



## Clinical trial results:

### A Randomized, Double-Blind, Four Treatment, Four period, Crossover Study, with Placebo, Tizanidine Immediate Release and Diphenhydramine to Study the Effect of Tizanidine Extended Release on Simulated Driving Performance, Cognitive, and Psychomotor Functioning

#### Summary

EudraCT number	2015-003770-32
Trial protocol	NL
Global end of trial date	11 July 2016

#### Results information

Result version number	v1 (current)
This version publication date	05 May 2021
First version publication date	05 May 2021

#### Trial information

##### Trial identification

Sponsor protocol code	CLR_14_05
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##### Additional study identifiers

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

Notes:

#### Sponsors

Sponsor organisation name	Sun Pharma Advanced Research Company Limited
Sponsor organisation address	17/B, Mahal Industrial Estate, Mahakali Caves Road, Andheri East., Mumbai, India, 400093
Public contact	Head- Clinical development, Sun Pharma Advanced Research Company, 91 2266455645, Clinical.Trials@sparcmail.com
Scientific contact	Head- Clinical development, Sun Pharma Advanced Research Company, 91 2266455645, Clinical.Trials@sparcmail.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	11 July 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 July 2016
Global end of trial reached?	Yes
Global end of trial date	11 July 2016
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To investigate effect of tizanidine ER 12 mg on simulated driving performance, cognitive and psychomotor functions compared with placebo and tizanidine IR 8 mg (two 4 mg doses given 6.5 hours apart) and active control (diphenhydramine) and placebo in healthy subjects

Protection of trial subjects:

At the start of each study day compliance was checked with alcohol breath test, urine drug screen and urine pregnancy test (females).

Participants were assigned a participant number. In this cross-over design all participants received all treatments, the order of which was based on a randomization table. The treatment codes are stored in a secure environment within TNO and accessible only to the medical expert and the principal investigator. The code was broken at the end of the trial when all participants had completed the study and after all, data was entered into the database, cleaned, and the database locked. After database lock, the results were analyzed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 April 2016
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: 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:

Adequate participants were enrolled to have twenty-four healthy participants (13 males and approximately 11 females) complete the study per protocol requirements. Participants were screened by means of a medical questionnaire and physical examination.

### Pre-assignment

Screening details:

30 participants screened, 27 unique subjects randomized.

### Period 1

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

### Arms

Are arms mutually exclusive?	No
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<b>Arm title</b>	Placebo Baseline
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Arm description: -

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

Dosage and administration details:

two doses separated by 6 .5 hours

<b>Arm title</b>	Active control baseline
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Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Diphenhydramine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

50 mg tablet (single dose) followed by placebo after 6.5 hours

<b>Arm title</b>	Tizanidine Immediate release Baseline
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Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Tizanidine immediate release tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

8 mg (two 4 mg doses separated by 6.5 hours)

<b>Arm title</b>	Tizanidine Extended release Baseline
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Tizanidine extended release tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

(single 12 mg dose) followed by placebo dose after 6.5 hours.

Number of subjects in period 1	Placebo Baseline	Active control baseline	Tizanidine Immediate release Baseline
Started	24	24	24
Completed	24	24	24

Number of subjects in period 1	Tizanidine Extended release Baseline
Started	24
Completed	24

## Period 2

Period 2 title	Assessment 1
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

## Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Placebo Assessment 1
Arm description: -	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
two doses separated by 6.5 hours	
<b>Arm title</b>	Active control Assessment 1

Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Diphenhydramine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
50 mg tablet (single dose) followed by placebo after 6.5 hours	
<b>Arm title</b>	Tizanidine Immediate release Assessment 1
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Tizanidine immediate release tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
8 mg (two 4 mg doses separated by 6.5 hours)	
<b>Arm title</b>	Tizanidine Extended release Assessment 1
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Tizanidine extended release tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
(single 12 mg dose) followed by placebo dose after 6. 5 hours.	

Number of subjects in period 2	Placebo Assessment 1	Active control Assessment 1	Tizanidine Immediate release Assessment 1
Started	24	24	24
Completed	24	24	24

Number of subjects in period 2	Tizanidine Extended release Assessment 1
Started	24
Completed	24

**Period 3**

Period 3 title	Assessment 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

**Arms**

Are arms mutually exclusive?	Yes
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<b>Arm title</b>	Placebo Assessment 2
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Arm description: -

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

Dosage and administration details:

two doses separated by 6 .5 hours

<b>Arm title</b>	Active control Assessment 2
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Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Diphenhydramine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

50 mg tablet (single dose) followed by placebo after 6.5 hours

<b>Arm title</b>	Tizanidine Immediate release Assessment 2
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Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Tizanidine immediate release tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

8 mg (two 4 mg doses separated by 6.5 hours)

<b>Arm title</b>	Tizanidine Extended release Assessment 2
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Arm description: -

Arm type	Experimental
Investigational medicinal product name	Tizanidine extended release tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

(single 12 mg dose) followed by placebo dose after 6. 5 hours.

Number of subjects in period 3	Placebo Assessment 2	Active control Assessment 2	Tizanidine Immediate release Assessment 2
Started	24	24	24
Completed	24	24	24

Number of subjects in period 3	Tizanidine Extended release Assessment 2
Started	24
Completed	24

#### Period 4

Period 4 title	Assessment 3
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

#### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Placebo Assessment 3
Arm description: -	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: two doses separated by 6 .5 hours	
<b>Arm title</b>	Active control Assessment 3
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Diphenhydramine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 50 mg tablet (single dose) followed by placebo after 6.5 hours	
<b>Arm title</b>	Tizanidine Immediate release Assessment 3



Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Tizanidine immediate release tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

8 mg (two 4 mg doses separated by 6.5 hours)

<b>Arm title</b>	Tizanidine Extended release Assessment 3
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Arm description: -

Arm type	Experimental
Investigational medicinal product name	Tizanidine extended release tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

(single 12 mg dose) followed by placebo dose after 6. 5 hours.

Number of subjects in period 4	Placebo Assessment 3	Active control Assessment 3	Tizanidine Immediate release Assessment 3
Started	24	24	24
Completed	24	24	24

Number of subjects in period 4	Tizanidine Extended release Assessment 3
Started	24
Completed	24

<b>Period 5</b>	
Period 5 title	Assessment 4
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

## Arms

Are arms mutually exclusive?	Yes
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<b>Arm title</b>	Placebo Assessment 4
Arm description: -	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: two doses separated by 6 .5 hours	
<b>Arm title</b>	Active control Assessment 4
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Diphenhydramine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 50 mg tablet (single dose) followed by placebo after 6.5 hours	
<b>Arm title</b>	Tizanidine Immediate release Assessment 4
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Tizanidine immediate release tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 8 mg (two 4 mg doses separated by 6.5 hours)	
<b>Arm title</b>	Tizanidine Extended release Assessment 4
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Tizanidine extended release tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: (single 12 mg dose) followed by placebo dose after 6. 5 hours.	

Number of subjects in period 5	Placebo Assessment 4	Active control Assessment 4	Tizanidine Immediate release Assessment 4
Started	24	24	24
Completed	24	24	24

Number of subjects in period 5	Tizanidine Extended release Assessment 4
Started	24
Completed	24

## Baseline characteristics

### Reporting groups

Reporting group title	Baseline
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Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	24	24	
Age categorical			
Units: Subjects			
Age continuous			
mean age			
Units: years			
arithmetic mean	32		
full range (min-max)	22 to 44	-	
Gender categorical			
Units: Subjects			
Female	11	11	
Male	13	13	

## End points

### End points reporting groups

Reporting group title	Placebo Baseline
Reporting group description: -	
Reporting group title	Active control baseline
Reporting group description: -	
Reporting group title	Tizanidine Immediate release Baseline
Reporting group description: -	
Reporting group title	Tizanidine Extended release Baseline
Reporting group description: -	
Reporting group title	Placebo Assessment 1
Reporting group description: -	
Reporting group title	Active control Assessment 1
Reporting group description: -	
Reporting group title	Tizanidine Immediate release Assessment 1
Reporting group description: -	
Reporting group title	Tizanidine Extended release Assessment 1
Reporting group description: -	
Reporting group title	Placebo Assessment 2
Reporting group description: -	
Reporting group title	Active control Assessment 2
Reporting group description: -	
Reporting group title	Tizanidine Immediate release Assessment 2
Reporting group description: -	
Reporting group title	Tizanidine Extended release Assessment 2
Reporting group description: -	
Reporting group title	Placebo Assessment 3
Reporting group description: -	
Reporting group title	Active control Assessment 3
Reporting group description: -	
Reporting group title	Tizanidine Immediate release Assessment 3
Reporting group description: -	
Reporting group title	Tizanidine Extended release Assessment 3
Reporting group description: -	
Reporting group title	Placebo Assessment 4
Reporting group description: -	
Reporting group title	Active control Assessment 4
Reporting group description: -	
Reporting group title	Tizanidine Immediate release Assessment 4
Reporting group description: -	
Reporting group title	Tizanidine Extended release Assessment 4
Reporting group description: -	

**Primary: Standard Deviation of the Lateral Position during highway driving**

End point title	Standard Deviation of the Lateral Position during highway driving <sup>[1]</sup>
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End point description:

End point type	Primary
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End point timeframe:

4 weeks

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: There was no statistically significant difference.

End point values	Placebo Baseline	Placebo Assessment 1	Placebo Assessment 2	Placebo Assessment 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23 <sup>[2]</sup>	23	23	23
Units: centimetres				
arithmetic mean (standard error)	18.88 (± 1.44)	19.73 (± 1.34)	22.18 (± 2.52)	23.43 (± 2.65)

Notes:

[2] - Placebo Baseline

End point values	Placebo Assessment 4	Active control baseline	Tizanidine Immediate release Baseline	Tizanidine Extended release Baseline
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	23	23	23
Units: centimetres				
arithmetic mean (standard error)	23.09 (± 4.03)	18.82 (± 1.16)	18.14 (± 1.36)	18.52 (± 1.62)

End point values	Active control Assessment 1	Tizanidine Immediate release Assessment 1	Tizanidine Extended release Assessment 1	Active control Assessment 2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	23	23	23
Units: centimetres				
arithmetic mean (standard error)	26.42 (± 3.09)	26.15 (± 2.03)	23.75 (± 2.31)	27.61 (± 2.68)

End point values	Tizanidine Immediate release Assessment 2	Tizanidine Extended release Assessment 2	Active control Assessment 3	Tizanidine Immediate release Assessment 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	23	23	23
Units: centimetres				
arithmetic mean (standard error)	24.12 (± 2.34)	26.81 (± 3.00)	28.19 (± 3.13)	20.73 (± 1.88)

End point values	Tizanidine Extended release Assessment 3	Active control Assessment 4	Tizanidine Immediate release Assessment 4	Tizanidine Extended release Assessment 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	23	23	23
Units: centimetres				
arithmetic mean (standard error)	26.00 (± 2.65)	23.54 (± 2.36)	28.59 (± 4.26)	21.81 (± 1.83)

## Statistical analyses

No statistical analyses for this end point

## Primary: Standard Deviation of the Lateral Position during rural road driving

End point title	Standard Deviation of the Lateral Position during rural road driving <sup>[3]</sup>
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End point description:

End point type	Primary
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End point timeframe:

4 weeks

Notes:

[3] - 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: There was no statistically significant difference.

End point values	Placebo Baseline	Placebo Assessment 1	Placebo Assessment 2	Placebo Assessment 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	23	23	23
Units: centimetre				
arithmetic mean (standard error)	15.81 (± 1.20)	17.38 (± 1.33)	19.34 (± 2.55)	20.91 (± 2.48)

End point values	Placebo Assessment 4	Active control baseline	Tizanidine Immediate release Baseline	Tizanidine Extended release Baseline
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	23	23	23
Units: centimetre				
arithmetic mean (standard error)	19.77 (± 2.43)	15.98 (± 1.35)	15.48 (± 1.49)	16.41 (± 1.64)

End point values	Active control	Tizanidine	Tizanidine	Active control
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	Assessment 1	Immediate release Assessment 1	Extended release Assessment 1	Assessment 2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	23	23	23
Units: centimetre				
arithmetic mean (standard error)	24.35 (± 2.43)	23.18 (± 2.00)	23.44 (± 2.84)	25.59 (± 2.44)

End point values	Tizanidine Immediate release Assessment 2	Tizanidine Extended release Assessment 2	Active control Assessment 3	Tizanidine Immediate release Assessment 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	23	23	23
Units: centimetre				
arithmetic mean (standard error)	22.88 (± 2.27)	28.52 (± 5.00)	26.46 (± 2.45)	19.90 (± 2.22)

End point values	Tizanidine Extended release Assessment 3	Active control Assessment 4	Tizanidine Immediate release Assessment 4	Tizanidine Extended release Assessment 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	23	23	23
Units: centimetre				
arithmetic mean (standard error)	25.49 (± 3.03)	20.99 (± 2.17)	26.98 (± 4.07)	21.19 (± 2.21)

### Statistical analyses

No statistical analyses for this end point

### Secondary: Standard deviation of speed

End point title	Standard deviation of speed
End point description:	
End point type	Secondary
End point timeframe:	
4 weeks	



End point values	Placebo Baseline	Placebo Assessment 1	Placebo Assessment 2	Placebo Assessment 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	23	23	23
Units: km/h				
arithmetic mean (standard error)				
during highway driving	3.53 (± 0.24)	3.72 (± 0.27)	3.76 (± 0.31)	4.17 (± 0.33)
during rural road driving	3.3993 (± 0.23800)	3.74 (± 0.32)	3.76 (± 0.29)	4.03 (± 0.35)

End point values	Placebo Assessment 4	Active control baseline	Tizanidine Immediate release Baseline	Tizanidine Extended release Baseline
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	23	23	23
Units: km/h				
arithmetic mean (standard error)				
during highway driving	3.90 (± 0.31)	3.66 (± 0.28)	3.49 (± 0.23)	3.53 (± 0.23)
during rural road driving	3.50 (± 0.28)	3.4239 (± 0.26391)	3.3572 (± 0.24878)	3.3493 (± 0.25766)

End point values	Active control Assessment 1	Tizanidine Immediate release Assessment 1	Tizanidine Extended release Assessment 1	Active control Assessment 2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	23	23	23
Units: km/h				
arithmetic mean (standard error)				
during highway driving	4.79 (± 0.41)	4.26 (± 0.28)	4.23 (± 0.27)	4.38 (± 0.32)
during rural road driving	4.67 (± 0.38)	4.45 (± 0.32)	4.33 (± 0.38)	4.61 (± 0.35)

End point values	Tizanidine Immediate release Assessment 2	Tizanidine Extended release Assessment 2	Active control Assessment 3	Tizanidine Immediate release Assessment 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	23	23	23
Units: km/h				
arithmetic mean (standard error)				
during highway driving	4.21 (± 0.29)	4.33 (± 0.32)	4.34 (± 0.32)	3.84 (± 0.23)
during rural road driving	3.94 (± 0.31)	4.15 (± 0.31)	4.46 (± 0.28)	3.90 (± 0.25)

End point values	Tizanidine	Active control	Tizanidine	Tizanidine
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	Extended release Assessment 3	Assessment 4	Immediate release Assessment 4	Extended release Assessment 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	23	23	23
Units: km/h				
arithmetic mean (standard error)				
during highway driving	4.15 (± 0.28)	4.10 (± 0.32)	4.03 (± 0.34)	3.83 (± 0.33)
during rural road driving	4.53 (± 0.34)	3.86 (± 0.35)	4.43 (± 0.36)	3.82 (± 0.29)

## Statistical analyses

No statistical analyses for this end point

## Secondary: Distance Headway in meters

End point title	Distance Headway in meters
End point description:	
End point type	Secondary
End point timeframe:	
4 weeks	

End point values	Placebo Baseline	Placebo Assessment 1	Placebo Assessment 2	Placebo Assessment 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	23	23	23
Units: meters				
arithmetic mean (standard error)				
Mean Distance Headway during highway driving	58.61 (± 2.09)	59.95 (± 3.05)	62.55 (± 2.89)	61.59 (± 3.48)
Mean Distance Headway during rural road driving	44.80 (± 1.56)	45.80 (± 2.23)	45.06 (± 2.00)	45.26 (± 2.08)

End point values	Placebo Assessment 4	Active control baseline	Tizanidine Immediate release Baseline	Tizanidine Extended release Baseline
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	23	23	23
Units: meters				
arithmetic mean (standard error)				
Mean Distance Headway during highway driving	63.43 (± 3.65)	61.92 (± 3.01)	58.73 (± 3.65)	56.41 (± 3.42)
Mean Distance Headway during rural road driving	47.82 (± 2.71)	46.44 (± 2.21)	44.09 (± 2.04)	44.02 (± 2.48)

End point values	Active control Assessment 1	Tizanidine Immediate release Assessment 1	Tizanidine Extended release Assessment 1	Active control Assessment 2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	23	23	23
Units: meters				
arithmetic mean (standard error)				
Mean Distance Headway during highway driving	66.04 (± 3.98)	63.20 (± 2.65)	60.94 (± 4.17)	63.57 (± 3.84)
Mean Distance Headway during rural road driving	46.25 (± 2.14)	47.56 (± 1.89)	45.70 (± 3.11)	45.43 (± 2.77)

End point values	Tizanidine Immediate release Assessment 2	Tizanidine Extended release Assessment 2	Active control Assessment 3	Tizanidine Immediate release Assessment 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	23	23	23
Units: meters				
arithmetic mean (standard error)				
Mean Distance Headway during highway driving	63.14 (± 3.80)	62.13 (± 3.93)	64.87 (± 4.26)	58.97 (± 3.20)
Mean Distance Headway during rural road driving	45.56 (± 2.21)	44.35 (± 2.13)	45.22 (± 2.81)	43.44 (± 1.98)

End point values	Tizanidine Extended release Assessment 3	Active control Assessment 4	Tizanidine Immediate release Assessment 4	Tizanidine Extended release Assessment 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	23	23	23
Units: meters				
arithmetic mean (standard error)				
Mean Distance Headway during highway driving	60.45 (± 4.00)	61.89 (± 3.83)	63.32 (± 3.30)	58.34 (± 3.92)
Mean Distance Headway during rural road driving	43.13 (± 2.44)	45.53 (± 2.50)	44.43 (± 1.78)	43.37 (± 2.83)

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to collision

End point title	Time to collision
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End point description:

End point type	Secondary
End point timeframe:	
4 weeks	

End point values	Placebo Baseline	Placebo Assessment 1	Placebo Assessment 2	Placebo Assessment 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	23	23	23
Units: seconds				
arithmetic mean (standard error)				
Minimum Time to collision during highway driving	10.00 (± 0.00)	9.68 (± 0.24)	9.86 (± 0.14)	9.58 (± 0.36)
Minimum time to collision during rural road drive	9.99 (± 0.01)	9.75 (± 0.16)	9.68 (± 0.15)	9.38 (± 0.35)

End point values	Placebo Assessment 4	Active control baseline	Tizanidine Immediate release Baseline	Tizanidine Extended release Baseline
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	23	23	23
Units: seconds				
arithmetic mean (standard error)				
Minimum Time to collision during highway driving	9.88 (± 0.12)	10.00 (± 0.00)	9.96 (± 0.04)	10.00 (± 0.00)
Minimum time to collision during rural road drive	9.52 (± 0.29)	9.71 (± 0.27)	9.75 (± 0.21)	9.67 (± 0.25)

End point values	Active control Assessment 1	Tizanidine Immediate release Assessment 1	Tizanidine Extended release Assessment 1	Active control Assessment 2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	23	23	23
Units: seconds				
arithmetic mean (standard error)				
Minimum Time to collision during highway driving	9.83 (± 0.16)	10.00 (± 0.00)	9.75 (± 0.15)	9.68 (± 0.22)
Minimum time to collision during rural road drive	7.94 (± 0.65)	9.50 (± 0.30)	9.08 (± 0.39)	8.59 (± 0.49)

End point values	Tizanidine Immediate release	Tizanidine Extended release	Active control Assessment 3	Tizanidine Immediate release
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	Assessment 2	Assessment 2		Assessment 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	23	23	23
Units: seconds				
arithmetic mean (standard error)				
Minimum Time to collision during highway driving	9.94 (± 0.06)	9.67 (± 0.24)	9.79 (± 0.21)	9.93 (± 0.07)
Minimum time to collision during rural road driving	9.31 (± 0.31)	9.10 (± 0.43)	8.35 (± 0.54)	9.69 (± 0.14)

End point values	Tizanidine Extended release Assessment 3	Active control Assessment 4	Tizanidine Immediate release Assessment 4	Tizanidine Extended release Assessment 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	23	23	23
Units: seconds				
arithmetic mean (standard error)				
Minimum Time to collision during highway driving	9.64 (± 0.28)	9.59 (± 0.24)	9.69 (± 0.23)	9.88 (± 0.12)
Minimum time to collision during rural road driving	8.65 (± 0.49)	9.07 (± 0.49)	9.44 (± 0.23)	9.27 (± 0.35)

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time Headway

End point title	Time Headway
End point description:	
End point type	Secondary
End point timeframe:	
4 weeks	

End point values	Placebo Baseline	Placebo Assessment 1	Placebo Assessment 2	Placebo Assessment 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	23	23	23
Units: seconds				
arithmetic mean (standard error)				
Mean Time Headway during highway driving	1.77 (± 0.06)	1.81 (± 0.09)	1.89 (± 0.09)	1.86 (± 0.11)
Mean Time Headway during rural road driving	2.03 (± 0.07)	2.07 (± 0.10)	2.04 (± 0.09)	2.05 (± 0.09)
Standard deviation during highway driving	0.30 (± 0.02)	0.35 (± 0.04)	0.40 (± 0.04)	0.43 (± 0.05)

Standard deviation during rural road driving	0.46 (± 0.04)	0.53 (± 0.06)	0.50 (± 0.04)	0.55 (± 0.05)
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End point values	Placebo Assessment 4	Active control baseline	Tizanidine Immediate release Baseline	Tizanidine Extended release Baseline
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	23	23	23
Units: seconds				
arithmetic mean (standard error)				
Mean Time Headway during highway driving	1.91 (± 0.11)	1.87 (± 0.09)	1.77 (± 0.11)	1.70 (± 0.10)
Mean Time Headway during rural road driving	2.17 (± 0.12)	2.10 (± 0.10)	2.00 (± 0.09)	1.99 (± 0.11)
Standard deviation during highway driving	0.46 (± 0.05)	0.38 (± 0.04)	0.31 (± 0.04)	0.33 (± 0.04)
Standard deviation during rural road driving	0.51 (± 0.05)	0.47 (± 0.05)	0.43 (± 0.04)	0.41 (± 0.04)

End point values	Active control Assessment 1	Tizanidine Immediate release Assessment 1	Tizanidine Extended release Assessment 1	Active control Assessment 2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	23	23	23
Units: seconds				
arithmetic mean (standard error)				
Mean Time Headway during highway driving	2.00 (± 0.12)	1.91 (± 0.08)	1.84 (± 0.13)	1.92 (± 0.12)
Mean Time Headway during rural road driving	2.11 (± 0.10)	2.16 (± 0.09)	2.07 (± 0.14)	2.07 (± 0.13)
Standard deviation during highway driving	0.53 (± 0.06)	0.44 (± 0.04)	0.44 (± 0.05)	0.47 (± 0.05)
Standard deviation during rural road driving	0.66 (± 0.07)	0.65 (± 0.06)	0.59 (± 0.07)	0.63 (± 0.06)

End point values	Tizanidine Immediate release Assessment 2	Tizanidine Extended release Assessment 2	Active control Assessment 3	Tizanidine Immediate release Assessment 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	23	23	23
Units: seconds				
arithmetic mean (standard error)				
Mean Time Headway during highway driving	1.91 (± 0.12)	1.87 (± 0.12)	1.96 (± 0.13)	1.78 (± 0.10)
Mean Time Headway during rural road driving	2.07 (± 0.10)	2.01 (± 0.10)	2.05 (± 0.13)	1.97 (± 0.09)

Standard deviation during highway driving	0.46 (± 0.05)	0.44 (± 0.05)	0.51 (± 0.06)	0.40 (± 0.04)
Standard deviation during rural road driving	0.57 (± 0.06)	0.58 (± 0.05)	0.61 (± 0.05)	0.54 (± 0.06)

End point values	Tizanidine Extended release Assessment 3	Active control Assessment 4	Tizanidine Immediate release Assessment 4	Tizanidine Extended release Assessment 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	23	23	23
Units: seconds				
arithmetic mean (standard error)				
Mean Time Headway during highway driving	1.83 (± 0.12)	1.87 (± 0.12)	1.91 (± 0.10)	1.76 (± 0.12)
Mean Time Headway during rural road driving	1.96 (± 0.11)	2.06 (± 0.11)	2.02 (± 0.08)	1.97 (± 0.13)
Standard deviation during highway driving	0.46 (± 0.06)	0.45 (± 0.05)	0.47 (± 0.06)	0.44 (± 0.06)
Standard deviation during rural road driving	0.61 (± 0.06)	0.59 (± 0.05)	0.66 (± 0.06)	0.54 (± 0.05)

## Statistical analyses

No statistical analyses for this end point

## Secondary: Peripheral Detection Task

End point title	Peripheral Detection Task
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End point description:

End point type	Secondary
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End point timeframe:

4 weeks

End point values	Placebo Baseline	Placebo Assessment 1	Placebo Assessment 2	Placebo Assessment 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	20	20	20
Units: milliseconds				
arithmetic mean (standard error)				
Mean reaction time PDT during highway driving	415 (± 20)	418 (± 22)	419 (± 28)	438 (± 31)
Mean reaction time PDT during rural road driving	437 (± 19)	457 (± 25)	467 (± 37)	486 (± 31)
Percentage missed targets PDT during highway driving	5.24 (± 2.44)	4.93 (± 1.78)	4.44 (± 1.42)	6.66 (± 2.25)
Percentage missed targets PDT during rural road driving	5.52 (± 1.88)	7.80 (± 2.19)	8.82 (± 3.09)	14.44 (± 4.61)

End point values	Placebo Assessment 4	Active control baseline	Tizanidine Immediate release Baseline	Tizanidine Extended release Baseline
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	20	20	20
Units: milliseconds				
arithmetic mean (standard error)				
Mean reaction time PDT during highway driving	427 (± 29)	415 (± 26)	397 (± 18)	421 (± 23)
Mean reaction time PDT during rural road driving	462 (± 31)	459 (± 30)	428 (± 22)	455 (± 26)
Percentage missed targets PDT during highway drive	5.29 (± 1.62)	5.11 (± 1.90)	3.78 (± 1.05)	3.72 (± 1.51)
Percentage missed targets PDT during rural road drive	9.45 (± 3.01)	6.47 (± 1.79)	4.56 (± 0.97)	5.92 (± 1.99)

End point values	Active control Assessment 1	Tizanidine Immediate release Assessment 1	Tizanidine Extended release Assessment 1	Active control Assessment 2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	20	20	20
Units: milliseconds				
arithmetic mean (standard error)				
Mean reaction time PDT during highway driving	462 (± 30)	452 (± 22)	441 (± 17)	478 (± 34)
Mean reaction time PDT during rural road driving	500 (± 31)	525 (± 34)	500 (± 19)	520 (± 33)
Percentage missed targets PDT during highway drive	7.15 (± 1.92)	8.23 (± 2.01)	4.54 (± 1.36)	7.61 (± 2.07)
Percentage missed targets PDT during rural road drive	15.51 (± 3.57)	14.35 (± 3.10)	12.06 (± 2.35)	17.12 (± 3.05)

End point values	Tizanidine Immediate release Assessment 2	Tizanidine Extended release Assessment 2	Active control Assessment 3	Tizanidine Immediate release Assessment 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	20	20	20
Units: milliseconds				
arithmetic mean (standard error)				
Mean reaction time PDT during highway driving	443 (± 24)	457 (± 25)	487 (± 32)	434 (± 26)
Mean reaction time PDT during rural road driving	504 (± 24)	523 (± 32)	554 (± 31)	478 (± 26)
Percentage missed targets PDT during highway drive	6.38 (± 1.46)	7.12 (± 1.61)	8.90 (± 2.27)	5.18 (± 1.39)



Percentage missed targets PDT during rural road dr	12.60 (± 2.41)	15.62 (± 3.14)	19.43 (± 3.43)	11.88 (± 2.73)
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End point values	Tizanidine Extended release Assessment 3	Active control Assessment 4	Tizanidine Immediate release Assessment 4	Tizanidine Extended release Assessment 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	20	20	20
Units: milliseconds				
arithmetic mean (standard error)				
Mean reaction time PDT during highway driving	448 (± 19)	452 (± 36)	471 (± 34)	441 (± 23)
Mean reaction time PDT during rural road driving	525 (± 21)	473 (± 30)	535 (± 28)	500 (± 29)
Percentage missed targets PDT during highway drivi	8.15 (± 1.98)	8.49 (± 2.40)	7.14 (± 1.86)	7.85 (± 3.37)
Percentage missed targets PDT during rural road dr	18.54 (± 3.24)	10.63 (± 3.29)	17.47 (± 2.87)	13.72 (± 3.28)

## Statistical analyses

No statistical analyses for this end point

## Secondary: Psychomotor vigilance test

End point title	Psychomotor vigilance test
End point description:	
End point type	Secondary
End point timeframe:	
4 weeks	

End point values	Placebo Baseline	Placebo Assessment 1	Placebo Assessment 2	Placebo Assessment 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	24	24	24	24
Units: milliseconds				
arithmetic mean (standard error)				
Mean reaction time	387 (± 13)	403 (± 15)	419 (± 14)	423 (± 17)
Number of lapses	10.13 (± 2.43)	12.17 (± 2.88)	14.67 (± 3.20)	15.04 (± 2.90)

End point values	Placebo Assessment 4	Active control baseline	Tizanidine Immediate release Baseline	Tizanidine Extended release Baseline
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Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	24	24	24	24
Units: milliseconds				
arithmetic mean (standard error)				
Mean reaction time	443 (± 25)	398 (± 16)	389 (± 14)	396 (± 10)
Number of lapses	16.04 (± 3.24)	12.00 (± 2.78)	11.50 (± 2.43)	9.75 (± 1.36)

End point values	Active control Assessment 1	Tizanidine Immediate release Assessment 1	Tizanidine Extended release Assessment 1	Active control Assessment 2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	24	24	24	24
Units: milliseconds				
arithmetic mean (standard error)				
Mean reaction time	488 (± 31)	458 (± 21)	421 (± 14)	504 (± 30)
Number of lapses	21.54 (± 3.89)	19.75 (± 3.03)	14.25 (± 2.59)	25.75 (± 3.46)

End point values	Tizanidine Immediate release Assessment 2	Tizanidine Extended release Assessment 2	Active control Assessment 3	Tizanidine Immediate release Assessment 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	24	24	24	24
Units: milliseconds				
arithmetic mean (standard error)				
Mean reaction time	455 (± 25)	468 (± 17)	461 (± 18)	435 (± 16)
Number of lapses	17.88 (± 2.91)	19.92 (± 2.39)	21.04 (± 3.34)	17.33 (± 2.90)

End point values	Tizanidine Extended release Assessment 3	Active control Assessment 4	Tizanidine Immediate release Assessment 4	Tizanidine Extended release Assessment 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	24	24	24	24
Units: milliseconds				
arithmetic mean (standard error)				
Mean reaction time	475 (± 18)	437 (± 19)	458 (± 15)	471 (± 28)
Number of lapses	21.04 (± 2.63)	18.96 (± 3.64)	21.33 (± 2.91)	19.83 (± 3.09)

## Statistical analyses

No statistical analyses for this end point

**Secondary: VigTrack**

End point title VigTrack

End point description:

End point type Secondary

End point timeframe:

4 weeks

End point values	Placebo Baseline	Placebo Assessment 1	Placebo Assessment 2	Placebo Assessment 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	24	24	24	24
Units: milliseconds				
arithmetic mean (standard error)				
Mean reaction time	576 ( $\pm$ 14)	663 ( $\pm$ 20)	659 ( $\pm$ 21)	667 ( $\pm$ 19)
Percentage targets missed	2.53 ( $\pm$ 1.01)	5.00 ( $\pm$ 1.62)	4.54 ( $\pm$ 0.97)	5.61 ( $\pm$ 1.64)
Trackin score	72.21 ( $\pm$ 11.00)	76.63 ( $\pm$ 11.47)	74.20 ( $\pm$ 11.76)	75.94 ( $\pm$ 11.55)

End point values	Placebo Assessment 4	Active control baseline	Tizanidine Immediate release Baseline	Tizanidine Extended release Baseline
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	24	24	24	24
Units: milliseconds				
arithmetic mean (standard error)				
Mean reaction time	678 ( $\pm$ 25)	609 ( $\pm$ 18)	586 ( $\pm$ 16)	611 ( $\pm$ 24)
Percentage targets missed	6.32 ( $\pm$ 1.52)	3.25 ( $\pm$ 0.96)	3.32 ( $\pm$ 1.56)	6.64 ( $\pm$ 3.82)
Trackin score	68.72 ( $\pm$ 7.40)	79.88 ( $\pm$ 10.34)	74.25 ( $\pm$ 9.48)	77.32 ( $\pm$ 14.37)

End point values	Active control Assessment 1	Tizanidine Immediate release Assessment 1	Tizanidine Extended release Assessment 1	Active control Assessment 2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	24	24	24	24
Units: milliseconds				
arithmetic mean (standard error)				
Mean reaction time	718 ( $\pm$ 25)	727 ( $\pm$ 23)	672 ( $\pm$ 26)	734 ( $\pm$ 29)
Percentage targets missed	16.14 ( $\pm$ 3.53)	17.03 ( $\pm$ 3.62)	9.43 ( $\pm$ 3.56)	14.48 ( $\pm$ 2.99)
Trackin score	118.73 ( $\pm$ 15.40)	123.35 ( $\pm$ 18.57)	82.33 ( $\pm$ 13.10)	111.66 ( $\pm$ 19.27)

End point values	Tizanidine Immediate release Assessment 2	Tizanidine Extended release Assessment 2	Active control Assessment 3	Tizanidine Immediate release Assessment 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	24	24	24	24
Units: milliseconds				
arithmetic mean (standard error)				
Mean reaction time	702 (± 19)	686 (± 21)	718 (± 25)	674 (± 21)
Percentage targets missed	9.11 (± 2.73)	12.22 (± 3.74)	10.28 (± 2.37)	6.49 (± 1.87)
Trackin score	90.36 (± 11.44)	86.36 (± 13.97)	97.24 (± 14.08)	79.30 (± 10.22)

End point values	Tizanidine Extended release Assessment 3	Active control Assessment 4	Tizanidine Immediate release Assessment 4	Tizanidine Extended release Assessment 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	24	24	24	24
Units: milliseconds				
arithmetic mean (standard error)				
Mean reaction time	679 (± 21)	692 (± 18)	709 (± 20)	702 (± 20)
Percentage targets missed	11.45 (± 3.45)	7.28 (± 1.49)	9.84 (± 1.57)	11.67 (± 3.25)
Trackin score	81.28 (± 12.04)	73.58 (± 8.05)	84.09 (± 10.97)	83.07 (± 12.76)

## Statistical analyses

No statistical analyses for this end point

## Secondary: Karolinska Sleepiness Scale

End point title	Karolinska Sleepiness Scale
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End point description:

End point type	Secondary
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End point timeframe:

4 weeks

<b>End point values</b>	Placebo Baseline	Placebo Assessment 1	Placebo Assessment 2	Placebo Assessment 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	24	24	24	24
Units: mean scores				
arithmetic mean (standard error)	3.75 (± 0.35)	4.13 (± 0.23)	4.17 (± 0.29)	4.17 (± 0.29)

<b>End point values</b>	Placebo Assessment 4	Active control baseline	Tizanidine Immediate release Baseline	Tizanidine Extended release Baseline
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	24	24	24	24
Units: mean scores				
arithmetic mean (standard error)	4.38 (± 0.31)	3.75 (± 0.33)	3.96 (± 0.30)	3.71 (± 0.20)

<b>End point values</b>	Active control Assessment 1	Tizanidine Immediate release Assessment 1	Tizanidine Extended release Assessment 1	Active control Assessment 2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	24	24	24	24
Units: mean scores				
arithmetic mean (standard error)	5.46 (± 0.40)	5.63 (± 0.39)	4.38 (± 0.29)	6.29 (± 0.37)

<b>End point values</b>	Tizanidine Immediate release Assessment 2	Tizanidine Extended release Assessment 2	Active control Assessment 3	Tizanidine Immediate release Assessment 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	24	24	24	24
Units: mean scores				
arithmetic mean (standard error)	5.58 (± 0.31)	5.46 (± 0.37)	5.25 (± 0.41)	4.46 (± 0.30)

<b>End point values</b>	Tizanidine Extended release Assessment 3	Active control Assessment 4	Tizanidine Immediate release Assessment 4	Tizanidine Extended release Assessment 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	24	24	24	24
Units: mean scores				
arithmetic mean (standard error)	4.96 (± 0.32)	5.04 (± 0.34)	5.38 (± 0.38)	5.25 (± 0.34)

## **Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

4 weeks (one day per week)

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	19
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### Reporting groups

Reporting group title	Non serious adverse events
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Reporting group description: -

Serious adverse events	Non serious adverse events		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 24 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Non serious adverse events		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 24 (75.00%)		
Surgical and medical procedures			
Sleepiness/Tired			
subjects affected / exposed	17 / 24 (70.83%)		
occurrences (all)	62		
Cardiac disorders			
Cold			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	5		
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 24 (25.00%)		
occurrences (all)	10		
Gastrointestinal disorders			

Nausea			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	2		



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported