Clinical trial results:
An Open-Label Study Of The Safety And Tolerability Of Memantine In Pediatric Patients With Autism, Asperger's Disorder, Or Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS).

Summary

EudraCT number	2012-001616-33
Trial protocol	GB HU BE ES NL EE IS IT
Global end of trial date	09 July 2013

Results information

Result version number	v1 (current)
This version publication date	10 August 2018
First version publication date	10 August 2018

Trial information

Trial identification

Sponsor protocol code	MEM-MD-91

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01592786
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, 001 201-427-8000 , 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	16 August 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 July 2013
Global end of trial reached?	Yes
Global end of trial date	09 July 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this study is to evaluate the safety and tolerability of memantine in pediatric (6-12 years old) patients with autism, Asperger's Disorder, or Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS) and to identify responders for participation in the follow-up randomized withdrawal study

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: -

Evidence for comparator: -

Actual start date of recruitment	01 June 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: 11
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Colombia: 8
Country: Number of subjects enrolled	Estonia: 6
Country: Number of subjects enrolled	France: 14
Country: Number of subjects enrolled	Hungary: 20
Country: Number of subjects enrolled	Iceland: 5
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Korea, Republic of: 25
Country: Number of subjects enrolled	New Zealand: 2
Country: Number of subjects enrolled	Poland: 37
Country: Number of subjects enrolled	Serbia: 21
Country: Number of subjects enrolled	Singapore: 1
Country: Number of subjects enrolled	South Africa: 2
Country: Number of subjects enrolled	Spain: 17
Country: Number of subjects enrolled	Ukraine: 16

Country: Number of subjects enrolled	United States: 714
Worldwide total number of subjects	906
EEA total number of subjects	116

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)	793
Adolescents (12-17 years)	113
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 eleven month period, from June of 2011 to May of 2012, at 118 study sites, located in the Untied States and 17 other countries.

Australia:
Belgium:
Canada:
Colombia
Estonia:
France:
Hungary:
Iceland:
Italy:
New Zealand:
Poland:
Singapore:
South Africa:
South Korea
Spain:
Ukraine

Pre-assignment

Screening details:

Enrolled patients went through a 2-week screening period.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Memantine Hydrochloride (HCl) ER

Arm description:

Memantine Hydrochloride (HCl) extended-release 3-mg capsules once daily, oral administration. Dosing was 3-mg, 6-mg, 9-mg, 12-mg, or 15-mg per day, based upon patient weight.

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 Hydrochloride (HCl) extended-release 3-mg capsules once daily, oral administration. Dosing was 3-mg, 6-mg, 9-mg, 12-mg, or 15-mg per day, based upon patient weight.

Number of subjects in period 1	Memantine Hydrochloride (HCl) ER
Started	906
Completed	765
Not completed	141
Consent withdrawn by subject	23
Adverse event, non-fatal	61
Other Reason	3
Lost to follow-up	21
Lack of efficacy	19
Protocol deviation	14

Baseline characteristics

Reporting groups

Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	906	906	
Age categorical Units: Subjects			
Children (6-12 years)	906	906	
Age continuous Units: years arithmetic mean standard deviation	 9 ± 1.9	 -	
Gender categorical Units: Subjects			
Female	144	144	
Male	762	762	

Subject analysis sets

Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

Of the 906 patients who enrolled in the study 903 received at least 1 dose of open-label treatment to comprise the Safety Population.

Subject analysis set title	Intent to Treat Population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The Intent to Treat (ITT) population included the 868 patients in the Safety population who also had at least 1 post–Visit 1 assessment of the SRS total raw score.

Reporting group values	Safety Population	Intent to Treat Population	
Number of subjects	903	868	
Age categorical Units: Subjects			
Children (6-12 years)	903		
Age continuous Units: years arithmetic mean standard deviation	 9 ± 1.9	 ±	
Gender categorical Units: Subjects			
Female	144		
Male	759		

End points

End points reporting groups

Reporting group title	Memantine Hydrochloride (HCl) ER
Reporting group description:	
Memantine Hydrochloride (HCl) extended-release 3-mg capsules once daily, oral administration. Dosing was 3-mg, 6-mg, 9-mg, 12-mg, or 15-mg per day, based upon patient weight.	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
Of the 906 patients who enrolled in the study 903 received at least 1 dose of open-label treatment to comprise the Safety Population.	
Subject analysis set title	Intent to Treat Population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The Intent to Treat (ITT) population included the 868 patients in the Safety population who also had at least 1 post–Visit 1 assessment of the SRS total raw score.	

Primary: Number of Social Responsiveness Scale (SRS) Confirmed Responders

End point title	Number of Social Responsiveness Scale (SRS) Confirmed Responders[1]
End point description:	
A confirmed SRS responder was defined as a patient who had at least 12 weeks of exposure to memantine, and a ≥ 10-point reduction in the SRS total raw score relative to baseline at 2 consecutive visits separated by at least 2 weeks. The SRS is a 65-item, caregiver-rated assessment scale that measures observable items on social behavior and social language use, as well as characteristics of autism in a naturalistic social setting. Each item is rated on a scale from 0 (never true) to 3 (almost always true). The SRS total raw score ranges from 0 to 195; a higher score indicates greater severity of social impairment.	
End point type	Primary
End point timeframe:	
Visit 1 (Baseline) to Visit 8 (week 48/Final Visit)	
Notes:	
[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: No inferential statistical analyses were performed for the efficacy parameters.	

End point values	Intent to Treat Population			
Subject group type	Subject analysis set			
Number of subjects analysed	868			
Units: Patients				
Confirmed Responders	517			
Non-Responders	351			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event data was collected over a 14 month period from June 2012 to August 2013 at 118 study sites in the US and 17 other countries.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	Memantine Hydrochloride (HCl)

Reporting group description:

Memantine Hydrochloride (HCl) extended-release 3-mg capsules once daily, oral administration. Dosing was 3-mg, 6-mg, 9-mg, 12-mg, or 15-mg per day, based upon patient weight.

Serious adverse events	Memantine Hydrochloride (HCl)		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 903 (0.66%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Accidental exposure			
subjects affected / exposed	1 / 903 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 903 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	1 / 903 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Abnormal behaviour			

subjects affected / exposed	2 / 903 (0.22%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Disinhibition			
subjects affected / exposed	1 / 903 (0.11%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Memantine Hydrochloride (HCl)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	193 / 903 (21.37%)		
Nervous system disorders			
Headache			
subjects affected / exposed	72 / 903 (7.97%)		
occurrences (all)	86		
General disorders and administration site conditions			
Irritability			
subjects affected / exposed	49 / 903 (5.43%)		
occurrences (all)	57		
Pyrexia			
subjects affected / exposed	52 / 903 (5.76%)		
occurrences (all)	59		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	57 / 903 (6.31%)		
occurrences (all)	69		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 March 2013	Amendment #1 specifies the following changes to the original protocol MEM-MD-91, dated April 05, 2012: Increasing sample size from approximately 192 enrolled patients to approximately 800 to 900 enrolled patients. Rationale: The Number of Patients (Planned and Analyzed) section has been amended to change the planned sample size such that a sufficient number of patients can be enrolled in MEM-MD-68 from this lead-in study. The sample size of MEM-MD-68 has been increased based on the discussion with the FDA. In order to provide sufficient patients transitioning to a follow-up randomized withdrawal study (MEM-MD-68), approximately 800 to 900 patients will be enrolled into this study. Adding information regarding the Data Safety Monitoring Board (DSMB) Rationale: This section has been added to include information about the DSMB. No safety issue necessitated the use of the DSMB. An Ethics Committee requested that a DSMB be established. Clarifying if administration of the Columbia-Suicide Severity Rating Scale (C-SSRS) is appropriate given a patient's developmental and/or situational status. Rationale: This section was revised to clarify if administration of the C-SSRS is appropriate given a patient's developmental and/or situational status. All references to the Social Responsiveness Scale (SRS) Patient Autoscore version have been revised. Rational: The Social Responsiveness Scale (SRS) Patient Autoscore version has not been provided to the sites. The SRS total raw score should be calculated before the patient/caregiver leave the site. Immediate Reporting of Serious Adverse Events Rationale: This section was revised to indicate where the SAE Form fax number and Medical Emergency phone number for sites outside the United States and Canada can be found. Contact Information Rationale: Appendix II was revised to indicate where the contact information and Medical Emergency phone number for sites outside the United States and Canada can be found.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported