



Clinical trial results:

A phase II, randomized, double-blind, parallel groups study to assess the efficacy and safety of Nimodipine 20 mg + Betahistine 16 mg versus Placebo + Betahistine 16 mg in the treatment of vertigo

Summary

EudraCT number	2013-005122-33
Trial protocol	IT
Global end of trial date	08 July 2015

Results information

Result version number	v1 (current)
This version publication date	20 December 2017
First version publication date	20 December 2017
Summary attachment (see zip file)	Synopsis CSR Nimobet vers. 1 date 16.12.2015 (Synopsis CSR Nimobet vers. 1 date 16.12.2015.pdf)

Trial information

Trial identification

Sponsor protocol code	NIMOBET-1
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	MDM S.p.A.
Sponsor organisation address	Via Volturbo 29/b, Monza, Italy, 20052
Public contact	Servizio Segreteria MDM, MDM S.p.A., 0039 039 3909110, mdm@mdmspa.com
Scientific contact	Servizio Segreteria MDM, MDM S.p.A., 0039 039 3909110, mdm@mdmspa.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	16 December 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 July 2015
Global end of trial reached?	Yes
Global end of trial date	08 July 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of Nimodipine 20 mg + Betahistine 16 mg (b.i.d) for the treatment of vertigo, compared to Betahistine 16 mg (b.i.d), as assessed by the Dizziness Handicap Inventory (DHI) after 4 weeks of treatment

Protection of trial subjects:

No specific measure was taken, other than good clinical practice procedures

Background therapy:

Betahistine dihydrochloride tablet 16 mg, 1 tablet b.i.d.

Evidence for comparator:

The rationale for using in this study a combination of betahistine and nimodipine in the symptomatic relief of vertigo is derived from their modes of action.

A recent retrospective study based on a ten-year experience with two long-term medical protocols prescribed to well defined Menière's disease patients showed a moderate reduction of the impact of vertigo on quality of life in betahistine-treated patients while a more significant effect was reported in those patients treated with the combination of nimodipine and betahistine. In addition, both protocols (betahistine alone versus betahistine + nimodipine) resulted in a better control of vertigo and postural control, but a greater reduction of frequency of the attacks and larger effects on body sway were obtained with the combination of drugs.

Actual start date of recruitment	01 April 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: 82
Worldwide total number of subjects	82
EEA total number of subjects	82

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)	30
From 65 to 84 years	49
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

Prior to performing any trial assessments, the Investigator will ensure that the patient has provided written informed according to the procedure described in the protocol. The first subject signed the informed consent and performed the Visit 1 (Screening Visit) on January 19th, 2015 and the last subject on May 12th, 2015.

Pre-assignment

Screening details:

Screening was performed on Visit 1 (Day -7). If eligible, the patients were instructed to discontinue their prestudy vestibular suppressants drugs for a 7 days wash out period. All screened subjects were eligible and entered the study.

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	Investigator, Subject, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

The treatment was provided in kits identified by a random code. The two study treatments (Nimodipine and placebo) were indistinguishable. The Investigator was provided with a set of sealed envelopes to unblind the codes for valid medical or safety reasons. The Investigator had to contact the Sponsor before breaking the blinded code. When the code was unblinded, the reason had to be fully documented on the CRF. The unblinding envelopes were checked for their integrity and returned to the Sponsor.

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment group A

Arm description:

Betahistine dihydrochloride tablet (30 tablets, 16 mg) plus Nimodipine drops (ISKIDROP, 25 ml, 30 mg/0.75 ml)

Arm type	Experimental
Investigational medicinal product name	Nimodipine drops: Iskidrop, 25 ml, 30 mg/0.75 ml
Investigational medicinal product code	C08CA06
Other name	
Pharmaceutical forms	Oral drops
Routes of administration	Oral use

Dosage and administration details:

20 drops twice a day

Investigational medicinal product name	Betahistine dihydrochloride: Betahistine ratiopharm 30 tablets, 16 mg
Investigational medicinal product code	N07CA01
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet twice a day

Arm title	Treatment group B
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Arm description:

Betahistine dihydrochloride tablet (30 tablets, 16 mg) plus Placebo drops (25 ml, 0 mg/0.75 ml)

Arm type	Placebo
Investigational medicinal product name	Placebo drops: 25 ml, 0 mg/0.75 ml
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral drops
Routes of administration	Oral use

Dosage and administration details:

20 drops twice a day

Investigational medicinal product name	Betahistine dihydrochloride: Betahistine ratiopharm 30 tablets, 16 mg
Investigational medicinal product code	N07CA01
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet twice a day

Number of subjects in period 1	Treatment group A	Treatment group B
Started	43	39
Completed	41	37
Not completed	2	2
Adverse event, non-fatal	1	2
Protocol deviation	1	-

Baseline characteristics

Reporting groups

Reporting group title	Treatment group A
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Reporting group description:

Betahistine dihydrochloride tablet (30 tablets, 16 mg) plus Nimodipine drops (ISKIDROP, 25 ml, 30 mg/0.75 ml)

Reporting group title	Treatment group B
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Reporting group description:

Betahistine dihydrochloride tablet (30 tablets, 16 mg) plus Placebo drops (25 ml, 0 mg/0.75 ml)

Reporting group values	Treatment group A	Treatment group B	Total
Number of subjects	43	39	82
Age categorical			
Units: Subjects			
Adults (18-64 years)	14	16	30
From 65-84 years	26	23	49
85 years and over	3	0	3
Age continuous			
Age at baseline			
Units: years			
arithmetic mean	66.84	65.64	
standard deviation	± 12.70	± 11.59	-
Gender categorical			
Gender			
Units: Subjects			
Female	30	29	59
Male	13	10	23
Vertigo			
Type of vertigo			
Units: Subjects			
Central	12	10	22
Mixed	10	8	18
Peripheral	21	21	42

End points

End points reporting groups

Reporting group title	Treatment group A
Reporting group description: Betahistine dihydrochloride tablet (30 tablets, 16 mg) plus Nimodipine drops (ISKIDROP, 25 ml, 30 mg/0.75 ml)	
Reporting group title	Treatment group B
Reporting group description: Betahistine dihydrochloride tablet (30 tablets, 16 mg) plus Placebo drops (25 ml, 0 mg/0.75 ml)	
Subject analysis set title	ITT Central A
Subject analysis set type	Sub-group analysis
Subject analysis set description: ITT patients with central vertigo at screening visit - Treatment group A	
Subject analysis set title	ITT Central B
Subject analysis set type	Sub-group analysis
Subject analysis set description: ITT patients with central vertigo at screening visit - Treatment group B	
Subject analysis set title	ITT Peripheral A
Subject analysis set type	Sub-group analysis
Subject analysis set description: ITT patients with peripheral vertigo at screening visit - Treatment group A	
Subject analysis set title	ITT Peripheral B
Subject analysis set type	Sub-group analysis
Subject analysis set description: ITT patients with peripheral vertigo at screening visit - Treatment group B	
Subject analysis set title	ITT Mixed A
Subject analysis set type	Sub-group analysis
Subject analysis set description: ITT patients with mixed vertigo at screening visit - Treatment group A	
Subject analysis set title	ITT Mixed B
Subject analysis set type	Sub-group analysis
Subject analysis set description: ITT patients with mixed vertigo at screening visit - Treatment group B	
Subject analysis set title	ITT Central/Mixed A
Subject analysis set type	Sub-group analysis
Subject analysis set description: ITT patients with central/mixed vertigo at screening visit - Treatment group A	
Subject analysis set title	ITT Central/Mixed B
Subject analysis set type	Sub-group analysis
Subject analysis set description: ITT patients with central/mixed vertigo at screening visit - Treatment group B	
Subject analysis set title	ITT Women A
Subject analysis set type	Sub-group analysis
Subject analysis set description: ITT female patients - Treatment group A	
Subject analysis set title	ITT Women B
Subject analysis set type	Sub-group analysis

Subject analysis set description:

ITT female patients - Treatment group B

Subject analysis set title	ITT Men A
Subject analysis set type	Sub-group analysis

Subject analysis set description:

ITT male patients - Treatment group A

Subject analysis set title	ITT Men B
Subject analysis set type	Sub-group analysis

Subject analysis set description:

ITT male patients - Treatment group B

Primary: Improvement of DHI score

End point title	Improvement of DHI score
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End point description:

The changes in DHI score between baseline and end of treatment have been compared between treatment groups

End point type	Primary
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End point timeframe:

Between baseline and end of treatment

End point values	Treatment group A	Treatment group B	ITT Central A	ITT Central B
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	41	37	11	9
Units: points				
arithmetic mean (standard deviation)	14.05 (\pm 10.40)	13.41 (\pm 9.81)	14.73 (\pm 10.52)	11.33 (\pm 6.00)

End point values	ITT Peripheral A	ITT Peripheral B	ITT Mixed A	ITT Mixed B
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20	20	10	8
Units: points				
arithmetic mean (standard deviation)	13.20 (\pm 10.89)	13.30 (\pm 12.14)	15.00 (\pm 10.21)	16.00 (\pm 6.32)

End point values	ITT Central/Mixed A	ITT Central/Mixed B	ITT Women A	ITT Women B
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	21	17	29	27
Units: points				
arithmetic mean (standard deviation)	14.86 (\pm 10.11)	13.53 (\pm 6.42)	13.38 (\pm 10.57)	14.00 (\pm 10.17)

End point values	ITT Men A	ITT Men B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	10		
Units: points				
arithmetic mean (standard deviation)	15.67 (\pm 10.23)	11.80 (\pm 9.07)		

Statistical analyses

Statistical analysis title	ANOVA on DHI improvement (ITT population)
Statistical analysis description: ANOVA model with factor for treatment on ITT population	
Comparison groups	Treatment group B v Treatment group A
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.78 ^[1]
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.93
upper limit	5.21

Notes:

[1] - The difference between treatment groups was not statistically significant

Statistical analysis title	ANCOVA on DHI improvement (ITT population)
Statistical analysis description: ANCOVA model with factors for treatment and baseline values on ITT population	
Comparison groups	Treatment group A v Treatment group B
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.843 ^[2]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.13
upper limit	5.04

Notes:

[2] - The difference between treatment groups was not statistically significant

Statistical analysis title	ANOVA on DHI improvement (Central Vertigo)
Statistical analysis description:	
ANOVA model with factor for treatment on patients with central vertigo	
Comparison groups	ITT Central A v ITT Central B
Number of subjects included in analysis	20
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.402 ^[3]
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	3.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.92
upper limit	11.7

Notes:

[3] - The difference between treatment groups was not statistically significant

Statistical analysis title	ANOVA on DHI improvement (Peripheral Vertigo)
Statistical analysis description:	
ANOVA model with factor for treatment on patients with peripheral vertigo	
Comparison groups	ITT Peripheral B v ITT Peripheral A
Number of subjects included in analysis	40
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.978 ^[4]
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.48
upper limit	7.28

Notes:

[4] - The difference between treatment groups was not statistically significant

Statistical analysis title	ANOVA on DHI improvement (Mixed Vertigo)
Statistical analysis description:	
ANOVA model with factor for treatment on patients with mixed vertigo	
Comparison groups	ITT Mixed A v ITT Mixed B

Number of subjects included in analysis	18
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.812 ^[5]
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.77
upper limit	7.77

Notes:

[5] - The difference between treatment groups was not statistically significant

Statistical analysis title	ANOVA on DHI improvement (Central/Mixed Vertigo)
Statistical analysis description:	
ANOVA model with factor for treatment on patients with central or mixed vertigo	
Comparison groups	ITT Central/Mixed A v ITT Central/Mixed B
Number of subjects included in analysis	38
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.642 ^[6]
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.41
upper limit	7.06

Notes:

[6] - The difference between treatment groups was not statistically significant

Statistical analysis title	ANOVA on DHI improvement (Women)
Statistical analysis description:	
ANOVA model with factor for treatment on female patients	
Comparison groups	ITT Women B v ITT Women A
Number of subjects included in analysis	56
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.824 ^[7]
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.19
upper limit	4.94

Notes:

[7] - The difference between treatment groups was not statistically significant

Statistical analysis title	ANOVA on DHI improvement (Men)
Statistical analysis description: ANOVA model with factor for treatment on male patients	
Comparison groups	ITT Men A v ITT Men B
Number of subjects included in analysis	22
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.364 [8]
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	3.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.82
upper limit	12.55

Notes:

[8] - The difference between treatment groups was not statistically significant

Secondary: Improvement of MVS score

End point title	Improvement of MVS score
End point description: The changes in MVS score between baseline and end of treatment have been compared between treatment groups	
End point type	Secondary
End point timeframe: Between baseline and end of treatment	

End point values	Treatment group A	Treatment group B	ITT Central A	ITT Central B
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	41	37	11	9
Units: points				
arithmetic mean (standard deviation)	2.61 (± 1.79)	2.32 (± 1.94)	2.09 (± 1.38)	1.56 (± 1.24)

End point values	ITT Peripheral A	ITT Peripheral B	ITT Mixed A	ITT Mixed B
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20	20	10	8
Units: points				
arithmetic mean (standard deviation)	2.60 (± 1.82)	2.60 (± 2.26)	3.20 (± 2.10)	2.50 (± 1.69)

End point values	ITT Central/Mixed A	ITT Central/Mixed B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	17		
Units: points				
arithmetic mean (standard deviation)	2.62 (\pm 1.80)	2.00 (\pm 1.50)		

Statistical analyses

Statistical analysis title	ANOVA on MVS improvement (ITT population)
Statistical analysis description: ANOVA model with factor for treatment	
Comparison groups	Treatment group A v Treatment group B
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.501
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.56
upper limit	1.13

Statistical analysis title	ANOVA on MVS improvement (Central Vertigo)
Statistical analysis description: ANOVA model with factor for treatment on patients with central vertigo	
Comparison groups	ITT Central A v ITT Central B
Number of subjects included in analysis	20
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.377 ^[9]
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.71
upper limit	1.78

Notes:

[9] - The difference between treatment groups was not statistically significant

Statistical analysis title	ANOVA on MVS improvement (Peripheral Vertigo)
Statistical analysis description:	
ANOVA model with factor for treatment on patients with peripheral vertigo	
Comparison groups	ITT Peripheral A v ITT Peripheral B
Number of subjects included in analysis	40
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 1 ^[10]
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.31
upper limit	1.31

Notes:

[10] - The difference between treatment groups was not statistically significant

Statistical analysis title	ANOVA on MVS improvement (Mixed Vertigo)
Statistical analysis description:	
ANOVA model with factor for treatment on patients with mixed vertigo	
Comparison groups	ITT Mixed A v ITT Mixed B
Number of subjects included in analysis	18
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.456 ^[11]
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.24
upper limit	2.64

Notes:

[11] - The difference between treatment groups was not statistically significant

Statistical analysis title	ANOVA on MVS improvement (Central/Mixed Vertigo)
Statistical analysis description:	
ANOVA model with factor for treatment on patients with central or mixed vertigo	
Comparison groups	ITT Central/Mixed A v ITT Central/Mixed B

Number of subjects included in analysis	38
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.265 ^[12]
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.49
upper limit	1.73

Notes:

[12] - The difference between treatment groups was not statistically significant

Secondary: Improvement of PCS-12 score

End point title	Improvement of PCS-12 score
End point description:	
The changes in PCS-12 score (SF-12) between baseline and end of treatment have been compared between treatment groups	
End point type	Secondary
End point timeframe:	
Between baseline and end of treatment	

End point values	Treatment group A	Treatment group B	ITT Central A	ITT Central B
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	41	37	11	9
Units: Points				
arithmetic mean (standard deviation)	2.49 (± 4.61)	1.97 (± 4.76)	2.86 (± 4.59)	2.09 (± 4.29)

End point values	ITT Peripheral A	ITT Peripheral B	ITT Mixed A	ITT Mixed B
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20	20	10	8
Units: Points				
arithmetic mean (standard deviation)	2.32 (± 4.02)	1.97 (± 5.18)	2.42 (± 6.04)	1.82 (± 4.75)

End point values	ITT Central/Mixed A	ITT Central/Mixed B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	17		
Units: Points				
arithmetic mean (standard deviation)	2.65 (± 5.19)	1.97 (± 4.37)		

Statistical analyses

Statistical analysis title	ANOVA on PCS-12 (ITT Population)
Statistical analysis description: ANOVA model with factor for treatment on ITT patients	
Comparison groups	Treatment group B v Treatment group A
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.625 ^[13]
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.59
upper limit	2.63

Notes:

[13] - The difference between treatment groups was not statistically significant

Statistical analysis title	ANOVA on PCS-12 (Central Vertigo)
Statistical analysis description: ANOVA model with factor for treatment on patients with central vertigo	
Comparison groups	ITT Central A v ITT Central B
Number of subjects included in analysis	20
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.704
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.44
upper limit	4.98

Statistical analysis title	ANOVA on PCS-12 (Peripheral Vertigo)
Statistical analysis description: ANOVA model with factor for treatment on patients with peripheral vertigo	
Comparison groups	ITT Peripheral A v ITT Peripheral B

Number of subjects included in analysis	40
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.815
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.62
upper limit	3.32

Statistical analysis title	ANOVA on PCS-12 (Mixed Vertigo)
Statistical analysis description:	
ANOVA model with factor for treatment on patients with mixed vertigo	
Comparison groups	ITT Mixed A v ITT Mixed B
Number of subjects included in analysis	18
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.822
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.95
upper limit	6.14

Statistical analysis title	ANOVA on PCS-12 (Central/Mixed Vertigo)
Statistical analysis description:	
ANOVA model with factor for treatment on patients with central or mixed vertigo	
Comparison groups	ITT Central/Mixed A v ITT Central/Mixed B
Number of subjects included in analysis	38
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.666
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.52
upper limit	3.89

Secondary: Improvement of MCS-12 score

End point title	Improvement of MCS-12 score
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End point description:

The changes in MCS-12 score (SF-12) between baseline and end of treatment have been compared between treatment groups

End point type	Secondary
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End point timeframe:

Between baseline and end of treatment

End point values	Treatment group A	Treatment group B	ITT Central A	ITT Central B
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	41	37	11	9
Units: POINTS				
arithmetic mean (standard deviation)	4.52 (± 9.57)	4.00 (± 6.18)	2.70 (± 6.77)	2.91 (± 4.74)

End point values	ITT Peripheral A	ITT Peripheral B	ITT Mixed A	ITT Mixed B
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20	20	10	8
Units: POINTS				
arithmetic mean (standard deviation)	4.96 (± 12.09)	3.00 (± 4.76)	5.64 (± 6.45)	7.71 (± 9.43)

End point values	ITT Central/Mixed A	ITT Central/Mixed B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	17		
Units: POINTS				
arithmetic mean (standard deviation)	4.10 (± 6.63)	5.17 (± 7.50)		

Statistical analyses

Statistical analysis title	ANOVA on MCS-12 (ITT Population)
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Statistical analysis description:

ANOVA model with factor for treatment on ITT population

Comparison groups	Treatment group A v Treatment group B
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Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.778
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.15
upper limit	4.2

Statistical analysis title	ANOVA on MCS-12 (Central Vertigo)
Statistical analysis description:	
ANOVA model with factor for treatment on patients with central vertigo	
Comparison groups	ITT Central A v ITT Central B
Number of subjects included in analysis	20
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.937
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.84
upper limit	5.41

Statistical analysis title	ANOVA on MCS-12 (Peripheral Vertigo)
Statistical analysis description:	
ANOVA model with factor for treatment on patients with peripheral vertigo	
Comparison groups	ITT Peripheral A v ITT Peripheral B
Number of subjects included in analysis	40
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.504
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.92
upper limit	7.84

Statistical analysis title	ANOVA on MCS-12 (Mixed Vertigo)
Statistical analysis description:	
ANOVA model with factor for treatment on patients with mixed vertigo	
Comparison groups	ITT Mixed A v ITT Mixed B
Number of subjects included in analysis	18
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.589
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10
upper limit	5.87

Statistical analysis title	ANOVA on MCS-12 (Central/Mixed Vertigo)
Statistical analysis description:	
ANOVA model with factor for treatment on patients with central or mixed vertigo	
Comparison groups	ITT Central/Mixed A v ITT Central/Mixed B
Number of subjects included in analysis	38
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.644
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.72
upper limit	3.58

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The reporting period for AEs is the period starting from the time of the first dose taken and lasting until Visit 6. At the end of this follow-up period, all unresolved AEs will be documented on the CRF as "ongoing".

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.0
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Reporting groups

Reporting group title	Treatment group A
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Reporting group description:

Betahistine dihydrochloride tablet (30 tablets, 16 mg) plus Nimodipine drops (ISKIDROP, 25 ml, 30 mg/0.75 ml)

Posology: 1 tablet plus 20 drops, twice in day.

Reporting group title	Treatment group B
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Reporting group description:

Betahistine dihydrochloride tablet (30 tablets, 16 mg) plus Placebo drops (25 ml, 0 mg/0.75 ml).

Posology: 1 tablet plus 20 drops, twice in day.

Serious adverse events	Treatment group A	Treatment group B	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 43 (0.00%)	0 / 39 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Treatment group A	Treatment group B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 43 (2.33%)	2 / 39 (5.13%)	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 43 (2.33%)	1 / 39 (2.56%)	
occurrences (all)	1	1	
Skin and subcutaneous tissue disorders			
Wheals			
subjects affected / exposed	1 / 43 (2.33%)	0 / 39 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 February 2014	<p>As a result of requests made by the Ethics Committee during the initial evaluation, some changes to protocol version no. 1 have been introduced. This has resulted in a new version of the protocol (version no. 2) and related documents.</p> <p>The present Amendment is intended to harmonize the documents submitted to AIFA with those requested and approved by the Ethics Committee.</p> <p>The requests for changes / additions made by the Ethics Committee have resulted in a new version of the following documents: 1) Study Protocol; 2) Synopsis 3) CTA Form 4) Information sheet and Informed Consent Form.</p> <p>The main changes made to the concerned protocol were as follows:</p> <p>1) In the eligibility criteria, the differential diagnosis of vertigo was better specified;</p> <p>2) A new exclusion criterion was introduced: patients with hypertension;</p> <p>3) In the study design an additional visit during the treatment phase (on day 14) was added, in order to better monitor the patients' safety.</p> <p>We finally took the opportunity to make some "Errata Corrige" to the initial text.</p>
30 September 2014	<p>The current exclusion criterion n. 1 provides for patients not be included in the study if affected by cerebellopontine lesions, multiple sclerosis, vascular dementia, migraine associated vertigo, phobic vertigo, motion sickness, acoustic neuroma or other CNS tumor, as documented by CT or MRI performed within 3 months of the screening visit.</p> <p>However, since patients who will be included in the study are already being treated for a long time at the center and their health conditions are well known to the Investigator and are periodically re-checked, it is considered sufficient that the exclusion criterion is verified by the Investigator on the basis of a previous instrumental examination (brain CT or MRI) and of the patient's medical history and any changes in the patient's health over time, since he/she is being treated at the center.</p> <p>The eligibility of the patient will be assessed by the Investigator, based also on a previous brain CT or MRI, although not necessarily carried out in the 3 months prior to the start of the study.</p> <p>For these reasons it is considered appropriate to remove the time limit of 3 months for the acceptability of cerebral CT or MRI, from the first exclusion criterion.</p> <p>We finally took the opportunity to update the period of the study, as communicated to the Ethical Committee with letter dated 23/07/2014, and to correct the investigator phone number indicated in the Information sheet and Informed Consent Form.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported