Clinical trial results:
Randomized, Double-Blind, Placebo-Controlled Study of Efficacy and Safety of Donepezil Hydrochloride in Preadolescent and Adolescent Children with Attention Impairment Following Cancer Treatment

Summary

EudraCT number	2007-005435-28
Trial protocol	GB ES NL FR DE
Global end of trial date	26 May 2009

Results information

Result version number	v2 (current)
This version publication date	19 June 2020
First version publication date	29 July 2016
Version creation reason	• Correction of full data set Updated the endpoint description

Trial information

Trial identification

Sponsor protocol code	E2020-G000-333

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00688376
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Eisai
Sponsor organisation address	100 Tice Boulevard, Woodcliff Lake, United States, 07677
Public contact	Eisai Ltd., EISAI Medical Information, +1 888-274-2378, esi_medinfo@eisai.com
Scientific contact	Eisai Ltd., EISAI Medical Information, +1 888-274-2378, 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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	26 May 2009
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 May 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to evaluate the efficacy, safety and tolerability of donepezil in children with persistent attention impairment that is present at least 12 months after the completion of cancer treatment.

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 Conference 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 Conference on Harmonisation 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	02 July 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	Spain: 4
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Argentina: 1
Country: Number of subjects enrolled	Australia: 2
Country: Number of subjects enrolled	Chile: 4
Country: Number of subjects enrolled	United States: 33
Country: Number of subjects enrolled	Belgium: 3

Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	South Africa: 9
Worldwide total number of subjects	71
EEA total number of subjects	21

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)	22
Adolescents (12-17 years)	49
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 22 centers in the United States, France, Germany, the Netherlands, Spain, the United Kingdom, Argentina, Chile, and Australia during the period of 02 July 2008 to 26 May 2009.

Pre-assignment

Screening details:

This trial had three phases: (1)pre-randomization to establish eligibility; (2) a 12-week, double-blind, placebo controlled, parallel-group phase with dose escalation based on body weight; (3) a 12-week, blinded extension phase during which all subjects received active drug. Eligible subjects were randomized to receive placebo or donepezil.

Period 1

Period 1 title	Double-Blind Phase
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

During the Blinded Extension Phase, study personnel, subjects, and parents/legal guardians continued to be blinded to the treatment that each subject received during the preceding Double-Blind Phase.

Arms

Are arms mutually exclusive?	Yes
Arm title	Donepezil

Arm description:

Donepezil 3 mg, 5 mg, or 10 mg donepezil Immediate Release (IR) orally, once daily.

Arm type	Experimental
Investigational medicinal product name	Donepezil
Investigational medicinal product code	
Other name	Aricept, E2020
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

During the Double-Blind Phase, all subjects randomized to receive donepezil started on 3 mg/day. Subjects who weighed 35 to 49.9 kg were titrated up to 5 mg/day final dose three weeks later. Subjects weighing 50.0 kg or more were titrated up after three weeks to 5 mg/day, then to a final dose of 10 mg/day three week later. No down-titrations were allowed. At Week 12, the Double-Blind Phase ended, and the Blinded Extension Phase began. Subjects who were randomized to receive active treatment during the Double-Blind Phase remained at the same dose level during the entire Blinded Extension Phase.

Arm title	Placebo

Arm description:

Placebo, matching 3 mg, 5 mg, or 10 mg placebo tablets administered orally, once daily.

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

Dosage and administration details:

During the Double-Blind Phase, matching 3 mg, 5 mg, and 10 mg placebo tablets were administered orally, once daily, to subjects receiving placebo. At Week 12, the Double-Blind Phase ended, and the

Blinded Extension Phase began. Subjects who had been on placebo during the Double-Blind Phase began receiving active treatment during the Blinded Extension Phase. Dose titration was applied for those subjects on final doses of 5 mg and 10 mg donepezil, according to the dose increment (titration) schedule that was applied to active treatment subjects during the Double-Blind Phase.

Number of subjects in period 1	Donepezil	Placebo
Started	40	31
Completed	34	25
Not completed	6	6
Consent withdrawn by subject	1	-
Adverse event, non-fatal	4	4
Protocol violation	1	2

Period 2

Period 2 title	Blinded Extension Phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Blinding implementation details:

During the Blinded Extension Phase, study personnel, subjects, and parents/legal guardians continued to be blinded to the treatment that each subject received during the preceding Double-Blind Phase.

Arms

Are arms mutually exclusive?	Yes
Arm title	Donepezil

Arm description:

Donepezil 3 mg, 5 mg, or 10 mg donepezil Immediate Release (IR) orally, once daily.

Arm type	Experimental
Investigational medicinal product name	Donepezil
Investigational medicinal product code	
Other name	Aricept, E2020
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

During the Double-Blind Phase, all subjects randomized to receive donepezil started on 3 mg/day. Subjects who weighed 35 to 49.9 kg were titrated up to 5 mg/day final dose three weeks later. Subjects weighing 50.0 kg or more were titrated up after three weeks to 5 mg/day, then to a final dose of 10 mg/day three weeks later. No down-titrations were allowed. At Week 12, the Double-Blind Phase ended, and the Blinded Extension Phase began. Subjects who were randomized to receive active treatment during the Double-Blind Phase remained at the same dose level during the entire Blinded Extension Phase.

Arm title	Placebo

Arm description:

Placebo, matching 3 mg, 5 mg, or 10 mg placebo tablets administered orally, once daily.

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

Dosage and administration details:

During the Double-Blind Phase, matching 3 mg, 5 mg, and 10 mg placebo tablets were administered orally, once daily, to subjects receiving placebo. At Week 12, the Double-Blind Phase ended, and the Blinded Extension Phase began. Subjects who had been on placebo during the Double-Blind Phase began receiving active treatment during the Blinded Extension Phase. Dose titration was applied for those subjects on final doses of 5 mg and 10 mg donepezil, according to the dose increment (titration) schedule that was applied to active treatment subjects during the Double-Blind Phase.

Number of subjects in period 2	Donepezil	Placebo
Started	34	25
Completed	29	20
Not completed	5	5
Physician decision	1	-
Consent withdrawn by subject	-	1
Adverse event, non-fatal	3	4
Other	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Donepezil
Reporting group description:	
Donepezil 3 mg, 5 mg, or 10 mg donepezil Immediate Release (IR) orally, once daily.	
Reporting group title	Placebo
Reporting group description:	
Placebo, matching 3 mg, 5 mg, or 10 mg placebo tablets administered orally, once daily.	

Reporting group values	Donepezil	Placebo	Total
Number of subjects	40	31	71
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
arithmetic mean	12.1	11.6	
standard deviation	± 3.06	± 2.83	-
Gender categorical			
Units: Subjects			
Female	15	21	36
Male	25	10	35

End points

End points reporting groups

Reporting group title	Donepezil
Reporting group description:	
Donepezil 3 mg, 5 mg, or 10 mg donepezil Immediate Release (IR) orally, once daily.	
Reporting group title	Placebo
Reporting group description:	
Placebo, matching 3 mg, 5 mg, or 10 mg placebo tablets administered orally, once daily.	
Reporting group title	Donepezil
Reporting group description:	
Donepezil 3 mg, 5 mg, or 10 mg donepezil Immediate Release (IR) orally, once daily.	
Reporting group title	Placebo
Reporting group description:	
Placebo, matching 3 mg, 5 mg, or 10 mg placebo tablets administered orally, once daily.	

Primary: Change From Baseline in the Test of Variables in Attention-Continuous Performance Test (TOVA-CPT) "d-prime" Standard Score (SS) at Week 12

End point title	Change From Baseline in the Test of Variables in Attention-Continuous Performance Test (TOVA-CPT) "d-prime" Standard Score (SS) at Week 12

End point description:

TOVA-CPT test has a standardized computer game-like format that tests attention and simple impulse control. It precisely measures a person’s reaction time to clicking on correct targets versus incorrect targets. Scores are based on the number of "Hits" (correct responses), omission errors (failure to respond), commission errors/”False Alarms” (incorrect responses), response time, and sensitivity ("d-prime"). “D-prime” is a measure of distractibility and reflects how well a person reacts correctly versus incorrectly. A higher value of "d-prime" is reached by having more "Hits" (correct response) and fewer "False Alarms" (incorrect response). Analysis was based on three factors: the “d-prime” standard score, the reaction time variability standard score, and the response time standard score.Standard scores less than or equal to 80 were significant for an attention deficit disorder. Standard scores greater than 80 were not significant for an attention deficit disorder.ITT population LOCF.

End point type	Primary

End point timeframe:

Baseline and Week 12

End point values	Donepezil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	30		
Units: "d-prime"				
arithmetic mean (standard deviation)	5.2 (± 8.77)	4.5 (± 7.39)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

P-values, least squares (LS) mean, and 95% confidence interval (CI) were obtained from Analysis of Covariance (ANCOVA) model with treatment group as a factor and Baseline value as covariate.

Comparison groups	Placebo v Donepezil
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.694
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.22
upper limit	4.8

Secondary: Change From Baseline in the TOVA-CPT "D-prime" Standard Score (SS) at Week 6

End point title	Change From Baseline in the TOVA-CPT "D-prime" Standard Score (SS) at Week 6

End point description:

The TOVA-CPT test has a standardized computer game-like format that tests attention and simple impulse control. It precisely measures a person's reaction time to clicking on correct targets versus incorrect targets. Scores are based on number of "Hits" (correct responses), omission errors (failure to respond), commission errors/"False Alarms" (incorrect responses), response time, and sensitivity ("d-prime")."D-prime" is a measure of distractibility and reflects how well a person reacts correctly versus incorrectly. A higher value of "d-prime" is reached by having more "Hits" (correct response) and fewer "False Alarms" (incorrect response).Analysis was based on three factors: the "d-prime" standard score, reaction time variability standard score, and response time standard score. Standard scores less than or equal to 80 were significant for an attention deficit disorder. Standard scores greater than 80 were not significant for an attention deficit disorder. ITT population LOCF.

End point type	Secondary

End point timeframe:

Baseline and Week 6

End point values	Donepezil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	30		
Units: d-prime				
arithmetic mean (standard deviation)	5.7 (± 8.41)	6.2 (± 9.49)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

P-values, LS mean, and 95% confidence intervals were obtained from ANCOVA model with treatment

group as a factor and baseline value as covariate.

Comparison groups	Donepezil v Placebo
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9458
Method	ANCOVA
Parameter estimate	LS mean difference]
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.38
upper limit	4.09

Secondary: Change From Baseline in the Reaction Time Variability Standard Score (RTVSS) and Response Time Standard Score (RTSS) at Weeks 6 and 12

End point title	Change From Baseline in the Reaction Time Variability Standard Score (RTVSS) and Response Time Standard Score (RTSS) at Weeks 6 and 12

End point description:

The Reaction Time Variability is defined as the time measurement of how consistently the switch is pressed. The Response Time is the measurement of how fast or slow information is processed and responded to by the subject. The testing process was as described in a previous outcome measure. Standard scores less than or equal to 80 were significant for an attention deficit disorder. Standard scores greater than 80 were not significant for an attention deficit disorder. Intent-to-Treat (ITT) Last Observed Carried Forward (LOCF) population included all safety subjects for whom the TOVA-CPT d-prime standard score was available at both Screening and at least one visit after the first dose of study drug during the Double-Blind Phase.

End point type	Secondary

End point timeframe:

Baseline, Weeks 6 and 12

End point values	Donepezil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	30		
Units: milliseconds				
arithmetic mean (standard deviation)				
RTVSS (Week 6)	-3.4 (± 18.44)	-3.2 (± 15.75)		
RTVSS (Week 12)	-3.9 (± 15.21)	-5.0 (± 17.00)		
RTSS (Week 6)	-6.9 (± 13.17)	-9.6 (± 13.25)		
RTSS (Week 12)	-9.0 (± 13.15)	-9.1 (± 12.79)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

RTVSS Change from Baseline to Week 6 (LOCF). P-values, LS mean, and 95% confidence intervals were obtained from ANCOVA model with treatment group as a factor
and baseline value as covariate.

Comparison groups	Placebo v Donepezil
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.743
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.56
upper limit	6.85

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

RTVSS Change from Baseline to Week 12 (LOCF). P-values, LS mean, and 95% confidence intervals were obtained from ANCOVA model with treatment group as a factor
and baseline value as covariate.

Comparison groups	Donepezil v Placebo
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9561
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.42
upper limit	7.84

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

RTSS Change from Baseline to Week 6 (LOCF). P-values, LS mean, and 95% confidence intervals were obtained from ANCOVA model with treatment group as a factor and baseline value as covariate.

Comparison groups	Donepezil v Placebo

Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4385
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.97
upper limit	9.04

Statistical analysis title	Statistical Analysis 4

Statistical analysis description:

RTSS Change from Baseline to Week 12 (LOCF). P-values, LS mean, and 95% confidence intervals were obtained from ANCOVA model with treatment group as a factor and baseline value as covariate.

Comparison groups	Donepezil v Placebo
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9088
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.74
upper limit	6

Secondary: Change From Baseline in the Global Executive Composite Score, Behavioral Regulation Index, Metacognition Index, and Working Memory Subscale

End point title	Change From Baseline in the Global Executive Composite Score, Behavioral Regulation Index, Metacognition Index, and Working Memory Subscale

End point description:

Behavioral Rating Inventory of Executive Functioning test evaluates impairment of executive function,memory,and sustained attention in children aged 5-18 years with wide range of developmental and acquired neurological conditions.Survey assess parent/guardian's perception of their child's executive functioning in home and school environments, which relate to daily function(as judged by parent).Each survey contains 86 items scored as;1(behavior is never a problem), 2(behavior is sometimes a problem),or 3(behavior is often a problem).Data were presented as t-scores(raw scale scores are used to generate t-scores)for Global Executive Composite Score(t-score range 72-216), Behavioral Regulation Index(t-score range 28-84;inhibit,shift,and emotional control),Metacognition Index (t-score range 44-132;initiate,working memory, plan/organize,organization of materials,and monitor),and Working Memory Subscale (t-score range 35-90). Higher scores indicate decline in performance.ITT population LOCF.

End point type	Secondary

End point timeframe:
Baseline and Week 12

End point values	Donepezil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	30		
Units: t-scores				
arithmetic mean (standard deviation)				
Global Executive Composite Score	-1.3 (± 6.73)	-3.8 (± 6.78)		
Behavioral Regulation Index	0.8 (± 7.54)	-1.9 (± 6.91)		
Metacognition Index	-2.3 (± 7.29)	-4.9 (± 6.99)		
Working Memory Scale	-3.6 (± 7.45)	-3.3 (± 6.59)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Global Executive Composite Score Analysis. P-values, LS mean, and 95% confidence intervals were obtained from ANCOVA model with treatment group as a factor and baseline value as covariate.

Comparison groups	Donepezil v Placebo
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2886
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	4.96

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Behavioral Regulation Index Analysis. P-values, LS mean, and 95% confidence intervals were obtained from ANCOVA model with treatment group as a factor and baseline value as covariate.

Comparison groups	Donepezil v Placebo

Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2555
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.54
upper limit	5.69

Statistical analysis title	Statistical Analysis 3
Statistical analysis description:	
Metacognition Index Analysis. P-values, LS mean, and 95% confidence intervals were obtained from ANCOVA model with treatment group as a factor and baseline value as covariate.	
Comparison groups	Donepezil v Placebo
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3155
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.63
upper limit	4.99

Statistical analysis title	Statistical Analysis 4
Statistical analysis description:	
Working Memory Scale Analysis. P-values, LS mean, and 95% confidence intervals were obtained from ANCOVA model with treatment group as a factor and baseline value as covariate.	
Comparison groups	Donepezil v Placebo
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9075
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-0.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.55
upper limit	3.16

Adverse events

Adverse events information

Timeframe for reporting adverse events:

For each subject, adverse events were collected from the time the subject signed the informed consent form up to 30 days after discontinuation, or approximately 203 days.

Adverse event reporting additional description:

Safety population included randomized subjects who received at least one dose of study medication and who had at least one post-Baseline safety assessment. Treatment-emergent adverse events (TEAEs), defined as an adverse event that started/increased in severity on/after the first dose of study medication are presented
in this section.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11.0

Reporting groups

Reporting group title	Donepezil Double-Blind Phase

Reporting group description:

Donepezil 3 mg, 5 mg, or 10 mg donepezil Immediate Release (IR) orally, once daily

Reporting group title	Placebo Double-Blind Phase

Reporting group description:

Placebo, matching 3 mg, 5 mg, or 10 mg placebo tablets administered orally, once daily

Reporting group title	Donepezil Blinded Extension Phase

Reporting group description:

Donepezil 3 mg, 5 mg, or 10 mg donepezil Immediate Release (IR) orally, once daily

Reporting group title	Placebo Blinded Extension Phase

Reporting group description:

Placebo, matching 3 mg, 5 mg, or 10 mg placebo tablets administered orally, once daily

Serious adverse events	Donepezil Double-Blind Phase	Placebo Double-Blind Phase	Donepezil Blinded Extension Phase
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 40 (2.50%)	1 / 31 (3.23%)	0 / 34 (0.00%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Rhabdomyosarcoma			
subjects affected / exposed	0 / 40 (0.00%)	1 / 31 (3.23%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Neutropenia			

subjects affected / exposed	1 / 40 (2.50%)	0 / 31 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	0 / 40 (0.00%)	0 / 31 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo Blinded Extension Phase		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 25 (4.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Rhabdomyosarcoma			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	1 / 25 (4.00%)		
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	Donepezil Double-Blind Phase	Placebo Double-Blind Phase	Donepezil Blinded Extension Phase
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 40 (62.50%)	17 / 31 (54.84%)	11 / 34 (32.35%)
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 40 (2.50%)	0 / 31 (0.00%)	0 / 34 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	10 / 40 (25.00%)	7 / 31 (22.58%)	2 / 34 (5.88%)
occurrences (all)	11	11	2
Memory impairment			
subjects affected / exposed	2 / 40 (5.00%)	0 / 31 (0.00%)	0 / 34 (0.00%)
occurrences (all)	2	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 40 (5.00%)	3 / 31 (9.68%)	2 / 34 (5.88%)
occurrences (all)	2	3	2
Pyrexia			
subjects affected / exposed	1 / 40 (2.50%)	2 / 31 (6.45%)	0 / 34 (0.00%)
occurrences (all)	1	2	0
Asthenia			
subjects affected / exposed	0 / 40 (0.00%)	2 / 31 (6.45%)	1 / 34 (2.94%)
occurrences (all)	0	2	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 40 (7.50%)	3 / 31 (9.68%)	1 / 34 (2.94%)
occurrences (all)	4	3	1
Abdominal pain upper			
subjects affected / exposed	2 / 40 (5.00%)	2 / 31 (6.45%)	2 / 34 (5.88%)
occurrences (all)	2	2	2
Diarrhoea			
subjects affected / exposed	3 / 40 (7.50%)	1 / 31 (3.23%)	2 / 34 (5.88%)
occurrences (all)	3	1	2
Nausea			
subjects affected / exposed	7 / 40 (17.50%)	2 / 31 (6.45%)	1 / 34 (2.94%)
occurrences (all)	9	2	1

Stomach discomfort			
subjects affected / exposed	0 / 40 (0.00%)	2 / 31 (6.45%)	0 / 34 (0.00%)
occurrences (all)	0	2	0
Vomiting			
subjects affected / exposed	2 / 40 (5.00%)	1 / 31 (3.23%)	2 / 34 (5.88%)
occurrences (all)	2	1	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 40 (10.00%)	1 / 31 (3.23%)	0 / 34 (0.00%)
occurrences (all)	4	1	0
Epistaxis			
subjects affected / exposed	0 / 40 (0.00%)	1 / 31 (3.23%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	3 / 40 (7.50%)	2 / 31 (6.45%)	0 / 34 (0.00%)
occurrences (all)	3	2	0
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	4 / 40 (10.00%)	1 / 31 (3.23%)	0 / 34 (0.00%)
occurrences (all)	4	1	0
Pain in extremity			
subjects affected / exposed	2 / 40 (5.00%)	0 / 31 (0.00%)	0 / 34 (0.00%)
occurrences (all)	2	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 40 (10.00%)	3 / 31 (9.68%)	2 / 34 (5.88%)
occurrences (all)	4	3	2
Upper respiratory tract infection			
subjects affected / exposed	1 / 40 (2.50%)	1 / 31 (3.23%)	2 / 34 (5.88%)
occurrences (all)	1	1	2

Non-serious adverse events	Placebo Blinded Extension Phase		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 25 (52.00%)		
Nervous system disorders			

Dizziness			
subjects affected / exposed	4 / 25 (16.00%)		
occurrences (all)	4		
Headache			
subjects affected / exposed	6 / 25 (24.00%)		
occurrences (all)	10		
Memory impairment			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Asthenia			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	4		
Abdominal pain upper			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	5		
Stomach discomfort			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Vomiting			

subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Epistaxis			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	3		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	3		
Pain in extremity			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Upper respiratory tract infection			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 March 2008	Changes to the study design and conduct included: • Updated the number of centers to be approximately 40. • Updated the list of abbreviations and definition of terms. • Added information pertaining to pharmacokinetics and safety of donepezil in pediatric subjects. • Revised the secondary objectives of the study. • Revised inclusion criteria #2, #3, #7 and #14. • Renumbered the exclusion criteria and revised criteria #3, #6, #7 and #10. • Added exclusion criteria #4 stating exclusion of subjects scoring higher than the t-score of 75 on oppositional scale of CPRS-R(S). • Added exclusion criteria #17 stating exclusion of subjects diagnosed with Attention Deficit Hyperactivity Disorder (DSM IV criteria) before or after cancer therapy. • Added that the dose to be received by each subject was to be based on body weight at Screening. • Added Conners' Parent Rating Scale – Revised (S). • Added section pertaining to warnings and precautions. Administrative changes included changes in Eisai contact information, and information about contract research organizations.
25 February 2009	Changes to the study design and conduct included: • Updated the number of centers to be approximately 50, and eliminated the use of centers in East Asia. • Revised the number of subjects from 300 to 70 and noted that data from studies E2020-G000-333 and E2020-G000-334 would be pooled. • Revised the TOVA-CPT measure to be used as the primary efficacy parameter (d' standard score) • Revised the definitions of the Safety and the ITT populations • Eliminated the category of efficacy assessments for simplification, since the information is contained in the SAP • Eliminated the stratification of inferential analyses by study center and/or geographic region • Revised exclusion criterion #8 to also exclude subjects with rare heredity disorders and exclusion criterion #9 to also exclude subjects with hypersensitivity to other excipients in study medication • Revised inclusion criterion #7 to allow the use of IQ scores available prior to Screening • Clarified the allowable interval between Screening and Baseline visits • Added a provision that the CPRS-R(S) may also be used as a safety assessment • Changed wording to clarify that glucose is to be assessed at other visits in addition to Screening Administrative changes included changes in the Eisai UK address and in contact information regarding reporting SAEs, pregnancies, deaths and life-threatening events.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported