



## Clinical trial results:

### Effects of Modafinil and Caffeine during the circadian trough on vigilance in healthy RNLAf aircrew: a randomized controlled trial

#### Summary

EudraCT number	2017-002288-16
Trial protocol	NL
Global end of trial date	25 June 2019

#### Results information

Result version number	v1 (current)
This version publication date	31 January 2022
First version publication date	31 January 2022

#### Trial information

##### Trial identification

Sponsor protocol code	MOCAFFE
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Dutch Trial Register: NTR6922

Notes:

#### Sponsors

Sponsor organisation name	Center for Man in Aviation
Sponsor organisation address	Kampweg 53, Soesterberg, Netherlands, 3769DE
Public contact	Y.Q. Wingelaar-Jagt, Center for Man in Aviation, +31 88 9530333 , YQ.Wingelaar.Jagt@mindef.nl
Scientific contact	Y.Q. Wingelaar-Jagt, Center for Man in Aviation, +31 88 9530333 , YQ.Wingelaar.Jagt@mindef.nl

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	01 November 2021
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	25 June 2019
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To investigate the effect of modafinil and caffeine on vigilance in low, medium and high caffeine consumers during the circadian trough in order to determine the best pharmacological agent to target fatigue.

Protection of trial subjects:

This clinical trial was conducted in accordance with the principles of the Declaration of Helsinki (1964), the International Conference on Harmonization, and the GCP guideline. This clinical trial is also conducted in accordance with the laws and regulations of the Netherlands, as well as any applicable guidelines. The study protocol was approved by the IEC (METC Brabant) at January 24, 2018.

Participants had already been medically examined in the previous year, so no medical or physical screening was necessary.

Vital signs including temperature, systolic (SBP) and diastolic (DBP) blood pressures and pulse were collected 4 times during each test day. Female subjects were tested for pregnancy.

Adverse events were collected throughout the study and at every visit after screening. During the trial day, subjects were continuously inquired about any adverse event. The medically-qualified investigator was available to provide clinical judgment on all trial-related medical issues including adverse events and clinical laboratory values.

Background therapy:

None

Evidence for comparator:

- The dosage of modafinil is 200 mg, compliant with the starting dose indicated for narcolepsy and which is regarded as an effective dose as a counter measurement for fatigue in military aviation.
- The dosage of caffeine is 300 mg, the usual dose administered to RNLAf aviators nowadays and considered a medium range but effective dose.
- The placebo will contain only a filler.

Actual start date of recruitment	12 November 2018
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	Netherlands: 32
Worldwide total number of subjects	32
EEA total number of subjects	32

Notes:

<b>Subjects enrolled per age group</b>	
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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	32
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Recruitment was initiated in november 2018 and continued during the first 4 months of 2019.

### Pre-assignment

Screening details:

All RNLAf personnel between 18 and 60 years of age were eligible to enter the study. Exclusion criteria were mainly based on possible side effects or interactions of one or both medicines, e.g., pregnancy or breastfeeding, the use of medication that is metabolized through CYP3A4/5, CYP2C19, or CYP2C9, and/or a history of psychiatric illness.

### Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Assessor

Blinding implementation details:

The study was double-blinded, both the subjects and investigators were unaware of the treatment given each day. For every subject, the Center received a treatment kit from BasicPharma, labeled with the subject number. Each treatment kit consisted of 3 separate containers, labeled test day 1, 2 or 3 as well as the subject number. Every test day, each subject was given the medication from his own treatment kit, from the corresponding container.

### Arms

Are arms mutually exclusive?	No
<b>Arm title</b>	Modafinil

Arm description:

The entire study consisted of 3 non-consecutive trial days for every participant during which modafinil, caffeine, and placebo were each administered once just after midnight. A wash-out period of at least 7 days was implemented to ensure that the investigational products were completely eliminated and would not interfere on subsequent trial days.

Arm type	Experimental
Investigational medicinal product name	Modafinil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

The dosage of modafinil is 200 mg, compliant with the starting dose indicated for narcolepsy and which is regarded as an effective dose as a counter measurement for fatigue in military aviation. Study medication will be administered orally with about 150 mL of water at ambient temperature.

<b>Arm title</b>	Caffeine
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Arm description:

The entire study consisted of 3 non-consecutive trial days for every participant during which modafinil, caffeine, and placebo were each administered once just after midnight. A wash-out period of at least 7 days was implemented to ensure that the investigational products were completely eliminated and would not interfere on subsequent trial days.

Arm type	Active comparator
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Investigational medicinal product name	Caffeine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

**Dosage and administration details:**

The dosage of caffeine is 300 mg, the usual dose administered to RNLAf aviators nowadays and considered a medium range but effective dose. Study medication will be administered orally with about 150 mL of water at ambient temperature.

<b>Arm title</b>	Placebo
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**Arm description:**

The entire study consisted of 3 non-consecutive trial days for every participant during which modafinil, caffeine, and placebo were each administered once just after midnight.

A wash-out period of at least 7 days was implemented to ensure that the investigational products were completely eliminated and would not interfere on subsequent trial days.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

**Dosage and administration details:**

The placebo will contain only a filler. Study medication will be administered orally with about 150 mL of water at ambient temperature.

<b>Number of subjects in period 1</b>	Modafinil	Caffeine	Placebo
Started	32	32	32
Completed	32	30	32
Not completed	0	2	0
Missed 1 trial day due to operational reasons	-	2	-

## Baseline characteristics

### Reporting groups

Reporting group title	Overall trial
Reporting group description: -	

Reporting group values	Overall trial	Total	
Number of subjects	32	32	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	32	32	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical			
Units: Subjects			
Female	5	5	
Male	27	27	

## End points

### End points reporting groups

Reporting group title	Modafinil
Reporting group description: The entire study consisted of 3 non-consecutive trial days for every participant during which modafinil, caffeine, and placebo were each administered once just after midnight. A wash-out period of at least 7 days was implemented to ensure that the investigational products were completely eliminated and would not interfere on subsequent trial days.	
Reporting group title	Caffeine
Reporting group description: The entire study consisted of 3 non-consecutive trial days for every participant during which modafinil, caffeine, and placebo were each administered once just after midnight. A wash-out period of at least 7 days was implemented to ensure that the investigational products were completely eliminated and would not interfere on subsequent trial days.	
Reporting group title	Placebo
Reporting group description: The entire study consisted of 3 non-consecutive trial days for every participant during which modafinil, caffeine, and placebo were each administered once just after midnight. A wash-out period of at least 7 days was implemented to ensure that the investigational products were completely eliminated and would not interfere on subsequent trial days.	

### Primary: VigTrack – Mean tracking error

End point title	VigTrack – Mean tracking error
End point description:	
End point type	Primary
End point timeframe: T = +6 h	

End point values	Modafinil	Caffeine	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	30	32	
Units: second				
number (confidence interval 95%)	83.26 (-25.20 to 191.73)	52.07 (-26.81 to 130.94)	272.59 (58.69 to 486.49)	

### Statistical analyses

Statistical analysis title	VigTrack – mean tracking error: Mod vs Caf
Comparison groups	Modafinil v Caffeine

Number of subjects included in analysis	62
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.666
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	31.197
Confidence interval	
level	95 %
sides	2-sided
lower limit	-115.784
upper limit	178.179
Variability estimate	Standard error of the mean
Dispersion value	71.366

<b>Statistical analysis title</b>	VigTrack – mean tracking error: Mod vs Plac
Comparison groups	Modafinil v Placebo
Number of subjects included in analysis	64
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.008
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-189.329
Confidence interval	
level	95 %
sides	2-sided
lower limit	-324.137
upper limit	-54.52
Variability estimate	Standard error of the mean
Dispersion value	65.456

<b>Statistical analysis title</b>	VigTrack – mean tracking error: Caf vs Plac
Comparison groups	Placebo v Caffeine
Number of subjects included in analysis	62
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.081
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-220.526
Confidence interval	
level	95 %
sides	2-sided
lower limit	-470.698
upper limit	29.646



Variability estimate	Standard error of the mean
Dispersion value	121.47

### Primary: SSS

End point title	SSS
End point description:	
End point type	Primary
End point timeframe:	
T= +6 h	

End point values	Modafinil	Caffeine	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	30	32	
Units: 1-7				
number (not applicable)	1.72	1.87	2.42	

### Statistical analyses

<b>Statistical analysis title</b>	SSS - Mod vs Caff
Comparison groups	Caffeine v Modafinil
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.191
Method	Wilcoxon (Mann-Whitney)

<b>Statistical analysis title</b>	SSS - Mod vs Plac
Comparison groups	Modafinil v Placebo
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Wilcoxon (Mann-Whitney)

<b>Statistical analysis title</b>	SSS - Caf vs Plac
Comparison groups	Placebo v Caffeine

Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.019
Method	Wilcoxon (Mann-Whitney)

### Primary: VigTrack - Mean Reaction Time

End point title	VigTrack - Mean Reaction Time
End point description:	
End point type	Primary
End point timeframe:	
T = +6 h	

End point values	Modafinil	Caffeine	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	30	32	
Units: second				
number (confidence interval 95%)	0.026 (-0.001 to 0.052)	0.044 (0.018 to 0.070)	0.093 (0.068 to 0.118)	

### Statistical analyses

<b>Statistical analysis title</b>	VigTrack - Mean RT: Mod vs Caf
Comparison groups	Modafinil v Caffeine
Number of subjects included in analysis	62
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.228
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.019
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	0.013
Variability estimate	Standard error of the mean
Dispersion value	0.015

<b>Statistical analysis title</b>	VigTrack - Mean RT: Mod vs Plac
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Comparison groups	Modafinil v Placebo
Number of subjects included in analysis	64
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.067
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.102
upper limit	-0.033
Variability estimate	Standard error of the mean
Dispersion value	0.017

<b>Statistical analysis title</b>	VigTrack - Mean RT: Caf vs Plac
Comparison groups	Placebo v Caffeine
Number of subjects included in analysis	62
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.003
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.049
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.079
upper limit	-0.019
Variability estimate	Standard error of the mean
Dispersion value	0.015

<b>Primary: PVT - 1/ mean RT</b>	
End point title	PVT - 1/ mean RT
End point description:	
End point type	Primary
End point timeframe:	
T = +6 h	

End point values	Modafinil	Caffeine	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	30	30	
Units: second				
number (confidence interval 95%)	0.000 (0.000 to 0.000)	0.000 (-0.001 to 0.000)	-0.001 (-0.001 to -0.001)	

## Statistical analyses

<b>Statistical analysis title</b>	PVT - 1/mean RT: Mod vs Caf
Comparison groups	Modafinil v Caffeine
Number of subjects included in analysis	62
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.08
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0000227
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0

<b>Statistical analysis title</b>	PVT - 1/mean RT: Mod vs Plac
Comparison groups	Modafinil v Placebo
Number of subjects included in analysis	62
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.001
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.001
Variability estimate	Standard error of the mean
Dispersion value	0

<b>Statistical analysis title</b>	PVT - 1/mean RT: Caf vs Plac
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Comparison groups	Caffeine v Placebo
Number of subjects included in analysis	60
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.001
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.001
Variability estimate	Standard error of the mean
Dispersion value	0

### Primary: PVT - Lapses

End point title	PVT - Lapses
End point description:	
End point type	Primary
End point timeframe:	
T = +6 h	

End point values	Modafinil	Caffeine	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	30	32	
Units: number				
number (confidence interval 95%)	5.355 (1.606 to 9.104)	9.615 (5.405 to 13.825)	19.914 (15.266 to 24.561)	

### Statistical analyses

<b>Statistical analysis title</b>	PVT - Lapses: Mod vs Caf
Comparison groups	Modafinil v Caffeine
Number of subjects included in analysis	62
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.159
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-4.26

Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.292
upper limit	1.772
Variability estimate	Standard error of the mean
Dispersion value	2.94

<b>Statistical analysis title</b>	PVT - Lapses: Mod vs Plac
Comparison groups	Modafinil v Placebo
Number of subjects included in analysis	64
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-14.559
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.936
upper limit	-9.182
Variability estimate	Standard error of the mean
Dispersion value	2.621

<b>Statistical analysis title</b>	PVT - Lapses: Caf vs Plac
Comparison groups	Placebo v Caffeine
Number of subjects included in analysis	62
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-10.299
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.171
upper limit	-5.426
Variability estimate	Standard error of the mean
Dispersion value	2.375

<b>Primary: VigTrack - Percentage Omissions</b>	
End point title	VigTrack - Percentage Omissions

End point description:

End point type	Primary
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End point timeframe:

T = +6 h

End point values	Modafinil	Caffeine	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	30	32	
Units: percentage				
number (confidence interval 95%)	2.565 (-0.591 to 5.721)	3.062 (-0.383 to 6.506)	8.580 (3.364 to 13.796)	

### Statistical analyses

Statistical analysis title	VigTrack - Omissions: Mod vs Caf
Comparison groups	Modafinil v Caffeine
Number of subjects included in analysis	62
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.816
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.497
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.841
upper limit	3.848
Variability estimate	Standard error of the mean
Dispersion value	2.11

Statistical analysis title	VigTrack - Omissions: Mod vs Plac
Comparison groups	Modafinil v Placebo
Number of subjects included in analysis	64
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.004
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-6.015

Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.864
upper limit	-2.166
Variability estimate	Standard error of the mean
Dispersion value	1.869

<b>Statistical analysis title</b>	VigTrack - Omissions: Caf vs Plac
Comparison groups	Placebo v Caffeine
Number of subjects included in analysis	62
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.048
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-5.518
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.971
upper limit	-0.065
Variability estimate	Standard error of the mean
Dispersion value	2.648



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Entire study

Adverse event reporting additional description:

Adverse events were collected throughout the study and at every visit after screening. During the trial day, subjects were continuously inquired about any adverse event. The medically-qualified investigator was available to provide clinical judgment on all trial-related medical issues including adverse events and clinical laboratory values.

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	24
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### Reporting groups

Reporting group title	Modafinil
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Reporting group description:

The entire study consisted of 3 non-consecutive trial days for every participant during which modafinil, caffeine, and placebo were each administered once just after midnight.

A wash-out period of at least 7 days was implemented to ensure that the investigational products were completely eliminated and would not interfere on subsequent trial days.

Reporting group title	Caffeine
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Reporting group description:

The entire study consisted of 3 non-consecutive trial days for every participant during which modafinil, caffeine, and placebo were each administered once just after midnight.

A wash-out period of at least 7 days was implemented to ensure that the investigational products were completely eliminated and would not interfere on subsequent trial days.

Reporting group title	Placebo
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Reporting group description:

The entire study consisted of 3 non-consecutive trial days for every participant during which modafinil, caffeine, and placebo were each administered once just after midnight.

A wash-out period of at least 7 days was implemented to ensure that the investigational products were completely eliminated and would not interfere on subsequent trial days.

Serious adverse events	Modafinil	Caffeine	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 32 (0.00%)	0 / 30 (0.00%)	0 / 32 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

<b>Non-serious adverse events</b>	Modafinil	Caffeine	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 32 (6.25%)	1 / 30 (3.33%)	1 / 32 (3.13%)
Cardiac disorders			
Syncope			
subjects affected / exposed	2 / 32 (6.25%)	1 / 30 (3.33%)	1 / 32 (3.13%)
occurrences (all)	2	1	1

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 February 2019	<ul style="list-style-type: none"><li>As advised by our laboratory specialist, we changed the scheduling of the blood samples (the number remained the same)<ul style="list-style-type: none"><li>Originally scheduled for: 08.00, 0.00, 02.00 and 07.00 hour</li><li>Performed at: 0.00, 03.00, 06.00 and 08.00 hour</li></ul></li></ul>
01 March 2019	As we had difficulty finding enough test subjects, we accepted all employees from the Royal Netherlands Defence Force, as long as they had a valid aeromedical examination or equivalent.
04 March 2019	<p>Because of logistics and in order to reduce the disruption of our subjects schedules, we slightly changed the testing schedule.</p> <p># Instead of welcoming the subjects in the morning at the testing location, they only arrived between 16.00 and 16.30 hour.</p> <p>*All subjects were briefed in detail about what activities they were and were not allowed to participate in during the day.</p> <p># Test moments:</p> <p>*The vital parameters and training of PVT and VigTrack were now done between 16.30 and 17.30 instead of in the morning at 08.00 hour.</p>
14 March 2019	<ul style="list-style-type: none"><li>In order to have a better flow during the night and more representative test results, we added one testing block (SSS, PVT and Vigtrack):<ul style="list-style-type: none"><li>Originally scheduled for: 02.00, 03.00, 04.00, 06.00 and 08.00 hour</li><li>Performed at: 01.00, 02.00, 03.00, 04.00, 06.00 and 08.00 hour</li></ul></li></ul>

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The testdays were relatively short, if the measurements had been continued after T = +8, it might have been possible to identify the duration of the effects of caffeine and modafinil on performance and vigilance.

Notes: