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

Summary

EudraCT number	2016-004946-27
Trial protocol	Outside EU/EEA
Global end of trial date	05 September 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-A001-219

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00570128
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., 011 888274-2378, esi_medinfo@eisai.com
Scientific contact	Eisai Medical Information, Eisai Inc., 011 888274-2378, 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	05 September 2008
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 September 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to determine whether donepezil hydrochloride (HCl) is effective and safe in improving cognitive dysfunction exhibited by children and adolescents with Down syndrome (DS). Effectiveness will be measured by rating communication, daily living skills, and social skills and relationships in subjects aged 12 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	16 November 2007
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	United States: 129
Worldwide total number of subjects	129
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)	129
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 35 centers in the United States during the period of 16 November 2007 to 05 September 2008.

Pre-assignment

Screening details:

A total of 158 subjects were screened, of which 29 were screen failures and 129 subjects were randomized to receive study treatment.

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, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Donepezil HCl

Arm description:

Blinded donepezil hydrochloride (HCl) 2.5 milligram per day (mg/day) (2.5 milliliter per day [mL/day]) orally for subjects with body weight (BW) 20 and less than (<) 25 kilogram (kg), 5 mg/day (5 mL/day) orally for subjects with BW 25 to <50 kg, and 10 mg/day (10 mL/day) orally for subjects with BW greater than or equal to (>=) 50 kg liquid formulation (1 milligram per 1 milliliter [1 mg/1 mL]) (titrated to 0.1 to 0.2 milligram per kilogram per day [mg/kg/day] based on BW).

Arm type	Active comparator
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 donepezil HCl 2.5 mg/day (2.5 mL/day) orally for subjects with BW 20 and <25 kg, 5 mg/day (5 mL/day) orally for subjects with BW 25 to <50 kg, and 10 mg/day (10 mL/day) orally for subjects with BW >=50 kg liquid formulation (1 mg/1 mL) (titrated to 0.1 to 0.2 mg/kg/day based on BW).

Arm title	Placebo

Arm description:

Liquid formulation matched to active treatment for oral administration.

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:

Liquid formulation matched to active treatment for oral administration.

Number of subjects in period 1	Donepezil HCl	Placebo
Started	64	65
Completed	60	65
Not completed	4	0
Consent withdrawn by subject	2	-
Adverse event, non-fatal	1	-
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Donepezil HCl
Reporting group description:	
Blinded donepezil hydrochloride (HCl) 2.5 milligram per day (mg/day) (2.5 milliliter per day [mL/day]) orally for subjects with body weight (BW) 20 and less than (<) 25 kilogram (kg), 5 mg/day (5 mL/day) orally for subjects with BW 25 to <50 kg, and 10 mg/day (10 mL/day) orally for subjects with BW greater than or equal to (>=) 50 kg liquid formulation (1 milligram per 1 milliliter [1 mg/1 mL]) (titrated to 0.1 to 0.2 milligram per kilogram per day [mg/kg/day] based on BW).	
Reporting group title	Placebo
Reporting group description:	
Liquid formulation matched to active treatment for oral administration.	

Reporting group values	Donepezil HCl	Placebo	Total
Number of subjects	64	65	129
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. The categorical age breakdown available (10 to 13 years and 14 to 17 years) is reported below.			
Units: subjects			
10 to 13 years	41	38	79
14 to 17 years	23	27	50
Age continuous			
Units: years			
arithmetic mean	13.0	13.0	
standard deviation	± 2.3	± 2.1	-
Gender categorical			
Units: Subjects			
Female	28	35	63
Male	36	30	66
Race			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	4	5
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	3	3	6
White	54	57	111
More than one race	0	0	0
Unknown or Not Reported	6	1	7

End points

End points reporting groups

Reporting group title	Donepezil HCl
Reporting group description:	
Blinded donepezil hydrochloride (HCl) 2.5 milligram per day (mg/day) (2.5 milliliter per day [mL/day]) orally for subjects with body weight (BW) 20 and less than (<) 25 kilogram (kg), 5 mg/day (5 mL/day) orally for subjects with BW 25 to <50 kg, and 10 mg/day (10 mL/day) orally for subjects with BW greater than or equal to (>=) 50 kg liquid formulation (1 milligram per 1 milliliter [1 mg/1 mL]) (titrated to 0.1 to 0.2 milligram per kilogram per day [mg/kg/day] based on BW).	
Reporting group title	Placebo
Reporting group description:	
Liquid formulation matched to active treatment for oral administration.	

Primary: Mean Change From Baseline in V-Scale Composite Score (Sum of 9 Sub-Domains) of Vineland Adaptive Behavior Scales Second Edition-Parent Caregiver Rating Form (VABS-II/PCRF) at Week 10-Last Observation Carried Forward (LOCF)

End point title	Mean Change From Baseline in V-Scale Composite Score (Sum of 9 Sub-Domains) of Vineland Adaptive Behavior Scales Second Edition-Parent Caregiver Rating Form (VABS-II/PCRF) at Week 10-Last Observation Carried Forward (LOCF)[1]
End point description:	
VABS-II/PCRF instrument:assess 3 domains(each with 3 subdomains):communication(subdomains:receptive,expressiveand writing), daily living skills(subdomains:personal,domestic,community), and socialization(subdomains:interpersonal relationships, play/leisure time, coping skills).Raw scores(2=always present, 1=sometimes present, 0=seldom or never present)rated by parent/caregiver from each subdomain were converted to standardized scores called V-scores. Each subdomain v-scale score ranged from 1(weakness)to 24(strength). V scores for 9 subdomains were summed to obtain composite V-score ranging from 9 to 216. Higher scores indicate higher level of adaptive functioning. ITT population: all randomized subjects who received at least 1 dose of study drug and had at least 1 postbaseline assessment for at least 1 efficacy variable irrespective of compliance and protocol violations. Here "Number of Subjects Analyzed" signifies subjects who were evaluable for this outcome measure.	
End point type	Primary
End point timeframe:	
Baseline, Week 10	

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	Donepezil HCl	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	65		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline	83.1 (± 15.5)	85.7 (± 15.8)		
Mean change from baseline at Week 10	4.74 (± 9.2)	4.22 (± 8.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in V-Scale Composite Score (Sum of 9 Sub-domains) of Vineland Adaptive Behavior Scales Second Edition-Parent Caregiver Rating Form (VABS-II/PCRF) at Week 4 and 10-Observed Cases (OC)

End point title	Mean Change From Baseline in V-Scale Composite Score (Sum of 9 Sub-domains) of Vineland Adaptive Behavior Scales Second Edition-Parent Caregiver Rating Form (VABS-II/PCRF) at Week 4 and 10-Observed Cases (OC)

End point description:

VABS-II/PCRF instrument:assess 3 domains(each with 3 subdomains):communication(subdomains:receptive, expressive, and writing),daily living skills(subdomains:personal,domestic, community),and socialization(subdomains:interpersonal relationships,play/leisure time, coping skills).Raw scores(2=always present,1=sometimes present,0=seldom or never present)rated by parent/caregiver from each subdomain were converted to standardized scores called V-scores.Each subdomain v-scale score ranged as 1(weakness)to 24(strength).V scores for 9 subdomains were summed to obtain composite V-score as 9 to 216.Higher scores indicate higher level of adaptive functioning.ITT population:all randomized subjects who received 1 dose of drug and had at least 1 postbaseline assessment for 1 efficacy variable irrespective of compliance and protocol violations.Number of subjects analysed:subjects who were evaluable for this outcome measure.n:subjects who were evaluable for this outcome measure at given time points.

End point type	Secondary

End point timeframe:

Baseline, Week 4 and Week 10

End point values	Donepezil HCl	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	65		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline	83.1 (± 15.5)	85.7 (± 15.8)		
Mean change from baseline at Week 4 (n=54, n=60)	1.5 (± 6.4)	2.6 (± 8.5)		
Mean change from baseline at Week 10 (n=55, n=63)	5.1 (± 9.6)	4.2 (± 8.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in Test of Verbal Expression and Reasoning (TOVER) Total Score at Week 4 and 10-OC

End point title	Mean Change From Baseline in Test of Verbal Expression and Reasoning (TOVER) Total Score at Week 4 and 10-OC

End point description:

TOVER:subject performance based measure of expressive language function and verbal reasoning in response to questions about series of stylized pictures showing identifiable scenarios.64-item test was specifically designed to assess language function in children and adults with down syndrome(DS)across a broad range of functional ability. The test used 23 multi-colored pictures to stimulate verbal responses to questions.The test was short(completed in 15 minutes)and fast-paced(2 to 4 questions per picture). Total score ranging from 0 to 64, was derived from 64 questions, where higher score indicates better functional ability.ITT population:all randomized subjects who received at least 1 dose of study drug and

had at least 1 post-baseline assessment for at least 1 efficacy variable irrespective of compliance and protocol violations.Number of subjects analysed:subjects who were evaluable for this outcome measure.n:subjects who were evaluable for this outcome measure at given time points.

End point type	Secondary

End point timeframe:

Baseline, Week 4 and Week 10

End point values	Donepezil HCl	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	64		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline	20.7 (± 12.2)	21.6 (± 11.4)		
Mean change from baseline at week 4 (n=56, n=59)	1.2 (± 6.4)	0.9 (± 8.5)		
Mean change from baseline at week 10 (n=56, n=62)	2.6 (± 6.2)	1.9 (± 5.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in Test of Verbal Expression and Reasoning (TOVER) Total Score at Week 10-LOCF

End point title	Mean Change From Baseline in Test of Verbal Expression and Reasoning (TOVER) Total Score at Week 10-LOCF

End point description:

TOVER: subject-performance-based measure of expressive language function and verbal reasoning in response to questions about series of stylized pictures showing identifiable scenarios. 64-item test was specifically designed to assess language function in children and adults with down syndrome (DS) across a broad range of functional ability. The test used 23 multi-colored pictures to stimulate verbal responses to questions. The test was short (completed in 15 minutes) and fast-paced (2 to 4 questions per picture). Total score ranging from 0 to 64, was derived from 64 questions, where higher score indicates better functional ability. ITT population: all randomized subjects who received at least 1 dose of study drug and had at least 1 post-baseline assessment for at least 1 efficacy variable irrespective of compliance and protocol violations. Here "Number of subjects analysed" signifies subjects who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Week 10

End point values	Donepezil HCl	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	64		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline	20.7 (± 12.2)	21.6 (± 11.4)		

Mean change from baseline at week 10	2.4 (± 6.0)	2.1 (± 5.5)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline up to 10 months	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	v11.0

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Liquid formulation matched to active treatment for oral administration.	
Reporting group title	Donepezil HCl
Reporting group description:	
Blinded donepezil HCl 2.5 mg/day (2.5 mL/day) orally for subjects with BW 20 and <25 kg, 5 mg/day (5 mL/ day) orally for subjects with BW 25 to <50 kg, and 10 mg/day (10 mL/day) orally for subjects with BW >=50 kg liquid formulation (1 mg/1 mL) (titrated to 0.1 to 0.2 mg/kg/day based on BW).	

Serious adverse events	Placebo	Donepezil HCl	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 65 (1.54%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Donepezil HCl	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	42 / 65 (64.62%)	45 / 64 (70.31%)	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 65 (3.08%)	5 / 64 (7.81%)	
occurrences (all)	2	7	
Lethargy			
subjects affected / exposed	0 / 65 (0.00%)	2 / 64 (3.13%)	
occurrences (all)	0	2	
Somnolence			
subjects affected / exposed	0 / 65 (0.00%)	2 / 64 (3.13%)	
occurrences (all)	0	5	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 65 (3.08%)	1 / 64 (1.56%)	
occurrences (all)	2	1	
Pyrexia			
subjects affected / exposed	2 / 65 (3.08%)	2 / 64 (3.13%)	
occurrences (all)	2	2	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 65 (1.54%)	2 / 64 (3.13%)	
occurrences (all)	1	2	
Constipation			
subjects affected / exposed	2 / 65 (3.08%)	0 / 64 (0.00%)	
occurrences (all)	2	0	
Diarrhoea			
subjects affected / exposed	10 / 65 (15.38%)	11 / 64 (17.19%)	
occurrences (all)	15	17	
Nausea			
subjects affected / exposed	2 / 65 (3.08%)	5 / 64 (7.81%)	
occurrences (all)	2	5	
Vomiting			
subjects affected / exposed	2 / 65 (3.08%)	8 / 64 (12.50%)	
occurrences (all)	2	8	
incontinence faecal			

subjects affected / exposed	0 / 65 (0.00%)	2 / 64 (3.13%)	
occurrences (all)	0	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 65 (1.54%)	4 / 64 (6.25%)	
occurrences (all)	1	4	
Nasal congestion			
subjects affected / exposed	2 / 65 (3.08%)	1 / 64 (1.56%)	
occurrences (all)	2	1	
Rhinitis allergic			
subjects affected / exposed	0 / 65 (0.00%)	2 / 64 (3.13%)	
occurrences (all)	0	2	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 65 (3.08%)	3 / 64 (4.69%)	
occurrences (all)	2	3	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 65 (3.08%)	0 / 64 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 65 (0.00%)	2 / 64 (3.13%)	
occurrences (all)	0	2	
Ear infection			
subjects affected / exposed	3 / 65 (4.62%)	1 / 64 (1.56%)	
occurrences (all)	4	1	
Gastroenteritis			
subjects affected / exposed	2 / 65 (3.08%)	0 / 64 (0.00%)	
occurrences (all)	2	0	
Gastroenteritis viral			
subjects affected / exposed	1 / 65 (1.54%)	2 / 64 (3.13%)	
occurrences (all)	1	2	
Nasopharyngitis			
subjects affected / exposed	4 / 65 (6.15%)	0 / 64 (0.00%)	
occurrences (all)	6	0	

Pharyngitis			
subjects affected / exposed	1 / 65 (1.54%)	3 / 64 (4.69%)	
occurrences (all)	1	3	
Sinusitis			
subjects affected / exposed	3 / 65 (4.62%)	1 / 64 (1.56%)	
occurrences (all)	4	1	
Upper respiratory tract infection			
subjects affected / exposed	5 / 65 (7.69%)	6 / 64 (9.38%)	
occurrences (all)	5	6	
Viral infection			
subjects affected / exposed	0 / 65 (0.00%)	2 / 64 (3.13%)	
occurrences (all)	0	3	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 65 (4.62%)	1 / 64 (1.56%)	
occurrences (all)	3	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 March 2008	Protocol amendment 01: 1. New pregnancy reporting language was added to the AE section. Rationale: Eisai and Pfizer SOPs. 2. Concomitant medication list was changed to reflect Section 9.7 of the protocol, which allows stable use of psychotropic medications that are not highly anticholinergic and to allow as needed (PRN) use of additional medications to reflect current medical practice (Protocol Amendment II). Rationale: Administrative change to make concomitant medication list consistent with the protocol and current medical practice.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported