

**Clinical trial results:****A Randomized, Open-Label Study to Characterize the Pharmacokinetics, Pharmacodynamics, and Safety of Single and Multiple Doses of Armodafinil (50, 100, and 150 mg/day) in Children and Adolescents with Excessive Sleepiness Associated With Narcolepsy****Summary**

EudraCT number	2012-005510-20
Trial protocol	FI
Global end of trial date	21 September 2015

**Results information**

Result version number	v1 (current)
This version publication date	23 November 2016
First version publication date	23 November 2016
Summary attachment (see zip file)	Sponsors statement concerning unavailability of paediatric clinical trial results_EudraCT 2012-005510-20 (Sponsors statement concerning unavailability of paediatric clinical trial results_EudraCT 2012-005510-20.pdf)

**Trial information****Trial identification**

Sponsor protocol code	C10953/1100
-----------------------	-------------

**Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01624480
WHO universal trial number (UTN)	-

Notes:

**Sponsors**

Sponsor organisation name	Teva Branded Pharmaceutical Products R&D, Inc
Sponsor organisation address	41 Moores Road, Frazer, Pennsylvania, United States, 19355
Public contact	Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc., 001 215-591-3000, ustevatrials@tevapharm.com
Scientific contact	Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc., 001 215-591-3000, ustevatrials@tevapharm.com

Notes:

**Paediatric regulatory details**

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

---

### Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 May 2016
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	21 September 2015
Was the trial ended prematurely?	No

Notes:

---

### General information about the trial

Main objective of the trial:

The primary objective of this study is to characterize the single- and multiple-dose pharmacokinetics of armodafinil and its major circulating metabolites (R-modafinil acid and modafinil sulfone) in children and adolescents with excessive sleepiness associated with narcolepsy.

Protection of trial subjects:

This study was conducted in full accordance with the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Consolidated Guideline (E6) and any applicable national and local laws and regulations (eg, Code of Federal Regulations [CFR] Title 21, Parts 50, 54, 56, 312, and 314; European Union (EU) Directive 2001/20/EC on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use). A signed and dated informed consent form was obtained from each parent/guardian and a signed and dated assent form was obtained from each patient before any study-specific procedures or assessments were done and after the aims, methods, anticipated benefits, and potential hazards were explained, according to local IRB/IEC requirements. The patient's willingness to participate in the study was documented in this assent form, which was signed by the patient with the date of that signature indicated. Each investigator kept the original consent/assent forms and copies were given to the patients. It was also explained to the patients that they were free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment.

Written and/or oral information about the study in a language understandable by the patient was given to all patients.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 July 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

---

### Population of trial subjects

#### Subjects enrolled per country

Country: Number of subjects enrolled	United States: 40
Worldwide total number of subjects	40
EEA total number of subjects	0

Notes:

---

**Subjects enrolled per age group**

---

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	10
Adolescents (12-17 years)	30
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

---

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Sixty-one patients were screened and 40 enrolled/randomized. Of the 21 not enrolled, 4 were withdrawn by patient, 6 did not meet inclusion criteria, 9 met exclusion criteria, 1 was lost to follow-up, and 1 whose reason was not specified.

### Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Armodafinil 50 mg

Arm description:

Patients received a single 50 mg dose of armodafinil on day 1. No intervention was administered on days 2+3. Patients received a single 50 mg daily dose of armodafinil on days 4-25. All doses of armodafinil must have been taken intact with up to 240 mL of water and the entire dose must have been consumed within 5 minutes.

Arm type	Experimental
Investigational medicinal product name	armodafinil
Investigational medicinal product code	
Other name	Nuvigil, CEP-10953
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Armodafinil was supplied as 50 mg tablets. Patients took the appropriate number of tablets for their assigned 50 mg, 100 mg or 150 mg daily dose. For a given patient, study drug was taken within the same 2-hour window in the morning on each day of study drug administration. Each patient's 2-hour window for study drug administration must have fallen between 0600 and 1000.

<b>Arm title</b>	Armodafinil 100 mg
------------------	--------------------

Arm description:

Patients received a single 50 mg dose of armodafinil on day 1. No intervention was administered on days 2+3. Patients received a single 50 mg dose on day 4 then daily 100 mg doses on days 5 - 25. All doses of armodafinil must have been taken intact with up to 240 mL of water and the entire dose must have been consumed within 5 minutes.

Arm type	Experimental
Investigational medicinal product name	armodafinil
Investigational medicinal product code	
Other name	Nuvigil, CEP-10953
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Armodafinil was supplied as 50 mg tablets. Patients took the appropriate number of tablets for their assigned 50 mg, 100 mg or 150 mg daily dose. For a given patient, study drug was taken within the same 2-hour window in the morning on each day of study drug administration. Each patient's 2-hour window for study drug administration must have fallen between 0600 and 1000.

<b>Arm title</b>	Armodafinil 150 mg
------------------	--------------------

**Arm description:**

Patients received a single 50 mg dose of armodafinil on day 1. No intervention was administered on days 2+3. Patients received a single 50 mg dose on day 4, 100 mg doses on days 5 and 6, then daily 150 mg doses on days 7 through 25. All doses of armodafinil must have been taken intact with up to 240 mL of water and the entire dose must have been consumed within 5 minutes.

Arm type	Experimental
Investigational medicinal product name	armodafinil
Investigational medicinal product code	
Other name	Nuvigil, CEP-10953
Pharmaceutical forms	Tablet
Routes of administration	Oral use

**Dosage and administration details:**

Armodafinil was supplied as 50 mg tablets. Patients took the appropriate number of tablets for their assigned 50 mg, 100 mg or 150 mg daily dose. For a given patient, study drug was taken within the same 2-hour window in the morning on each day of study drug administration. Each patient's 2-hour window for study drug administration must have fallen between 0600 and 1000.

<b>Number of subjects in period 1</b>	Armodafinil 50 mg	Armodafinil 100 mg	Armodafinil 150 mg
Started	14	13	13
Safety analysis set	14	13	13
Pharmacodynamic analysis set	14	13	13
Pharmacokinetic analysis set	14	12	12
Completed	13	12	11
Not completed	1	1	2
Consent withdrawn by subject	-	1	1
Lost to follow-up after first PK visit	1	-	-
Sponsor decision on day 24	-	-	1

## Baseline characteristics

### Reporting groups

Reporting group title	Armodafinil 50 mg
-----------------------	-------------------

Reporting group description:

Patients received a single 50 mg dose of armodafinil on day 1. No intervention was administered on days 2+3. Patients received a single 50 mg daily dose of armodafinil on days 4-25. All doses of armodafinil must have been taken intact with up to 240 mL of water and the entire dose must have been consumed within 5 minutes.

Reporting group title	Armodafinil 100 mg
-----------------------	--------------------

Reporting group description:

Patients received a single 50 mg dose of armodafinil on day 1. No intervention was administered on days 2+3. Patients received a single 50 mg dose on day 4 then daily 100 mg doses on days 5 - 25. All doses of armodafinil must have been taken intact with up to 240 mL of water and the entire dose must have been consumed within 5 minutes.

Reporting group title	Armodafinil 150 mg
-----------------------	--------------------

Reporting group description:

Patients received a single 50 mg dose of armodafinil on day 1. No intervention was administered on days 2+3. Patients received a single 50 mg dose on day 4, 100 mg doses on days 5 and 6, then daily 150 mg doses on days 7 through 25. All doses of armodafinil must have been taken intact with up to 240 mL of water and the entire dose must have been consumed within 5 minutes.

Reporting group values	Armodafinil 50 mg	Armodafinil 100 mg	Armodafinil 150 mg
Number of subjects	14	13	13
Age categorical			
Units: Subjects			
Children (6-11 years)	4	3	3
Adolescents (12-17 years)	10	10	10
Age continuous			
Units: years			
arithmetic mean	13.1	13.3	13
standard deviation	± 2.38	± 3.07	± 2.68
Gender categorical			
Units: Subjects			
Female	6	4	7
Male	8	9	6
Race			
Units: Subjects			
White	7	5	4
Black	4	8	8
Asian	1	0	0
Other	2	0	1
Ethnicity			
Units: Subjects			
Not Hispanic or Latino	12	12	13
Hispanic or Latino	2	1	0
Clinical Global Impression of Severity (CGI-S) for Depression			
The CGI-S is an observer-rated scale that measures illness severity on a 7-point scale, with the severity of illness scale using a range of responses from 1 (normal) through to 7 (amongst the most severely ill patients).			

Units: Subjects			
Normal (no signs of illness)	1	1	0
Borderline ill	0	0	0
Mildly (slightly ill)	0	1	1
Moderately ill	7	7	4
Markedly ill	4	3	5
Severely ill	2	1	3
Among the most extremely ill patients	0	0	0
Skin Evaluation			
Units: Subjects			
Abnormal at baseline	0	0	1
Normal at baseline	14	13	12
Electrocardiogram (ECG)			
Units: Subjects			
Normal at baseline	9	10	10
Abnormal at baseline	5	3	3
Body Mass Index			
Units: kg/m <sup>2</sup>			
arithmetic mean	29	24.9	25.6
standard deviation	± 7.28	± 6.77	± 5.43

<b>Reporting group values</b>	Total		
Number of subjects	40		
Age categorical			
Units: Subjects			
Children (6-11 years)	10		
Adolescents (12-17 years)	30		
Age continuous			
Units: years			
arithmetic mean	-		
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	17		
Male	23		
Race			
Units: Subjects			
White	16		
Black	20		
Asian	1		
Other	3		
Ethnicity			
Units: Subjects			
Not Hispanic or Latino	37		
Hispanic or Latino	3		
Clinical Global Impression of Severity (CGI-S) for Depression			
The CGI-S is an observer-rated scale that measures illness severity on a 7-point scale, with the severity of illness scale using a range of responses from 1 (normal) through to 7 (amongst the most severely ill patients).			
Units: Subjects			

Normal (no signs of illness)	2		
Borderline ill	0		
Mildly (slightly ill)	2		
Moderately ill	18		
Markedly ill	12		
Severely ill	6		
Among the most extremely ill patients	0		
Skin Evaluation			
Units: Subjects			
Abnormal at baseline	1		
Normal at baseline	39		
Electrocardiogram (ECG)			
Units: Subjects			
Normal at baseline	29		
Abnormal at baseline	11		
Body Mass Index			
Units: kg/m <sup>2</sup>			
arithmetic mean			
standard deviation	-		

## End points

### End points reporting groups

Reporting group title	Armodafinil 50 mg
Reporting group description: Patients received a single 50 mg dose of armodafinil on day 1. No intervention was administered on days 2+3. Patients received a single 50 mg daily dose of armodafinil on days 4-25. All doses of armodafinil must have been taken intact with up to 240 mL of water and the entire dose must have been consumed within 5 minutes.	
Reporting group title	Armodafinil 100 mg
Reporting group description: Patients received a single 50 mg dose of armodafinil on day 1. No intervention was administered on days 2+3. Patients received a single 50 mg dose on day 4 then daily 100 mg doses on days 5 - 25. All doses of armodafinil must have been taken intact with up to 240 mL of water and the entire dose must have been consumed within 5 minutes.	
Reporting group title	Armodafinil 150 mg
Reporting group description: Patients received a single 50 mg dose of armodafinil on day 1. No intervention was administered on days 2+3. Patients received a single 50 mg dose on day 4, 100 mg doses on days 5 and 6, then daily 150 mg doses on days 7 through 25. All doses of armodafinil must have been taken intact with up to 240 mL of water and the entire dose must have been consumed within 5 minutes.	

### Primary: Maximum observed plasma concentration (C<sub>max</sub>) for Armodafinil after a Single Dose (Day 1) and after Multiple Doses (Day 25)

End point title	Maximum observed plasma concentration (C <sub>max</sub> ) for Armodafinil after a Single Dose (Day 1) and after Multiple Doses (Day 25) <sup>[1]</sup>
End point description:	
End point type	Primary
End point timeframe: Days 1 and 25: prior to and 0.5, 1, 2, 4, 6, 8, 12, 24, 48 and 72 hours after administration of armodafinil	
Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: No intention to make inference based on stat analysis; the intent is to support clinical judgement.	

End point values	Armodafinil 50 mg	Armodafinil 100 mg	Armodafinil 150 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14 <sup>[2]</sup>	12 <sup>[3]</sup>	12 <sup>[4]</sup>	
Units: micrograms/mL				
arithmetic mean (standard deviation)				
Single-dose (Day 1)	1.3 (± 0.214)	3.05 (± 1.388)	4.27 (± 1.048)	
Multiple-dose (Day 25)	1.76 (± 0.359)	4.22 (± 1.553)	5.78 (± 1.19)	

Notes:

[2] - PK analysis set

Day 1: n=14

Day 25: n=11

[3] - PK analysis set  
 Day 1: n=12  
 Day 25: n=11  
 [4] - PK analysis set  
 Day 1: n=12  
 Day 25: n=10

### Statistical analyses

No statistical analyses for this end point

### Primary: Time To Maximum Observed Drug Concentration (tmax) for Armodafinil after a Single Dose (Day 1) and after Multiple Doses (Day 25)

End point title	Time To Maximum Observed Drug Concentration (tmax) for Armodafinil after a Single Dose (Day 1) and after Multiple Doses (Day 25) <sup>[5]</sup>
-----------------	---

End point description:

End point type	Primary
----------------	---------

End point timeframe:

Days 1 and 25: prior to and 0.5, 1, 2, 4, 6, 8, 12, 24, 48 and 72 hours after administration of armodafinil

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No intention to make inference based on stat analysis; the intent is to support clinical judgement.

End point values	Armodafinil 50 mg	Armodafinil 100 mg	Armodafinil 150 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14 <sup>[6]</sup>	12 <sup>[7]</sup>	12 <sup>[8]</sup>	
Units: hours				
median (full range (min-max))				
Single-dose (Day 1)	2 (0.5 to 4.5)	2.4 (0.5 to 4.5)	2.3 (0.5 to 6.6)	
Multiple-dose (Day 25)	1 (0.5 to 4.4)	2.3 (1 to 4.5)	2.4 (1 to 6.5)	

Notes:

[6] - PK analysis set  
 Day 1: n=14  
 Day 25: n=11

[7] - PK analysis set  
 Day 1: n=12  
 Day 25: n=11

[8] - PK analysis set  
 Day 1: n=12  
 Day 25: n=10

### Statistical analyses

No statistical analyses for this end point

### Primary: Area Under The Plasma Concentration-Time Curve From Time 0 To The Time Of The Last Measurable Drug Concentration (AUC0-t) for Armodafinil after a Single Dose (Day 1) and after Multiple Doses (Day 25)

End point title	Area Under The Plasma Concentration-Time Curve From Time 0 To The Time Of The Last Measurable Drug Concentration (AUC0-t) for Armodafinil after a Single Dose (Day 1) and after
-----------------	---

End point description:

End point type Primary

End point timeframe:

Days 1 and 25: prior to and 0.5, 1, 2, 4, 6, 8, 12, 24, 48 and 72 hours after administration of armodafinil

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No intention to make inference based on stat analysis; the intent is to support clinical judgement.

End point values	Armodafinil 50 mg	Armodafinil 100 mg	Armodafinil 150 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14 <sup>[10]</sup>	12 <sup>[11]</sup>	12 <sup>[12]</sup>	
Units: µg·h/mL				
arithmetic mean (standard deviation)				
Single-dose (Day 1)	15.6 (± 3.88)	49.1 (± 31.88)	74.4 (± 23.38)	
Multiple-dose (Day 25)	24.6 (± 7.66)	85 (± 27.35)	119.8 (± 19.99)	

Notes:

[10] - PK analysis set

Day 1: n=14

Day 25: n=11

[11] - PK analysis set

Day 1: n=12

Day 25: n=11

[12] - PK analysis set

Day 1: n=12

Day 25: n=10

### Statistical analyses

No statistical analyses for this end point

### Primary: Area Under The Plasma Concentration-Time Curve From Time 0 To Infinity (AUC<sub>0-∞</sub>) for Armodafinil after a Single Dose (Day 1)

End point title	Area Under The Plasma Concentration-Time Curve From Time 0 To Infinity (AUC <sub>0-∞</sub> ) for Armodafinil after a Single Dose (Day 1) <sup>[13]</sup>
-----------------	--

End point description:

End point type Primary

End point timeframe:

Day 1: prior to and 0.5, 1, 2, 4, 6, 8, 12, 24, 48 and 72 hours after administration of armodafinil

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No intention to make inference based on stat analysis; the intent is to support clinical judgement.

<b>End point values</b>	Armodafinil 50 mg	Armodafinil 100 mg	Armodafinil 150 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	13 <sup>[14]</sup>	10 <sup>[15]</sup>	12 <sup>[16]</sup>	
Units: µg·h/mL				
arithmetic mean (standard deviation)	21.1 (± 5.06)	57.2 (± 33.33)	82.8 (± 24.06)	

Notes:

[14] - PK analysis set

[15] - PK analysis set

[16] - PK analysis set

## Statistical analyses

No statistical analyses for this end point

### Primary: Extrapolation for Armodafinil after a Single Dose (Day 1)

End point title	Extrapolation for Armodafinil after a Single Dose (Day 1) <sup>[17]</sup>
-----------------	---

End point description:

End point type	Primary
----------------	---------

End point timeframe:

Day 1: prior to and 0.5, 1, 2, 4, 6, 8, 12, 24, 48 and 72 hours after administration of armodafinil

Notes:

[17] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No intention to make inference based on stat analysis; the intent is to support clinical judgement.

<b>End point values</b>	Armodafinil 50 mg	Armodafinil 100 mg	Armodafinil 150 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	13 <sup>[18]</sup>	10 <sup>[19]</sup>	12 <sup>[20]</sup>	
Units: percentage				
arithmetic mean (standard deviation)	26.4 (± 8.41)	18.9 (± 8.1)	10.8 (± 5)	

Notes:

[18] - PK analysis set

[19] - PK analysis set

[20] - PK analysis set

## Statistical analyses

No statistical analyses for this end point

### Primary: Area Under The Plasma Concentration-Time Curve For One Dosing Interval Of A Multiple-Dose Regimen (AUC<sub>T</sub>) for Armodafinil (Day 25)

End point title	Area Under The Plasma Concentration-Time Curve For One Dosing Interval Of A Multiple-Dose Regimen (AUC <sub>T</sub> ) for Armodafinil (Day 25) <sup>[21]</sup>
-----------------	--

End point description:

End point type	Primary
----------------	---------

End point timeframe:

Day 25: prior to and 0.5, 1, 2, 4, 6, 8, 12, 24, 48 and 72 hours after administration of armodafinil

Notes:

[21] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No intention to make inference based on stat analysis; the intent is to support clinical judgement.

<b>End point values</b>	Armodafinil 50 mg	Armodafinil 100 mg	Armodafinil 150 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11 <sup>[22]</sup>	11 <sup>[23]</sup>	10 <sup>[24]</sup>	
Units: µg·h/mL				
arithmetic mean (standard deviation)	23.3 (± 4.91)	61.6 (± 20.33)	86.2 (± 13.83)	

Notes:

[22] - PK analysis set

[23] - PK analysis set

[24] - PK analysis set

### Statistical analyses

No statistical analyses for this end point

### Primary: Half-Life (t<sub>1/2</sub>) for Armodafinil after a Single Dose (Day 1) and after Multiple Doses (Day 25)

End point title	Half-Life (t <sub>1/2</sub> ) for Armodafinil after a Single Dose (Day 1) and after Multiple Doses (Day 25) <sup>[25]</sup>
-----------------	---

End point description:

End point type	Primary
----------------	---------

End point timeframe:

Days 1 and 25: prior to and 0.5, 1, 2, 4, 6, 8, 12, 24, 48 and 72 hours after administration of armodafinil

Notes:

[25] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No intention to make inference based on stat analysis; the intent is to support clinical judgement.

<b>End point values</b>	Armodafinil 50 mg	Armodafinil 100 mg	Armodafinil 150 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14 <sup>[26]</sup>	12 <sup>[27]</sup>	12 <sup>[28]</sup>	
Units: hours				
arithmetic mean (standard deviation)				
Single-dose (Day 1)	11.1 (± 2.15)	12.1 (± 2.23)	12.8 (± 4.18)	
Multiple-dose (Day 25)	12.6 (± 1.98)	14.1 (± 2.54)	13.8 (± 2.88)	

Notes:

[26] - PK analysis set

Day 1: n=13

Day 25: n=11

[27] - PK analysis set

Day 1: n=10

Day 25: n=11

[28] - PK analysis set

Day 1: n=12

Day 25: n=10

## Statistical analyses

No statistical analyses for this end point

### Primary: Apparent Total Clearance (CL/F) for Armodafinil after a Single Dose (Day 1) and after Multiple Doses (Day 25)

End point title	Apparent Total Clearance (CL/F) for Armodafinil after a Single Dose (Day 1) and after Multiple Doses (Day 25) <sup>[29]</sup>
-----------------	---

End point description:

End point type	Primary
----------------	---------

End point timeframe:

Days 1 and 25: prior to and 0.5, 1, 2, 4, 6, 8, 12, 24, 48 and 72 hours after administration of armodafinil

Notes:

[29] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No intention to make inference based on stat analysis; the intent is to support clinical judgement.

End point values	Armodafinil 50 mg	Armodafinil 100 mg	Armodafinil 150 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14 <sup>[30]</sup>	12 <sup>[31]</sup>	12 <sup>[32]</sup>	
Units: mL/minute				
arithmetic mean (standard deviation)				
Single-dose (Day 1)	41.7 (± 10.77)	34.7 (± 11.95)	32.4 (± 8.86)	
Multiple-dose (Day 25)	37.3 (± 8.27)	28.9 (± 6.42)	29.7 (± 4.97)	

Notes:

[30] - PK analysis set

Day 1: n=13

Day 25: n=11

[31] - PK analysis set

Day 1: n=10

Day 25: n=11

[32] - PK analysis set

Day 1: n=12

Day 25: n=10

## Statistical analyses

No statistical analyses for this end point

### Primary: Apparent Volume of Distribution (V<sub>z</sub>/F) for Armodafinil after a Single Dose (Day 1) and after Multiple Doses (Day 25)

End point title	Apparent Volume of Distribution (V <sub>z</sub> /F) for Armodafinil after a Single Dose (Day 1) and after Multiple Doses (Day 25) <sup>[33]</sup>
-----------------	---

End point description:

End point type	Primary
----------------	---------

End point timeframe:

Days 1 and 25: prior to and 0.5, 1, 2, 4, 6, 8, 12, 24, 48 and 72 hours after administration of armodafinil

Notes:

[33] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No intention to make inference based on stat analysis; the intent is to support clinical judgement.

<b>End point values</b>	Armodafinil 50 mg	Armodafinil 100 mg	Armodafinil 150 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14 <sup>[34]</sup>	12 <sup>[35]</sup>	12 <sup>[36]</sup>	
Units: liters				
arithmetic mean (standard deviation)				
Single-dose (Day 1)	39 (± 8.33)	35.3 (± 10.55)	34 (± 6.71)	
Multiple-dose (Day 25)	40.2 (± 8.93)	35.5 (± 9.84)	35.6 (± 12.68)	

Notes:

[34] - PK analysis set

Day 1: n=13

Day 25: n=11

[35] - PK analysis set

Day 1: n=10

Day 25: n=11

[36] - PK analysis set

Day 1: n=12

Day 25: n=10

## Statistical analyses

No statistical analyses for this end point

## Primary: Predicted Accumulation Ratio (Rpred) for Armodafinil after a Single Dose (Day 1)

End point title	Predicted Accumulation Ratio (Rpred) for Armodafinil after a Single Dose (Day 1) <sup>[37]</sup>
-----------------	--

End point description:

End point type	Primary
----------------	---------

End point timeframe:

Day 1: prior to and 0.5, 1, 2, 4, 6, 8, 12, 24, 48 and 72 hours after administration of armodafinil

Notes:

[37] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No intention to make inference based on stat analysis; the intent is to support clinical judgement.

<b>End point values</b>	Armodafinil 50 mg	Armodafinil 100 mg	Armodafinil 150 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	13 <sup>[38]</sup>	10 <sup>[39]</sup>	12 <sup>[40]</sup>	
Units: ratio				
arithmetic mean (standard deviation)	1.3 (± 0.11)	1.4 (± 0.15)	1.5 (± 0.26)	

Notes:

[38] - PK analysis set

[39] - PK analysis set

[40] - PK analysis set

## Statistical analyses

No statistical analyses for this end point

### Primary: Observed Accumulation Ratio (Robs) for Armodafinil after Multiple Doses (Day 25)

End point title	Observed Accumulation Ratio (Robs) for Armodafinil after Multiple Doses (Day 25) <sup>[41]</sup>
-----------------	--

End point description:

End point type	Primary
----------------	---------

End point timeframe:

Day 25: prior to and 0.5, 1, 2, 4, 6, 8, 12, 24, 48 and 72 hours after administration of armodafinil

Notes:

[41] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No intention to make inference based on stat analysis; the intent is to support clinical judgement.

End point values	Armodafinil 50 mg	Armodafinil 100 mg	Armodafinil 150 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11 <sup>[42]</sup>	11 <sup>[43]</sup>	10 <sup>[44]</sup>	
Units: ratio				
arithmetic mean (standard deviation)	1.5 (± 0.24)	1.6 (± 0.28)	1.5 (± 0.24)	

Notes:

[42] - PK analysis set

[43] - PK analysis set

[44] - PK analysis set

## Statistical analyses

No statistical analyses for this end point

### Primary: Steady-State Accumulation Ratio (Rss) for Armodafinil after Multiple Doses (Day 25)

End point title	Steady-State Accumulation Ratio (Rss) for Armodafinil after Multiple Doses (Day 25) <sup>[45]</sup>
-----------------	---

End point description:

End point type	Primary
----------------	---------

End point timeframe:

Day 25: prior to and 0.5, 1, 2, 4, 6, 8, 12, 24, 48 and 72 hours after administration of armodafinil

Notes:

[45] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No intention to make inference based on stat analysis; the intent is to support clinical judgement.

<b>End point values</b>	Armodafinil 50 mg	Armodafinil 100 mg	Armodafinil 150 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10 <sup>[46]</sup>	9 <sup>[47]</sup>	10 <sup>[48]</sup>	
Units: ratio				
arithmetic mean (standard deviation)	1.1 (± 0.18)	1.2 (± 0.27)	1 (± 0.22)	

Notes:

[46] - PK analysis set

[47] - PK analysis set

[48] - PK analysis set

## Statistical analyses

No statistical analyses for this end point

## Primary: Mean Trough Plasma Armodafinil Concentrations Following Once-Daily Oral Doses of Armodafinil on Days 11, 18 and 25

End point title	Mean Trough Plasma Armodafinil Concentrations Following Once-Daily Oral Doses of Armodafinil on Days 11, 18 and 25 <sup>[49]</sup>
-----------------	--

End point description:

End point type	Primary
----------------	---------

End point timeframe:

Days 11, 18, 25

Notes:

[49] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No intention to make inference based on stat analysis; the intent is to support clinical judgement.

<b>End point values</b>	Armodafinil 50 mg	Armodafinil 100 mg	Armodafinil 150 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14 <sup>[50]</sup>	12 <sup>[51]</sup>	12 <sup>[52]</sup>	
Units: µg/mL				
arithmetic mean (standard deviation)				
Day 11	0.566 (± 0.303)	1.472 (± 0.5004)	2.075 (± 0.9509)	
Day 18	0.511 (± 0.1695)	1.558 (± 0.4242)	2.348 (± 0.4494)	
Day 25	0.478 (± 0.2355)	1.456 (± 0.7369)	1.976 (± 0.6857)	

Notes:

[50] - PK analysis set

Day 11: 12 patients

Day 18: 10 patients

Day 25: 11 patients

[51] - PK analysis set

Day 11: 9 patients

Day 18: 8 patients

Day 25: 10 patients

[52] - PK analysis set

Day 11: 10 patients

Day 18: 10 patients

Day 25: 10 patients

## Statistical analyses

No statistical analyses for this end point

**Primary: Maximum observed plasma concentration (C<sub>max</sub>) for R-Modafinil Acid after a Single Dose (Day 1) and after Multiple Doses (Day 25)**

End point title | Maximum observed plasma concentration (C<sub>max</sub>) for R-Modafinil Acid after a Single Dose (Day 1) and after Multiple Doses (Day 25)<sup>[53]</sup>

End point description:

End point type | Primary

End point timeframe:

Days 1 and 25: prior to and 0.5, 1, 2, 4, 6, 8, 12, 24, 48 and 72 hours after administration of armodafinil

Notes:

[53] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No intention to make inference based on stat analysis; the intent is to support clinical judgement.

End point values	Armodafinil 50 mg	Armodafinil 100 mg	Armodafinil 150 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14 <sup>[54]</sup>	12 <sup>[55]</sup>	12 <sup>[56]</sup>	
Units: µg/mL				
arithmetic mean (standard deviation)				
Single-dose (Day 1)	0 (± 0)	0.17 (± 0.161)	0.37 (± 0.207)	
Multiple-dose (Day 25)	0.04 (± 0.087)	0.39 (± 0.093)	0.51 (± 0.162)	

Notes:

[54] - K analysis set

Day 1: n=14

Day 25: n=11

[55] - K analysis set

Day 1: n=12

Day 25: n=11

[56] - K analysis set

Day 1: n=12

Day 25: n=10

**Statistical analyses**

No statistical analyses for this end point

**Primary: Time To Maximum Observed Drug Concentration (t<sub>max</sub>) for R-Modafinil Acid after a Single Dose (Day 1) and after Multiple Doses (Day 25)**

End point title | Time To Maximum Observed Drug Concentration (t<sub>max</sub>) for R-Modafinil Acid after a Single Dose (Day 1) and after Multiple Doses (Day 25)<sup>[57]</sup>

End point description:

Values of 9999 = not calculable

End point type | Primary

End point timeframe:

Days 1 and 25: prior to and 0.5, 1, 2, 4, 6, 8, 12, 24, 48 and 72 hours after administration of armodafinil

Notes:

[57] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No intention to make inference based on stat analysis; the intent is to support clinical judgement.

<b>End point values</b>	Armodafinil 50 mg	Armodafinil 100 mg	Armodafinil 150 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14 <sup>[58]</sup>	12 <sup>[59]</sup>	12 <sup>[60]</sup>	
Units: hours				
median (full range (min-max))				
Single-dose (Day 1)	9999 (9999 to 9999)	2.5 (1 to 4.5)	2.5 (1 to 4.9)	
Multiple-dose (Day 25)	2.4 (2.4 to 2.5)	2.4 (0.6 to 4.5)	4.1 (2 to 5.1)	

Notes:

[58] - PK analysis set

Day 1: n=14

Day 25: n=2

[59] - PK analysis set

Day 1: n=7

Day 25: n=11

[60] - PK analysis set

Day 1: n=10

Day 25: n=10

## Statistical analyses

No statistical analyses for this end point

### **Primary: Area Under The Plasma Concentration-Time Curve From Time 0 To The Time Of The Last Measurable Drug Concentration (AUC<sub>0-t</sub>) for R-Modafinil Acid after a Single Dose (Day 1) and after Multiple Doses (Day 25)**

End point title	Area Under The Plasma Concentration-Time Curve From Time 0 To The Time Of The Last Measurable Drug Concentration (AUC <sub>0-t</sub> ) for R-Modafinil Acid after a Single Dose (Day 1) and after Multiple Doses (Day 25) <sup>[61]</sup>
-----------------	---

End point description:

End point type	Primary
----------------	---------

End point timeframe:

Days 1 and 25: prior to and 0.5, 1, 2, 4, 6, 8, 12, 24, 48 and 72 hours after administration of armodafinil

Notes:

[61] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No intention to make inference based on stat analysis; the intent is to support clinical judgement.

<b>End point values</b>	Armodafinil 50 mg	Armodafinil 100 mg	Armodafinil 150 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14 <sup>[62]</sup>	12 <sup>[63]</sup>	12 <sup>[64]</sup>	
Units: µg·h/mL				
arithmetic mean (standard deviation)				
Single-dose (Day 1)	0 (± 0)	1 (± 1.06)	3.4 (± 2.19)	
Multiple-dose (Day 25)	0 (± 0)	3.7 (± 1.82)	7.3 (± 4.28)	

Notes:

[62] - PK analysis set

Day 1: n=14

Day 25: n=11

[63] - PK analysis set

Day 1: n=12

Day 25: n=11

[64] - PK analysis set

Day 1: n=12

Day 25: n=10

## Statistical analyses

No statistical analyses for this end point

### Primary: Area Under The Plasma Concentration-Time Curve From Time 0 To Infinity (AUC<sub>0-∞</sub>) for R-Modafinil Acid after a Single Dose (Day 1)

End point title	Area Under The Plasma Concentration-Time Curve From Time 0 To Infinity (AUC <sub>0-∞</sub> ) for R-Modafinil Acid after a Single Dose (Day 1) <sup>[65]</sup>
-----------------	---

End point description:

Values of 9999 = not calculable

End point type	Primary
----------------	---------

End point timeframe:

Day 1: prior to and 0.5, 1, 2, 4, 6, 8, 12, 24, 48 and 72 hours after administration of armodafinil

Notes:

[65] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No intention to make inference based on stat analysis; the intent is to support clinical judgement.

End point values	Armodafinil 50 mg	Armodafinil 100 mg	Armodafinil 150 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14 <sup>[66]</sup>	12 <sup>[67]</sup>	12 <sup>[68]</sup>	
Units: µg·h/mL				
arithmetic mean (standard deviation)	9999 (± 9999)	9999 (± 9999)	8.8 (± 2.54)	

Notes:

[66] - PK analysis set

[67] - PK analysis set

[68] - PK analysis set

## Statistical analyses

No statistical analyses for this end point

### Primary: Extrapolation for R-Modafinil Acid after a Single Dose (Day 1)

End point title	Extrapolation for R-Modafinil Acid after a Single Dose (Day 1)
-----------------	--

End point description:

Values of 9999 = not calculable

End point type	Primary
----------------	---------

End point timeframe:

Day 1: prior to and 0.5, 1, 2, 4, 6, 8, 12, 24, 48 and 72 hours after administration of armodafinil

Notes:

[69] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No intention to make inference based on stat analysis; the intent is to support clinical judgement.

<b>End point values</b>	Armodafinil 50 mg	Armodafinil 100 mg	Armodafinil 150 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14 <sup>[70]</sup>	12 <sup>[71]</sup>	8 <sup>[72]</sup>	
Units: percentage				
arithmetic mean (standard deviation)	9999 (± 9999)	9999 (± 9999)	48.8 (± 8.75)	

Notes:

[70] - PK analysis set

[71] - PK analysis set

[72] - PK analysis set

### Statistical analyses

No statistical analyses for this end point

### Primary: Area Under The Plasma Concentration-Time Curve For One Dosing Interval Of A Multiple-Dose Regimen (AUC<sub>T</sub>) for R-Modafinil Acid (Day 25)

End point title	Area Under The Plasma Concentration-Time Curve For One Dosing Interval Of A Multiple-Dose Regimen (AUC <sub>T</sub> ) for R-Modafinil Acid (Day 25) <sup>[73]</sup>
End point description:	
Values of 9999 = not calculable	
End point type	Primary

End point timeframe:

Day 25: prior to and 0.5, 1, 2, 4, 6, 8, 12, 24, 48 and 72 hours after administration of armodafinil

Notes:

[73] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No intention to make inference based on stat analysis; the intent is to support clinical judgement.

<b>End point values</b>	Armodafinil 50 mg	Armodafinil 100 mg	Armodafinil 150 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14 <sup>[74]</sup>	4 <sup>[75]</sup>	8 <sup>[76]</sup>	
Units: µg·h/mL				
arithmetic mean (standard deviation)	9999 (± 9999)	6.8 (± 0.98)	8.5 (± 2.89)	

Notes:

[74] - PK analysis set

[75] - PK analysis set

[76] - PK analysis set

### Statistical analyses

No statistical analyses for this end point

### Primary: Half-Life (t<sub>1/2</sub>) for R-Modafinil Acid after a Single Dose (Day 1) and after Multiple Doses (Day 25)

End point title	Half-Life (t1/2) for R-Modafinil Acid after a Single Dose (Day 1) and after Multiple Doses (Day 25) <sup>[77]</sup>
-----------------	---

End point description:

Values of 9999 = not calculable

End point type	Primary
----------------	---------

End point timeframe:

Days 1 and 25: prior to and 0.5, 1, 2, 4, 6, 8, 12, 24, 48 and 72 hours after administration of armodafinil

Notes:

[77] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No intention to make inference based on stat analysis; the intent is to support clinical judgement.

End point values	Armodafinil 50 mg	Armodafinil 100 mg	Armodafinil 150 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14 <sup>[78]</sup>	12 <sup>[79]</sup>	12 <sup>[80]</sup>	
Units: hours				
arithmetic mean (standard deviation)				
Single-dose (Day 1)	9999 (± 9999)	9999 (± 9999)	11.8 (± 3.97)	
Multiple-dose (Day 25)	9999 (± 9999)	14.4 (± 4.41)	16.6 (± 2.88)	

Notes:

[78] - PK analysis set

[79] - PK analysis set

Day 1: n=12

Day 25: n=4

[80] - PK analysis set

Day 1: n=8

Day 25: n=6

## Statistical analyses

No statistical analyses for this end point

## Primary: Maximum observed plasma concentration (Cmax) for Modafinil Sulfone after a Single Dose (Day 1) and after Multiple Doses (Day 25)

End point title	Maximum observed plasma concentration (Cmax) for Modafinil Sulfone after a Single Dose (Day 1) and after Multiple Doses (Day 25) <sup>[81]</sup>
-----------------	--

End point description:

End point type	Primary
----------------	---------

End point timeframe:

Days 1 and 25: prior to and 0.5, 1, 2, 4, 6, 8, 12, 24, 48 and 72 hours after administration of armodafinil

Notes:

[81] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No intention to make inference based on stat analysis; the intent is to support clinical judgement.

<b>End point values</b>	Armodafinil 50 mg	Armodafinil 100 mg	Armodafinil 150 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14 <sup>[82]</sup>	12 <sup>[83]</sup>	12 <sup>[84]</sup>	
Units: µg/mL				
arithmetic mean (standard deviation)				
Single-dose (Day 1)	0 (± 0)	0.23 (± 0.34)	0.33 (± 0.203)	
Multiple-dose (Day 25)	0.28 (± 0.212)	1.86 (± 2.179)	2.58 (± 1.766)	

Notes:

[82] - PK analysis set

Day 1: n=14

Day 25: n=11

[83] - PK analysis set

Day 1: n=12

Day 25: n=11

[84] - PK analysis set

Day 1: n=12

Day 25: n=10

### Statistical analyses

No statistical analyses for this end point

### Primary: Time To Maximum Observed Drug Concentration (tmax) for Modafinil Sulfone after a Single Dose (Day 1) and after Multiple Doses (Day 25)

End point title	Time To Maximum Observed Drug Concentration (tmax) for Modafinil Sulfone after a Single Dose (Day 1) and after Multiple Doses (Day 25) <sup>[85]</sup>
-----------------	--

End point description:

Values of 9999 = not calculable

End point type	Primary
----------------	---------

End point timeframe:

Days 1 and 25: prior to and 0.5, 1, 2, 4, 6, 8, 12, 24, 48 and 72 hours after administration of armodafinil

Notes:

[85] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No intention to make inference based on stat analysis; the intent is to support clinical judgement.

<b>End point values</b>	Armodafinil 50 mg	Armodafinil 100 mg	Armodafinil 150 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14 <sup>[86]</sup>	12 <sup>[87]</sup>	12 <sup>[88]</sup>	
Units: hours				
median (full range (min-max))				
Single-dose (Day 1)	9999 (9999 to 9999)	24.1 (11.9 to 48)	24 (11.7 to 48.6)	
Multiple-dose (Day 25)	2.8 (0 to 8.2)	8.6 (0 to 23.7)	8.2 (0 to 22)	

Notes:

[86] - PK analysis set

Day 1: n=14

Day 25: n=8

[87] - PK analysis set

Day 1: n=7

Day 25: n=11

[88] - PK analysis set

Day 1: n=10  
Day 25: n=10

## Statistical analyses

No statistical analyses for this end point

### Primary: Area Under The Plasma Concentration-Time Curve From Time 0 To The Time Of The Last Measurable Drug Concentration (AUC<sub>0-t</sub>) for Modafinil Sulfone after a Single Dose (Day 1) and after Multiple Doses (Day 25)

End point title	Area Under The Plasma Concentration-Time Curve From Time 0 To The Time Of The Last Measurable Drug Concentration (AUC <sub>0-t</sub> ) for Modafinil Sulfone after a Single Dose (Day 1) and after Multiple Doses (Day 25) <sup>[89]</sup>
-----------------	--

End point description:

End point type	Primary
----------------	---------

End point timeframe:

Days 1 and 25: prior to and 0.5, 1, 2, 4, 6, 8, 12, 24, 48 and 72 hours after administration of armodafinil

Notes:

[89] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No intention to make inference based on stat analysis; the intent is to support clinical judgement.

End point values	Armodafinil 50 mg	Armodafinil 100 mg	Armodafinil 150 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14 <sup>[90]</sup>	12 <sup>[91]</sup>	12 <sup>[92]</sup>	
Units: µg·h/mL				
arithmetic mean (standard deviation)				
Single-dose (Day 1)	0 (± 0)	8.4 (± 19.28)	12.6 (± 11.92)	
Multiple-dose (Day 25)	8.6 (± 8.46)	93 (± 119.28)	114.4 (± 78.36)	

Notes:

[90] - PK analysis set

Day 1: n=14

Day 25: n=11

[91] - PK analysis set

Day 1: n=12

Day 25: n=11

[92] - PK analysis set

Day 1: n=12

Day 25: n=10

## Statistical analyses

No statistical analyses for this end point

### Primary: Area Under The Plasma Concentration-Time Curve For One Dosing Interval Of A Multiple-Dose Regimen (AUC) for Modafinil Sulfone (Day 25)

End point title	Area Under The Plasma Concentration-Time Curve For One
-----------------	--

End point description:

End point type Primary

End point timeframe:

Day 25: prior to and 0.5, 1, 2, 4, 6, 8, 12, 24, 48 and 72 hours after administration of armodafinil

Notes:

[93] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No intention to make inference based on stat analysis; the intent is to support clinical judgement.

End point values	Armodafinil 50 mg	Armodafinil 100 mg	Armodafinil 150 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5 <sup>[94]</sup>	11 <sup>[95]</sup>	10 <sup>[96]</sup>	
Units: µg·h/mL				
arithmetic mean (standard deviation)	9.7 (± 2.21)	39 (± 46.39)	56.8 (± 38.34)	

Notes:

[94] - PK analysis set

[95] - PK analysis set

[96] - PK analysis set

### Statistical analyses

No statistical analyses for this end point

### Primary: Half-Life (t<sub>1/2</sub>) for Modafinil Sulfone after a Single Dose (Day 1) and after Multiple Doses (Day 25)

End point title Half-Life (t<sub>1/2</sub>) for Modafinil Sulfone after a Single Dose (Day 1) and after Multiple Doses (Day 25)<sup>[97]</sup>

End point description:

Values of 9999 = not calculable

End point type Primary

End point timeframe:

Days 1 and 25: prior to and 0.5, 1, 2, 4, 6, 8, 12, 24, 48 and 72 hours after administration of armodafinil

Notes:

[97] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No intention to make inference based on stat analysis; the intent is to support clinical judgement.

End point values	Armodafinil 50 mg	Armodafinil 100 mg	Armodafinil 150 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14 <sup>[98]</sup>	12 <sup>[99]</sup>	12 <sup>[100]</sup>	
Units: hours				
arithmetic mean (standard deviation)				
Single-dose (Day 1)	9999 (± 9999)	9999 (± 9999)	38.6 (± 9999)	
Multiple-dose (Day 25)	42.7 (± 11.13)	32.5 (± 5.83)	35.9 (± 15.46)	

Notes:

[98] - PK analysis set

Day 1: n=14

Day 25: n=3

[99] - PK analysis set

Day 1: n=14

Day 25: n=10

[100] - PK analysis set

Day 1: n=1

Day 25: n=6

## Statistical analyses

No statistical analyses for this end point

## Secondary: Patients with Treatment-Emergent Adverse Events (AE)

End point title Patients with Treatment-Emergent Adverse Events (AE)

End point description:

An adverse event was defined as any untoward medical occurrence that develops or worsens in severity during the conduct of a clinical study and does not necessarily have a causal relationship to the study drug. Treatment-emergent AEs refer to those that began or worsened after treatment start.

Severity was rated by the investigator on a scale of mild, moderate and severe, with severe= an AE which prevents normal daily activities. Relation of AE to treatment was determined by the investigator. Serious AEs include death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, a congenital anomaly or birth defect, OR an important medical event that jeopardized the patient and required medical intervention to prevent the previously listed serious outcomes.

End point type Secondary

End point timeframe:

Day 1 up to Day 35

End point values	Armodafinil 50 mg	Armodafinil 100 mg	Armodafinil 150 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14 <sup>[101]</sup>	13 <sup>[102]</sup>	13 <sup>[103]</sup>	
Units: patients				
Any AE	9	4	9	
Severe AE	0	1	0	
Treatment-related AE	3	3	3	
Deaths	0	0	0	
Other serious AEs	0	0	0	
Withdrawn from study due to AE	0	0	0	

Notes:

[101] - Safety analysis set

[102] - Safety analysis set

[103] - Safety analysis set

## Statistical analyses

No statistical analyses for this end point

## Secondary: Patients with Clinically Significant Post Baseline Laboratory Test Results

End point title Patients with Clinically Significant Post Baseline Laboratory Test Results

End point description:

Outcome summarizes the number of patients with post-baseline clinically significant serum chemistry, hematology or urinalysis tests.

End point type Secondary

End point timeframe:

Day 1 to Day 25

End point values	Armodafinil 50 mg	Armodafinil 100 mg	Armodafinil 150 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14 <sup>[104]</sup>	13 <sup>[105]</sup>	13 <sup>[106]</sup>	
Units: patients	0	0	0	

Notes:

[104] - Safety analysis set

[105] - Safety analysis set

[106] - Safety analysis set

### Statistical analyses

No statistical analyses for this end point

### Secondary: Patients with Clinically Significant Post Baseline Vital Sign Results

End point title Patients with Clinically Significant Post Baseline Vital Sign Results

End point description:

Summary of patients with at least one post baseline vital sign abnormality. Significance criteria for vital signs with findings are:

Pulse rate (high):  $\geq 120$  and increase over baseline of  $\geq 15$  beats/minute

Sitting systolic blood pressure (high):  $\geq 130$  and increase over baseline  $\geq 20$  mmHg

Sitting diastolic blood pressure (high):  $\geq 85$  and increase over baseline  $\geq 15$  mmHg

Sitting diastolic blood pressure (low):  $\leq 50$  and decrease over baseline  $\geq 15$  mmHg

End point type Secondary

End point timeframe:

Day 1 to Day 35

End point values	Armodafinil 50 mg	Armodafinil 100 mg	Armodafinil 150 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14 <sup>[107]</sup>	13 <sup>[108]</sup>	13 <sup>[109]</sup>	
Units: patients				
Pulse rate (high)	0	2	1	
Sitting systolic blood pressure (high)	7	5	5	
Sitting diastolic blood pressure (high)	3	5	5	
Sitting diastolic blood pressure (low)	2	0	1	

Notes:

[107] - Safety analysis set

[108] - Safety analysis set

[109] - Safety analysis set

## Statistical analyses

No statistical analyses for this end point

### Secondary: Electrocardiogram (ECG) Findings Shift From Baseline to Overall

End point title	Electrocardiogram (ECG) Findings Shift From Baseline to Overall
-----------------	---

End point description:

Resting 12-lead ECG were taken at baseline and Day 25 or early withdrawal. The worst post baseline finding for each patient is summarized.

Shifts are read as: Baseline / Overall

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline (Day -1), Day 25 or early withdrawal

End point values	Armodafinil 50 mg	Armodafinil 100 mg	Armodafinil 150 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14 <sup>[110]</sup>	13 <sup>[111]</sup>	13 <sup>[112]</sup>	
Units: patients				
Normal / Normal	7	8	9	
Normal / Abnormal	2	2	1	
Abnormal / Normal	1	1	1	
Abnormal / Abnormal	4	1	2	

Notes:

[110] - Safety analysis set

[111] - Safety analysis set

One patient did not have both a baseline and post baseline ECG

[112] - Safety analysis set

## Statistical analyses

No statistical analyses for this end point

### Secondary: Patients with Post Baseline Changes in Body Weight or Body Temperature

End point title	Patients with Post Baseline Changes in Body Weight or Body Temperature
-----------------	--

End point description:

Patients with post baseline changes in body weight or body temperature are counted.

End point type	Secondary
----------------	-----------

End point timeframe:

Days 1 - 25

<b>End point values</b>	Armodafinil 50 mg	Armodafinil 100 mg	Armodafinil 150 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14 <sup>[113]</sup>	13 <sup>[114]</sup>	13 <sup>[115]</sup>	
Units: patients	0	0	0	

Notes:

[113] - Safety analysis set

[114] - Safety analysis set

[115] - Safety analysis set

### Statistical analyses

No statistical analyses for this end point

### Secondary: Patients with Post Baseline Abnormal Skin Evaluations

End point title	Patients with Post Baseline Abnormal Skin Evaluations
End point description:	Special attention was paid to skin rashes or hypersensitivity reactions.
End point type	Secondary
End point timeframe:	Day 1 – Day 35

<b>End point values</b>	Armodafinil 50 mg	Armodafinil 100 mg	Armodafinil 150 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14 <sup>[116]</sup>	13 <sup>[117]</sup>	13 <sup>[118]</sup>	
Units: patients	1	0	2	

Notes:

[116] - Safety analysis set

[117] - Safety analysis set

[118] - Safety analysis set

### Statistical analyses

No statistical analyses for this end point

### Secondary: Patients with Post Baseline Suicidal Ideation as Measured by the Columbia Suicide Severity Rating Scale (C-SSRS) Scale for Children

End point title	Patients with Post Baseline Suicidal Ideation as Measured by the Columbia Suicide Severity Rating Scale (C-SSRS) Scale for Children
End point description:	The C-SSRS-Children's Since Last Visit version was used post baseline at day 1 discharge from the study center, each weekly outpatient visit on days 11 and 18, check-in to the study center on day 24, at the final assessment (or early withdrawal), and at the follow-up visit (approximately day 32). Any abnormal finding is summarized.
End point type	Secondary
End point timeframe:	Day 1 to Day 35

<b>End point values</b>	Armodafinil 50 mg	Armodafinil 100 mg	Armodafinil 150 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14 <sup>[119]</sup>	13 <sup>[120]</sup>	13 <sup>[121]</sup>	
Units: patients	0	0	0	

Notes:

[119] - Safety analysis set

[120] - Safety analysis set

[121] - Safety analysis set

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline after a Single Dose (Day 1) and after Multiple Doses (Day 25) in Multiple Sleep Latency Test (MSLT)

End point title	Change from Baseline after a Single Dose (Day 1) and after Multiple Doses (Day 25) in Multiple Sleep Latency Test (MSLT)
-----------------	--

End point description:

The MSLT is an objective assessment of sleepiness that measures the likelihood of falling asleep (Carskadon et al 1986). The test consists of five 20-minute naps performed at 1000, 1200, 1400, 1600, and 1800. Every effort should have been made to perform each MSLT assessment at the specified time relative to dose administration. The date and time of MSLT assessment were reflected on the case report form.

MSLT was performed on the day before study drug administration (day -1), on the day of study drug administration on days 1 and 25. No napping was permitted between MSLT naps. For each nap, sleep latency was measured as the elapsed time from lights-out to the first epoch scored as sleep. MSLT tracings from all centers were sent to an independent evaluator to be scored. Mean sleep latency was the average of the sleep latencies from the 5 naps performed at each time point.

Positive change from baseline scores indicate longer periods of wakefulness.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline (Day -1), Days 1 and 25

<b>End point values</b>	Armodafinil 50 mg	Armodafinil 100 mg	Armodafinil 150 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14 <sup>[122]</sup>	13 <sup>[123]</sup>	13 <sup>[124]</sup>	
Units: minutes				
arithmetic mean (standard deviation)				
Single Dose (Day 1)	1.9 (± 3.69)	4.3 (± 5.02)	4.9 (± 5.82)	
Multiple Doses (Day 25)	2.1 (± 4.81)	2.1 (± 3.14)	2.3 (± 6.4)	

Notes:

[122] - Pharmacodynamic analysis set

Day 1: n=14

Day 25: n=12

[123] - Pharmacodynamic analysis set

Day 1: n=13

Day 25: n=12

[124] - Pharmacodynamic analysis set

Day 1: n=13

Day 25: n=10

## Statistical analyses

No statistical analyses for this end point

### Secondary: Clinical Global Impression of Change (GCI-C) of Excessive Sleepiness after a Single Dose (Day 1) and after Multiple Doses (Day 25)

End point title	Clinical Global Impression of Change (GCI-C) of Excessive Sleepiness after a Single Dose (Day 1) and after Multiple Doses (Day 25)
-----------------	--

End point description:

The CGI-C is an assessment by the investigator of change in the patient's severity of excessive sleepiness (ES) during the course of the study. The scale has been used in child/adolescent studies with modafinil, is easily administered, and provides useful information regarding clinical benefit. At each time point, the physician (or another qualified clinician, if other than the physician) asked the parent or legal guardian to assess the child's home behavior over the past week. If possible, the rater and the parent/legal guardian respondent should have remained consistent for each child for the duration of the study. The CGI-C ratings were assessed using the following 7 categories and scoring assignments:

1=very much improved

2=much improved

3=minimally improved

4=no change

5=minimally worse

6=much worse

7=very much worse

End point type	Secondary
----------------	-----------

End point timeframe:

Day 1 and 25

End point values	Armodafinil 50 mg	Armodafinil 100 mg	Armodafinil 150 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14 <sup>[125]</sup>	13 <sup>[126]</sup>	13 <sup>[127]</sup>	
Units: patients				
Day 1: Very much improved	1	0	1	
Day 1: Much improved	4	7	6	
Day 1: Minimally improved	4	4	5	
Day 1: No change	5	2	1	
Day 1: Minimally worse	0	0	0	
Day 1: Much worse	0	0	0	
Day 1: Very much worse	0	0	0	
Day 1: Not assessed	0	0	0	
Day 25: Very much improved	0	0	2	
Day 25: Much improved	5	7	6	
Day 25: Minimally improved	3	3	1	
Day 25: No change	2	2	1	

Day 25: Minimally worse	2	0	0	
Day 25: Much worse	0	0	0	
Day 25: Very much worse	0	0	0	
Day 25: Not assessed	0	0	0	

Notes:

[125] - Pharmacodynamic analysis set

Day 1: n=14

Day 25: n=12

[126] - Pharmacodynamic analysis set

Day 1: n=13

Day 25: n=12

[127] - Pharmacodynamic analysis set

Day 1: n=13

Day 25: n=10

## **Statistical analyses**

---

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Day 1 up to Day 35

Assessment type	Systematic
-----------------	------------

### Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	18.1
--------------------	------

### Reporting groups

Reporting group title	Armodafinil 50 mg
-----------------------	-------------------

Reporting group description:

Patients received a single 50 mg dose of armodafinil on day 1. No intervention was administered on days 2+3. Patients received a single 50 mg daily dose of armodafinil on days 4-25. All doses of armodafinil must have been taken intact with up to 240 mL of water and the entire dose must have been consumed within 5 minutes.

Reporting group title	Armodafinil 100 mg
-----------------------	--------------------

Reporting group description:

Patients received a single 50 mg dose of armodafinil on day 1. No intervention was administered on days 2+3. Patients received a single 50 mg dose on day 4 then daily 100 mg doses on days 5 - 25. All doses of armodafinil must have been taken intact with up to 240 mL of water and the entire dose must have been consumed within 5 minutes.

Reporting group title	Armodafinil 150 mg
-----------------------	--------------------

Reporting group description:

Patients received a single 50 mg dose of armodafinil on day 1. No intervention was administered on days 2+3. Patients received a single 50 mg dose on day 4, 100 mg doses on days 5 and 6, then daily 150 mg doses on days 7 through 25. All doses of armodafinil must have been taken intact with up to 240 mL of water and the entire dose must have been consumed within 5 minutes.

<b>Serious adverse events</b>	Armodafinil 50 mg	Armodafinil 100 mg	Armodafinil 150 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 13 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 5 %

<b>Non-serious adverse events</b>	Armodafinil 50 mg	Armodafinil 100 mg	Armodafinil 150 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 14 (64.29%)	4 / 13 (30.77%)	9 / 13 (69.23%)
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	0 / 14 (0.00%)	2 / 13 (15.38%)	0 / 13 (0.00%)
occurrences (all)	0	2	0
Pyrexia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
Chest pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Feeling jittery			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	2
Vessel puncture site pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	2
Irritability			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	0 / 13 (0.00%)
occurrences (all)	2	0	0
Hunger			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Sneezing			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Cough			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	0 / 13 (0.00%)
occurrences (all)	0	2	0
Upper respiratory tract congestion			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Epistaxis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			

Middle insomnia subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 13 (0.00%) 0	1 / 13 (7.69%) 1
Depression subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 13 (0.00%) 0	1 / 13 (7.69%) 1
Agitation subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 13 (0.00%) 0	1 / 13 (7.69%) 1
Nightmare subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 13 (0.00%) 0	0 / 13 (0.00%) 0
Intermittent explosive disorder subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 13 (0.00%) 0	0 / 13 (0.00%) 0
Emotional disorder subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 13 (0.00%) 0	0 / 13 (0.00%) 0
Aggression subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 13 (0.00%) 0	0 / 13 (0.00%) 0
Investigations			
Blood pressure systolic increased subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 13 (0.00%) 0	0 / 13 (0.00%) 0
Electrocardiogram Q wave abnormal subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 13 (0.00%) 0	0 / 13 (0.00%) 0
Injury, poisoning and procedural complications			
Subcutaneous haematoma subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 13 (0.00%) 0	1 / 13 (7.69%) 1
Excoriation subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 13 (0.00%) 0	1 / 13 (7.69%) 1
Contusion			

subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 13 (0.00%) 0	1 / 13 (7.69%) 1
Fall subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 13 (0.00%) 0	1 / 13 (7.69%) 1
Foreign body subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 13 (0.00%) 0	0 / 13 (0.00%) 0
Cardiac disorders Tachycardia subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 13 (0.00%) 0	1 / 13 (7.69%) 1
Palpitations subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 13 (7.69%) 1	0 / 13 (0.00%) 0
Nervous system disorders Headache subjects affected / exposed occurrences (all)	3 / 14 (21.43%) 7	1 / 13 (7.69%) 2	4 / 13 (30.77%) 8
Somnolence subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 2	0 / 13 (0.00%) 0	1 / 13 (7.69%) 1
Lethargy subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 13 (0.00%) 0	1 / 13 (7.69%) 1
Dizziness subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 13 (0.00%) 0	1 / 13 (7.69%) 1
Disturbance in attention subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 13 (0.00%) 0	0 / 13 (0.00%) 0
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 13 (0.00%) 0	1 / 13 (7.69%) 1
Ear pain			

subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 13 (7.69%) 1	0 / 13 (0.00%) 0
<b>Gastrointestinal disorders</b>			
<b>Nausea</b>			
subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	1 / 13 (7.69%) 1	2 / 13 (15.38%) 3
<b>Abdominal pain upper</b>			
subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 2	1 / 13 (7.69%) 2	0 / 13 (0.00%) 0
<b>Vomiting</b>			
subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 13 (0.00%) 0	1 / 13 (7.69%) 1
<b>Gingival pruritus</b>			
subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 13 (7.69%) 1	0 / 13 (0.00%) 0
<b>Dry mouth</b>			
subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 13 (0.00%) 0	1 / 13 (7.69%) 1
<b>Tongue pruritus</b>			
subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 13 (7.69%) 1	0 / 13 (0.00%) 0
<b>Constipation</b>			
subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 13 (0.00%) 0	1 / 13 (7.69%) 1
<b>Toothache</b>			
subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 13 (7.69%) 1	0 / 13 (0.00%) 0
<b>Skin and subcutaneous tissue disorders</b>			
<b>Rash</b>			
subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 13 (7.69%) 1	0 / 13 (0.00%) 0
<b>Ingrowing nail</b>			
subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 13 (0.00%) 0	1 / 13 (7.69%) 1
<b>Ecchymosis</b>			

subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 13 (0.00%) 0	1 / 13 (7.69%) 1
Dermatitis contact subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 13 (0.00%) 0	0 / 13 (0.00%) 0
Acne subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 13 (0.00%) 0	0 / 13 (0.00%) 0
Renal and urinary disorders Pollakiuria subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 13 (7.69%) 1	0 / 13 (0.00%) 0
Musculoskeletal and connective tissue disorders Musculoskeletal chest pain subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 13 (7.69%) 1	0 / 13 (0.00%) 0
Muscle twitching subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 13 (7.69%) 1	0 / 13 (0.00%) 0
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 13 (0.00%) 0	1 / 13 (7.69%) 1
Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 13 (7.69%) 1	0 / 13 (0.00%) 0
Herpes simplex subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 13 (0.00%) 0	1 / 13 (7.69%) 1
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	2 / 13 (15.38%) 2	1 / 13 (7.69%) 1

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 May 2012	Amendment 1 (dated 22 May 2012) to the protocol was issued before any patients were enrolled into the study. The primary reason for this amendment was to add a blood sample for measurement of hemoglobin obtained at the week 5 visit during period 2.
07 November 2012	Amendment 2 (dated 07 November 2012) to the protocol was issued after 1 patient was enrolled into the study. Changes to the protocol were considered to have no negative impact on the safety of the patient already enrolled into the study. The primary reason for this amendment was to add a pregnancy test and C-SSRS assessment at the follow-up visit. Criteria for the need for pregnancy testing were also modified and pharmacokinetic sampling added at each period 2 outpatient visit.
24 April 2013	Amendment 3 (dated 24 April 2013) to the protocol was issued after 3 patients were enrolled into the study. Changes to the protocol were considered to have no negative impact on the safety of patients already enrolled into the study. The primary reason for this amendment was to revise the overall study design from 2 periods to 1 while accommodating both single- and multiple-dose treatments.

Notes:

---

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported