 (2)
Protocol violation <sup>a</sup>	2 (2)	2 (2)	4 (2)	0	4 (1)
Lost to follow-up	0	1 (<1)	1 (<1)	1 (<1)	2 (<1)
Noncompliance to study drug	1 (<1)	0	1 (<1)	0	1 (<1)
Noncompliance to study procedures	1 (<1)	0	1 (<1)	1 (<1)	2 (<1)
Other <sup>b</sup>	1 (<1)	1 (<1)	2 (<1)	1 (<1)	3 (<1)

A total of 19 (11 in drug and 8 in placebo) patients with known minor infractions of protocol or inclusion/exclusion criteria were allowed to continue in the study and included in the full set analysis as an exception. These predominately included patients who failed to meet inclusion and exclusion criteria. A large number of these (n=6) were exceptions for a positive urine drug screen for medications that were prescribed for a medical condition. Another large group of exceptions were granted to patients for not fulfilling CPAP criteria (n=5).

Thirteen patients were in violation to protocol. These are presented in the table below. Violations were seen for a number of reasons in all groups. Most commonly, the patient did not adequately meet inclusion exclusion criteria. A number of patients were in violation for reasons of GCO guidelines involving issues of informed consent. These represent a small number of the total patients studied and will likely not affect the final results of the study. Two of these patients were withdrawn from the study; one of these had a history of insomnia (1681549) and the other suffered (0981403) from an “uncontrolled medical condition” (“severe increase in blood pressure”).

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Patient	Study Visit	Event description	Outcome/Action
<b>250 mg/day armodafinil</b>			
0121683	1A	Inclusion criteria: UDS incomplete	Enrolled/continued
1021718	1B	Inclusion criteria: Patient randomized with 11 days of nCPAP use	Enrolled/continued
1041669	4	Primary endpoint criteria: CGI-C not done at visit 4	Enrolled/continued
1681549	1B	Exclusion criteria: Patient enrolled with current insomnia diagnosis	Rejected/terminated
3003418	1B	Inclusion criteria: No double barrier method of birth control was used in addition to medroxyprogesterone acetate injection	Enrolled/continued
<b>150 mg/day armodafinil</b>			
0261457	5	GCP guidelines: Revised informed consent form not signed prior to the patient's completing the study	Enrolled/continued
0981403	—	Inclusion/exclusion criteria: Patient randomized but did not meet inclusion and exclusion criteria	Rejected/terminated
1021722	1B	Inclusion criteria: Patient had 9 days of nCPAP usage prior to randomization	Enrolled/continued
1081436	3	GCP guidelines: Revised informed consent form not signed at correct visit	Enrolled/continued
1081506	3	GCP guidelines: Patient did not sign revised informed consent form at the next visit	Enrolled/continued
<b>Placebo</b>			
1041708	1A	Exclusion criteria: Patient consumes 8-10 cups of coffee per day	Enrolled/continued
2021741	1A	GCP guidelines: Informed consent form was not given to patient	Enrolled/continued
3163440	1B	Inclusion criteria: Patient enrolled with nCPAP compliance <70%	Enrolled/continued

### 1.36.2 Study in Narcolepsy (3020)

#### 1.36.2.1 Design

This was a 12-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of armodafinil at 150 and 250 mg/day as treatment for adults with excessive sleepiness associated with narcolepsy. Patients were randomized (1:1:1) to receive 150 or 250 mg/day of armodafinil or placebo once daily for a 12-week double-blind treatment period.

#### 1.36.2.2 Schedule

The schedule for the present study is presented in the table below.

	Screening		Baseline	Double-blind Treatment Period			
	Visit 1A	Visit 1B	Visit 2	Telephone contact (2 weeks)	Visit 3 Week 4	Visit 4 Week 8	Visit 5 Week 12 <sup>a</sup>
<b>Procedures and assessments</b>							
Informed consent	X						
Inclusion and exclusion criteria	X		X				
Medical and psychiatric history	X						
Prior medication history	X						
Full physical examination <sup>b</sup>	X		X <sup>c</sup>				X
Clinical laboratory tests <sup>d</sup> (serum chemistry and hematology)	X		X		X	X	X
Urinalysis and urine drug screen (UDS) <sup>e</sup>	X						X
Vital signs measurements <sup>f</sup>	X	X	X		X	X	X
Clinical Global Impression of Severity of Illness (CGI-S)	X						
Electrocardiography (12-lead)	X		X		X	X	X
Dispense/review/collect diary <sup>g</sup>	X	X	X	X	X	X	X
Multiple Sleep Latency Test (MSLT)		X					
Nocturnal polysomnography (PSG)			X				X
Adverse event inquiry		X	X	X	X	X	X
Concomitant medication inquiry		X	X	X	X	X	X
Cognitive Drug Research (CDR) system training		X					
Clinical Global Impression of Change (CGI-C)					X	X	X
Epworth Sleepiness Scale (ESS)		X			X	X	X
Brief Fatigue Inventory (BFI)			X		X	X	X
Maintenance of Wakefulness Test (MWT)			X		X	X	X
CDR system testing <sup>h</sup>			X		X	X	X
Blood samples for drug assay <sup>i</sup>			X		X	X	X
Administer/dispense/collect study drug			X		X	X	X

Potential patients who had a current diagnoses of narcolepsy according to the ICSD (American Sleep Disorders Association 2000) diagnostic criteria came to the clinic (visit 1A) for preliminary screening assessments, after a washout period from medications excluded by the protocol, that included the administration of the Clinical Global Impression of Severity of Illness (CGI-S) scale. If the criteria were met, patients returned to the clinic (visit 1B) for additional screening assessments, including the ESS and Multiple Sleep Latency Test (MSLT). Patients who met the inclusion/exclusion and screening criteria returned to the clinic the evening before the baseline visit, with baseline assessments commencing the next morning. Baseline outcome assessments included the MWT administered 6 times (naps at 0900, 1100, 1300, 1500, 1700, and 1900), CDR system testing (tests of attention and memory) administered between MWT naps, and the BFI assessed prior to the first MWT nap. Nocturnal PSG started (ie, lights out) within 30 minutes of the patient's habitual bedtime (as determined by sleep history), but no earlier than 2130 and after other procedures/ assessments were performed. The patient was discharged the following morning. For each remaining clinic visit, patients arrived at the clinic the evening before and stayed overnight. They were administered study drug at 0700 ( $\pm$  15 minutes) the next day, about 30 minutes before breakfast. The MWT was administered 6 times (naps at 0900, 1100, 1300, 1500, 1700, and 1900) 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/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, nighttime sleep, and cataplexy were reviewed at weeks 4, 8, and 12. For the purposes of assessing effect on nighttime sleep, the week-12 visit or the last postbaseline observation also included a nocturnal PSG (conducted overnight after other procedures/assessment were performed), with the patient discharged the following morning. Adverse events were recorded throughout the study. Safety was also assessed by evaluating clinical laboratory test results and vital signs measurements as

described in the above table. Blood was collected at the baseline visit and before study drug administration at weeks 4, 8, and 12 for determination of trough plasma concentrations of armodafinil. Patients who completed 12 weeks of treatment and patients who discontinued from the study at any time before the completion of the study had final procedures performed and assessments made.

### 1.36.2.3 Drug Dose and Concomitant Medications

Patients were randomized to receive armodafinil at two dosages (150 mg/day and 250 mg/day) or placebo in a 1:1:1 ratio. Armodafinil treatment was so that patients received 50 mg on the first day followed by an increase in an additional 50 mg for each consecutive day, until the appropriate dosage was reached. On visit days at weeks 4, 8, and 12, study drug or placebo was taken in the clinic at 0700 ( $\pm 15$  minutes), about 30 minutes before breakfast. On other study days, patients took their study drug or placebo before 0800, about 30 minutes before breakfast. Study drug was taken in the fasted state in order to avoid any potential food effects.

Any prior and concomitant medication given to a patient within 30 days before and up to the end of the study, including all medication given before, during, and after study drug administration, was recorded on the CRF. Any medication that would make the patient feel sleepy was not to be used during the study. The following specific medications were not allowed during the study: modafinil, melatonin, sodium oxybate, lithium, St. John's Wort, methylphenidate, amphetamines, pemoline, antipsychotic agents, benzodiazepines, zolpidem, monoamine oxidase (MAO) inhibitors, anticoagulants (eg, warfarin sodium), anticonvulsants (unless used for other than seizure disorders), and barbiturates. Patients were not to have used prohibited medications for at least 7 days prior to the second screening visit. In some cases, the investigator could elect to extend the screening period to accomplish this goal. Anticatataplectic medications, with the exception of sodium oxybate, were permitted during the study if they did not contribute to the **patient's sleepiness**. A **patient's** current dosage of anticatataplectic medication had to be stable for at least 1 month before the second screening visit. At the time of enrollment in to the study, the investigator was not to anticipate any need to change the **patient's anticatataplectic medication** during the study. Selective serotonin reuptake inhibitors (SSRIs) were permitted if the patient did not have a history of sedation caused by SSRIs and if the patient was on a stable dosage of an SSRI (at least 3 months for fluoxetine or 1 month for other SSRIs) before the screening visit. Women participating in this study were allowed to use steroidal contraceptives only if taken in conjunction with the use of a barrier contraceptive method. At each clinic visit after the screening visit, the investigator queried about the use of any medication including OTC and herbal preparations.

#### 1.36.2.4 Number of Patients Planned for Study

Approximately 210 patients were planned to be enrolled. Data from 194 patients were analyzed for safety and 176 patients for efficacy.

#### 1.36.2.5 Endpoints

Primary and secondary efficacy endpoints are described in the integrated summary of efficacy. Along with routine adverse event monitoring (see schedule above), patients will be evaluated for effects on nighttime sleep by nighttime diaries and week 12 PSG (see integrated summary of safety). Diaries include questions on sleep and cataplexy. Blood samples were also collected for trough levels at weeks 4, 8 and 12 (see schedule above).

#### 1.36.2.6 Principal Inclusion Criteria

- The patient is an outpatient, man or woman, 18 to 65 years of age.
- The patient has a complaint of excessive sleepiness.
- The patient has a current diagnosis of narcolepsy according to the ICSD (International Classification of Sleep Disorders ) criteria.
- The patient is in good health as determined by a medical and psychiatric history, physical examination, electrocardiogram (ECG), and serum chemistry, hematology, and urinalysis.
- Women have to be surgically sterile, 2 years postmenopausal, or, if of child-bearing potential, must be using a medically accepted method of birth control and agree to continued use. Acceptable methods include steroidal contraceptive in conjunction with a barrier method, barrier method with spermicide, intrauterine device (IUD).
- The patient must have a mean sleep latency of 6 minutes or less as determined by the MSLT (performed at 0900, 1100, 1300, and 1500) during screening.
- The patient must have CGI-S rating of 4 or more, assessed during screening and if necessary after the washout of medication disallowed by the protocol.
- The patient must not have any medical or psychiatric disorders that could account for the excessive daytime sleepiness.

#### 1.36.2.7 Principal Exclusion Criteria

- The patient has any clinically significant, uncontrolled medical or psychiatric conditions (treated or untreated).
- The patient has a probable diagnosis of a current sleep disorder other than narcolepsy.

- The patient consumes caffeine including coffee, tea and/or other caffeine-containing beverages or food averaging more than 600 mg of caffeine per day.
- The patient uses any prescription drugs disallowed by the protocol or has clinically significant use of over-the-counter (OTC) drugs within 7 days before the second screening visit.
- The patient has a history of alcohol, narcotic, or any other drug abuse as defined by the Diagnostic and Statistical Manual of Mental Disorder, 4th Edition (DSM-IV).
- The patient has a positive urine drug screen (UDS), without medical explanation, at the screening visit.
- The patient has a clinically significant deviation from normal in the physical examination.
- The patient is a pregnant or lactating woman. (Any woman becoming pregnant during the study is to be withdrawn.)
- The patient has used an investigational drug within 1 month before the screening visit.
- The patient has any disorder that could interfere with drug absorption, distribution, metabolism, or excretion.
- The patient has a known clinically significant drug sensitivity to stimulants or modafinil.

#### 1.36.2.8 Amendments

Two amendments were made to this protocol, Amendment 1 on March 9, 2004 and Amendment 2 on October 21, 2004. The changes in the amendment are reflected in the protocol as presented in this review.

Amendment 1: This amendment was issued prior to any patient enrolment and, in view of an obvious flaw in the protocol as presented above, is unlikely to influence the protocol adversely.

Amendment 2: Most changes in this were for minor corrections and clarifications. More significant changes are listed below. As the protocol was altered prior to unblinding these changes should equally apply to both experimental groups and not bias results.

- If a patient has not taken study drug for more than 2 days, prior to final evaluation, only safety procedures will be performed at the final evaluation.
- Number of patients studied was reduced so that the power was changed from 90% to 80%. This would have an effect of biasing against finding a therapeutic effect.

#### 1.36.2.9 Patient Disposition

The table below presents an accounting of the disposition of patients randomized to the study. The majority of patients randomized originated in US centers (n=111) with the second highest randomization coming from Canada (n=36). A similar percent of drug and placebo patients randomized to the study was used in the full efficacy analysis set: i.e. 89% for drug and 91% for placebo. A small percent was withdrawn for reasons of adverse events but was slightly higher in

drug group. All other reasons for withdrawal were similar except for “other” which was substantially higher in the drug group (compare 6% to 2%). A slightly greater percent of patients completed the study in placebo; the difference is probably accounted for by differences in “other” and adverse event reasons for dropping out. Six of the 8 patients withdrawn from the armodafinil treatment group for other reasons were withdrawn for administrative reasons or due to study termination by the sponsor.

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(All Patients)

Patient disposition	Number (%) of patients				
	Armodafinil 250 mg/day (N=67)	Armodafinil 150 mg/day (N=65)	Armodafinil combined (N=132)	Placebo (N=64)	Total (N=196)
Screened	—	—	—	—	326
Randomized	67 (100)	65 (100)	132 (100)	64 (100)	196 (100)
Randomized, not treated	0	1 (2)	1 (<1)	1 (2)	2 (1)
Safety analysis set	67 (100)	64 (98)	131 (>99)	63 (98)	194 (99)
Full analysis set	60 (90)	58 (89)	118 (89)	58 (91)	176 (90)
Completed	56 (84)	49 (75)	105 (80)	55 (86)	160 (82)
Discontinued	11 (16)	16 (25)	27 (20)	9 (14)	36 (18)
Adverse event	2 (3)	5 (8)	7 (5)	1 (2)	8 (4)
Lack of efficacy	2 (3)	0	2 (2)	2 (3)	4 (2)
Consent withdrawn	3 (4)	4 (6)	7 (5)	4 (6)	11 (6)
Protocol violation	0	0	0	0	0
Lost to follow-up	0	1 (2)	1 (<1)	1 (2)	2 (1)
Noncompliance to study drug	1 (1)	0	1 (<1)	0	1 (<1)
Noncompliance to study procedures	1 (1)	0	1 (<1)	0	1 (<1)
Other <sup>a</sup>	2 (3)	6 (9)	8 (6)	1 (2)	9 (5)

SOURCE: Summary 15.1; Listing 2 and Listing 3.

<sup>a</sup> “Other” was the reason for discontinuation for 9 patients: patient 1441101 (250 mg/day, administrative reason), patient 2281106 (250 mg/day, study termination), patient 0421042 (150 mg/day, positive pregnancy test; subsequently, patient had an elective abortion), patient 0501012 (150 mg/day, moved out of state), patients 1261098 and 6047013 (150 mg/day, administrative reason), patients 1461107 and 2281102 (150 mg/day, study termination), and patient 6047012 (placebo, administrative reason).

### 1.36.3 Study in SWSD (3022)

#### 1.36.3.1 Design

This was a 10- to 12-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of armodafinil at 150 mg on nights worked as treatment for adults with excessive sleepiness associated with chronic SWSD. Patients were randomized (1:1) to receive 150 mg of armodafinil or placebo to be taken 30 minutes to 1 hour before the start of the night shift, but no later than 2300, only on nights worked for a 10- to 12-week double-blind treatment period. Depending upon the shift work schedule, a patient could be considered to have completed the study after 10 weeks of double-blind treatment.

#### 1.36.3.2 Schedule

The schedule for the present study is presented in the table below.

Procedures and assessments	Initial screening	Further screening and baseline period		Double-blind treatment period			
	Visit 1	Visit 2	Visit 3	Telephone contact (2 weeks)	Visit 4 Week 4	Visit 5 Week 8	Visit 6 Week 12 <sup>a</sup>
Informed consent	X						
Inclusion and exclusion criteria	X	X	X				
Medical and psychiatric history	X						
Prior medication history	X						
Full physical examination	X		X <sup>b</sup>				X
Clinical laboratory tests <sup>c</sup> (serum chemistry and hematology)	X		X		X	X	X
Urinalysis and urine drug screen (UDS) <sup>d</sup>	X						X
Vital signs measurements <sup>e</sup>	X	X	X		X	X	X
Clinical Global Impression of Severity (CGI-S)	X						
Electrocardiography (12-lead)	X	X			X	X	X
Dispense/review/collect diary <sup>f</sup>	X	X	X	X	X	X	X
Multiple Sleep Latency Test (MSLT)		X			X	X	X
Daytime polysomnography (PSG) (8-hour)		X					X
Adverse event inquiry		X	X	X	X	X	X
Concomitant medication inquiry		X	X	X	X	X	X
Clinical Global Impression of Change (CGI-C)					X	X	X
Karolinska Sleepiness Scale (KSS) <sup>g</sup>		X			X	X	X
Brief Fatigue Inventory (BFI)		X			X	X	X
Cognitive Drug Research (CDR) system testing <sup>h</sup>		X <sup>i</sup>			X	X	X
Verification of shift work status	X	X	X	X	X	X	X
Administer/dispense/collect study drug			X <sup>j</sup>		X	X	X

With the exception of the first screening visit and the study drug dispensing visit, all visits include an overnight stay in the clinic which simulates a night shift, where ambient light intensity

in patient rooms is maintained at 70 lux or less. These visits immediately followed the last night of a night shift work period of least 3 consecutive night shifts.

Potential patients will come to the clinic for preliminary screening assessments, including administration of the Clinical Global Impression of Severity of Illness (CGI-S). If criteria are met, the patients will return to the clinic (at approximately 1900) for additional screening/baseline assessments including the MSLT and 8-hour daytime PSG. If a patient is taking a medication excluded by this protocol at visit 1, there must be a washout period of 7 days before CGI-S evaluation, which will be done at visit 2 along other baseline sleepiness measures. Outcome sleepiness assessments at visit 2 include the MSLT administered 5 times in 2-hour intervals after study drug administration (at 2400 [midnight], 0200, 0400, 0600, and 0800  $\pm$ 30 minutes relative to study drug administration), the BFI assessed before the first MSLT nap, KSS administered before each MSLT nap, CDR system testing administered between MSLT naps, and the CGI-C (as related to sleepiness during night shifts including the commute to and from work) assessed after the last CDR system testing session. There is at least 7 days between the initial screening visit (visit 1) and the study drug dispensing visit (visit 3) in order to collect 7 days of diary data.

For each remaining clinic visit (on treatment), patients refrained from eating/drinking (except bottled water) after arrival at the clinic at approximately 1900; study drug will be administered at 2200 ( $\pm$ 30 minutes) followed by a meal. The MSLT is administered 5 times in 2-hour intervals after study drug administration (at 2400 [midnight], 0200, 0400, 0600, and 0800  $\pm$  30 minutes relative to study drug administration) at weeks 4, 8, and 12. At weeks 4, 8, and 12, the BFI is administered before the first MSLT nap, the KSS is administered before each MSLT nap, CDR system testing is administered between MSLT naps, and the CGI-C (as related to sleepiness during night shifts including the commute to and from work) is performed after the last CDR system testing session. Data from diaries, on the effect on sleepiness and its consequences during the night shift and the commute home, and the effect on daytime sleep is reviewed at weeks 4, 8, and 12. (Patients are to make daily diary entries, including after overnight testing in the clinic and after daytime PSG.) For the purposes of assessing effect on daytime sleep, the week-12/final visit also includes an 8-hour daytime PSG (conducted beginning at 1015 after other procedures/assessment are performed), with the patient discharged following the testing and a meal.

Adverse events are recorded throughout the study. Safety assessment also included clinical laboratory test results, and vital signs measurements (performed during the overnight clinic visits before the first and after the last CDR system testing session, and before discharge from the clinic) as baseline assessments and at weeks 4, 8, and 12; ECGs (performed at 0100, after the first CDR system testing) as a baseline assessment and at weeks 4, 8, and 12; physical examination findings as a baseline assessment and at week 12; and concomitant medication usage throughout the study. Patients who complete 12 weeks of treatment and patients who discontinue from the study at any time before the completion where to have a final procedures performed and assessments made.

### 1.36.3.3 Drug Dose and Concomitant Medications

Patients are to administer armodafinil or placebo 30 minutes to 1 hour before the start of the night shift on nights worked, but no later than 2300. It was recommended that patients refrain from eating/drinking (except bottled water) for at least 2 hours before taking study drug. When in clinic dosage was administered within 30 minutes of 2200, followed by a meal. For the overnight clinic visits during the treatment period, patients were to refrain from eating/drinking (except bottled water) after arrival at the clinic (1900).

Armodafinil treatment was titrated by initiating 50 mg on the first day and increasing by 50 mg/day each subsequent day till a final dosage of 150 mg/day is achieved.

Any prior and concomitant medication given to a patient within 30 days before and up to the end of the study, including all medication given before, during, and after study drug administration, was recorded on the CRF. Generic or trade name, indication, and dosage were recorded.

Any medication that would make the patient feel sleepy was not to be used during the study. The following specific medications were not allowed during the study: modafinil, melatonin, sodium oxybate, lithium, St. John's Wort, methylphenidate, amphetamines, pemoline, antipsychotic agents, benzodiazepines, zolpidem, monoamine oxidase (MAO) inhibitors, anticoagulants (eg., warfarin sodium), anticonvulsants (unless used for other than seizure disorders), and barbiturates. Patients were not to have used prohibited medications for at least 7 days prior to the second screening visit. In some cases, the investigator could elect to extend the screening period to accomplish this goal. Selective serotonin reuptake inhibitors (SSRIs) were permitted if the patient did not have a history of sedation caused by SSRIs. Patients who were smokers were allowed to use a low-dosage (7 mg/24 hr) nicotine patch during the overnight clinic visits. This patch could be prescribed by the investigator. Women participating in this study were allowed to use steroidal contraceptives only if taken in conjunction with the use of a barrier contraceptive method. At each clinic visit after the screening visit, the investigator asked the patient whether any medications (other than study drug), including OTC medications and herbal preparations had been taken since the previous visit.

### 1.36.3.4 Number of Patients Planned for Study

Approximately 250 patients were planned to be enrolled. Two hundred and forty five patients were analyzed for safety and from 216 patients for efficacy.

### 1.36.3.5 Endpoints

Primary and secondary efficacy endpoints are described in the integrated summary of efficacy. Along with routine adverse event monitoring (see schedule above), patients will be evaluated for

effects on daytime sleep by diaries and week 12 PSG (see integrated summary of safety). Diaries include questions on sleep along with questions regarding accidents and near misses. Blood samples were also collected for trough levels at weeks 4, 8 and 12 (see schedule above).

#### 1.36.3.6 Principal Inclusion Criteria

- The patient is a man or woman, 18 to 65 years of age.
- The patient has a complaint of excessive sleepiness.
- The patient has a diagnosis of SWSD according to the ICSD criteria with excessive sleepiness during night shifts for at least 3 months.
- The patient has to work at least 5 night shifts per month, of which at least 3 nights are consecutive. The patient also plans to maintain this schedule.
- The patient has to work night shifts that included at least 6 hours between 2200 and 0800 and are no longer than 12 hours in duration.
- The patient has no more than 87.5% sleep efficiency (sleep duration ÷ time in bed x 100%) as determined by 8-hour daytime PSG at screening.
- The patient is in good health as determined by a medical and psychiatric history, physical examination, ECG, and serum chemistry, hematology, and urinalysis.
- Women have to be surgically sterile, 2 years postmenopausal, or, if of child-bearing potential, must be using a medically accepted method of birth control and agree to continued use. Acceptable methods include steroidal contraceptive in conjunction with a barrier method, barrier method with spermicide, intrauterine device (IUD).
- The patient has a mean sleep latency of 6 minutes or less as determined by the MSLT performed at (mean at 0200, 0400, 0600, and 0800 ±30 minutes).
- The patient has a CGI-S rating of 4 or more, performed at screening, as it pertains to sleepiness during night shifts including the commute to and from work.
- The patient did not have any medical or psychiatric disorders that could account for the excessive sleepiness during the night shift.
- The patient was able to complete self-rating scales and computer-based testing.

#### 1.36.3.7 Principal Exclusion Criteria

- The patient has any clinically significant, uncontrolled medical or psychiatric conditions (treated or untreated).
- The patient has a probable diagnosis of a current sleep disorder other than SWSD.
- The patient consumes caffeine including coffee, tea and/or other caffeine-containing beverages or food averaging more than 600 mg of caffeine per day within 7 days before the second screening/baseline visit (visit 2).

- The patient uses any prescription drugs disallowed by the protocol or clinically significant use of over-the-counter (OTC) drugs within 7 days before the second screening/baseline visit (visit 2).
- The patient has a history of alcohol, narcotic, or any other drug abuse as defined by the Diagnostic and Statistical Manual of Mental Disorders, 4<sup>th</sup> Edition (DSM-IV).
- The patient has a positive urine drug screen (UDS) without medical explanation at the screening visit.
- The patient has a clinically significant deviation from normal in the physical examination.
- The patient is pregnant or lactating woman. (Any woman becoming pregnant during the study was to be withdrawn from the study.)
- The patient had used an investigational drug within 1 month before the screening visit.
- The patient has any disorder that could interfere with drug absorption, distribution, metabolism, or excretion.
- The patient had a known clinically significant drug sensitivity to stimulants or modafinil.

#### 1.36.3.8 Amendments

Two amendments were made to this protocol, Amendment 1 on March 21, 2004 and Amendment 2 on October 10, 2004. The changes in the amendment are reflected in the protocol as presented in this review.

Amendment 1: This amendment was issued before any patients were enrolled and would therefore not be expected to impact on the study. Its changes are reflected in the protocol as it is presented.

Amendment 2: This amendment was issued after all patients had been enrolled, but before blind was lifted. These changes should therefore equally and randomly apply to each treatment group and should therefore not influence the study outcome. This amendment consisted of a number of changes most of which consisted of only minor clarifications or corrections. Because of this only those changes deemed significant by this reviewer are listed below.

- The number of weeks that patients have to participate in the study (in compliance with the protocol) before being considered to have completed the study was changed from 12 weeks to 10 weeks. This change was executed to address observed variability in work schedules and conditions over a 3-month period. Presumably this is to capture individuals whose work schedule shifts to the daytime after a 10 to a 11 week period.
- In most cases, when a patient withdraws from the study and has not taken study drug for more than 2 days prior to final evaluation, only safety measures will be performed at the

final evaluation. The Sponsor noted **that this was a “clarification” of the procedures to be performed at the final evaluation for patients who discontinue treatment for more than 2 days were clarified.**

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### 1.36.3.9 Patient Disposition

The table below presents an accounting for patient disposition. Compared to other studies in these series of studies, this study exhibited a large percent of patients who withdrew from the study. Most of these were in the placebo group and **were classified as “withdrew consent**). It is unclear why there is such a large disparity. Thus 13% of patients in the placebo group withdrew consent whereas only 2% in the drug groups withdrew consent. Other reasons for withdrawal were less frequent and somewhat well matched between groups except for a somewhat greater frequency for withdrawal for adverse events in the drug as compared to the placebo group, as may be expected and a greater incidence of noncompliance in the drug group.

Patient disposition	Number (%) of patients		
	Armodafinil 150 mg (N=127)	Placebo (N=127)	Total (N=254)
Screened	—	—	747
Randomized	127 (100)	127 (100)	254 (100)
Randomized, not treated	4 (3)	5 (4)	9 (4)
Safety analysis set	123 (97)	122 (96)	245 (96)
Full analysis set	112 (88)	104 (82)	216 (85)
Completed study	97 (76)	89 (70)	186 (73)
Discontinued from study	30 (24)	38 (30)	68 (27)
Adverse event	7 (6)	4 (3)	11 (4)
Lack of efficacy	0	0	0
Consent withdrawn	3 (2)	16 (13)	19 (7)
Protocol violation	0	0	0
Lost to follow-up	3 (2)	5 (4)	8 (3)
Non-compliance to study drug	0	0	0
Non-compliance to study procedures	6 (5)	2 (2)	8 (3)
Other	11 (9)	11 (9)	22 (9)

SOURCE: Summary 15.1, Listing 2 and Listing 3.

NOTE: Other=change in shift work status (7 patients); administrative reasons (4 patients); closure of study enrollment (3 patients); and pregnancy, elevated blood pressure, panic attack, family reasons, excluded medication, patient had to leave the country, did not meet inclusion criteria, and unspecified (1 patient each).

A number of minor deviations were considered by the Sponsor to have no meaningful impact on the results of the study. The most common deviations were those related to study procedures, safety procedures (e.g. missed performance of the study procedure), and study drug compliance

or missed doses. Perusal of these by this reviewer did not suggest these to have a significant effect on the study.

Protocol driven exceptions are presented in the table below. The types of exceptions were similar across studies (e.g. failure to meet criteria in sleep efficiency), but cases were more common for placebo group. The magnitude of the deviations were small and likely do not affect the results. An additional 6 exceptions were granted for reasons of protocol-specific deviations (3 patients receiving armodafinil and 3 patients receiving placebo). These are not described in any detail in the submission.

<b>Treatment</b>	
<b>Patient Number</b>	<b>Event description</b>
<b>Armodafinil</b>	
0449152	Inclusion criterion: sleep efficiency more than 87.5% (86%) <sup>a</sup>
0529025	Inclusion criterion: sleep efficiency more than 87.5% (89.4%)
0669106	Inclusion criterion: sleep efficiency more than 87.5% (88.4%)
1349074	Inclusion criterion: sleep efficiency more than 87.5% (89.6%)
2069005	Inclusion criterion: mean sleep latency more than 6 minutes on MSLT (6.875)
2669136	Inclusion criterion: mean sleep latency more than 6 minutes on MSLT (6.125)
<b>Placebo</b>	
0469209	Inclusion criterion: mean sleep latency more than 6 minutes on MSLT (6.125)
0529100	Inclusion criterion: patient works 5.5 hours 5 nights a week
0669097	Inclusion criterion: sleep efficiency more than 87.5% (91.9%)
0849029	Inclusion criterion: sleep efficiency more than 87.5% (82.9%) <sup>a</sup>
0849121	Inclusion criterion: sleep efficiency more than 87.5% (89.3%)
0849131	Inclusion criterion: sleep efficiency more than 87.5% (90.2%)
0969155	Exclusion criterion: positive UDS (butalbital taken for migraine)
1289026	Inclusion criterion: sleep efficiency more than 87.5% (88%)
1529035	Inclusion criterion: sleep efficiency more than 87.5% (90.0%)
3129308	Exclusion criterion: positive UDS (codeine taken for knee pain)
3189314	Inclusion criterion: mean sleep latency more than 6 minutes on MSLT (6.125)

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The table below presents a listing of patients in violation of the protocol. All patients were included in the final analysis. There was no pattern of error between the two experimental groups that may lead to biasing of the study.

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<b>Treatment</b>	
<b>Patient number</b>	<b>Event description</b>
<b>Armodafinil</b>	
0309030	GCP guidelines: patient improperly administered study drug
0449170	Primary endpoint criteria: CGI-S not redone after a 7-day washout period
0529082	Exclusion criterion: patient history of alcoholism and recreational drug use
0529183	Exclusion criterion: patient history of alcoholism and recreational drug use
0829055	Primary endpoint criteria: CGI-S not done after washout of prohibited medication
0969058	Primary endpoint criteria: at visit 4, study drug given at 1930 and meal at 2245
2029101	GCP guidelines: informed consent <sup>a</sup>
2069005	Inclusion criterion: patient randomized in error (MSLT 6.8 minutes)
<b>Placebo</b>	
0269002	Primary endpoint criteria: CGI-C not done at visit 6
0469234	Primary endpoint criteria: CGI-C not done at week 4
0589137	Exclusion criterion: urine drug screen not done prior to randomization
2029133	GCP guidelines: informed consent <sup>a</sup>

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### 1.37 APPENDIX B: Cognitive Drug Research (CDR) System

The CDR is a computerized testing system that tests various cognitive functions. All tasks are presented on VGA color monitors, and the responses recorded via response modules containing **two buttons, one marked “NO” and the other “YES”**. The CDR is carried out with the following tasks in the order of presentation:

- *Word presentation:* A list of 15 words was presented on the monitor at the rate of 1 every 2 s for the patients to remember.
- *Immediate word recall:* The patient was given 1 min to recall as many of the words as possible. The measures from the task were the percentage of words correctly recalled, the number of words recalled in error and the number of intrusions from previous lists.
- *Picture presentation* A series of 20 pictures is presented on the monitor at the rate of one every 3 s for the patient to remember.
- *Simple reaction time:* The patient was instructed to press the YES response button as quickly as possible every time the word YES was presented on the monitor. Thirty stimuli were presented with a varying inter-stimulus interval. The outcome measure was the average reaction time in milliseconds.
- *Digit vigilance task:* A target digit was randomly selected and constantly displayed to the right of the monitor screen. A series of digits was presented in the centre of the screen at the rate of 150 per minute and the patient was required to press the YES button as quickly as possible every time the digit in the series matched the target digit. There were 45 targets. The outcome measures were the percentage of targets correctly detected, the average reaction time of these detections and the number of false positive responses (false alarms).
- *Choice reaction time:* Either the word NO or the word YES was presented on the monitor and the patient was instructed to press the corresponding button as quickly as possible. There were 30 trials, for each of which the stimulus word was chosen randomly with equal probability and there was a varying inter-stimulus interval. The outcome measures were the percentage of correct responses and the average reaction time of these responses in milliseconds.
- *Spatial working memory:* A picture of a house is presented on the screen with four of its nine windows lit. The patient memorized the position of the lit windows. For each of the 36 subsequent presentations of the house, the patient decided whether or not the one window, which is lit, was also lit in the original presentation. The patient recorded his response by pressing the YES or NO response button as appropriate. The measures are the percentage of correct responses and the average reaction time.
- *Numeric working memory:* A series of 5 digits was presented for the patient to hold in memory. This was followed by a series of 30 probe digits for each of which the patient decided whether or not it was in the original series and press the YES or NO response button as appropriate. The measures are the percentage of correct responses and the average reaction time.
- *Joystick tracking task:* In this task the patient used a joystick to move an object on the screen in pursuit of a randomly moving target. The task lasted for 1 min. The measure is the average distance (mm) off target.
- *Delayed word recall:* The patient was again given 1 min to recall as many of the words as possible. The measures from the task were the percentage of words correctly recalled, the number of words recalled in error and the number of intrusions from previous lists.
- *Word recognition:* The original words plus 15 distraction words were presented one at a time in a randomized order. For each word the patient indicated whether or not he or she recognized it as being from the original list of words by pressing the YES or NO button as appropriate. The measures are the percentage of words correctly classified (either as original or new) and the average reaction time.
- *Picture recognition:* The original pictures plus 20 distractor pictures were presented one at a time in a randomized order. For each picture the patient indicated whether or not he or she recognized it as being from the original series by pressing the YES or NO button as appropriate. The measures are the percentage of pictures correctly classified (either as original or new) and the average reaction time.

Using the above testing the Sponsor derived the following measures:

1. **The Power of attention:** This was computed as the speed from the simple reaction time test plus the speed from the digit vigilance task plus the speed from the choice reaction time test.
2. **The continuity of attention:** This was computed as the targets detected from the digit vigilance task plus the accurate responses from the choice reaction time test minus the false alarms from the digit vigilance task.
3. **The Speed of memory:** was computed as the speed from the numeric working memory test plus the speed from the word recognition test plus the speed from the picture recognition test.
4. **Quality of episodic secondary memory:** This was computed as follows: for the word recall tasks, the number of words recalled correctly was adjusted for the number of words falsely recalled. The score for each task was then calculated as a percentage of the 15 words originally presented. For the word and picture recognition tasks, the number of items correctly recognized and the number of items not previously presented that were correctly rejected were averaged to obtain an overall percentage of accuracy. This number was adjusted for chance responding (50%), to yield a score that reflects the pure recognition ability for the words and pictures. The scores from the 4 memory tasks (immediate word recall test, delayed word recall test, word recognition, and picture recognition), which are all of a comparable weight, were then summed to derive the quality of episodic secondary memory.

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**1.38 Appendix C: Shifts from Baseline Baseline to endpoint in blood chemistry testing for patients in OSAHS placebo-control phase 3 trials.**

Test	Baseline Endpoint	CES-10983											
		250 MG (N=131)			150 MG (N=260)			Combined (N=391)			Placebo (N=260)		
		Low	Normal	High	Low	Normal	High	Low	Normal	High	Low	Normal	High
Sodium (mmol/L)	Low	0	0	0	0	0	0	0	0	0	0	1	0
	Normal	0	128	0	0	249	0	0	377	0	0	253	2
	High	0	0	1	0	2	0	0	2	1	0	2	0
Potassium (mmol/L)	Low	0	1	0	0	2	0	0	4	0	0	2	0
	Normal	0	127	0	1	247	0	1	374	0	0	255	1
	High	0	0	0	0	0	0	0	0	0	0	0	0
Chloride (mmol/L)	Low	0	0	0	0	0	0	0	0	0	0	0	0
	Normal	0	129	0	0	250	1	0	379	1	1	257	0
	High	0	0	0	0	0	0	0	0	0	0	0	0
Bicarbonate / CO2 content (mmol/L)	Low	0	0	0	0	1	0	0	1	0	0	0	0
	Normal	1	115	2	1	221	14	2	336	17	0	237	9
	High	0	9	2	0	11	3	0	19	5	0	10	2
Glucose (mmol/L)	Low	0	0	1	1	2	0	1	2	1	0	1	0
	Normal	2	93	12	1	157	25	2	240	37	3	162	22
	High	1	6	24	0	22	41	1	28	65	0	19	51
Blood urea nitrogen (mmol/L)	Low	0	0	0	0	0	0	0	0	0	0	0	0
	Normal	0	119	4	0	221	14	0	329	18	0	226	15
	High	0	3	4	0	12	4	0	15	8	0	10	7
Creatinine (umol/L)	Low	0	0	0	0	1	0	0	1	0	0	0	0
	Normal	0	125	0	1	242	5	1	367	5	0	247	4
	High	0	0	4	0	1	1	0	1	5	0	2	5
Calcium (mmol/L)	Low	0	0	0	0	1	0	0	1	0	0	0	0
	Normal	0	126	2	1	244	1	1	370	3	0	254	0
	High	0	1	0	0	1	3	0	2	3	0	4	0
Phosphorus (mmol/L)	Low	0	0	0	0	1	0	0	1	0	0	0	0
	Normal	0	127	1	1	242	3	1	369	4	1	249	5
	High	0	1	0	0	4	0	0	5	0	0	3	1
Total protein (g/L)	Low	0	0	0	0	2	0	0	2	0	0	2	0
	Normal	0	128	0	0	247	0	0	375	0	0	255	0
	High	0	1	0	0	2	0	0	3	0	0	1	0
Albumin (g/L)	Low	1	2	0	0	2	0	1	4	0	0	1	0
	Normal	1	124	1	0	246	0	1	370	1	0	256	0
	High	0	0	0	0	3	0	0	3	0	0	1	0
Uric acid (umol/L)	Low	0	0	0	0	0	0	0	0	0	0	0	0
	Normal	0	111	7	0	210	11	0	321	18	0	202	24
	High	0	5	6	0	7	23	0	12	29	0	19	14
SGOT (AST) (U/L)	Low	0	0	0	1	0	0	1	0	0	0	0	0
	Normal	1	114	4	0	216	7	1	330	11	1	224	6
	High	0	5	4	0	13	14	0	18	18	0	12	14
SGPT (ALT) (U/L)	Low	0	0	0	0	0	0	0	0	0	0	0	0
	Normal	0	99	13	0	190	20	0	288	32	0	196	15
	High	0	9	9	0	16	25	0	25	33	0	14	33
Alk phos (U/L)	Low	0	0	0	0	0	0	0	0	0	0	0	0
	Normal	0	119	3	0	242	2	0	360	5	0	243	5
	High	0	4	4	0	6	1	0	10	5	0	2	8
GGT (U/L)	Low	1	0	0	0	1	0	1	1	0	1	0	0
	Normal	0	116	1	0	209	5	0	316	6	0	216	7
	High	0	5	6	0	21	24	0	26	30	0	4	30
Total bilirubin (umol/L)	Low	7	12	0	6	14	0	13	26	0	5	12	0
	Normal	5	104	1	8	221	1	12	328	2	9	226	1
	High	0	0	0	0	0	1	0	0	1	0	2	1
Cholesterol (mmol/L)	Low	13	5	0	35	16	0	48	21	0	44	26	0
	Normal	14	92	2	28	147	1	38	259	2	10	170	2
	High	0	2	1	0	5	3	0	7	4	0	2	4

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**1.39 Appendix D: Selected Blood chemistries Central tendency analysis for pivotal control trials.**

Chemistry variable*	Time point Statistic	Narcolepsy		OSAS		SWSD		
		Armodafinil (N=131)	Placebo (N=63)	Armodafinil (N=391)	Placebo (N=269)	Armodafinil (N=123)	Placebo (N=122)	
Alkaline phosphatase, U/L	Baseline							
	n	131	62	391	260	123	121	
	Mean	75.7	74.3	78.1	81.1	79.2	76.8	
	SD	21.03	18.13	20.99	23.42	25.70	21.04	
	Median	71.0	74.0	77.0	78.0	74.0	72.0	
	Min, max	35.0, 153.0	43.0, 119.0	36.0, 174.0	38.0, 198.0	35.0, 212.0	42.0, 144.0	
	Change from baseline							
	n	126	60	380	259	120	112	
	Mean	4.4	-0.7	3.3	-1.1	2.7	0.9	
	SD	9.35	8.66	10.63	10.25	9.83	8.10	
	Median	3.0	0.0	3.0	-1.0	2.0	1.0	
	Min, max	-15.0, 43.0	-26.0, 20.0	-31.0, 55.0	-64.0, 31.0	-30.0, 34.0	-17.0, 40.0	
	GGT, U/L	Baseline						
		n	131	62	391	260	123	121
Mean		26.0	30.8	34.3	39.0	26.3	27.4	
SD		23.69	26.30	23.81	37.32	17.92	25.62	
Median		21.0	21.5	29.0	29.0	20.0	21.0	
Min, max		6.0, 214.0	7.0, 131.0	8.0, 190.0	8.0, 326.0	6.0, 111.0	7.0, 234.0	
Change from baseline								
n		126	59	380	259	120	112	
Mean		7.0	0.9	7.8	0.6	5.6	0.9	
SD		13.88	9.48	20.94	15.77	30.75	7.48	
Median		4.0	0.0	5.0	1.0	2.0	1.0	
Min, max		-22.0, 104.0	-29.0, 30.0	-101.0, 182.0	-142.0, 75.0	-25.0, 330.0	-36.0, 44.0	
ALT, U/L		Baseline						
		n	131	62	391	260	123	121
	Mean	23.2	25.6	31.1	31.8	26.5	25.4	
	SD	12.52	16.48	17.00	16.57	16.06	13.68	
	Median	21.0	22.5	27.0	28.0	22.0	21.0	
	Min, max	6.0, 72.0	7.0, 85.0	9.0, 153.0	8.0, 120.0	10.0, 98.0	4.0, 68.0	
	Change from baseline							
	n	126	60	379	259	120	112	
	Mean	1.0	0.9	-0.4	0.6	1.4	1.4	
	SD	9.95	8.23	12.24	12.35	13.76	10.23	
	Median	0.0	0.0	0.0	1.0	0.0	1.0	
	Min, max	-35.0, 60.0	-27.0, 26.0	-96.0, 77.0	-46.0, 127.0	-27.0, 92.0	-36.0, 64.0	
	AST, U/L	Baseline						
		n	131	62	391	259	123	121
Mean		22.1	23.2	24.2	24.9	22.9	22.8	
SD		7.88	6.87	10.66	11.45	8.59	6.80	
Median		21.0	22.0	22.0	22.0	21.0	22.0	
Min, max		10.0, 59.0	12.0, 44.0	9.0, 119.0	10.0, 129.0	10.0, 78.0	11.0, 50.0	
Change from baseline								
n		126	60	379	258	120	112	
Mean		0.6	0.2	0.2	0.8	-0.5	-0.1	
SD		10.95	5.90	7.73	7.70	8.32	6.92	
Median		0.0	1.0	0.0	0.0	-2.0	0.0	
Min, max		-25.0, 99.0	-17.0, 22.0	-79.0, 26.0	-20.0, 40.0	-49.0, 40.0	-24.0, 30.0	

Creatinine (umol/L)	Baseline	Narcolepsy		OSAHS		SWSD	
		Armodafinil (N=131)	Placebo (N=63)	Armodafinil (N=391)	Placebo (N=269)	Armodafinil (N=123)	Placebo (N=122)
n		131	62	391	260	123	121
Mean		72.9	78.7	79.1	79.0	77.3	75.1
SD		14.34	17.51	18.00	18.84	16.23	15.27
Median		70.7	79.6	79.6	79.6	79.6	70.7
Min, max		44.2, 123.8	44.2, 132.6	26.5, 150.3	44.2, 185.6	35.4, 123.8	44.2, 123.8
Change from baseline							
n		126	60	380	259	120	112
Mean		-1.9	-1.6	-1.6	0.9	-2.2	-3.2
SD		10.64	10.10	9.33	10.26	10.58	11.87
Median		0.0	0.0	0.0	0.0	0.0	0.0
Min, max		-70.7, 26.5	-26.5, 17.7	-35.4, 26.5	-35.4, 35.4	-35.4, 35.4	-35.4, 26.5

Chemistry variable*	Time point	Narcolepsy		OSAHS		SWSD	
		Armodafinil (N=131)	Placebo (N=63)	Armodafinil (N=391)	Placebo (N=269)	Armodafinil (N=123)	Placebo (N=122)
Bilirubin (total), µmol/L	Statistic						
	Baseline						
	n	131	62	391	260	123	121
	Mean	7.6	7.1	7.8	8.0	8.9	8.2
	SD	4.21	4.03	3.90	4.11	5.57	4.42
	Median	6.8	6.8	6.8	6.8	6.8	6.8
	Min, max	3.2, 25.7	3.2, 20.5	3.2, 34.2	3.2, 25.7	3.2, 35.9	3.2, 25.7
	Change from baseline						
	n	126	60	380	259	120	112
	Mean	-1.5	0.0	-0.8	-0.2	-1.2	-0.9
SD	3.21	3.12	3.23	3.06	3.32	2.99	
Median	-1.7	0.0	0.0	0.0	-1.7	-0.2	
Min, max	-15.4, 5.3	-10.3, 5.1	-17.1, 8.6	-12.0, 15.4	-10.3, 8.6	-12.0, 6.8	

Blood urea nitrogen (BUN), mmol/L	Baseline	Narcolepsy		OSAHS		SWSD	
		Armodafinil (N=131)	Placebo (N=63)	Armodafinil (N=391)	Placebo (N=269)	Armodafinil (N=123)	Placebo (N=122)
n		131	62	391	260	123	121
Mean		5.0	5.3	6.1	6.2	5.1	5.4
SD		1.27	1.22	1.66	1.66	1.29	1.70
Median		4.6	5.4	6.1	6.1	5.0	5.0
Min, max		2.5, 8.6	2.9, 8.9	2.9, 13.9	2.5, 13.9	2.5, 8.6	2.1, 12.9
Change from baseline							
n		126	60	380	259	120	112
Mean		0.0	-0.0	-0.1	-0.0	0.2	-0.1
SD		1.23	1.11	1.30	1.24	1.38	1.47
Median		0.0	0.0	0.0	0.0	0.2	0.0
Min, max		-3.2, 5.0	-2.5, 2.5	-3.6, 3.9	-5.0, 3.6	-3.6, 4.3	-5.0, 3.6

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**1.40 Appendix e: Shifts from Baseline to endpoint in hematology indices for patients in OSAHS placebo-control phase 3 trials.**

Test	Baseline Endpoint	CEP-10952											
		250 MG (N=131)			150 MG (N=280)			COMBINED (N=291)			Placebo (N=260)		
		Low	Normal	High	Low	Normal	High	Low	Normal	High	Low	Normal	High
Eosinophils (%)	Low	0	0	0	0	0	0	0	0	0	0	0	0
	Normal	0	124	1	0	245	1	0	369	4	0	251	0
	High	0	2	1	0	2	1	0	4	2	0	3	0
Platelets (10E9/L)	Low	0	1	0	0	2	0	0	2	0	2	1	0
	Normal	2	121	1	1	236	2	3	357	3	3	237	2
	High	0	2	0	0	1	6	0	2	6	0	3	4
Monocytes ABS (10E9/L)	Low	0	2	0	0	1	0	0	3	0	0	0	0
	Normal	2	123	0	0	245	2	2	368	2	3	252	1
	High	0	1	0	0	3	0	0	4	0	0	0	1
Eosinophils ABS (10E9/L)	Low	0	0	0	0	0	0	0	0	0	0	0	0
	Normal	0	126	1	0	248	2	0	374	3	0	255	1
	High	0	1	0	0	1	0	0	2	0	0	1	0
Basophils ABS (10E9/L)	Low	0	0	0	0	0	0	0	0	0	0	0	0
	Normal	0	127	1	0	249	2	0	376	3	0	256	0
	High	0	0	0	0	0	0	0	0	0	0	1	0
Neutrophils (%)	Low	0	2	0	3	2	0	3	4	0	2	3	0
	Normal	1	120	3	3	237	2	4	357	5	7	243	1
	High	0	2	0	0	4	0	0	6	0	0	0	1
Lymphocytes ABS (10E9/L)	Low	1	0	0	0	0	0	1	0	0	1	1	0
	Normal	0	123	1	0	240	7	0	363	8	0	247	3
	High	0	2	1	0	1	3	0	3	4	0	1	4
WBC (10E9/L)	Low	0	5	0	2	7	0	3	2	0	5	14	0
	Normal	2	167	6	5	627	6	4	214	5	11	1008	17
	High	0	3	6	0	19	16	0	2	5	0	24	27
RBC (10E12/L)	Low	2	7	0	15	19	0	3	7	0	20	33	0
	Normal	4	176	0	25	623	0	7	216	1	36	1015	1
	High	0	0	0	0	0	0	0	0	1	0	0	1
Hemoglobin (g/L)	Low	3	7	0	18	12	0	6	5	0	27	24	0
	Normal	2	176	1	10	640	1	6	217	0	18	1033	2
	High	0	0	0	0	1	0	0	0	1	0	1	1
Hematocrit (L/L)	Low	0	5	0	7	18	0	1	2	0	8	25	0
	Normal	3	180	0	2	646	7	4	226	0	9	1052	7
	High	0	0	0	0	0	0	0	0	0	0	0	0
ANC (10E9/L)	Low	2	4	0	4	5	0	6	4	0	12	13	0
	Normal	3	168	6	12	615	12	8	206	4	23	989	22
	High	0	2	4	0	25	9	0	5	2	0	32	15
Lymphocytes (%)	Low	0	4	0	0	7	0	0	2	0	0	11	0
	Normal	2	169	8	4	658	8	2	205	8	8	1032	24
	High	0	4	2	0	2	3	0	7	11	0	13	16
Monocytes (%)	Low	0	2	0	0	7	0	0	6	0	0	15	0
	Normal	4	181	0	10	647	15	0	224	4	14	1052	19
	High	0	1	1	0	2	1	0	1	0	0	4	2
Basophils (%)	Low	0	0	0	0	0	0	0	0	0	0	0	0
	Normal	0	180	5	0	670	10	0	232	3	0	1082	18
	High	0	4	0	0	1	1	0	0	0	0	5	1

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**1.41 Appendix F: Changes in EKG parameters (excluding QT) in placebo control phase 3 trials.**

Variable	Time point Statistic	Narcolepsy		OSAHS		SWSB		
		Armodafinil (N=131)	Placebo (N=63)	Armodafinil (N=391)	Placebo (N=260)	Armodafinil (N=123)	Placebo (N=122)	
Ventricular rate, bpm	Baseline							
	n	131	62	391	260	123	122	
	Mean	64.4	63.9	64.5	64.3	63.8	64.9	
	SD	10.55	9.98	10.44	9.68	9.34	10.26	
	Median	63.0	62.0	64.0	64.0	62.0	65.0	
	Min, max	42, 110	43, 86	38, 100	40, 93	43, 90	42, 91	
	Change from baseline							
	n	125	59	378	258	119	114	
	Mean	3.9	1.6	2.7	1.1	2.8	1.5	
	SD	9.46	7.22	8.37	7.38	8.48	8.71	
	Median	4.0	1.0	3.0	1.0	3.0	3.0	
	Min, max	-20, 25	-12, 21	-26, 36	-26, 32	-20, 26	-22, 28	
	PR interval, msec	Baseline						
		n	131	62	391	260	123	122
Mean		153.8	150.7	163.9	163.6	161.0	161.2	
SD		21.40	21.25	23.58	22.54	24.15	21.68	
Median		154.0	148.0	162.0	162.0	160.0	161.0	
Min, max		94, 224	103, 235	101, 292	96, 237	110, 258	113, 221	
Change from baseline								
n		125	59	378	258	119	114	
Mean		-2.2	2.0	-2.4	0.9	-3.4	-0.8	
SD		14.12	12.88	13.75	15.12	15.15	11.31	
Median		-2.0	3.0	-2.0	0.0	-3.0	-1.0	
Min, max		-53, 36	-34, 33	-51, 44	-45, 55	-50, 39	-39, 31	
QRS interval, msec		Baseline						
		n	131	62	391	260	123	122
	Mean	92.7	93.6	98.5	98.2	95.4	92.8	
	SD	9.65	10.76	14.51	12.57	11.94	11.63	
	Median	92.0	92.0	97.0	97.0	94.0	93.0	
	Min, max	71, 124	74, 119	65, 191	71, 157	69, 158	56, 122	
	Change from baseline							
	n	125	59	378	258	119	114	
	Mean	0.8	0.0	-0.3	0.0	1.2	0.2	
	SD	8.39	8.81	10.40	10.07	10.31	10.87	
	Median	0.0	0.0	-1.0	0.0	2.0	0.5	
	Min, max	-21, 21	-21, 20	-34, 35	-29, 35	-27, 25	-25, 36	

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1.42 Appendix G: Change in staged sleep from baseline at endpoint across the various placebo controlled phase 3 studied disorders.

Variable	Time point Statistic	Narcolepsy		OSAHS		SWSD		
		Armodafinil (N=131)	Placebo (N=63)	Armodafinil (N=391)	Placebo (N=260)	Armodafinil (N=123)	Placebo (N=122)	
Sleep efficiency (%)	Baseline							
	n	130	60	382	255	123	122	
	Mean	84.4	81.3	82.4	82.0	71.1	70.9	
	SD	11.97	12.76	10.87	12.10	16.00	15.44	
	Median	87.7	85.2	84.6	84.9	73.4	75.2	
	Min, max	32.2, 99.1	51.5, 97.9	36.3, 98.8	26.5, 99.5	19.6, 99.1	15.7, 93.1	
	Change from baseline							
	n	107	54	327	232	102	91	
	Mean	-0.6	-0.9	-0.4	-0.7	-2.1	0.5	
	SD	10.25	10.91	12.53	11.80	19.28	18.49	
	Median	-0.7	0.9	-0.1	-0.8	-1.4	-0.6	
	Min, max	-43.9, 27.9	-26.3, 24.6	-98.1, 48.1	-46.4, 38.4	-76.8, 49.0	-39.9, 82.3	
	Stage 2 sleep (%)	Baseline						
		n	130	60	382	255	123	122
Mean		57.1	56.1	59.3	58.8	57.1	56.5	
SD		9.82	12.05	9.75	10.11	10.90	12.09	
Median		56.9	55.8	59.9	58.2	56.9	56.4	
Min, max		31.9, 79.0	20.7, 84.0	24.6, 85.2	35.2, 88.0	33.1, 81.1	29.5, 82.8	
Change from baseline								
n		107	54	327	232	102	91	
Mean		-0.0	0.6	-0.5	-0.9	-1.2	-0.4	
SD		8.36	11.68	11.10	10.66	13.36	12.83	
Median		0.4	1.5	-0.5	-0.6	-0.5	0.6	
Min, max		-19.9, 19.1	-24.2, 31.0	-65.9, 37.6	-46.0, 25.7	-72.6, 21.6	-56.1, 31.9	
Stage 3/4 sleep (%)		Baseline						
		n	130	60	382	255	123	122
	Mean	11.5	11.7	10.6	10.8	13.2	14.6	
	SD	8.63	11.40	9.03	9.57	11.02	11.54	
	Median	10.7	9.6	9.1	9.4	11.7	13.5	
	Min, max	0.0, 36.9	0.0, 69.1	0.0, 47.2	0.0, 45.6	0.0, 45.2	0.0, 58.4	
	Change from baseline							
	n	107	54	327	232	102	91	
	Mean	0.5	0.6	-0.3	0.0	1.2	0.3	
	SD	7.04	7.39	8.62	9.58	10.16	10.24	
	Median	-0.3	0.4	0.0	0.0	0.3	-0.1	
	Min, max	-19.3, 23.5	-28.4, 14.3	-33.2, 39.4	-32.3, 41.1	-39.9, 30.2	-23.6, 45.5	
	REM sleep (%)	Baseline						
		n	130	60	382	255	123	122
Mean		18.9	19.3	18.9	19.5	18.1	17.9	
SD		6.45	6.96	6.91	7.22	8.00	8.70	
Median		19.0	20.2	19.1	19.7	18.0	18.0	
Min, max		0.0, 36.9	1.8, 35.3	0.0, 45.4	0.00, 41.4	0.0, 41.6	0.0, 42.7	
Change from baseline								
n		107	54	327	232	102	91	
Mean		-0.4	-0.4	1.0	1.2	-1.1	-0.0	
SD		6.82	8.24	8.23	7.53	8.56	7.79	
Median		0.0	0.3	1.0	1.5	-1.6	0.4	
Min, max		-26.3, 21.7	-19.1, 23.9	-29.6, 29.1	-20.2, 39.2	-22.2, 22.4	-17.5, 19.3	

Clinical Review  
Norman Hershkowitz, MD, PhD  
21,875 (000)  
Nuvigil (armodafinil)

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**1.43 Appendix H Criteria for clinically significant abnormal values in selected pertinent laboratories.**

Parameter	Criterion Value
Alanine aminotransferase (ALT)	≥3x upper limit of normal (ULN)
Aspartate aminotransferase (AST)	≥3x ULN
Alkaline phosphatase	≥3x ULN
Gamma-glutamyl transpeptidase (GGT)	≥3x ULN
Lactate dehydrogenase (LDH)	≥3x ULN
Blood urea nitrogen (BUN)	≥10.71 mmol/L
Creatinine	≥177 μmol/L
Uric acid Men	≥625 μmol/L
Women	≥506 μmol/L
Bilirubin (total)	≥34.2 μmol/L
Hematocrit Men	<37%
Women	<32%
Hemoglobin Men	≤115 g/L
Women	≤95 g/L
White blood cell (WBC) counts	≤3 x 10 <sup>9</sup> /L or ≥20 x 10 <sup>9</sup> /L
Eosinophils	≥10%
Absolute neutrophil counts (ANC)	≤1 x 10 <sup>9</sup> /L
Platelet count	<75 x 10 <sup>9</sup> /L or >700 x 10 <sup>9</sup> /L

ULN=upper limit of normal range.

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