Clinical trial results:
An Open-Label Study To Evaluate The Safety Of Donepezil Hydrochloride (Aricept) For Up To 1 Year In The Treatment Of The Cognitive Dysfunction Exhibited By Children With Down Syndrome - Follow-Up To A 10-Week, Double-Blind, Placebo-Controlled Trial

Summary

EudraCT number	2016-004947-35
Trial protocol	Outside EU/EEA
Global end of trial date	15 December 2008

Results information

Result version number	v1 (current)
This version publication date	23 May 2021
First version publication date	23 May 2021

Trial information

Trial identification

Sponsor protocol code	E2020-A001-220

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00675025
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Eisai Medical Research Inc.
Sponsor organisation address	100 Tice Boulevard, Woodcliff Lake, New Jersey, United States, 07677
Public contact	Eisai Medical Information, Eisai Inc., 888 274-2378, esi-medinfo@eisai.com
Scientific contact	Eisai Medical Information, Eisai Inc., 888 274-2378, esi-medinfo@eisai.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	15 December 2008
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 December 2008
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to determine the safety of donepezil hydrochloride (Aricept) in children with Down syndrome who have finished the preceding 10-week, double-blind study of donepezil hydrochloride. Medical tests for drug safety will be conducted at each clinic visit.

Protection of trial subjects:

This study was conducted in accordance with standard operating procedures (SOPs) of the sponsor (or designee), which are designed to ensure adherence to Good Clinical Practice (GCP) guidelines as required by the following: - Principles of the World Medical Association Declaration of Helsinki (World Medical Association, 2008) - International Council on Harmonisation (ICH) E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use - Title 21 of the United States (US) Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and Institutional Review Board (IRB) regulations and applicable sections of US 21 CFR Part 312 - European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any European Union (EU) country. All suspected unexpected serious adverse reactions were reported, as required, to the Competent Authorities of all involved EU member states. - Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan’s GCP Subject Information and Informed Consent.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 April 2008
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	United States: 117
Worldwide total number of subjects	117
EEA total number of subjects	0

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)	113
Adults (18-64 years)	4
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was recruited at 24 centers in the United States during the period of 04 Apr 2008 to 15 Dec 2008. All subjects who completed the double-blind (DB) placebo-controlled, 10 week study (Study 2020-A001-219 [NCT00570128]) were offered enrollment in this study.

Pre-assignment

Screening details:

The Screening and baseline activities for this study took place on the same day as the Week 10 final visit of the double-blind (DB) study (2020-A001-219 [NCT00570128]).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Prior Donepezil-DB

Arm description:

Subjects who received donepezil in the double-blind study E2020-A001-219 (NCT00570128) were continued in this OLE study to be treated with donepezil titrated to achieve a final dose of 0.1 - 0.2 mg/kg/day using liquid formulated at 5 mg/5 mL for up to approximately Week 42.

Arm type	Experimental
Investigational medicinal product name	Donepezil Hydrochloride
Investigational medicinal product code	
Other name	Aricept
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:

Subjects received donepezil titrated to a final dose of 0.1 - 0.2 mg/kg/day using liquid formulated at 5 mg/5 mL.

Arm title	Prior Placebo-DB

Arm description:

Subjects who received matched placebo in the double-blind study E2020-A001-219 (NCT00570128) were continued in this OLE study to be treated with donepezil titrated to achieve a final dose of 0.1 - 0.2 mg/kg/day using liquid formulated at 5 mg/5 mL for up to approximately Week 42.

Arm type	Experimental
Investigational medicinal product name	Donepezil Hydrochloride
Investigational medicinal product code	
Other name	Aricept
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:

Subjects received donepezil titrated to a final dose of 0.1 - 0.2 mg/kg/day using liquid formulated at 5 mg/5 mL.

Number of subjects in period 1	Prior Donepezil-DB	Prior Placebo-DB
Started	54	63
Completed	0	0
Not completed	54	63
Consent withdrawn by subject	4	6
Adverse event, non-fatal	6	11
Study Terminated by Sponsor	38	42
Lost to follow-up	6	4

Baseline characteristics

Reporting groups	
Reporting group title	Prior Donepezil-DB
Reporting group description:	
Subjects who received donepezil in the double-blind study E2020-A001-219 (NCT00570128) were continued in this OLE study to be treated with donepezil titrated to achieve a final dose of 0.1 - 0.2 mg/kg/day using liquid formulated at 5 mg/5 mL for up to approximately Week 42.	
Reporting group title	Prior Placebo-DB
Reporting group description:	
Subjects who received matched placebo in the double-blind study E2020-A001-219 (NCT00570128) were continued in this OLE study to be treated with donepezil titrated to achieve a final dose of 0.1 - 0.2 mg/kg/day using liquid formulated at 5 mg/5 mL for up to approximately Week 42.	

Reporting group values	Prior Donepezil-DB	Prior Placebo-DB	Total
Number of subjects	54	63	117
Age categorical			
Individual subject ages were not available for this study so the categorical age breakdown in the Trial Information Section could not be populated. Instead, all subjects were reported in the 'Adolescents (12-17 years)' category with the exception of four subjects who was aged over 17 years. The categorical age breakdown available (10 to 13 years, 14 to 17 years and >17 years) is reported below.			
Units: subjects			
10 to 13 years	32	36	68
14 to 17 years	20	25	45
>17 years	2	2	4
Age continuous			
Units: years			
arithmetic mean	13.4	13.2	
standard deviation	± 2.4	± 2.2	-
Gender categorical			
Units: Subjects			
Female	23	34	57
Male	31	29	60
Race			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	4	4
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	2	3	5
White	46	55	101
More than one race	0	0	0
Unknown or Not Reported	6	1	7

End points

End points reporting groups

Reporting group title	Prior Donepezil-DB

Reporting group description:

Subjects who received donepezil in the double-blind study E2020-A001-219 (NCT00570128) were continued in this OLE study to be treated with donepezil titrated to achieve a final dose of 0.1 - 0.2 mg/kg/day using liquid formulated at 5 mg/5 mL for up to approximately Week 42.

Reporting group title	Prior Placebo-DB

Reporting group description:

Subjects who received matched placebo in the double-blind study E2020-A001-219 (NCT00570128) were continued in this OLE study to be treated with donepezil titrated to achieve a final dose of 0.1 - 0.2 mg/kg/day using liquid formulated at 5 mg/5 mL for up to approximately Week 42.

Primary: Change From Visit 1 (Baseline) to Visit 4 (or Early Termination) in the Vineland Adaptive Behavior Scales, 2nd Edition, Parent/Caregiver Rating Form (VABS-II/PCRF) Sum of the 9 Sub-domain V-scores

End point title	Change From Visit 1 (Baseline) to Visit 4 (or Early Termination) in the Vineland Adaptive Behavior Scales, 2nd Edition, Parent/Caregiver Rating Form (VABS-II/PCRF) Sum of the 9 Sub-domain V-scores[1]

End point description:

VABS-II/PCRF assessed subject's adaptive behaviors on 3 domains (each has 3 sub-domains): Communication (receptive, expressive, written), Daily Living Skills (personal, domestic, community), Socialization (interpersonal relationships, play a leisure time, coping skills). Parent/caregiver rated subject's behavior for sub-domains from 0 (never present) to 2 (always present). Raw scores from sub-domains converted into standardized score(V-scale scores) ranged:1-24 for each sub-domain, mean=15,standard deviation(SD)=3,higher scores=higher level of adaptive functioning and were summed to obtain V-scale composite score ranged 9-216, mean=100,SD=15,higher scores=higher level of adaptive functioning, positive change=improvement in adaptive functioning. Composite and individual analyses, both raw and standardized scores, were not performed due to lack of significant differences between donepezil and placebo in parent study. Analyses was performed on the Intent-to-treat population.

End point type	Primary

End point timeframe:

Visit 1 (Baseline); Visit 4 (Week 42)

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: Only descriptive data were planned to be analyzed for this endpoint.

End point values	Prior Donepezil-DB	Prior Placebo-DB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	63		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline (Week 10 of DB study)	87.73 (± 16.58)	92.02 (± 17.51)		
Early termination visit	89.37 (± 16.58)	91.25 (± 18.45)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to early termination visit (Week 36)

Adverse event reporting additional description:

Individual counts of non-serious adverse events (SAEs) were not available for this study, so the minimum number of events (i.e. the number of subject's experiencing an event) has been reported. Occurrences of non-SAEs may potentially have been higher than reported if one subject experienced the same event more than once.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11.1

Reporting groups

Reporting group title	Prior Donepezil-DB

Reporting group description:

Subjects received donepezil titrated to a final dose of 0.1 - 0.2 mg/kg/day using liquid formulated at 5 mg/5 mL.

Reporting group title	Prior Placebo-DB

Reporting group description:

Subjects received donepezil titrated to a final dose of 0.1 - 0.2 mg/kg/day using liquid formulated at 5 mg/5 mL.

Serious adverse events	Prior Donepezil-DB	Prior Placebo-DB	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 54 (0.00%)	0 / 63 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Prior Donepezil-DB	Prior Placebo-DB	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 54 (68.52%)	48 / 63 (76.19%)	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 54 (1.85%)	4 / 63 (6.35%)	
occurrences (all)	1	4	
Somnolence			

subjects affected / exposed	4 / 54 (7.41%)	1 / 63 (1.59%)	
occurrences (all)	4	1	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 54 (1.85%)	3 / 63 (4.76%)	
occurrences (all)	1	3	
Pyrexia			
subjects affected / exposed	1 / 54 (1.85%)	3 / 63 (4.76%)	
occurrences (all)	1	3	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	2 / 54 (3.70%)	1 / 63 (1.59%)	
occurrences (all)	2	1	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	5 / 54 (9.26%)	4 / 63 (6.35%)	
occurrences (all)	5	4	
Diarrhoea			
subjects affected / exposed	8 / 54 (14.81%)	15 / 63 (23.81%)	
occurrences (all)	8	15	
Flatulence			
subjects affected / exposed	0 / 54 (0.00%)	2 / 63 (3.17%)	
occurrences (all)	0	2	
Frequent bowel movements			
subjects affected / exposed	0 / 54 (0.00%)	2 / 63 (3.17%)	
occurrences (all)	0	2	
Nausea			
subjects affected / exposed	2 / 54 (3.70%)	4 / 63 (6.35%)	
occurrences (all)	2	4	
Vomiting			
subjects affected / exposed	4 / 54 (7.41%)	4 / 63 (6.35%)	
occurrences (all)	4	4	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 54 (0.00%)	4 / 63 (6.35%)	
occurrences (all)	0	4	

Nasal congestion			
subjects affected / exposed	0 / 54 (0.00%)	4 / 63 (6.35%)	
occurrences (all)	0	4	
Oropharyngeal pain			
subjects affected / exposed	0 / 54 (0.00%)	2 / 63 (3.17%)	
occurrences (all)	0	2	
Rhinitis allergic			
subjects affected / exposed	3 / 54 (5.56%)	1 / 63 (1.59%)	
occurrences (all)	3	1	
Wheezing			
subjects affected / exposed	0 / 54 (0.00%)	2 / 63 (3.17%)	
occurrences (all)	0	2	
Skin and subcutaneous tissue disorders			
Furuncle			
subjects affected / exposed	2 / 54 (3.70%)	1 / 63 (1.59%)	
occurrences (all)	2	1	
Rash			
subjects affected / exposed	0 / 54 (0.00%)	2 / 63 (3.17%)	
occurrences (all)	0	2	
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	1 / 54 (1.85%)	3 / 63 (4.76%)	
occurrences (all)	1	3	
Aggression			
subjects affected / exposed	0 / 54 (0.00%)	2 / 63 (3.17%)	
occurrences (all)	0	2	
Initial insomnia			
subjects affected / exposed	2 / 54 (3.70%)	0 / 63 (0.00%)	
occurrences (all)	2	0	
Irritability			
subjects affected / exposed	3 / 54 (5.56%)	1 / 63 (1.59%)	
occurrences (all)	3	1	
Infections and infestations			
Ear infection			
subjects affected / exposed	1 / 54 (1.85%)	2 / 63 (3.17%)	
occurrences (all)	1	2	
Gastroenteritis viral			

subjects affected / exposed	0 / 54 (0.00%)	2 / 63 (3.17%)	
occurrences (all)	0	2	
Nasopharyngitis			
subjects affected / exposed	2 / 54 (3.70%)	0 / 63 (0.00%)	
occurrences (all)	2	0	
Pharyngitis streptococcal			
subjects affected / exposed	2 / 54 (3.70%)	0 / 63 (0.00%)	
occurrences (all)	2	0	
Sinusitis			
subjects affected / exposed	6 / 54 (11.11%)	8 / 63 (12.70%)	
occurrences (all)	6	8	
Upper respiratory tract infection			
subjects affected / exposed	2 / 54 (3.70%)	7 / 63 (11.11%)	
occurrences (all)	2	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 June 2008	The following administrative changes were identified and were made to the Protocol 111 Amendment 01 after the original (19 Dec 2007) protocol was finalized: 1. Header, footer, and title page changed to reflect new amendment date and version. 2. Pfizer Study Manager was changed (Protocol Sections 1.3 and 15). 3. Person's title was changed (Protocol Sections 1.3 and 15). 4. Typographic error in second paragraph corrected; changed from "will be given in a final protocol appendix" to "is in Appendix II" (Protocol Section 9.7). 5. Typographic error in last bullet point corrected; changed from "16 weeks" to "18 weeks" (Protocol Section 10.3 .5). 6. Concomitant medication list revised to reflect changes in concomitant medication allowed and not allowed during the study (Protocol Appendix II).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

This was an open-label trial that was terminated early by the Sponsor. Sufficient evidence of efficacy not met. Discontinuation was not based on any safety concerns.

Notes: