Clinical trial results:
An Open-Label Extension 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	2012-001630-33
Trial protocol	GB HU BE ES NL EE FR IS IT
Global end of trial date	31 January 2014

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-69

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01592773
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 March 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 January 2014
Global end of trial reached?	Yes
Global end of trial date	31 January 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the long-term safety and tolerability of memantine in the treatment of pediatric patients with autism, Asperger's Disorder or Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS).

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	09 April 2012
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	Poland: 36
Country: Number of subjects enrolled	Spain: 14
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Estonia: 5
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	Hungary: 14
Country: Number of subjects enrolled	Iceland: 5
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	United States: 586
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Colombia: 8
Country: Number of subjects enrolled	Korea, Republic of: 22
Country: Number of subjects enrolled	New Zealand: 1
Country: Number of subjects enrolled	Serbia: 21
Country: Number of subjects enrolled	South Africa: 1
Country: Number of subjects enrolled	Ukraine: 14

Worldwide total number of subjects	747
EEA total number of subjects	93

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)	634
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 October of 2012 to September of 2013, at 106 study sites, located in the United States and 15 other countries.

Pre-assignment

Screening details:

Patients who took open-label memantine in the preceding study, MEM-MD-67 orMEM-MD-91, will receive 48 weeks of open-label memantine at their maximum tolerated weight-based target dosage.

Patients who participated in the double-blind study MEM-MD-68 will undergo 6 weeks of double-blind dosing followed by 42 weeks of open-label dosing. During the

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)

Arm description:

Memantine Hydrochloride (HCl) extended-release 3-mg capsules once daily, oral administration.... more 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	Namenda, Axura, Akatinol, Ebixa, Abixa, Memox
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Memantine extended-release 3mg capsules; oral administration. The maximum target dosage was identified during the prior studies for each patient. Dosing was once daily.

The weight-based dose limits in this study were as follows:
Group A: ≥ 60 kg; maximum 15 mg/day Group B: 40-59 kg; maximum 9 mg/day Group C: 20-39 kg; maximum 6 mg/day Group D: < 20 kg; maximum 3 mg/day

Number of subjects in period 1	Memantine Hydrochloride (HCl)
Started	747
Completed	81
Not completed	666
Consent withdrawn by subject	35
'Study Terminated by Sponsor '	582
'Inclusion/exclusion not meet '	1
Adverse event, non-fatal	17
Other Reason	1

Lost to follow-up	19
Lack of efficacy	9
Protocol deviation	2

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	747	747	
Age categorical Units: Subjects			
Children (6-12 years)	747	747	
Age continuous Units: years			
arithmetic mean	9		
standard deviation	± 1.9	-	
Gender categorical Units: Subjects			
Female	627	627	
Male	120	120	
Race/Ethnicity, Customized 1 Units: Subjects			
White	636	636	
Black or African American	42	42	
Asian	44	44	
American Indian or Alaska Native	2	2	
Native Hawaiian or Other Pacific Islander	3	3	
Other Race	20	20	
Race/Ethnicity, Customized 2 Units: Subjects			
Hispanic or Latino	88	88	
Not Hispanic or Latino	659	659	

End points

End points reporting groups

Reporting group title	Memantine Hydrochloride (HCl)

Reporting group description:

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

Primary: Patients With Any Treatment-emergent Adverse Event

End point title	Patients With Any Treatment-emergent Adverse Event[1]

End point description:

Number of patients who experienced 1 or more Treatment Emergent Adverse Event

End point type	Primary

End point timeframe:

Visit 1 (Week 0) up to 30 days after Visit 8 (up to Week 48) or 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: This was an exploratory study with an emphasis on safety.

End point values	Memantine Hydrochloride (HCl)			
Subject group type	Reporting group			
Number of subjects analysed	747[2]			
Units: Number	424			

Notes:

[2] - Analysis was performed on the 747 patients who took at least 1 dose of investigational product (Safe

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Event data was collected from study participants for 48 weeks at 106 sites in the US and 15 other countries.

Adverse event reporting additional description:

Safety results are based on the safety population (ie, all patients who took at least one dose of investigational product).

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.... more 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	8 / 747 (1.07%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Dehydration			
subjects affected / exposed	1 / 747 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Foreign body			
subjects affected / exposed	1 / 747 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rectal prolapse			
subjects affected / exposed	1 / 747 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			

Abnormal behaviour				
subjects affected / exposed	1 / 747 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dysphoria				
subjects affected / exposed	1 / 747 (0.13%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Homicidal ideation				
subjects affected / exposed	1 / 747 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Suicidal ideation				
subjects affected / exposed	1 / 747 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	1 / 747 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal pain lower				
subjects affected / exposed	1 / 747 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	1 / 747 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Appendicitis				
subjects affected / exposed	1 / 747 (0.13%)			
occurrences causally related to treatment / all	0 / 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	150 / 747 (20.08%)		
Nervous system disorders			
Headache			
subjects affected / exposed	41 / 747 (5.49%)		
occurrences (all)	41		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	47 / 747 (6.29%)		
occurrences (all)	47		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	51 / 747 (6.83%)		
occurrences (all)	51		
Infections and infestations			
Nasopharymgitis			
subjects affected / exposed	55 / 747 (7.36%)		
occurrences (all)	55		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 March 2013	1. Increasing sample size from about 220 to about 800-900; Rationale: The sample size has been increased based on the increased enrollment of the lead-in studies MEM-MD-91 and MEM-MD-68. 2. 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 has been amended to clarify if administration of the C-SSRS is appropriate given a patient's developmental and/or situational status. 3. Removing reference to the CGI-I being performed at Visit 1; a. Clarify that laboratory and ECG results received after randomization should be done with respect to the eligibility criteria; b. Remove the Clinical Global Impression - Improvement (CGI-I) scale from the section "If Visit 1 is being held more than 14 days after the final visit of the preceding study, the following procedures must be performed:" 4. Adding information regarding the Data Safety Monitoring Board; 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.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported