



Clinical trial results:

A Double-Blind, Placebo-Controlled, Randomized Withdrawal Study of the Safety and Efficacy of Memantine in Pediatric Patients with Autism, Asperger's Disorder, or Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS) Previously Treated with Memantine Summary

EudraCT number	2012-001568-31
Trial protocol	GB HU BE ES NL EE FR IT IS
Global end of trial date	11 September 2013

Results information

Result version number	v1 (current)
This version publication date	09 August 2018
First version publication date	09 August 2018

Trial information

Trial identification

Sponsor protocol code	MEM-MD-68
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01592747
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Forest Laboratories LLC, a subsidiary of Allergan, plc
Sponsor organisation address	1 Grand Canal Square, Docklands, Ireland, Dublin 2
Public contact	Clinical Trial Information Desk, Forest Laboratories LLC, a subsidiary of Allergan, plc, 001 866-369-5227,
Scientific contact	Joel Trugman, Forest Laboratories LLC, a subsidiary of Allergan, plc, 001 201-427-8681, Joel.Trugman@actavis.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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 October 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 September 2013
Global end of trial reached?	Yes
Global end of trial date	11 September 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety, tolerability, and efficacy of memantine therapy compared with placebo in pediatric patients with autism, Asperger's Disorder, or Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS) previously on stable memantine therapy utilizing a randomized withdrawal paradigm.

Protection of trial subjects:

At each study center, the Investigator was responsible for ensuring that the investigation was conducted according to the signed Investigator agreement, the protocol, good clinical practice guidelines, and applicable regulations; for protecting the rights, safety, and welfare of patients under the Investigator's care; and for the control of investigational products under investigation. The Investigator at each study center was responsible for the management of the study, which consisted of maintaining the study file and patient records, corresponding with the IRB/IEC, and completing the electronic case report forms (eCRFs).

Background therapy:

Not Applicable

Evidence for comparator:

Not Applicable

Actual start date of recruitment	10 September 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Colombia: 5
Country: Number of subjects enrolled	Estonia: 2
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Hungary: 8
Country: Number of subjects enrolled	Iceland: 3
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	Korea, Republic of: 14
Country: Number of subjects enrolled	New Zealand: 2
Country: Number of subjects enrolled	Poland: 21
Country: Number of subjects enrolled	Serbia: 14
Country: Number of subjects enrolled	South Africa: 1
Country: Number of subjects enrolled	Spain: 2

Country: Number of subjects enrolled	Ukraine: 6
Country: Number of subjects enrolled	United States: 386
Worldwide total number of subjects	479
EEA total number of subjects	51

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)	418
Adolescents (12-17 years)	61
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patient recruitment occurred over an ten month period, from September of 2012 to June of 2013, at 92 study sites, located in 15 countries.

Belgium
Colombia
Estonia
France
Hungary
Iceland
Italy
Korea, Republic of
New Zealand
Poland
Serbia
South Africa
Spain
Ukraine
United States

Pre-assignment

Screening details:

Patients who completed at least 12 weeks of exposure to open-label memantine and met the responder criterion at 2 consecutive visits separated by at least 2 weeks during lead-in study 2012-001568-31 (MEM-MD-91) were eligible to be randomized into this study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Dose-matched placebo, oral administration, once per day.

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

Dosage and administration details:

Dose-matched placebo, oral administration, once per day.

Arm title	Memantine Reduced Dose
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Arm description:

Memantine, 3mg every other day, 3mg per day, or 6mg per day depending on weight group and tolerability. Oral administration once per day.

Arm type	Experimental
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Investigational medicinal product name	Memantine
Investigational medicinal product code	
Other name	Ebixa, Namenda, Axura, Akatinol, Abixa, Memox
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Memantine, 3mg every other day, 3mg per day, or 6mg per day depending on weight group and tolerability. Oral administration once per day.

Arm title	Memantine Full-Dose
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Arm description:

Memantine, 3mg, 6mg, 9mg, 12mg or 15mg depending on weight group and tolerability. Oral administration, once per day.

Arm type	Experimental
Investigational medicinal product name	Memantine
Investigational medicinal product code	
Other name	Ebixa, Namenda, Axura, Akatinol, Abixa, Memox
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Memantine, 3mg, 6mg, 9mg, 12mg or 15mg depending on weight group and tolerability. Oral administration, once per day.

Number of subjects in period 1	Placebo	Memantine Reduced Dose	Memantine Full-Dose
Started	160	161	158
Completed	44	50	50
Not completed	116	111	108
Loss of Therapeutic Response	107	108	100
Consent withdrawn by subject	2	-	2
Adverse event, non-fatal	1	-	-
Other Reasons	1	1	-
Lost to follow-up	1	-	1
Did meet Inclusion/Exclusion criteria	-	1	1
Protocol deviation	4	-	4
Lack of efficacy	-	1	-

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description: Dose-matched placebo, oral administration, once per day.	
Reporting group title	Memantine Reduced Dose
Reporting group description: Memantine, 3mg every other day, 3mg per day, or 6mg per day depending on weight group and tolerability. Oral administration once per day.	
Reporting group title	Memantine Full-Dose
Reporting group description: Memantine, 3mg, 6mg, 9mg, 12mg or 15mg depending on weight group and tolerability. Oral administration, once per day.	

Reporting group values	Placebo	Memantine Reduced Dose	Memantine Full-Dose
Number of subjects	160	161	158
Age categorical Units: Subjects			
Children (6-12 years)	160	161	158
Age continuous Units: years			
arithmetic mean	8.9	9.2	9.2
standard deviation	± 2	± 1.9	± 1.9
Gender categorical Units: Subjects			
Female	18	28	26
Male	142	133	132

Reporting group values	Total		
Number of subjects	479		
Age categorical Units: Subjects			
Children (6-12 years)	479		
Age continuous Units: years			
arithmetic mean	-		
standard deviation			
Gender categorical Units: Subjects			
Female	72		
Male	407		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Dose-matched placebo, oral administration, once per day.	
Reporting group title	Memantine Reduced Dose
Reporting group description:	
Memantine, 3mg every other day, 3mg per day, or 6mg per day depending on weight group and tolerability. Oral administration once per day.	
Reporting group title	Memantine Full-Dose
Reporting group description:	
Memantine, 3mg, 6mg, 9mg, 12mg or 15mg depending on weight group and tolerability. Oral administration, once per day.	
Subject analysis set title	Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All efficacy analyses were based on the Intent-to-treat (ITT) Population. Of the 479 randomized patients, 471 patients were in the ITT Population (ie, had at least 1 dose of double-blind investigational product and at least 1 assessment of the Social Responsiveness Scale (SRS) total raw score during the double-blind treatment period.)	
Subject analysis set title	Memantine Reduced Dose
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All efficacy analyses were based on the Intent-to-treat (ITT) Population. Of the 479 randomized patients, 471 patients were in the ITT Population (ie, had at least 1 dose of double-blind investigational product and at least 1 assessment of the Social Responsiveness Scale (SRS) total raw score during the double-blind treatment period.)	
Subject analysis set title	Memantine Full Dose
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All efficacy analyses were based on the Intent-to-treat (ITT) Population. Of the 479 randomized patients, 471 patients were in the ITT Population (ie, had at least 1 dose of double-blind investigational product and at least 1 assessment of the Social Responsiveness Scale (SRS) total raw score during the double-blind treatment period.)	

Primary: Proportion of Patients Meeting the Criterion for Loss of Therapeutic Response (LTR) by the End of the Study

End point title	Proportion of Patients Meeting the Criterion for Loss of Therapeutic Response (LTR) by the End of the Study
End point description:	
Loss of Therapeutic response is defined as an increase of at least 10 points (worsening) in Social Responsiveness Scale (SRS) total raw score at any double-blind visit (Visits 2, 3, 4, 5, 6, or 7) relative to the Visit 1 (randomization) score.	
The Social Responsiveness Scale (SRS) is a 65-item informant-rated assessment with total raw score, ranging from 0 (no impairment) to 195 (severe social impairment).	
Each item is associated with 1 of 5 subscales (social awareness, social cognition, social communication, social motivation and autistic mannerisms). Each item is rated on a 4-point scale from 1 (not true) to 4 (almost always true). The scores are then transposed to a scale from 0 to 3 and scores are summed within each of the 5 subscales. A higher score indicates greater severity of social impairment.	
End point type	Primary
End point timeframe:	
Baseline (Visit 1) to week 12	

End point values	Placebo	Memantine Reduced Dose	Memantine Full Dose	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	158	160	153	
Units: Percentage of patients with LTR				
number (not applicable)	69	67.5	66.7	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Memantine Full Dose v Placebo
Number of subjects included in analysis	311
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.659 ^[1]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.8

Notes:

[1] - Cochran-Mantel-Haensze test controlling for Autistic Spectrum Disorder subtype.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Memantine Reduced Dose
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7839 ^[2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.7

Notes:

[2] - Cochran-Mantel-Haenszel test controlling for Autistic Spectrum Disorder subtype.

Secondary: Time to First Loss of Therapeutic (LTR) Response

End point title	Time to First Loss of Therapeutic (LTR) Response
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End point description:	
Time to the first visit when a patient shows LTR following randomization to memantine or placebo.	
End point type	Secondary
End point timeframe:	
Baseline to week 12	

End point values	Placebo	Memantine Reduced Dose	Memantine Full Dose	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	158	160	153	
Units: Days				
median (confidence interval 95%)	29 (28 to 42)	33 (28 to 56)	30 (28 to 44)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Children's Communication Checklist-2 (CCC-2) - Speech Subscale

End point title	Change in Children's Communication Checklist-2 (CCC-2) - Speech Subscale
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End point description:

The Children's Communication Checklist-2 (CCC-2) Speech Subscale consists of 7 items rated from 0 (less than once a week or never) to 3 (several times [more than twice] a day or always), with a total raw score of 0 (mildest) to 21 (most severe).

The Children's Communication Checklist-2 (CCC-2) is a validated, norm-referenced, informant-rated scale that evaluates difficulties children may have (across 10 different subscales, consisting of 7 items each) that affect communication (items 1-50), as well as strengths that children may demonstrate when communicating with others (items 51-70).

End point type	Secondary
End point timeframe:	
Baseline (Visit 1) to week 12	

End point values	Placebo	Memantine Reduced Dose	Memantine Full-Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	153	160	158	
Units: Units on a Scale				
arithmetic mean (standard deviation)	0.2 ($\pm$ 2.7)	0.2 ($\pm$ 2.7)	0.3 ($\pm$ 2.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Children's Communication Checklist-2 (CCC-2) - Syntax Subscale

End point title	Change in Children's Communication Checklist-2 (CCC-2) - Syntax Subscale
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End point description:

The Children's Communication Checklist-2 (CCC-2) Syntax Subscale consists of 7 items rated from 0 (less than once a week or never) to 3 (several times [more than twice] a day or always), with a total raw score of 0 (mildest) to 21 (most severe).

The Children's Communication Checklist-2 (CCC-2) is a validated, norm-referenced, informant-rated scale that evaluates difficulties children may have (across 10 different subscales, consisting of 7 items each) that affect communication (items 1-50), as well as strengths that children may demonstrate when communicating with others (items 51-70).

End point type	Secondary
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End point timeframe:

Baseline (Visit 1) to week 12

End point values	Placebo	Memantine Reduced Dose	Memantine Full-Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	158	160	153	
Units: Units on a Scale				
arithmetic mean (standard deviation)	0.1 (± 2.9)	0.6 (± 2.9)	0.4 (± 2.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Children's Communication Checklist-2 (CCC-2) - Semantics Subscale

End point title	Change in Children's Communication Checklist-2 (CCC-2) - Semantics Subscale
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End point description:

The Children's Communication Checklist-2 (CCC-2) Semantics Subscale consists of 7 items rated from 0 (less than once a week or never) to 3 (several times [more than twice] a day or always), with a total raw score of 0 (mildest) to 21 (most severe).

The Children's Communication Checklist-2 (CCC-2) is a validated, norm-referenced, informant-rated scale that evaluates difficulties children may have (across 10 different subscales, consisting of 7 items each) that affect communication (items 1-50), as well as strengths that children may demonstrate when communicating with others (items 51-70).

End point type	Secondary
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End point timeframe:

Baseline (Visit 1) to week 12

End point values	Placebo	Memantine Reduced Dose	Memantine Full-Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	158	160	153	
Units: Units on a Scale				
arithmetic mean (standard deviation)	0.5 (± 2.6)	1 (± 2.9)	0.7 (± 2.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Children's Communication Checklist-2 (CCC-2) - Coherence Subscale

End point title	Change in Children's Communication Checklist-2 (CCC-2) - Coherence Subscale
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End point description:

The Children's Communication Checklist-2 (CCC-2) Coherence Subscale consists of 7 items rated from 0 (less than once a week or never) to 3 (several times [more than twice] a day or always), with a total raw score of 0 (mildest) to 21 (most severe).

The Children's Communication Checklist-2 (CCC-2) is a validated, norm-referenced, informant-rated scale that evaluates difficulties children may have (across 10 different subscales, consisting of 7 items each) that affect communication (items 1-50), as well as strengths that children may demonstrate when communicating with others (items 51-70).

End point type	Secondary
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End point timeframe:

Baseline (Visit 1) to week 12

End point values	Placebo	Memantine Reduced Dose	Memantine Full-Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	158	160	153	
Units: Units on a Scale				
arithmetic mean (standard error)	0.8 (± 3.4)	1.2 (± 3.8)	1.2 (± 3.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Children's Communication Checklist-2 (CCC-2) - Initiation Subscale

End point title	Change in Children's Communication Checklist-2 (CCC-2) - Initiation Subscale
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End point description:

The Children's Communication Checklist-2 (CCC-2) Initiation Subscale consists of 7 items rated from 0 (less than once a week or never) to 3 (several times [more than twice] a day or always), with a total raw score of 0 (mildest) to 21 (most severe).

The Children's Communication Checklist-2 (CCC-2) is a validated, norm-referenced, informant-rated scale that evaluates difficulties children may have (across 10 different subscales, consisting of 7 items each) that affect communication (items 1-50), as well as strengths that children may demonstrate when communicating with others (items 51-70).

End point type	Secondary
End point timeframe:	
Baseline (Visit 1) to week 12	

End point values	Placebo	Memantine Reduced Dose	Memantine Full-Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	158	160	153	
Units: Units on a Scale				
arithmetic mean (standard error)	1.3 (± 3.1)	1.5 (± 3.7)	1.1 (± 3.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Children's Communication Checklist-2 (CCC-2) - Scripted Language Subscale

End point title	Change in Children's Communication Checklist-2 (CCC-2) - Scripted Language Subscale
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End point description:

The Children's Communication Checklist-2 (CCC-2) Scripted language Subscale consists of 7 items rated from 0 (less than once a week or never) to 3 (several times [more than twice] a day or always), with a total raw score of 0 (mildest) to 21 (most severe).

The Children's Communication Checklist-2 (CCC-2) is a validated, norm-referenced, informant-rated scale that evaluates difficulties children may have (across 10 different subscales, consisting of 7 items each) that affect communication (items 1-50), as well as strengths that children may demonstrate when communicating with others (items 51-70).

End point type	Secondary
End point timeframe:	
Baseline (Visit 1) to week 12	

End point values	Placebo	Memantine Reduced Dose	Memantine Full-Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	158	160	153	
Units: Units on a Scale				
arithmetic mean (standard error)	0.8 (± 2.9)	1.2 (± 3.2)	1 (± 3.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Children's Communication Checklist-2 (CCC-2) - Context Subscale

End point title	Change in Children's Communication Checklist-2 (CCC-2) - Context Subscale
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End point description:

The Children's Communication Checklist-2 (CCC-2) Context Subscale consists of 7 items rated from 0 (less than once a week or never) to 3 (several times [more than twice] a day or always), with a total raw score of 0 (mildest) to 21 (most severe).

The Children's Communication Checklist-2 (CCC-2) is a validated, norm-referenced, informant-rated scale that evaluates difficulties children may have (across 10 different subscales, consisting of 7 items each) that affect communication (items 1-50), as well as strengths that children may demonstrate when communicating with others (items 51-70).

End point type	Secondary
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End point timeframe:

Baseline (Visit 1) to week 12

End point values	Placebo	Memantine Reduced Dose	Memantine Full-Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	158	160	153	
Units: Units on a Scale				
arithmetic mean (standard deviation)	0.9 (± 3)	0.9 (± 3.8)	0.9 (± 3.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Children's Communication Checklist-2 (CCC-2) - Nonverbal Communication Subscale

End point title	Change in Children's Communication Checklist-2 (CCC-2) - Nonverbal Communication Subscale
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End point description:

The Children's Communication Checklist-2 (CCC-2) Nonverbal communication Subscale consists of 7 items rated from 0 (less than once a week or never) to 3 (several times [more than twice] a day or always), with a total raw score of 0 (mildest) to 21 (most severe).

The Children's Communication Checklist-2 (CCC-2) is a validated, norm-referenced, informant-rated scale that evaluates difficulties children may have (across 10 different subscales, consisting of 7 items each) that affect communication (items 1-50), as well as strengths that children may demonstrate when communicating with others (items 51-70).

End point type	Secondary
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End point timeframe:

Baseline (Visit 1) to week 12

End point values	Placebo	Memantine Reduced Dose	Memantine Full-Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	158	160	153	
Units: Units on a Scale				
arithmetic mean (standard deviation)	1.3 ($\pm$ 3.2)	1.6 ($\pm$ 3.8)	1.7 ($\pm$ 3.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Children's Communication Checklist-2 (CCC-2) - Social Relations Subscale

End point title	Change in Children's Communication Checklist-2 (CCC-2) - Social Relations Subscale
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End point description:

The Children's Communication Checklist-2 (CCC-2) Social Relations Subscale consists of 7 items rated from 0 (less than once a week or never) to 3 (several times [more than twice] a day or always), with a total raw score of 0 (mildest) to 21 (most severe).

The Children's Communication Checklist-2 (CCC-2) is a validated, norm-referenced, informant-rated scale that evaluates difficulties children may have (across 10 different subscales, consisting of 7 items each) that affect communication (items 1-50), as well as strengths that children may demonstrate when communicating with others (items 51-70).

End point type	Secondary
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End point timeframe:

Baseline (Visit 1) to week 12

End point values	Placebo	Memantine Reduced Dose	Memantine Full-Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	158	160	153	
Units: Units on a Scale				
arithmetic mean (standard deviation)	1.6 ($\pm$ 2.9)	1.9 ($\pm$ 3.7)	1.7 ($\pm$ 3.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Children's Communication Checklist-2 (CCC-2) - Interests Subscale

End point title	Change in Children's Communication Checklist-2 (CCC-2) - Interests Subscale
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End point description:

The Children's Communication Checklist-2 (CCC-2) Interests Subscale consists of 7 items rated from 0 (less than once a week or never) to 3 (several times [more than twice] a day or always), with a total raw score of 0 (mildest) to 21 (most severe).

The Children's Communication Checklist-2 (CCC-2) is a validated, norm-referenced, informant-rated scale that evaluates difficulties children may have (across 10 different subscales, consisting of 7 items each) that affect communication (items 1-50), as well as strengths that children may demonstrate when communicating with others (items 51-70).

End point type	Secondary
End point timeframe:	
Baseline (Visit 1) to week 12	

End point values	Placebo	Memantine Reduced Dose	Memantine Full-Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	158	160	158	
Units: Units on a Scale				
arithmetic mean (standard deviation)	0.8 ($\pm$ 3.3)	1.3 ($\pm$ 3.7)	1.2 ($\pm$ 3.2)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected for a 14 month period from September of 2012 to October of 2013 at 92 study centers in 15 countries.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	15.0
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Reporting groups

Reporting group title	Placebo
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Reporting group description:

Dose-matched placebo, oral administration, once per day.

Reporting group title	Memantine Reduced Dose
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Reporting group description:

Memantine, 3mg every other day, 3mg per day, or 6mg per day depending on weight group and tolerability. Oral administration once per day.

Reporting group title	Memantine Full-Dose
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Reporting group description:

Memantine, 3mg, 6mg, 9mg, 12mg or 15mg depending on weight group and tolerability. Oral administration, once per day.

Serious adverse events	Placebo	Memantine Reduced Dose	Memantine Full-Dose
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 160 (0.00%)	1 / 160 (0.63%)	0 / 157 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Infections and infestations			
Furuncle			
subjects affected / exposed	0 / 160 (0.00%)	1 / 160 (0.63%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo	Memantine Reduced Dose	Memantine Full-Dose
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 160 (5.00%)	5 / 160 (3.13%)	4 / 157 (2.55%)
General disorders and administration site conditions			

Irritability			
subjects affected / exposed	8 / 160 (5.00%)	5 / 160 (3.13%)	4 / 157 (2.55%)
occurrences (all)	8	5	4

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 March 2013	The following changes have been made globally to the protocol: All references to the Social Responsiveness Scale (SRS) Parent Autoscore version have been revised because the SRS Parent Autoscore version has not been provided to the sites. The SRS total raw score should be calculated before the caregiver leaves the site. The global change is as follows, "If for any reason the data cannot be entered in EDC, Forest must be contacted immediately before the patient/caregiver leave the site.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported