



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 | <ul style="list-style-type: none">• Correction of full data setUpdated 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 (\pm 8.77) | 4.5 (\pm 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 |
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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 occurrences (all) | 0 / 40 (0.00%) 0 | 2 / 31 (6.45%) 2 | 0 / 34 (0.00%) 0 |
| Vomiting subjects affected / exposed occurrences (all) | 2 / 40 (5.00%) 2 | 1 / 31 (3.23%) 1 | 2 / 34 (5.88%) 2 |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 4 / 40 (10.00%) 4 | 1 / 31 (3.23%) 1 | 0 / 34 (0.00%) 0 |
| Epistaxis subjects affected / exposed occurrences (all) | 0 / 40 (0.00%) 0 | 1 / 31 (3.23%) 1 | 0 / 34 (0.00%) 0 |
| Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) | 3 / 40 (7.50%) 3 | 2 / 31 (6.45%) 2 | 0 / 34 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders Muscle spasms subjects affected / exposed occurrences (all) | 4 / 40 (10.00%) 4 | 1 / 31 (3.23%) 1 | 0 / 34 (0.00%) 0 |
| Pain in extremity subjects affected / exposed occurrences (all) | 2 / 40 (5.00%) 2 | 0 / 31 (0.00%) 0 | 0 / 34 (0.00%) 0 |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) | 4 / 40 (10.00%) 4 | 3 / 31 (9.68%) 3 | 2 / 34 (5.88%) 2 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 1 / 40 (2.50%) 1 | 1 / 31 (3.23%) 1 | 2 / 34 (5.88%) 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 occurrences (all) | 3 / 25 (12.00%) 3 | | |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 2 / 25 (8.00%) 3 | | |
| Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | | |
| Musculoskeletal and connective tissue disorders Muscle spasms subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all) | 2 / 25 (8.00%) 3 0 / 25 (0.00%) 0 | | |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 1 / 25 (4.00%) 1 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 21 March 2008 | <p>Changes to the study design and conduct included:</p> <ul style="list-style-type: none">• 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. <p>Administrative changes included changes in Eisai contact information, and information about contract research organizations.</p> |
| 25 February 2009 | <p>Changes to the study design and conduct included:</p> <ul style="list-style-type: none">• 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 <p>Administrative changes included changes in the Eisai UK address and in contact information regarding reporting SAEs, pregnancies, deaths and life-threatening events.</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported