Clinical trial results:
Effects of MagneB6® (470.0 mg Magnesium Lactate Dihydrate + 5.0 mg Pyridoxine Hydrochloride, Coated Tablet) Supplementation (8 Weeks) on Stress Levels of Chronically Stressed Subjects, with Suboptimal Serum Magnesium Levels- A Randomized, Single-blind Active Comparator, Multicentric Clinical Trial - Comparison with Magnespasmyl® (465.4 mg Magnesium Lactate Dihydrate, Coated Tablet)

Summary

EudraCT number	2015-003749-24
Trial protocol	FR
Global end of trial date	04 April 2017

Results information

Result version number	v1 (current)
This version publication date	19 April 2018
First version publication date	19 April 2018

Trial information

Trial identification

Sponsor protocol code	MGLACC07810

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Study Name: MB6 SUPERIORITY

Notes:

Sponsors

Sponsor organisation name	Sanofi-Aventis Group
Sponsor organisation address	54 Rue La Boétie, Paris, France, 75008
Public contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.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	30 June 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 April 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the superiority of Magne B6® (Magnesium [Mg] + vitamin B6) versus Magnespasmyl® (Mg only) supplementation on stress level, evaluated by the stress subscale from the Depression Anxiety Stress Scale (DASS)-42 test, in chronically stressed subjects, with suboptimal serum Mg levels.

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency. Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 May 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	France: 264
Worldwide total number of subjects	264
EEA total number of subjects	264

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)	264

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 4 centres in France. A total of 854 subjects were screened between 04 May 2016 and 25 January 2017 of whom 586 were screen failures. Screen failures were mainly due to exclusion criteria met.

Pre-assignment

Screening details:

A total of 268 subjects were randomized in the study. Of which, 264 subjects were treated in 1:1 ratio to the MagneB6® and Magnespasmyl® arms. The randomization was stratified by sex on a 1:1 ratio.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Investigator[1]

Arms

Are arms mutually exclusive?	Yes
Arm title	MagneB6®

Arm description:

Subjects received two tablets of MagneB6® (470.0 mg Mg lactate dihydrate + 5.0 mg pyridoxime hydrochloride) three times per day during the 8 week treatment period.

Arm type	Experimental
Investigational medicinal product name	MagneB6®
Investigational medicinal product code	Z0889
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received 6 coated tablets of MagneB6® per day, divided in three intakes, at meal time (2 tablets to be swallowed during each meal: breakfast, lunch, dinner).

Arm title	Magnespasmyl®

Arm description:

Subjects received two tablets of Magnespasmyl® 47.4 mg three times per day during the 8 week treatment period.

Arm type	Active comparator
Investigational medicinal product name	Magnespasmyl®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received 6 coated tablets of Magnespasmyl® (465.4 mg Mg lactate dihydrate) per day, divided in three intakes, at meal time (2 tablets to be swallowed during each meal: breakfast, lunch, dinner).

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: Only investigator was blinded in this trial.

Number of subjects in period 1	MagneB6®	Magnespasmyl®
Started	132	132
Completed	130	130
Not completed	2	2
Consent withdrawn by subject	2	1
Adverse event	-	1

Baseline characteristics

Reporting groups	
Reporting group title	MagneB6®
Reporting group description:	
Subjects received two tablets of MagneB6® (470.0 mg Mg lactate dihydrate + 5.0 mg pyridoxime hydrochloride) three times per day during the 8 week treatment period.	
Reporting group title	Magnespasmyl®
Reporting group description:	
Subjects received two tablets of Magnespasmyl® 47.4 mg three times per day during the 8 week treatment period.	

Reporting group values	MagneB6®	Magnespasmyl®	Total
Number of subjects	132	132	264
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 31.2 ± 8.4	 32.1 ± 8.6	 -
Gender categorical Units: Subjects			
Female	98	97	195
Male	34	35	69

End points

End points reporting groups

Reporting group title	MagneB6®
Reporting group description:	
Subjects received two tablets of MagneB6® (470.0 mg Mg lactate dihydrate + 5.0 mg pyridoxime hydrochloride) three times per day during the 8 week treatment period.	
Reporting group title	Magnespasmyl®
Reporting group description:	
Subjects received two tablets of Magnespasmyl® 47.4 mg three times per day during the 8 week treatment period.	

Primary: Change From Baseline in DASS-42 Stress Subscale at Week 8: Modified Intent to Treat (mITT) Population

End point title	Change From Baseline in DASS-42 Stress Subscale at Week 8: Modified Intent to Treat (mITT) Population
End point description:	
DASS-42 is a 42-item questionnaire consisting of 3 sub-scales (depression, anxiety and stress) to measure the negative emotional states of depression, anxiety and stress. Each sub-scale contains 14 items. The stress sub-scale items were scored on a 4-point rating scale: 0 (Did not apply to me at all) to 3 (Applies to me most of the time). The sub-scale score ranges from 0 to 42, where cut-off score from 0-14= normal, 15-18= mild, 19-25= moderate, 26-33= severe and 34-42= extremely severe stress level. Analysis was performed on mITT population which included all subjects randomized in the study with at least one consumption of study product (MagneB6® or Magnespasmyl®) and an evaluable DASS-42 stress score at baseline and at least one during the treatment period.	
End point type	Primary
End point timeframe:	
Baseline, Week 8	

End point values	MagneB6®	Magnespasmyl®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	132	132		
Units: units on a scale				
arithmetic mean (confidence interval 95%)	-12.44 (-13.83 to -11.05)	-11.72 (-13.10 to -10.33)		

Statistical analyses

Statistical analysis title	MagneB6® vs. Magnespasmyl®
Statistical analysis description:	
Difference in adjusted mean was analysed from analysis of covariance (ANCOVA), adjusted on sex and interaction between visit and DASS-42 stress at Day 1 (Baseline). Missing data was imputed by last observation carried forward (LOCF) method.	
Comparison groups	MagneB6® v Magnespasmyl®

Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4472
Method	ANCOVA
Parameter estimate	Difference in adjusted means
Point estimate	0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.15
upper limit	2.59

Primary: Change From Baseline in DASS-42 Stress Subscale at Week 8: Strict Per Protocol Set (SPPS) Population

End point title	Change From Baseline in DASS-42 Stress Subscale at Week 8: Strict Per Protocol Set (SPPS) Population

End point description:

DASS-42 is a 42-item questionnaire consisting of 3 sub-scales (depression, anxiety and stress) to measure the negative emotional states of depression, anxiety and stress. Each sub-scale contains 14 items. The stress sub-scale items were scored on a 4-point rating scale: 0 (Did not apply to me at all) to 3 (Applies to me most of the time). The sub-scale score ranges from 0 to 42, where cut-off score from 0-14= normal, 15-18= mild, 19-25= moderate, 26-33= severe and 34-42= extremely severe stress level. Analysis was performed on SPPS population which included all subjects of the mITT without any major protocol deviation, analysed in the group to which they were allocated by randomization with a DASS-42 scale for chronic stress at Day 1 (baseline) >18.

End point type	Primary

End point timeframe:

Baseline, Week 8

End point values	MagneB6®	Magnespasmyl®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	116		
Units: units on a scale				
arithmetic mean (confidence interval 95%)	-13.26 (-14.81 to -11.71)	-12.21 (-13.73 to -10.68)		

Statistical analyses

Statistical analysis title	MagneB6® vs. Magnespasmyl®

Statistical analysis description:

Difference in adjusted mean was analysed from ANCOVA, adjusted on sex and interaction between visit and DASS-42 stress at Day 1 (Baseline). Missing data was imputed by LOCF method.

Comparison groups	Magnespasmyl® v MagneB6®

Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3095
Method	ANCOVA
Parameter estimate	Difference in adjusted means
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.99
upper limit	3.1

Primary: Change From Baseline in DASS-42 Stress Subscale (for Subjects with Normal to Moderate DASS-42 Stress Scale) at Week 8 - mITT Population

End point title	Change From Baseline in DASS-42 Stress Subscale (for Subjects with Normal to Moderate DASS-42 Stress Scale) at Week 8 - mITT Population

End point description:

DASS-42 is a 42-item questionnaire consisting of 3 sub-scales (depression, anxiety and stress) to measure the negative emotional states of depression, anxiety and stress. Each sub-scale contains 14 items. The stress sub-scale items were scored on a 4-point rating scale: 0 (Did not apply to me at all) to 3 (Applies to me most of the time). The sub-scale score ranges from 0 to 42, where cut-off score from 0-14= normal, 15-18= mild, 19-25= moderate, 26-33= severe and 34-42= extremely severe stress level. Analysis was performed on mITT population. Number of subjects analysed=subjects with available data for this end point.

End point type	Primary

End point timeframe:

Baseline, Week 8

End point values	MagneB6®	Magnespasmyl®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	35		
Units: units on a scale				
arithmetic mean (confidence interval 95%)	-8.20 (-10.01 to -6.40)	-10.56 (-12.48 to -8.65)		

Statistical analyses

Statistical analysis title	MagneB6® vs. Magnespasmyl®

Statistical analysis description:

Difference in adjusted mean was analysed from ANCOVA, adjusted on sex. Missing data were imputed by LOCF method.

Comparison groups	MagneB6® v Magnespasmyl®

Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0784
Method	ANCOVA
Parameter estimate	Difference in adjusted means
Point estimate	-2.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.99
upper limit	0.27

Primary: Change From Baseline in DASS-42 Stress Subscale (for Subjects with Normal to Moderate DASS-42 Stress Scale) at Week 8 - SPPS Population

End point title	Change From Baseline in DASS-42 Stress Subscale (for Subjects with Normal to Moderate DASS-42 Stress Scale) at Week 8 - SPPS Population

End point description:

DASS-42 is a 42-item questionnaire consisting of 3 sub-scales (depression, anxiety and stress) to measure the negative emotional states of depression, anxiety and stress. Each sub-scale contains 14 items. The stress sub-scale items were scored on a 4-point rating scale: 0 (Did not apply to me at all) to 3 (Applies to me most of the time). The sub-scale score ranges from 0 to 42, where cut-off score from 0-14= normal, 15-18= mild, 19-25= moderate, 26-33= severe and 34-42= extremely severe stress level. Analysis was performed on SPPS population. Number of subjects analysed=subjects with available data for this end point.

End point type	Primary

End point timeframe:

Baseline, Week 8

End point values	MagneB6®	Magnespasmyl®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	32		
Units: units on a scale				
arithmetic mean (confidence interval 95%)	-9.73 (-11.82 to -7.65)	-11.69 (-14.05 to -9.33)		

Statistical analyses

Statistical analysis title	MagneB6® vs. Magnespasmyl®

Statistical analysis description:

Difference in adjusted mean was analysed from ANCOVA, adjusted on sex. Missing data were imputed by LOCF method.

Comparison groups	MagneB6® v Magnespasmyl®

Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2199
Method	ANCOVA
Parameter estimate	Difference in adjusted means
Point estimate	-1.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.11
upper limit	1.2

Primary: Change From Baseline in DASS-42 Stress Subscale (for Subjects with Severe or Extremely Severe DASS-42 Stress Scale) at Week 8 - mITT Population

End point title	Change From Baseline in DASS-42 Stress Subscale (for Subjects with Severe or Extremely Severe DASS-42 Stress Scale) at Week 8 - mITT Population

End point description:

DASS-42 is a 42-item questionnaire consisting of 3 sub-scales (depression, anxiety and stress) to measure the negative emotional states of depression, anxiety and stress. Each sub-scale contains 14 items. The stress sub-scale items were scored on a 4-point rating scale: 0 (Did not apply to me at all) to 3 (Applies to me most of the time). The sub-scale score ranges from 0 to 42, where cut-off score from 0-14= normal, 15-18= mild, 19-25= moderate, 26-33= severe and 34-42= extremely severe stress level. Analysis was performed on mITT population. Number of subjects analysed=subjects with available data for this end point.

End point type	Primary

End point timeframe:

Baseline, Week 8

End point values	MagneB6®	Magnespasmyl®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	84		
Units: units on a scale				
arithmetic mean (confidence interval 95%)	-16.36 (-18.27 to -14.44)	-13.20 (-15.05 to -11.36)		

Statistical analyses

Statistical analysis title	MagneB6® vs. Magnespasmyl®

Statistical analysis description:

Difference in adjusted mean was analysed from ANCOVA, adjusted on sex. Missing data were imputed by LOCF method.

Comparison groups	MagneB6® v Magnespasmyl®

Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0203
Method	ANCOVA
Parameter estimate	Difference in adjusted means
Point estimate	3.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	5.82

Primary: Change From Baseline in DASS-42 Stress Subscale (for Subjects with Severe or Extremely Severe DASS-42 Stress Scale) at Week 8 - SPPS Population

End point title	Change From Baseline in DASS-42 Stress Subscale (for Subjects with Severe or Extremely Severe DASS-42 Stress Scale) at Week 8 - SPPS Population

End point description:

DASS-42 is a 42-item questionnaire consisting of 3 sub-scales (depression, anxiety and stress) to measure the negative emotional states of depression, anxiety and stress. Each sub-scale contains 14 items. The stress sub-scale items were scored on a 4-point rating scale: 0 (Did not apply to me at all) to 3 (Applies to me most of the time). The sub-scale score ranges from 0 to 42, where cut-off score from 0-14= normal, 15-18= mild, 19-25= moderate, 26-33= severe and 34-42= extremely severe stress level. Analysis was performed on SPPS population. Number of subjects analysed=subjects with available data for this end point.

End point type	Primary

End point timeframe:

Baseline, Week 8

End point values	MagneB6®	Magnespasmyl®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76	84		
Units: units on a scale				
arithmetic mean (confidence interval 95%)	-16.09 (-18.02 to -14.16)	-13.20 (-15.04 to -11.36)		

Statistical analyses

Statistical analysis title	MagneB6® vs. Magnespasmyl®

Statistical analysis description:

Difference in adjusted mean was analysed from ANCOVA, adjusted on sex. Missing data were imputed by LOCF method.

Comparison groups	MagneB6® v Magnespasmyl®

Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0339
Method	ANCOVA
Parameter estimate	Difference in adjusted means
Point estimate	2.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.22
upper limit	5.56

Secondary: Change From Baseline in DASS-42 Stress Subscale at Week 4

End point title	Change From Baseline in DASS-42 Stress Subscale at Week 4

End point description:

DASS-42 is a 42-item questionnaire consisting of 3 sub-scales (depression, anxiety and stress) to measure the negative emotional states of depression, anxiety and stress. Each sub-scale contains 14 items. The stress sub-scale items were scored on a 4-point rating scale: 0 (Did not apply to me at all) to 3 (Applies to me most of the time). The sub-scale score ranges from 0 to 42, where cut-off score from 0-14= normal, 15-18= mild, 19-25= moderate, 26-33= severe and 34-42= extremely severe stress level. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Baseline, Week 4

End point values	MagneB6®	Magnespasmyl®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	132	132		
Units: units on a scale				
arithmetic mean (confidence interval 95%)	-8.94 (-10.22 to -7.65)	-7.58 (-8.86 to -6.30)		

Statistical analyses

Statistical analysis title	MagneB6® vs. Magnespasmyl®

Statistical analysis description:

Difference in adjusted mean was analysed from analysis of covariance (ANCOVA), adjusted on sex. Missing data were imputed by LOCF method.

Comparison groups	MagneB6® v Magnespasmyl®

Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1203
Method	ANCOVA
Parameter estimate	Difference in adjusted means
Point estimate	1.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.36
upper limit	3.06

Secondary: Change From Baseline in Anxiety Subscore at Week 4 and 8

End point title	Change From Baseline in Anxiety Subscore at Week 4 and 8

End point description:

DASS-42 is a 42-item questionnaire consisting of 3 sub-scales (depression, anxiety and stress) to measure the negative emotional states of depression, anxiety and stress. Each sub-scale contains 14 items. The anxiety sub-scale items were scored on a 4-point rating scale: 0 (Did not apply to me at all) to 3 (Applies to me most of the time). The sub-scale score ranges from 0 to 42, where cut-off score from 0-7= normal, 8-9= mild, 10-14= moderate, 15-19= severe and 20-42= extremely severe anxiety level. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Baseline, Week 4 and Week 8

End point values	MagneB6®	Magnespasmyl®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	132	132		
Units: units on a scale				
arithmetic mean (confidence interval 95%)				
Change at Week 4	-5.30 (-6.29 to -4.31)	-5.66 (-6.65 to -4.68)		
Change at Week 8	-7.98 (-8.95 to -7.01)	-8.60 (-9.57 to -7.63)		

Statistical analyses

Statistical analysis title	Change at Week 4: MagneB6® vs. Magnespasmyl®

Statistical analysis description:

Difference in adjusted mean was analysed from ANCOVA, adjusted on sex and interaction between visit and DASS-42 anxiety at D1. Missing data were imputed by LOCF method.

Comparison groups	MagneB6® v Magnespasmyl®

Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	ANCOVA
Parameter estimate	Difference in adjusted means
Point estimate	-0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.69
upper limit	0.95

Statistical analysis title	Change at Week 8: MagneB6® v Magnespasmyl®

Statistical analysis description:

Difference in adjusted mean was analysed from ANCOVA, adjusted on sex and interaction between visit and DASS-42 anxiety at D1. Missing data were imputed by LOCF method.

Comparison groups	MagneB6® v Magnespasmyl®
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	ANCOVA
Parameter estimate	Difference in adjusted means
Point estimate	-0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.91
upper limit	0.68

Secondary: Change From Baseline in Depression Subscore at Week 4 and 8

End point title	Change From Baseline in Depression Subscore at Week 4 and 8

End point description:

DASS-42 is a 42-item questionnaire consisting of 3 sub-scales (depression, anxiety and stress) to measure the negative emotional states of depression, anxiety and stress. Each sub-scale contains 14 items. The depression sub-scale items were scored on a 4-point rating scale: 0 (Did not apply to me at all) to 3 (Applies to me most of the time). The sub-scale score ranges from 0 to 42, where cut-off score from 0-9= normal, 10-13= mild, 14-20= moderate, 21-27= severe and 28-42= extremely severe depression. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Baseline, Week 4 and Week 8

End point values	MagneB6®	Magnespasmyl ®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	132	132		
Units: units on a scale				
arithmetic mean (confidence interval 95%)				
Change at Week 4	-5.42 (-6.47 to -4.37)	-5.01 (-6.05 to -3.96)		
Change at Week 8	-7.71 (-8.85 to -6.57)	-7.69 (-8.83 to -6.55)		

Statistical analyses

Statistical analysis title	Change at Week 4: MagneB6® vs. Magnespasmyl®
Statistical analysis description:	
Difference in adjusted mean was analysed from ANCOVA, adjusted on sex and interaction between visit and DASS-42 depression at Day 1 (Baseline). Missing data were imputed by LOCF method.	
Comparison groups	Magnespasmyl® v MagneB6®
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	ANCOVA
Parameter estimate	Difference in adjusted means
Point estimate	0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.98
upper limit	1.81

Statistical analysis title	Change at Week 8: MagneB6® vs. Magnespasmyl®
Statistical analysis description:	
Difference in adjusted mean was analysed from ANCOVA, adjusted on sex and interaction between visit and DASS-42 depression at Day 1 (Baseline). Missing data were imputed by LOCF method.	
Comparison groups	MagneB6® v Magnespasmyl®
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	ANCOVA
Parameter estimate	Difference in adjusted means
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.51
upper limit	1.55

Secondary: Change From Baseline in Total DASS-42 Scale at Week 4 and 8

End point title	Change From Baseline in Total DASS-42 Scale at Week 4 and 8

End point description:

DASS-42 is a 42-item questionnaire consisting of 3 sub-scales (depression, anxiety and stress) to measure the negative emotional states of depression, anxiety and stress. Each sub-scale containing 14 items were scored on a 4-point rating scale: 0 (Did not apply to me at all) to 3 (Applies to me most of the time). The total scores (DASS-42 stress + DASS-42 depression + DASS-42 anxiety) ranged from 0 to 126, where higher scores indicated higher level of depression, anxiety or/and stress. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Baseline, Week 4 and Week 8

End point values	MagneB6®	Magnespasmyl ®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	132	132		
Units: units on a scale				
arithmetic mean (confidence interval 95%)				
Change at Week 4	-19.66 (-22.55 to -16.78)	-18.28 (-21.15 to -15.41)		
Change at Week 8	-28.14 (-31.28 to -25.00)	-28.03 (-31.16 to -24.90)		

Statistical analyses

Statistical analysis title	Change at Week 4: MagneB6® v Magnespasmyl®

Statistical analysis description:

Difference in adjusted mean was analysed from ANCOVA, adjusted on sex and interaction between visit and DASS-42 total at D1. Missing data were imputed by LOCF method.

Comparison groups	Magnespasmyl® v MagneB6®
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	ANCOVA
Parameter estimate	Difference in adjusted means
Point estimate	1.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.44
upper limit	5.2

Statistical analysis title	Change at Week 8: MagneB6® vs. Magnespasmyl®

Statistical analysis description:

Difference in adjusted mean was analysed from ANCOVA, adjusted on sex and interaction between visit and DASS-42 total at D1. Missing data were imputed by LOCF method.

Comparison groups	MagneB6® v Magnespasmyl®
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	ANCOVA
Parameter estimate	Difference in adjusted means
Point estimate	0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.1
upper limit	4.31

Secondary: Change from Baseline in Cortisol Awakening Response (CAR) at Week 4 and 8

End point title	Change from Baseline in Cortisol Awakening Response (CAR) at Week 4 and 8

End point description:

CAR is an allostatic indicator used as a biomarker to quantify stress levels. This test was done by subjects at home on 2 days (the day before visit & day of visit [except for baseline visit)]). Three saliva samples were collected by day: 0, 30 & 45 minutes after awakening & before breakfast on Day 2 and 3 (for baseline), Day 27 and 28 (for Week 4) and Day 55 and 56 (for Week 8). CAR kits were dispensed to subjects for saliva cortisol sampling. Change from baseline at Week 4 and Week 8 was measured by the mean over 2 days of total area under the curve (AUCt) (0, 30 and 45 minutes) of CAR. Difference in adjusted mean was analysed from ANCOVA, adjusted on sex. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Baseline, Week 4 and Week 8

End point values	MagneB6®	Magnespasmyl®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	132	132		
Units: nmol/L				
arithmetic mean (confidence interval 95%)				
Change at Week 4	-14.04 (-53.48 to 25.40)	-5.42 (-44.71 to 33.87)		
Change at Week 8	-2.62 (-47.07 to 41.84)	6.29 (-37.99 to 50.58)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Absolute Increase of Cortisol (AINC) at Week 4 and 8

End point title	Change from Baseline in Absolute Increase of Cortisol (AINC) at Week 4 and 8

End point description:

Change from baseline at Week 4 and Week 8 was measured by the mean over 2 days of AINC (maximum value of cortisol at 30 and 45 minutes minus 0 minutes). Difference in adjusted mean was analysed from ANCOVA, adjusted on sex. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Baseline, Week 4 and Week 8

End point values	MagneB6®	Magnespasmyl®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	132	132		
Units: nmol/L				
arithmetic mean (confidence interval 95%)				
Change at Week 4	0.11 (-1.27 to 1.49)	0.30 (-1.08 to 1.67)		
Change at Week 8	-0.01 (-1.26 to 1.24)	0.80 (-0.45 to 2.04)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Mean Increase of Cortisol (MINC) at Week 4 and 8

End point title	Change from Baseline in Mean Increase of Cortisol (MINC) at Week 4 and 8

End point description:

Change from baseline at Week 4 and Week 8 was measured by mean over 2 days of MINC (mean value of cortisol at 30 and 45 minutes minus 0 minutes). Difference in adjusted mean was analysed from ANCOVA, adjusted on sex. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Baseline, Week 4 and Week 8

End point values	MagneB6®	Magnespasmyl ®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	132	132		
Units: nmol/L				
arithmetic mean (confidence interval 95%)				
Change at Week 4	0.36 (-0.74 to 1.47)	0.14 (-0.96 to 1.25)		
Change at Week 8	0.21 (-0.79 to 1.20)	0.63 (-0.36 to 1.63)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Local Erythrocyte (Red Blood Cells [RBCs]) Magnesium at Week 4 and 8

End point title	Change from Baseline in Local Erythrocyte (Red Blood Cells [RBCs]) Magnesium at Week 4 and 8

End point description:

Difference in adjusted means were analysed. Adjusted mean from ANCOVA, adjusted on sex. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Baseline, Week 4 and Week 8

End point values	MagneB6®	Magnespasmyl ®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	132	132		
Units: mmol/L				
arithmetic mean (confidence interval 95%)				
Change at Week 4	0.03 (-0.01 to 0.08)	0.04 (-0.01 to 0.09)		
Change at Week 8	0.01 (-0.03 to 0.06)	0.02 (-0.03 to 0.06)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AEs) were collected from signature of the informed consent form up to the last visit (Week 8) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported AEs are treatment-emergent AEs that is AEs that developed/worsened from first study drug intake up to 8 weeks. Safety population included all subjects included in the study with at least one consumption of study product. Subjects were analysed according to the actual treatment received.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	MagneB6®

Reporting group description:

Subjects received two tablets of MagneB6® (470.0 mg Mg lactate dihydrate + 5.0 mg pyridoxime hydrochloride) three times per day during the 8 week treatment period.

Reporting group title	Magnespasmyl®

Reporting group description:

Subjects received two tablets of Magnespasmyl® 47.4 mg three times per day during the 8 week treatment period.

Serious adverse events	MagneB6®	Magnespasmyl®	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	MagneB6®	Magnespasmyl®	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	54 / 132 (40.91%)	52 / 132 (39.39%)	
Injury, poisoning and procedural complications			

Ligament sprain			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences (all)	1	0	
Rib fracture			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Sunburn			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 132 (2.27%)	1 / 132 (0.76%)	
occurrences (all)	3	1	
Formication			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	2	
Headache			
subjects affected / exposed	11 / 132 (8.33%)	13 / 132 (9.85%)	
occurrences (all)	11	16	
Hypersomnia			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Migraine			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences (all)	1	0	
Presyncope			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 132 (0.76%)	1 / 132 (0.76%)	
occurrences (all)	1	1	
Fatigue			
subjects affected / exposed	1 / 132 (0.76%)	1 / 132 (0.76%)	
occurrences (all)	1	1	
Vessel puncture site haematoma			

subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences (all)	1	0	
Abdominal distension			
subjects affected / exposed	2 / 132 (1.52%)	0 / 132 (0.00%)	
occurrences (all)	2	0	
Abdominal pain			
subjects affected / exposed	3 / 132 (2.27%)	8 / 132 (6.06%)	
occurrences (all)	3	12	
Abdominal pain upper			
subjects affected / exposed	0 / 132 (0.00%)	2 / 132 (1.52%)	
occurrences (all)	0	2	
Constipation			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	7 / 132 (5.30%)	12 / 132 (9.09%)	
occurrences (all)	8	21	
Dry mouth			
subjects affected / exposed	2 / 132 (1.52%)	0 / 132 (0.00%)	
occurrences (all)	2	0	
Dyspepsia			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Dysphagia			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences (all)	1	0	
Faeces soft			
subjects affected / exposed	3 / 132 (2.27%)	2 / 132 (1.52%)	
occurrences (all)	3	2	
Flatulence			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	

Frequent bowel movements			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal inflammation			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	2 / 132 (1.52%)	3 / 132 (2.27%)	
occurrences (all)	2	3	
Vomiting			
subjects affected / exposed	2 / 132 (1.52%)	2 / 132 (1.52%)	
occurrences (all)	5	2	
Reproductive system and breast disorders			
Metrorrhagia			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences (all)	1	0	
Epistaxis			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal pain			
subjects affected / exposed	1 / 132 (0.76%)	1 / 132 (0.76%)	
occurrences (all)	1	1	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Dermatitis acneiform			
subjects affected / exposed	1 / 132 (0.76%)	1 / 132 (0.76%)	
occurrences (all)	1	1	
Rash			
subjects affected / exposed	1 / 132 (0.76%)	1 / 132 (0.76%)	
occurrences (all)	1	1	

Rash papular			
subjects affected / exposed	2 / 132 (1.52%)	1 / 132 (0.76%)	
occurrences (all)	2	1	
Skin reaction			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Urticaria			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Depression			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Sleep disorder			
subjects affected / exposed	2 / 132 (1.52%)	0 / 132 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	4 / 132 (3.03%)	2 / 132 (1.52%)	
occurrences (all)	4	2	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal stiffness			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Myalgia			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Neck pain			
subjects affected / exposed	3 / 132 (2.27%)	0 / 132 (0.00%)	
occurrences (all)	3	0	
Infections and infestations			

Bronchitis			
subjects affected / exposed	0 / 132 (0.00%)	2 / 132 (1.52%)	
occurrences (all)	0	2	
Cystitis			
subjects affected / exposed	0 / 132 (0.00%)	2 / 132 (1.52%)	
occurrences (all)	0	2	
Eczema infected			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis			
subjects affected / exposed	3 / 132 (2.27%)	2 / 132 (1.52%)	
occurrences (all)	3	2	
Influenza			
subjects affected / exposed	1 / 132 (0.76%)	1 / 132 (0.76%)	
occurrences (all)	1	1	
Nasopharyngitis			
subjects affected / exposed	4 / 132 (3.03%)	1 / 132 (0.76%)	
occurrences (all)	4	1	
Rhinitis			
subjects affected / exposed	6 / 132 (4.55%)	1 / 132 (0.76%)	
occurrences (all)	6	1	
Sinusitis			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Tonsillitis			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Vaginal infection			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Increased appetite			

subjects affected / exposed occurrences (all)	0 / 132 (0.00%) 0	1 / 132 (0.76%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 February 2016	Following changes were made: - Change in names and addresses of team's representative. - Addition of a table summarizing blood sample volume per subject during the study. - Procedures for the analysis of Erythrocyte Mg, Serum vitamin B6 and CAR.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported