Clinical trial results:
Evaluation in patients affected by middle of the night (MONT) awakenings using different dosages of triazolam

Summary

EudraCT number	2013-000078-30
Trial protocol	IT
Global end of trial date	09 December 2014

Results information

Result version number	v1 (current)
This version publication date	04 August 2021
First version publication date	04 August 2021

Trial information

Trial identification

Sponsor protocol code	MB0612/1860/02

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Valeas Spa
Sponsor organisation address	Via Vallisneri 10, Milano, Italy,
Public contact	Medical Direction, Valeas SpA, +39 2236901, dir.medica@valeas.it
Scientific contact	Medical Direction, Valeas SpA, +39 2236901, dir.medica@valeas.it

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 February 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 December 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of different triazolam dosage in patients affected by difficulty returning to sleep following a nocturnal awakening

Protection of trial subjects:

None

Background therapy:

None

Evidence for comparator:

None

Actual start date of recruitment	08 January 2014
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	Italy: 24
Worldwide total number of subjects	24
EEA total number of subjects	24

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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	24
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Adult men and women, aged 18–64, meeting diagnostic criteria for primary insomnia according to the Diagnostic and Statistical Manual of Mental Disorder were enrolled in Italy. 40 patients were assessed for eligibility; 16 were excluded because they did not meet inclusion criteria (15) or declined to participate (1).

Pre-assignment

Screening details:

Key exclusion criteria for the study included clinical significant ongoing medical/neurologic conditions; any sleep disorder other than insomnia as determined by sleep history, or regular night shift worker within the past 6 months prior to screening; history of psychiatric disorder; use of any other central nervous system medication.

Period 1

Period 1 title	T0
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	T0 - 0.0625 mg

Arm description:

0.0625 mg

Arm type	Experimental
Investigational medicinal product name	Triazolam
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral drops, solution
Routes of administration	Oral use

Dosage and administration details:

0.0625 mg
Eligible patients underwent a 7-day washout period, if necessary, and then a two-night PSG evaluation was performed. After the first adaption night in the sleep laboratory, two consecutive nights were evaluated by means of PSG and actigraphy. During the first night (T0), after the awakening, patients received placebo drops (single-blind), whereas after awakening during the second night (T1), one of the three randomized dosages of triazolam was given (in single-dose containers).

Arm title	T0 - 0.125 mg

Arm description:

0.125 mg

Arm type	Experimental
Investigational medicinal product name	Triazolam
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral drops, solution
Routes of administration	Oral use

Dosage and administration details:

0.125 mg
Eligible patients underwent a 7-day washout period, if necessary, and then a two-night PSG evaluation was performed. After the first adaption night in the sleep laboratory, two consecutive nights were evaluated by means of PSG and actigraphy. During the first night (T0), after the awakening, patients

received placebo drops (single-blind), whereas after awakening during the second night (T1), one of the three randomized dosages of triazolam was given (in single-dose containers).

Arm title	T0 - 0.250 mg
Arm description: 0.250 mg	
Arm type	Experimental
Investigational medicinal product name	Triazolam
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral drops, solution
Routes of administration	Oral use

Dosage and administration details:

0.250 mg
Eligible patients underwent a 7-day washout period, if necessary, and then a two-night PSG evaluation was performed. After the first adaption night in the sleep laboratory, two consecutive nights were evaluated by means of PSG and actigraphy. During the first night (T0), after the awakening, patients received placebo drops (single-blind), whereas after awakening during the second night (T1), one of the three randomized dosages of triazolam was given (in single-dose containers).

Number of subjects in period 1	T0 - 0.0625 mg	T0 - 0.125 mg	T0 - 0.250 mg
Started	8	8	8
Completed	8	8	8

Period 2	
Period 2 title	T1
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	T1 - 0.0625 mg
Arm description: 0.0625 mg	
Arm type	Experimental

Investigational medicinal product name	Triazolam
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral drops, solution
Routes of administration	Oral use

Dosage and administration details:

0.0625 mg
Eligible patients underwent a 7-day washout period, if necessary, and then a two-night PSG evaluation was performed. After the first adaption night in the sleep laboratory, two consecutive nights were evaluated by means of PSG and actigraphy. During the first night (T0), after the awakening, patients received placebo drops (single-blind), whereas after awakening during the second night (T1), one of the three randomized dosages of triazolam was given (in single-dose containers).

Arm title	T1 - 0.125 mg

Arm description:

0.125 mg

Arm type	Experimental
Investigational medicinal product name	Triazolam
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral drops, solution
Routes of administration	Oral use

Dosage and administration details:

0.125 mg
Eligible patients underwent a 7-day washout period, if necessary, and then a two-night PSG evaluation was performed. After the first adaption night in the sleep laboratory, two consecutive nights were evaluated by means of PSG and actigraphy. During the first night (T0), after the awakening, patients received placebo drops (single-blind), whereas after awakening during the second night (T1), one of the three randomized dosages of triazolam was given (in single-dose containers).

Arm title	T1 - 0.250 mg

Arm description:

0.250 mg

Arm type	Experimental
Investigational medicinal product name	Triazolam
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral drops, solution
Routes of administration	Oral use

Dosage and administration details:

0.250 mg
Eligible patients underwent a 7-day washout period, if necessary, and then a two-night PSG evaluation was performed. After the first adaption night in the sleep laboratory, two consecutive nights were evaluated by means of PSG and actigraphy. During the first night (T0), after the awakening, patients received placebo drops (single-blind), whereas after awakening during the second night (T1), one of the three randomized dosages of triazolam was given (in single-dose containers).

Number of subjects in period 2	T1 - 0.0625 mg	T1 - 0.125 mg	T1 - 0.250 mg
Started	8	8	8
Completed	8	8	8

Baseline characteristics

Reporting groups	
Reporting group title	T0 - 0.0625 mg
Reporting group description: 0.0625 mg	
Reporting group title	T0 - 0.125 mg
Reporting group description: 0.125 mg	
Reporting group title	T0 - 0.250 mg
Reporting group description: 0.250 mg	

Reporting group values	T0 - 0.0625 mg	T0 - 0.125 mg	T0 - 0.250 mg
Number of subjects	8	8	8
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
arithmetic mean	41.13	40.63	41.25
standard deviation	± 10.12	± 11.94	± 10.62
Gender categorical Units: Subjects			
Female	5	2	3
Male	3	6	5
Weight Units: kg			
arithmetic mean	67.4	69.5	65.6
standard deviation	± 4.7	± 3.9	± 3.1
Height Units: meter			
arithmetic mean	1.7	1.7	1.7
standard deviation	± 0.0	± 0.0	± 0.0
Body Mass Index Units: kg/m			
arithmetic mean	23.0	23.0	22.7
standard deviation	± 1.0	± 0.9	± 0.9
Total Sleep Time			

Units: Minutes			
arithmetic mean	353.41	364.35	343.87
standard deviation	± 28.27	± 27.48	± 25.12
Sleep Latency			
Units: Minutes			
arithmetic mean	10.20	17.00	13.08
standard deviation	± 2.12	± 5.12	± 3.77
Wake after sleep onset			
Units: minutes			
arithmetic mean	97.90	74.90	98.37
standard deviation	± 20.92	± 20.71	± 15.57
Sleep Efficiency			
Units: percent			
arithmetic mean	76.01	80.42	75.44
standard deviation	± 4.94	± 5.67	± 4.03
Number of awakenings			
Units: Number			
arithmetic mean	18.64	14.85	20.45
standard deviation	± 2.13	± 2.55	± 4.57
Stage 1 NREM			
Units: percent			
arithmetic mean	9.81	7.14	9.31
standard deviation	± 1.44	± 1.38	± 1.54
Stage 2 NREM			
Units: percent			
arithmetic mean	47.77	48.57	42.75
standard deviation	± 2.56	± 3.54	± 2.51
Slow-wave Sleep			
Units: percent			
arithmetic mean	24.34	26.77	26.44
standard deviation	± 2.07	± 3.68	± 2.32
REM			
Units: percent			
arithmetic mean	16.88	17.88	21.57
standard deviation	± 2.54	± 1.67	± 1.13

Reporting group values	Total		
Number of subjects	24		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	0		
From 65-84 years	0		
85 years and over	0		

Age continuous Units: years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Female Male	10 14		
Weight Units: kg arithmetic mean standard deviation	- -		
Height Units: meter arithmetic mean standard deviation	- -		
Body Mass Index Units: kg/m arithmetic mean standard deviation	- -		
Total Sleep Time Units: Minutes arithmetic mean standard deviation	- -		
Sleep Latency Units: Minutes arithmetic mean standard deviation	- -		
Wake after sleep onset Units: minutes arithmetic mean standard deviation	- -		
Sleep Efficiency Units: percent arithmetic mean standard deviation	- -		
Number of awakenings Units: Number arithmetic mean standard deviation	- -		
Stage 1 NREM Units: percent arithmetic mean standard deviation	- -		
Stage 2 NREM Units: percent arithmetic mean standard deviation	- -		
Slow-wave Sleep Units: percent arithmetic mean standard deviation	- -		

REM Units: percent arithmetic mean standard deviation	-		

End points

End points reporting groups	
Reporting group title	T0 - 0.0625 mg
Reporting group description: 0.0625 mg	
Reporting group title	T0 - 0.125 mg
Reporting group description: 0.125 mg	
Reporting group title	T0 - 0.250 mg
Reporting group description: 0.250 mg	
Reporting group title	T1 - 0.0625 mg
Reporting group description: 0.0625 mg	
Reporting group title	T1 - 0.125 mg
Reporting group description: 0.125 mg	
Reporting group title	T1 - 0.250 mg
Reporting group description: 0.250 mg	

Primary: Change in Wake after sleep onset	
End point title	Change in Wake after sleep onset
End point description: The data recorded by polysomnography during the 3 days spent in the hospital by the patient, i.e. the night T-1 (night of adaptation), the night T0 (the night when he took Placebo (P)), and the night T1 (the night when he took the experimental drug).	
End point type	Primary
End point timeframe: Second night in the hospital	

End point values	T0 - 0.0625 mg	T0 - 0.125 mg	T0 - 0.250 mg	T1 - 0.0625 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	8	8	8
Units: minute				
arithmetic mean (standard error)	97.90 (± 20.92)	74.90 (± 20.71)	98.37 (± 15.57)	43.14 (± 13.96)

End point values	T1 - 0.125 mg	T1 - 0.250 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	8		
Units: minute				

arithmetic mean (standard error)	19.50 (± 4.51)	41.30 (± 8.32)		

Statistical analyses

Statistical analysis title	T test
Statistical analysis description: Difference between baseline and T1	
Comparison groups	T0 - 0.0625 mg v T1 - 0.0625 mg
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.009
Method	t-test, 2-sided

Statistical analysis title	T test
Statistical analysis description: Difference between baseline and T1	
Comparison groups	T0 - 0.125 mg v T1 - 0.125 mg
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.009
Method	t-test, 2-sided

Statistical analysis title	T test
Statistical analysis description: Difference between baseline and T1	
Comparison groups	T0 - 0.250 mg v T1 - 0.250 mg
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.007
Method	t-test, 2-sided

Primary: Change in the Number of nightime awakenings

End point title	Change in the Number of nightime awakenings

End point description:

The data recorded by polysomnography during the 3 days spent in the hospital by the patient, i.e. the night T-1 (night of adaptation), the night T0 (the night when he took Placebo (P)), and the night T1 (the night when he took the experimental drug).

End point type	Primary
End point timeframe: Second night in the hospital	

End point values	T0 - 0.0625 mg	T0 - 0.125 mg	T0 - 0.250 mg	T1 - 0.0625 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	8	8	8
Units: unit(s)				
arithmetic mean (standard error)	18.64 (± 2.13)	14.85 (± 2.55)	20.45 (± 4.57)	10.64 (± 2.31)

End point values	T1 - 0.125 mg	T1 - 0.250 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	8		
Units: unit(s)				
arithmetic mean (standard error)	6.81 (± 1.60)	9.61 (± 2.70)		

Statistical analyses

Statistical analysis title	T test
Comparison groups	T0 - 0.0625 mg v T1 - 0.0625 mg
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.036
Method	t-test, 2-sided

Statistical analysis title	T test
Comparison groups	T0 - 0.125 mg v T1 - 0.125 mg
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.036
Method	t-test, 2-sided

Statistical analysis title	T test
Comparison groups	T0 - 0.250 mg v T1 - 0.250 mg

Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.006
Method	t-test, 2-sided

Primary: Change in Sleep Efficiency

End point title	Change in Sleep Efficiency

End point description:

The data recorded by polysomnography during the 3 days spent in the hospital by the patient, i.e. the night T-1 (night of adaptation), the night T0 (the night when he took Placebo (P)), and the night T1 (the night when he took the experimental drug).

End point type	Primary

End point timeframe:

Second night in the hospital

End point values	T0 - 0.0625 mg	T0 - 0.125 mg	T0 - 0.250 mg	T1 - 0.0625 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	8	8	8
Units: percent				
arithmetic mean (standard error)	76.01 (± 4.94)	80.42 (± 5.67)	75.44 (± 4.03)	89.31 (± 3.23)

End point values	T1 - 0.125 mg	T1 - 0.250 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	8		
Units: percent				
arithmetic mean (standard error)	93.12 (± 1.66)	89.28 (± 2.01)		

Statistical analyses

Statistical analysis title	T test
Comparison groups	T0 - 0.0625 mg v T1 - 0.0625 mg
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.012
Method	t-test, 2-sided

Statistical analysis title	T test
Comparison groups	T0 - 0.125 mg v T1 - 0.125 mg
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.017
Method	t-test, 2-sided

Statistical analysis title	T test
Comparison groups	T0 - 0.250 mg v T1 - 0.250 mg
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.01
Method	t-test, 2-sided

Primary: Change in Total Sleep Time

End point title	Change in Total Sleep Time

End point description:

The data recorded by polysomnography during the 3 days spent in the hospital by the patient, i.e. the night T-1 (night of adaptation), the night T0 (the night when he took Placebo (P)), and the night T1 (the night when he took the experimental drug).

End point type	Primary

End point timeframe:

Second night in the hospital

End point values	T0 - 0.0625 mg	T0 - 0.125 mg	T0 - 0.250 mg	T1 - 0.0625 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	8	8	8
Units: minute				
arithmetic mean (standard error)	353.41 (± 28.27)	364.35 (± 27.48)	343.87 (± 25.12)	428.84 (± 17.04)

End point values	T1 - 0.125 mg	T1 - 0.250 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	8		
Units: minute				
arithmetic mean (standard error)	447.22 (± 8.84)	412.36 (± 8.86)		

Statistical analyses

Statistical analysis title	T test
Comparison groups	T0 - 0.0625 mg v T1 - 0.0625 mg
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.009
Method	t-test, 2-sided

Statistical analysis title	T test
Comparison groups	T0 - 0.125 mg v T1 - 0.125 mg
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.005
Method	t-test, 2-sided

Statistical analysis title	T test
Comparison groups	T0 - 0.250 mg v T1 - 0.250 mg
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.017
Method	t-test, 2-sided

Primary: Change in DSST	
End point title	Change in DSST
End point description:	
The DSST (Digit symbol substitution test) is a pencil-and-paper test of psychomotor performance. The test consists of filling as many empty boxes as possible with a symbol matching each number.	
End point type	Primary
End point timeframe:	
Second night in the hospital	

End point values	T0 - 0.0625 mg	T0 - 0.125 mg	T0 - 0.250 mg	T1 - 0.0625 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	8	8	8
Units: score				
arithmetic mean (standard deviation)	53.75 (± 11.65)	61.38 (± 12.49)	54.13 (± 13.81)	58.25 (± 10.42)

End point values	T1 - 0.125 mg	T1 - 0.250 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	8		
Units: score				
arithmetic mean (standard deviation)	63.25 (± 15.03)	58.63 (± 11.50)		

Statistical analyses

Statistical analysis title	T test
Comparison groups	T0 - 0.0625 mg v T1 - 0.0625 mg
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05 [1]
Method	t-test, 2-sided

Notes:

[1] - Not significant

Statistical analysis title	T test
Comparison groups	T0 - 0.125 mg v T1 - 0.125 mg
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05 [2]
Method	t-test, 2-sided

Notes:

[2] - Not significant

Statistical analysis title	T test
Comparison groups	T0 - 0.250 mg v T1 - 0.250 mg
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05 [3]
Method	t-test, 2-sided

Notes:

[3] - Not significant

Secondary: Change in ESS

End point title	Change in ESS

End point description:

Following the two PSG/actigraphy recording nights, patients continued the 2-week treatment with one of the three dosages assigned at T2 at home. During this time, patients had to wear an actigraph and to complete every morning a visual analog scale for the assessment of vigilance, as well as a sleep log in order to control, in particular, the number of awakenings and drug assumption.
The ESS (Epworth Sleepiness scale) questionnaire was used to evaluate the quality of sleep.

End point type	Secondary

End point timeframe:

At the end of the 2-week treatment

End point values	T0 - 0.0625 mg	T0 - 0.125 mg	T0 - 0.250 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	8	8	
Units: score				
arithmetic mean (standard error)	4.00 (± 2.98)	2.88 (± 2.36)	4.38 (± 3.70)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in ISI

End point title	Change in ISI

End point description:

The ISI (insomnia severity index) questionnaire assesses insomnia severity

End point type	Secondary

End point timeframe:

At the end of the 2-week treatment

End point values	T0 - 0.0625 mg	T0 - 0.125 mg	T0 - 0.250 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	8	8	
Units: score				
arithmetic mean (standard error)	11.38 (± 4.07)	11.50 (± 3.51)	7.88 (± 4.49)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events: From screening to the final visit	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.1

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

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: No adverse events were reported in the study

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28584913