

**Clinical trial results:****A 10-Week, Double-Blind, Placebo-Controlled Study To Evaluate The Efficacy And Safety Of Donepezil Hydrochloride (Aricept) In The Treatment Of The Cognitive Dysfunction Exhibited By Children With Down Syndrome, Aged 11 To 17****Summary**

EudraCT number	2016-004948-11
Trial protocol	Outside EU/EEA
Global end of trial date	11 December 2008

Results information

Result version number	v1 (current)
This version publication date	07 April 2019
First version publication date	07 April 2019

Trial information**Trial identification**

Sponsor protocol code	E2020-A001-335
-----------------------	----------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00754052
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Eisai Medical Services Inc.
Sponsor organisation address	100 Tice Boulevard, Woodcliff Lake, United States,
Public contact	Eisai Medical Information, Eisai Inc., 011 888247-2378, esi_medinfo@eisai.com
Scientific contact	Eisai Medical Information, Eisai Inc., 011 888247-2378, 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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 December 2008
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	11 December 2008
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to determine the efficacy and safety of donepezil hydrochloride (Aricept) in the treatment of the cognitive dysfunction shown by children with Down syndrome, aged 11 to 17.

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	30 September 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: 8
Worldwide total number of subjects	8
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	8
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Due to early termination of the study by the Sponsor, only 8 participants were enrolled into the 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	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Donepezil HCl

Arm description:

Blinded oral donepezil HCl, was started at 2.5 mL daily, followed by 2-week titration intervals over a period of 6 weeks until a maximum dose of 5 mg/kg/day or 10 mg/kg/day was reached. Due to early termination of the study, no participant reached either targeted maximum.

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

Dosage and administration details:

Blinded oral donepezil hydrochloride (HCl), was started at 2.5 mL daily, followed by 2-week titration intervals over a period of 6 weeks until a maximum dose of 5 mg/kg/day or 10 mg/kg/day was reached. Due to early termination of the study, no participant reached either targeted maximum.

Arm title	Placebo
------------------	---------

Arm description:

Participants received matching placebo in a 1:1:1 ratio.

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

Dosage and administration details:

Participants received matching placebo in a 1:1:1 ratio.

Number of subjects in period 1	Donepezil HCl	Placebo
Started	5	3
Completed	0	0
Not completed	5	3
Study terminated by Sponsor	5	3

Baseline characteristics

Reporting groups

Reporting group title	Donepezil HCl
-----------------------	---------------

Reporting group description:

Blinded oral donepezil HCl, was started at 2.5 mL daily, followed by 2-week titration intervals over a period of 6 weeks until a maximum dose of 5 mg/kg/day or 10 mg/kg/day was reached. Due to early termination of the study, no participant reached either targeted maximum.

Reporting group title	Placebo
-----------------------	---------

Reporting group description:

Participants received matching placebo in a 1:1:1 ratio.

Reporting group values	Donepezil HCl	Placebo	Total
Number of subjects	5	3	8
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean full range (min-max)	12.8 11 to 16	15 13 to 17	-
Gender categorical Units: Subjects			
Female	1	1	2
Male	4	2	6

End points

End points reporting groups

Reporting group title	Donepezil HCl
Reporting group description: Blinded oral donepezil HCl, was started at 2.5 mL daily, followed by 2-week titration intervals over a period of 6 weeks until a maximum dose of 5 mg/kg/day or 10 mg/kg/day was reached. Due to early termination of the study, no participant reached either targeted maximum.	
Reporting group title	Placebo
Reporting group description: Participants received matching placebo in a 1:1:1 ratio.	

Primary: Mean Change from Baseline in Vineland-II Adaptive Behavior Scale (VABS-II) Parent/Caregiver Rating Form (PCRF) Score Using Last Observation Carried Forward (LOCF)

End point title	Mean Change from Baseline in Vineland-II Adaptive Behavior Scale (VABS-II) Parent/Caregiver Rating Form (PCRF) Score Using Last Observation Carried Forward (LOCF) ^[1]
End point description: VABS-II/PCRF assesses the social abilities of an individual in the age range of preschool to 18 years old. The test measures 5 main domains; (Communication, Daily Living Skills, Socialization, Motor Skills, and Maladaptive Behavior (optional)), each with 2-3 subdomains. It is in the form of a questionnaire and administered as a semi-structured interview. Each item is rated on a scale of 0 to 2, along with the codes ("N") for instances when the child has never had the opportunity to perform the activity, and a code ("DK") when the caregiver does not know if the child performed the activity. Sum-domain raw scores are obtained by summing the numerical values of the responses then compared to a table in the manual to obtain a standard score (with a mean of 100 and standard deviation of 15), percentile ranks, stanines, and age equivalents. The plan for this trial was to include 3 scores for each of the domains, communication, daily living skills, and socialization domains.	
End point type	Primary
End point timeframe: Baseline (Day 0) to Visit 3 (Week 10) or at early termination	

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: Due to early termination of the study, analyses were not performed.

End point values	Donepezil HCl	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[2]	0 ^[3]		
Units: None				
number (not applicable)				

Notes:

[2] - This study was terminated early. Analyses were not performed.

[3] - This study was terminated early. Analyses were not performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline in Additional Analyses of the VABS-11/PCRF Sustained sub-tests of the Leiter-R

End point title	Mean Change from Baseline in Additional Analyses of the
-----------------	---

End point description:

Additional analyses were to be performed using the VABS-II/PCRF test, (as described in the primary outcome section of this document). In addition, observed cases analyses of these assessments at Week 4 and Week 10 were planned. Efficacy data were collected on the 8 participants already enrolled in the study at the time of early termination. Analyses were not performed due to study medication exposure being limited and variable, limited efficacy data were collected, and no participant reached their maximum targeted dose.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline (Day 0) to Visit 3 (Week 10) or early termination

End point values	Donepezil HCl	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[4]	0 ^[5]		
Units: None				
number (not applicable)				

Notes:

[4] - This study was terminated early. Analyses were not performed.

[5] - This study was terminated early. Analyses were not performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline in Test of Verbal Expression and Reasoning (TOVER)

End point title	Mean Change from Baseline in Test of Verbal Expression and Reasoning (TOVER)
-----------------	--

End point description:

Additional analyses were to be performed using the TOVER test. In addition, observed cases analyses of these assessments at Week 4 and Week 10 were planned. Efficacy data were collected on the 8 participants already enrolled in the study at the time of early termination. Analyses were not performed due to study medication exposure being limited and variable, limited efficacy data were collected, and no participant reached their maximum targeted dose.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline (Day 0) to Visit 3 (Week 10) or early termination

End point values	Donepezil HCl	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[6]	0 ^[7]		
Units: None				
number (not applicable)				

Notes:

[6] - This study was terminated early. Analyses were not performed.

[7] - This study was terminated early. Analyses were not performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline if the Forward Memory and Attention Sustained Sub-tests of the Leiter-R

End point title	Mean Change from Baseline if the Forward Memory and Attention Sustained Sub-tests of the Leiter-R
-----------------	---

End point description:

Additional analyses were to be performed using the Forward Memory and Attention Sustained sub-tests of the Leiter-R (revised scale). In addition, observed cases analyses of these assessments at Week 4 and Week 10 were planned. Efficacy data were collected on the 8 participants already enrolled in the study at the time of early termination. Analyses were not performed due to study medication exposure being limited and variable, limited efficacy data were collected, and no participant reached their maximum targeted dose.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline (Day 0) to Visit 3 (Week 10) or early termination

End point values	Donepezil HCl	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[8]	0 ^[9]		
Units: None				
number (not applicable)				

Notes:

[8] - This study was terminated early. Analyses were not performed.

[9] - This study was terminated early. Analyses were not performed.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) and treatment emergent AEs (TEAEs) were collected from the time of screening (prior to start of study medication) until termination of the study.

Adverse event reporting additional description:

The Safety Population included all 8 participants who received at least 1 dose of study medication.

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	11.1
--------------------	------

Reporting groups

Reporting group title	Donepezil HCl
-----------------------	---------------

Reporting group description:

Blinded oral donepezil HCl, was started at 2.5 mL daily, followed by 2-week titration intervals over a period of 6 weeks until a maximum dose of 5 mg/kg/day or 10 mg/kg/day was reached. Due to early termination of the study no participant reached either targeted maximum.

Reporting group title	Placebo
-----------------------	---------

Reporting group description:

Participants received matching placebo in a 1:1:1 ratio.

Serious adverse events	Donepezil HCl	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Donepezil HCl	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 5 (40.00%)	1 / 3 (33.33%)	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 5 (20.00%)	1 / 3 (33.33%)	
occurrences (all)	1	1	
Diarrhea			
subjects affected / exposed	1 / 5 (20.00%)	1 / 3 (33.33%)	
occurrences (all)	1	1	

Infections and infestations			
Ear infection			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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 10-week double blind placebo-controlled trial was terminated early after the results of a similarly-designed study showing lack of effect and therefore there was no benefit to continue this study.

Notes: