CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022568

MEDICAL REVIEW(S)

Review and Evaluation of Clinical Data

NDA	**22568**
Sponsor:	**Eisai**
Drug:	**Aricept 23 Mg Tablet**
Proposed Indication:	**Alzheimer's Disease**
Material Submitted:	**New Drug Application**
Correspondence Date:	**9/24/09**
Date Received / Agency:	**9/24/09**
Date Review Completed:	**7/23/10**
Reviewer:	**Ranjit B. Mani, M.D.**

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EXECUTIVE SUMMARY

Recommendation

I recommend that this application, which seeks the approval of Aricept® in a new dose strength of 23 mg, administered once daily, for the treatment of moderate to severe dementia of the Alzheimer's type not be approved.

Proposed Indication

This New Drug Application (NDA) seeks the approval of a new formulation of Aricept® (donepezil hydrochloride) for the treatment of moderate to severe dementia of the Alzheimer's type.

The proposed new formulation of Aricept® is a 23 mg tablet. During the review of this application it was determined by the Agency that the proposed new formulation did not have the characteristics of an extended-release tablet, contrary to statements made in the original submission under this application.

Aricept® is currently approved as standard and orally disintegrating tablets, of 5 mg and 10 mg strength for each type of tablet, for the treatment of mild, moderate, and severe Alzheimer's Disease. An oral solution formulation of Aricept® containing 1 mg/mL of donepezil hydrochloride is also approved for the treatment of mild to moderate Alzheimer's Disease, but is not marketed in this country.

All currently-approved formulations of Aricept® are administered once daily. In the current application, it is proposed that the 23 mg tablet formulation of Aricept® also be administered once daily.

Summary Of Clinical Findings

Efficacy

The sponsor has submitted the results of a single efficacy study, E2020-G000-326 (also referred to as "Study 326") to support the approval of the proposed new 23 mg formulation of donepezil This study was conducted at 220 sites in 23 countries.

The design and efficacy data for Study 326 are described further below.

Design

The primary objective of Study 326 was to compare the efficacy of the 23 mg QD dose of donepezil with that of the 10 mg QD dose in the treatment of moderate to severe Alzheimer's Disease. Among the secondary objectives of the study was to

evaluate the safety and tolerability of the 23 mg QD dose of donepezil in Alzheimer's Disease.

This was a randomized, double-blind, double-dummy, active-controlled, parallel-arm study of 24 weeks duration

The key inclusion criteria for this study were a diagnosis of Probable Alzheimer's Disease, using the National Institute for Neurological and Communicative Diseases and Stroke – Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria, an entry Mini-Mental Status Examination (MMSE) score of 0-20, a Severe Impairment Battery score ≤ 90 at entry, and use of donepezil at a stable daily dose of 10 mg QD for at least 3 months prior to study entry.

Patients enrolled in this study were randomized to the following treatment groups for the 24-week duration of the study.

- Donepezil 23 mg QD
- Donepezil 10 mg QD

(Patients assigned to the 23 mg QD dose received that dose without titration).

The primary efficacy measures for the study were:

- A measure of cognition, the Severe Impairment Battery (SIB)
- A measure of global function, the Clinician Interview-Based Impression of Change-Plus (CIBIC-Plus).

The secondary efficacy measures for this study consisted of a 19-item version of the Alzheimer's Disease Cooperative Study – Activities of Daily Living Scale (ADCS-ADL) specially designed for patients with moderate to severe dementia, and the MMSE.

Safety measures included adverse events, vital signs, physical and basic neurological examinations, safety laboratory tests, and electrocardiograms.

The primary efficacy parameters were the change from baseline in the total SIB score at Week 24 and the CIBIC-Plus score at Week 24. The primary efficacy analysis was performed on the intent-to-treat dataset at Week 24, using the last-observation-carried-forward method of imputation. The intent-to-treat dataset consisted of all randomized patients who received at least one dose of study medication and had at least one post-baseline evaluation of the SIB or CIBIC-Plus.

The analysis of the Severe Impairment Battery data was to be performed using an analysis of covariance model with terms for baseline, country, and treatment.

The CIBIC-Plus was to be analyzed using a non-parametric analysis of covariance with a Cochran-Mantel-Haenszel test component. The analysis was to adjust for Clinician Interview-Based Impression of Severity-Plus (CIBIS-Plus) score at baseline with a stratification adjustment for country.

The superiority of the 23 mg/day sustained-release group over the 10 mg/day donepezil immediate-release group must to have been demonstrated on the Severe Impairment Battery and CIBIC-Plus, during the primary efficacy analysis, for the study to be considered positive. Superiority was to have been demonstrated at a significance level of 0.05 (2-sided) for each primary efficacy measure.

Results

A total of 1467 patients were enrolled in this study. The number randomized to the 2 treatment groups and the number completing the study in each group is in the following table.

Category	Treatment Group	
	Donepezil SR 23 mg/day N (%)	Donepezil IR 10 mg/day N (%)
Randomized	981 (100.0)	486 (100.0)
Completed	685 (69.8)	399 (82.1)

The actual MMSE scores for patients enrolled in the study ranged from 0-22 with a mean score of 13.1 (standard deviation ± 4.91).

The results of the primary efficacy analysis revealed the following:

- A least squares mean change from baseline of 2.6 points in the donepezil 23 mg QD group and 0.4 points in the donepezil 10 mg QD group, on the SIB, with the difference between groups being statistically significant (p = 0.0001)

- A mean score of 4.23 points in the donepezil 23 mg QD group and 4.29 points in the donepezil 10 mg QD group, on the CIBIC-Plus, with the difference between groups not being statistically significant (p = 0.1789).

Sensitivity and other analyses of the SIB, including post-hoc analyses confined to subsets with and within an entry Mini-Mental Status Examination score range of 0 to 16, were all consistent with the primary efficacy analysis. Additional analyses of the CIBIC-Plus showed a nominally statistically significant treatment difference favoring the 23 mg QD group over the 10 mg QD group for the subset with an entry MMSE score of 0-16, but not consistently for subsets either close to or within that range.

No statistically significant treatment difference was seen between the treatment groups on the 2 secondary efficacy measures, the ADCS-ADL and the MMSE.

Indeed, there was no difference at all between the treatment groups on the mean change from baseline to Week 24 in the ADCS-ADL

Reviewer's Conclusion

The results of Study 326 did not satisfy the pre-specified criteria for demonstrating the efficacy of the higher dose of donepezil (23 mg QD).

Although the primary efficacy analysis showed a small, but clearly statistically significant, effect of donepezil (23 mg QD) on the SIB, that was maintained on at least some sensitivity analyses, and in a post-hoc analysis of the subset with an entry MMSE score in the 0-16 range, the primary efficacy analysis of the CIBIC-Plus did not show a statistically significant benefit, thus failing to provide confirmation that the small effect on the SIB was clinically meaningful.

Safety

The safety data reviewed under this application were submitted in the following.

- The Summary of Clinical Safety, submitted with the original application
- The 120-Day Safety Update

Each of these components is further summarized below.

Summary Of Clinical Safety

Studies included in the Summary of Clinical Safety were the following.

- Study E2020-G000-326 ("Study 326"), which is already described above.

- Study E2020-G000-328 (also referred to as "Study 328"), a 12-month open-label uncontrolled extension to Study E2020-G000-326, which is currently ongoing.

- Four completed clinical pharmacology studies (E2020-A001-020, -021, 022, and 0-23), all of which involved testing presumed sustained-release formulations of Aricept®, including the 23 mg tablet proposed for approval in the current application. All 4 studies were conducted in healthy subjects.

Safety outcome measures in the majority of these studies included adverse events, vital signs, safety laboratory tests, and electrocardiograms.

The cut-off date for safety data from Study 328 included in the original NDA submission was June 30, 2009, except for discontinuations due to adverse events for which the cut-off date was April 1, 2009.

In Study 326, the incidence of deaths and of all serious adverse events was similar in the 2 treatment groups, while the incidence of all adverse events and of adverse events leading to treatment discontinuation was clearly higher in the

donepezil 23 mg QD group than in the donepezil 10 mg QD group. The individual adverse events that were substantially more common in the higher dose donepezil group were nausea, vomiting, and anorexia; vomiting, notably, had an incidence of 9.2% in the 23 mg QD group and only 2.5 % in the 10 mg QD group, with the difference in incidence of gastrointestinal adverse events between the 2 treatment groups being particularly apparent during the first month of the study. The sponsor-provided descriptions of deaths and serious adverse events that occurred in this study suggested that they were most unlikely to be attributable to donepezil. The same applies to adverse events that led to treatment discontinuation, with the exception of nausea, vomiting, diarrhea, and dizziness, the incidence of which was notably higher in the donepezil 23 mg QD group than in the 10 mg QD group. Other safety data analyzed, including vital signs, safety laboratory tests, and electrocardiograms showed no areas of concern when comparing the two treatment groups.

The safety results of Study 326 raised a very significant concern about the safety of the 23 mg QD dose of donepezil (in addition to a lack of evidence that that dose had a clinically meaningful benefit). The introduction of that dose in Study 326 was associated with an incidence of vomiting of 9.2%, as compared with several-fold lower incidence of only 2.5% in those continuing to receive donepezil in a dose of 10 mg QD; the occurrence of vomiting can lead to even greater morbidity in patients with Alzheimer's Disease, that includes pneumonia, massive gastrointestinal bleeding, esophageal rupture, or death. Thus, in addition to lacking any evidence of a clinically meaningful benefit, at least in comparison with the 10 mg QD dose of donepezil, the use of a 23 mg QD dose (i.e., an escalation in dose from 10 mg QD to 23 mg QD) is also associated with a significant risk to patient safety.

However, the available data for Study 328 and the safety data for the clinical pharmacology studies do not raise any additional clinically significant safety concerns.

120-Day Safety Update

The 120-Day Safety Update for this application contained a full summary of available safety data from all the studies included in the earlier-submitted Summary of Clinical Safety. However, the new safety data provided in the Update were exclusively for Study 328 and consisted of the following.

- Council for International Organizations of Medical Sciences (CIOMS) forms for deaths and serious adverse events that occurred through a cut-off date of November 25, 2009
- Listings of deaths and serious adverse events that occurred through a cut-off date of July 25, 2009
- Narratives for discontinuations due to non-serious adverse events that occurred through a cut-off date of July 25, 2009

Data included in the Update indicated that of 915 patients had been enrolled in Study 328, of whom the participation of 589 patients remained ongoing.

The data presented in the 120-Day Safety Update for donepezil did not raise any new concerns about the safety and tolerability of the 23 mg QD dose of donepezil.

Pharmacokinetics

The sponsor drew the following conclusions from the results of the Phase I studies (E2020-A001-020, -021, 022, and 0-23) included in this application, regarding the 23 mg tablet formulation of Aricept® proposed for approval.

- The selected formulation for the 23 mg tablet had a longer T_{max}, a lower dose-normalized C_{max}, and a slightly lower dose-normalized AUC than the approved immediate-release formulation.

- With the 23 mg tablet, plasma concentrations of donepezil reached steady state over 14 days. After cessation of treatment, plasma concentrations of donepezil declined exponentially reaching asymptote within 2 weeks.

- There was no clinically significant effect of food on the bioavailability of the selected 23 mg formulation.

Additional conclusions drawn from a population pharmacokinetic analysis of Study 326 included the following:

- The AUC at steady-state was about two-fold higher for the 23 mg donepezil formulation than for the 10 mg tablets (as might be expected)

- The T_{max} following the administration of the 23 mg formulation was about twice as long as for the 10 mg

- A small difference in relative bioavailability was seen between the 23 mg and 10 mg formulations

- CYP2D6 phenotype, age, and weight were predictive of donepezil clearance. Gender and the co-administration of CYP2D6 inhibitors also had an effect on donepezil clearance.

The Agency Clinical Pharmacology reviewer concluded, based on data provided by the sponsor, that there was no evidence that the proposed 23 mg tablet formulation of Aricept® was in fact a controlled-release formulation.

Overall Conclusions

The sponsor has not provided substantial evidence for the efficacy or safety of Aricept® administered in a dose of 23 mg QD to patients with moderate to severe Alzheimer's Disease.

1. Background

This New Drug Application (NDA) seeks the approval of a new formulation (b) (4) and comprised of donepezil hydrochloride extended-release tablets of 23 mg strength, as stated by the sponsor in the original cover letter to this application) for the treatment of moderate to severe dementia of the Alzheimer's type.

During review of the current application, the Agency concluded that the proposed new 23 mg tablet of donepezil did not meet the criteria for an extended-release formulation, and the sponsor was informed accordingly.

Earlier in the review of the current application, the Agency judged that the name (b) (4) was not an acceptable one for the proposed 23 mg tablet. The sponsor then proposed the name (b) (4) for the proposed new formulation which the Agency had preliminarily judged as being satisfactory, until it was eventually concluded by the Agency that the proposed new 23 mg formulation of donepezil hydrochloride did not meet the criteria for an extended-release tablet, and thus merely qualified to be considered as a higher strength of the currently-approved Aricept® standard tablet formulation (see below).

Donepezil (Aricept®) is an acetylcholinesterase inhibitor initially approved in this country on November 25, 1996 as a standard tablet formulation (in 5 mg and 10 mg strengths), under NDA 20690, for the treatment of mild to moderate dementia of the Alzheimer's type. The Agency then approved an extension of that indication to include severe dementia of the Alzheimer's type, on October 13, 2006, based on the review of a Supplemental NDA (NDA 20690; SE1-026) submitted on March 20, 2006.

Oral solution and orally disintegrating tablet formulations of donepezil were approved for the treatment of mild to moderate dementia of the Alzheimer's type on October 18, 2004 under NDA 21719 and NDA 21720, respectively. The orally disintegrating tablet formulation of donepezil was later also approved for the treatment of severe dementia of the Alzheimer's type (under NDA 21720; SE1-003) at the same time that the standard tablet formulation was approved for that indication.

Only the standard and orally-disintegrating tablet formulations of Aricept® are currently marketed in the United States.

The proposed new formulation of donepezil has been developed under IND 35974, as were the previously approved formulations of the same compound.

Although the proposed 23 mg formulation of donepezil was not eventually judged to qualify as an extended-release tablet for regulatory purposes, it has been referred to using the following terms in the application itself: "donepezil sustained release;" "donepezil sustained release (SR);" "donepezil SR;" "E2020-SR;" and "Aricept SR." Thus, tables in this review that have been directly copied from the

application also use the same terms in describing the new formulation. Similar terms have occasionally been used in the text of this review to refer to the proposed new formulation.

The words “donepezil” and “Aricept®” are used interchangeably in this review.

2. Contents Of Submission

Individual submissions under this application that have provided clinical data and have been reviewed by me in detail are as follows:

- The original submission of September 24, 2009
- The 120-Day Safety Update submitted on January 21, 2010
- Draft product labeling submitted on June 3, 2010.

Other submissions under this application include those listed in the following table. Several have contributed in a minor way to my review of this application.

Nature of submission	Letter date
Request for proprietary name review	October 6, 2009
Withdrawal of request for proprietary name review	December 10, 2009
Statistical datasets for population pharmacokinetic analysis	December 21, 2009
Request for proprietary name review	January 7, 2010
Chemistry stability data	January 21, 2010
Amendment to request for proprietary name review	January 25, 2010
Labeling amendment	February 22, 2010
Response to information request (chemistry)	May 27, 2010
Proposed container labels	June 30, 2010
Response to information request (chemistry)	July 6, 2010
Proposed container labels and commitments regarding blister labels	July 22, 2010

All submissions under this application have been in electronic Common Technical Document format.

3. Contents Of Review

The contents of this submission have been reviewed under the following main headings and in the same order as below:

- History of development of Aricept® 23 mg tablet
- Summary table for all clinical studies for which data has been included in this application
- Description of main controlled clinical trial (E2020-G000-326) supporting current application
- Integrated Summary of Safety (Summary of Clinical Safety)
- 120-Day Safety Update

- Sponsor's summary of clinical pharmacokinetics of new formulation
- Description of new drug product formulation
- Summary of additional agency reviews
- Review of labeling
- Financial disclosure certification
- Study site inspection report
- Overall conclusions
- Recommendation.

4. History Of Development Of Aricept 23 Mg Tablet

4.1 Rationale For Development Of Aricept® 23 Mg Tablet

The rationale for developing the 23 mg tablet of Aricept® (originally designated by the sponsor as a sustained-release formulation) is explained in the introductory section of the original submission under this application, and may be summarized as follows:

- To evaluate the hypothesis that patients with more advanced Alzheimer's Disease can benefit from a higher dose of donepezil than that currently approved

(b) (4)

An identical rationale for developing the proposed new formulation of donepezil was conveyed to the Agency during the interactions that preceded the submission of this application and are described in the next section.

4.2 Interactions Between Sponsor And Agency Regarding Development Of Aricept® 23 Mg Tablet

The main interactions between the Agency and sponsor regarding the development of the 23 mg tablet of donepezil were under the following circumstances.

- An End-of-Phase 2 Meeting held on March 19, 2007. The Briefing Package for the meeting was submitted as Serial #1137 under IND 35974 on February 16, 2007

- A Special Protocol Assessment of the key efficacy study under this application, submitted as Serial #1151 under IND 35974 on September 17, 2007. The sponsor responded to an Agency letter that addressed the request for a Special Protocol Assessment in a further submission (Serial #1171 under IND 35974) on March 3, 2008

- A planned Pre-NDA Meeting for which a Briefing Package was submitted as Serial #1240 under IND 35974 on January 13, 2009. After preliminary responses to the sponsor's questions in the Briefing Package were received (by the sponsor), the meeting was cancelled at the sponsor's request.

Among the key agreements related to the clinical aspects of this submission that were reached during the course of the above interactions were the following:

- A single adequate and well-controlled study that demonstrated substantial evidence of effectiveness was likely to be sufficient to obtain approval of the proposed new formulation of donepezil. While Protocol E2020-G000-326 conformed in its design to such a study, it could be considered to provide substantial evidence of effectiveness for the 23 mg/day dose of the sustained-release formulation of Aricept® only if that dose was demonstrated to have a statistically significant superiority over the 10 mg/day dose of the immediate-release formulation on both primary efficacy measures, the Severe Impairment Battery (SIB) and the Clinician Interview-Based Impression of Change-Plus (CIBIC-Plus).

- The available data and prior experience supported the use of the SIB as a cognitive outcome measure as being most appropriate for those with a Mini-Mental Status Examination score at entry that is ≤ 14. While the Agency remained to be fully convinced about the appropriateness of using the Severe Impairment Battery as an efficacy measure in patients with an entry Mini-Mental Status Examination score ≥ 15, it did judge that there was also sufficient additional information supplied by the sponsor to support the enrollment of patients with entry Mini-Mental Status Examination scores up to 20 in Study E2020-G000-326, and to perform the primary analysis of the Severe Impairment Battery data using all enrolled patients (i.e., those an entry Mini-Mental Status Examination score ≤ 20).

Please see the above submissions and related Agency reviews, letters, and meeting minutes for full details.

5. Summary Table For All Clinical Studies For Which Data Has Been Included In This Application

The studies for which clinical data has been included in this application are as follows:

- Phase 3 efficacy and safety studies, consisting of:

- E2020-G000-326, a randomized, double-blind, active-controlled, parallel-arm study comparing donepezil 23 mg QD with donepezil 10 mg QD
- E2020-G000-328, an open-label uncontrolled extension to Study E2020-G000-326, that is currently ongoing.

- Four clinical pharmacology studies listed below:

  - E2020-A001-020
  - E2020-A001-021
  - E2020-A001-022
  - E2020-A001-023.

The studies listed above are further outlined in the next table, which I have copied from the submission.

Study ID	Design	Number of Study Centers (Locations)	# Patients by Arm; Entered/ Completed	Diagnosis Inclusion Criteria	Gender M/F Median age (Range)	Duration	Study and Control Drugs Dose, Route, Regimen	Frequency of Dosing
Completed Pivotal Phase III Study								
E2020-G000-326	Double-blind, double-dummy, parallel-group, superiority trial comparing donepezil SR 23 mg to donepezil IR 10 mg	220 (Asia, Oceania, Europe, North America, Africa, and South America)	donepezil SR 981/685 donepezil IR 486/399	Men or women 45 to 90 yrs with probable AD consistent with DSM-IV, NINCDS-ADRDA criteria; MMSE (1 to 20); CSDD < 12; SIB ≤ 90	donepezil SR 23 mg 356/607 75 yrs (47 to 90) donepezil IR 10 mg: 177/294 75 yrs (49 to 90)	24 weeks	donepezil SR 23 mg orally QD for 24 weeks donepezil IR 10 mg orally QD for 24 weeks	QD

Study ID	Design	Number of Study Centers (Locations)	# Patients by Arm; Entered/ Completed	Diagnosis Inclusion Criteria	Gender M/F Median age (Range)	Duration	Study and Control Drugs Dose, Route, Regimen	Frequency of Dosing
Ongoing Long-term Extension Study								
E2020-G000-328 (extension of E2020-G000-326)	Open-label, multicenter study to evaluate safety and efficacy of long-term treatment with donepezil SR	181	donepezil SR 915 entered/ (ongoing)	Completed E2020-G000-326 with no ongoing SAEs or serious adverse drug reactions during the study	ongoing	12 months	donepezil SR 23 mg orally QD for 12 months	QD

Study ID	Design	Number of Study Centers (Locations)	# Patients by Arm; Entered/ Completed	Diagnosis Inclusion Criteria	Gender M/F Median age (Range)	Duration	Study and Control Drugs Dose, Route, Regimen	Frequency of Dosing
Completed Phase I Studies								
E2020-A001-020	Randomized, open-label, two-period, two-sequence crossover study to evaluate the relative bio-availability of three donepezil SR formulations	1 (US)	donepezil SR-4H 29/24	healthy subjects	donepezil SR-4H 11/18 39 yrs (22 to 46)	two single doses (SR and IR) in a crossover design separated by a ~3 week washout	a single dose of donepezil SR 10 mg (4H-, or 8H-, or 12H) or donepezil IR 10 mg under fasting conditions	QD
			donepezil SR-8H 26/25		donepezil SR-8H 14/12 36 yrs (21 to 44)			
			donepezil SR-12H 27/24		donepezil SR-12H 11/16 36 yrs (19 to 45)			

Study ID	Design	Number of Study Centers (Locations)	# Patients by Arm; Entered/ Completed	Diagnosis Inclusion Criteria	Gender M/F Median age (Range)	Duration	Study and Control Drugs Dose, Route, Regimen	Frequency of Dosing
Completed Phase I Studies								
E2020-A001-020	Randomized, open-label, two-period, two-sequence crossover study to evaluate the relative bio-availability of three donepezil SR formulations	1 (US)	donepezil SR-4H 29/24	healthy subjects	donepezil SR-4H 11/18 39 yrs (22 to 46)	two single doses (SR and IR) in a crossover design separated by a ~3 week washout	a single dose of donepezil SR 10 mg (4H-, or 8H-, or 12H) or donepezil IR 10 mg under fasting conditions	QD
			donepezil SR-8H 26/25		donepezil SR-8H 14/12 36 yrs (21 to 44)			
			donepezil SR-12H 27/24		donepezil SR-12H 11/16 36 yrs (19 to 45)			

Study ID	Design	Number of Study Centers (Locations)	# Patients by Arm; Entered/ Completed	Diagnosis Inclusion Criteria	Gender M/F Median age (Range)	Duration	Study and Control Drugs Dose, Route, Regimen	Frequency of Dosing
E2020-A001-021	Double-blind, single-dose PK and PD study	1 (US)	donepezil SR 23 mg 34/23	healthy subjects	donepezil SR 23 mg 17/17 24 yrs (19 to 38)	single dose	single, oral dose of donepezil SR 23 mg under fasting conditions	QD
			donepezil SR 14 mg 23/19		donepezil SR 14 mg 9/14 29 yrs (19 to 43)		single, oral dose of donepezil SR 14 mg under fasting conditions	
			donepezil IR 10 mg 27/19		donepezil IR 10 mg 8/19 25 yrs (19 to 40)		single, oral dose of donepezil IR 10 mg under fasting conditions	

Study ID	Design	Number of Study Centers (Locations)	# Patients by Arm; Entered/ Completed	Diagnosis Inclusion Criteria	Gender M/F Median age (Range)	Duration	Study and Control Drugs Dose, Route, Regimen	Frequency of Dosing
E2020-A001-022	Placebo-controlled, multiple-dose PK and PD study of E2020-SR tablets	1 (US)	Group 1[a] placebo/ SR 14 mg/ SR 23 mg 15/8	healthy subjects	Group 1[a] 11/4 35 yrs (22 to 44)	5 weeks	placebo or donepezil IR 5 mg orally QD for 7 days under fasting conditions during Period 1 placebo or donepezil SR 14 mg orally QD for 14 days under fasting conditions during Period 2 placebo or donepezil SR 23 mg orally QD for 14 days under fasting conditions during Period 3	QD
			Group 2[a] placebo/ placebo/ placebo 15/13		Group 2[a] 6/9 39 yrs (19 to 45)			
			Group 3[a] placebo/ SR 14 mg/ placebo 16/13		Group 3[a] 6/10 37 yrs (22 to 45)			
			Group 4[a] IR 5 mg/ SR 14 mg/ SR 23 mg 15/12		Group 4[a] 9/6 41 yrs (21 to 45)			
			Group 5[a] IR 5 mg/ SR 14 mg/ placebo 16/12		Group 5[a] 12/4 41 yrs (21 to 44)			

Study ID	Design	Number of Study Centers (Locations)	# Patients by Arm; Entered/ Completed	Diagnosis Inclusion Criteria	Gender M/F Median age (Range)	Duration	Study and Control Drugs Dose, Route, Regimen	Frequency of Dosing
E2020-A001-023	Open-label, single and repeated dose study to evaluate the effect of food on the bio-availability (PK profile) of the donepezil SR tablet	1 (US)	Panel 1 donepezil SR 14 mg 17/15	healthy subjects	Panel 1 9/8 27 yrs (19 to 41)	Panel 1 & Panel 2 two single doses in a crossover design separated by a 2-week washout	single, oral dose of either donepezil SR 14 mg or 23 mg under fasting conditions and under fed conditions	QD
			Panel 2 donepezil SR 23 mg 35/16		Panel 2 18/17 27 yrs (21 to 43)			
			Panel 3 7 days with donepezil SR 14 mg followed by a single dose of donepezil SR 23 mg 27/13		Panel 3 17/10 30 yrs (20 to 45)	Panel 3 16 days in a crossover design separated by a 2-week washout	donepezil SR 14 mg orally QD for 7 days followed by a single, oral dose of donepezil SR 23 mg taken under fasting conditions and under fed conditions	

[a] Treatments are shown as follows: Period 1/Period 2/Period 3. Period 1 was 7 days in duration. Period 2 and Period 3 were each 14 days in duration.

Abbreviations: IR – immediate release; SR –sustained release; AD – Alzheimer's disease; CRF – case report form; CSDD – Cornell Scale for Depression in Dementia; DSM-IV – Diagnostic and Statistical Manual for Mental Disorders–Version IV; ID – identification; MMSE – Mini-Mental State Examination; NINCDS-ADRDA – National Institute of Neurological and Communicative Diseases and Stroke–Alzheimer's Disease and Related Disorders Association; PD – pharmacodynamic; PK – pharmacokinetic; SAE – serious adverse event; QD – once daily; US – United States.

6. Description Of Main Controlled Clinical Trial (E2020-G000-326) Supporting Current Application

The results of a single randomized, double-blind, controlled clinical study have been submitted to support the approval of the proposed new formulation of donepezil as a treatment for moderate to severe Alzheimer's Disease. That study is E2020-G000-326, also referred to as Study 326 in both the application and this review.

The final clinical protocol for and results of Study 326 are summarized below.

6.1 Study Protocol

The study protocol summarized below is the final protocol dated June 2008.

6.1.1 Title

Double-Blind, Parallel-Group Comparison Of 23 Mg Donepezil Sustained-Release To 10 mg Donepezil Immediate-Release In Patients With Moderate To Severe Alzheimer's Disease

6.1.2 Objectives

6.1.2.1 Primary

To compare the efficacy of the 23 mg sustained-release tablet of donepezil with that of the 10 mg immediate-release tablet of donepezil in the treatment of patients with moderate to severe Alzheimer's Disease.

6.1.2.2 Secondary

To compare the effects of the 23 mg sustained-release tablet of donepezil on secondary efficacy parameters in support of the primary efficacy parameters.

To compare the effects of the 23 mg sustained-release tablet of donepezil with that of the 10 mg immediate-release tablet of donepezil on exploratory quality-of-life parameters.

To evaluate the safety and tolerability of the 23 mg sustained-release tablet of donepezil when administered to patients with Alzheimer's Disease.

To determine, in an exploratory manner, whether the response to treatment with the 23 mg sustained-release tablet of donepezil is related to the rate of drug metabolism as modified by CYP2D6 alleles, and whether the treatment response is related to the presence of the Alzheimer's Disease risk factor APOE ε4.

6.1.3 Design

This will be a randomized, double-blind, double-dummy, active-controlled, parallel-arm study.

Patients randomized to the study will be assigned to 2 parallel treatment groups:

- Sustained-release donepezil 23 mg/day (this group will also receive the placebo equivalent of the 10 mg immediate-release table of donepezil)
- Immediate-release donepezil 10 mg/day (this group will also receive the placebo equivalent of the 23 mg sustained-release table of donepezil).

6.1.4 Duration

24 weeks of double-blind, parallel-arm treatment.

6.1.5 Sample Size

About 1200 patients are to be enrolled and randomized in a 2:1 ratio to 23 mg/day of sustained-release donepezil and 10 mg/day of immediate-release donepezil.

6.1.6 Selection

6.1.6.1 Key Inclusion Criteria

- Male or female; aged 45 to 90 years. If female must be surgically sterile or at least one year post-menopausal (i.e., of non-childbearing-potential)

- Probable Alzheimer's Disease by NINCDS-ADRDA and DSM-IV 290.00 and DSM-IV 290.10 criteria

- Mini Mental Status Examination scores ranging from 1 to 20 (at screening and baseline)

- Cornell Scale for Depression in Dementia score < 12 at screening

- Severe Impairment Battery score ≤ 90 at screening and baseline

- Receiving a stable dose of immediate-release Aricept® (or generic equivalent) of 10 mg once daily for ≥ 3 months at entry, without splitting the daily dose, or without crushing or breaking individual tablets

- CT scan or MRI within the previous 12 months without focal disease that could account for dementia

- Generally healthy and ambulatory with or without a walking aid

- Vision and hearing (with or without eyeglasses and/or a hearing aid) sufficient for compliance with testing procedures

- Clinical laboratory data within normal limits, and within the sponsor's guidelines, or abnormalities considered not clinically significant

- Patients with hypertension and cardiac disease may be enrolled provided that the hypertension is medication-controlled, with a supine diastolic pressure < 95 mm, and cardiac disease is stable on appropriate medication for 3 months, prior to screening. Peripheral vascular disease must also have been stable for 3 months prior to screening

- Patients with diabetes mellitus or risk factors for diabetes mellitus may be enrolled in the study provided that the patient's disease is stable and provided that there have been no recent (within 3 months) hospitalizations for diabetic ketoacidosis, hyperosmolar coma, or hypoglycemia. Patients with non-insulin-dependent diabetes may enroll in the study if controlled on diet or oral medication. All diabetic patients must have a HbA_1C concentration of < 10% and a fasting (8 hours) serum glucose concentration of < 170 mg/dl or a random serum glucose concentration of < 250 mg/dL at screening

- Patients undergoing treatment with a selective serotonin reuptake inhibitor may enter the study provided the dose of drug being taken is equal to or less than the approved dose range

- Patients who do not have acceptable serum Vitamin B_{12} levels at screening may, nonetheless, be admitted to the study if they show normal levels at baseline

- Patients with hypothyroidism who are on a stable dose of medication for at least 12 weeks prior to screening, have normal serum TSH and free T4 at screening, and are considered euthyroid will be eligible

- No history of life-threatening arrhythmias

- Written informed consent is to be obtained from the patient (if possible) or from the patient's legal guardian or other representative prior to beginning screening activities. Even if unable to provide written informed consent, the patient must assent verbally to participating in the study and the record should note this assent

- Reliable caregiver, who must also give informed consent for his or her own participation in the study, and must satisfy a separate set of inclusion criteria

- Patients taking the following concomitant medications under the conditions listed below may be enrolled in the study under the conditions specified.

    - Chronic daily benzodiazepines, if doses are stable, within an approved dose range, and consistent with accepted standards of practice for at least 1 year prior to screening. Intermittent use of benzodiazepines is also permitted, but not within 48 hours of a scheduled assessment. All benzodiazepine use must be approved by the Medical Monitor

    - Bronchodilator treatment for chronic obstructive pulmonary disease, if the drug is administered by metered dose inhaler and within an approved dose range

    - Memantine at doses ≤ 20 mg/day, if the dose has been stable for at least 3 months prior to screening.

    - Vitamin E, fish oil, or Ginkgo biloba, if the dose has been stable for at least 3 months prior to screening, and if the doses are not to be changed during the study.

6.1.6.2 Key Exclusion Criteria

- No measurable concentrations of donepezil in plasma
- Unreliable caregiver

- Neurological disorder other than Alzheimer's Disease which is capable of affecting cognition or the assessment of cognition (examples provided)
- Dementia complicated by other organic disease, or Alzheimer's Disease with delirium
- Psychiatric disorders that could influence the ability to evaluate cognition (examples provided)
- Any clinically significant condition that could interfere with absorption, distribution, or elimination of study drug
- Drug or alcohol abuse by DSM-IV criteria within previous 5 years
- Clinically significant active gastrointestinal, renal, hepatic, respiratory, endocrine or cardiovascular system disease
- Known hypersensitivity to cholinesterase inhibitors or memantine
- History of malignant neoplasms (other than basal or squamous cell carcinoma) treated within 5 years prior to study entry, current evidence of malignant neoplasm or recurrent metastatic disease
- Planned elective surgery during treatment period that would require general anesthesia and administration of neuromuscular blocking agents such as succinylcholine
- Donation of blood or blood products within 30 days prior to screening or plans to donate blood while participating in the study or within 30 days of its completion
- Unwilling or unable to fulfill the commitments of the study. Otherwise considered unsuitable for the study
- Use of an investigational drug within the preceding 3 months or likely involvement in such a trial within the course of the current study
- Use of concomitant antidepressants known to have significant anticholinergic effects
- Inability to swallow or difficulty swallowing whole tablets
- Patients with fecal or urinary incontinence who are unable to cooperate with urinary or fecal specimen collection
- Use of prohibited prior or concomitant medication
- Use of any alternative medical techniques such as acupuncture or acupressure for the treatment of Alzheimer's Disease.

6.1.6.3 Prohibited Concomitant Medications

A comprehensive listing is provided in an appendix to the protocol. These consist of specific analgesics, anesthetics/muscle relaxants, anticholinergics, anticonvulsants, antidepressants, antipsychotics, anti-hypertensive agents, anxiolytics, anti-Parkinsonian drugs, stimulants and appetite suppressants, cholinomimetic agents, antipsychotics, sympathomimetics, NMDA antagonists, and other agents.

Apart from memantine and Vitamin E, drugs for the treatment of Alzheimer's Disease are prohibited. If memantine is being taken, it should have been used in a stable dose of 20 mg/day for at least 3 months prior to study entry.

6.1.7 Dosage

Both active formulations of donepezil and their placebo counterparts are to be packaged as appropriate for a “double-dummy” presentation.

Both doses to be administered (23 mg/day of the sustained-release formulation and 10 mg/day of the immediate-release formulation) will be administered without titration during the study.

6.1.8 Schedule

The study schedule is copied below from the submission:

Assessments and Activities[a]	Screening (−4 weeks to Day 0)	Base-line visit	3 week visit (Safety only)	6 week visit	12 week visit	18 week visit	Final Visit (24 weeks) or Early Termination
Informed Consent, caregiver	X						
Informed Consent, patient[b]	X						
Inclusion/Exclusion Criteria, caregiver	X						
Inclusion/Exclusion Criteria, patient	X	X					
Medical history (patient) and demographics (patient and caregiver)	X						
MMSE[c], caregiver	X						
CES-D[c], caregiver	X						
MMSE[d]	X	X		X	X	X	X
CSDD[d]	X						
SIB[d]	X	X		X	X	X	X
CIBIS+, patient and caregiver		X					
CIBIC+, patient and caregiver				X	X	X	X
ADCS-ADL, caregiver		X		X	X	X	X
QoL-AD, patient and caregiver		X					X
EQ-5D, caregiver proxy assessment		X					X
SCB, caregiver (non-professional)		X					X
TES, caregiver (non-professional)		X					
TOS, caregiver							X
GAtS, patient and caregiver		X					X
Vitals (with Weight)[e]	X	X	X	X	X	X	X
Height	X						
Complete physical examination	X	X	X	X	X	X	X
Complete neurological examination	X						X
Basic neurological examination		X	X	X	X	X	
12-Lead ECG	X	X[f]	X	X	X	X	X
Clinical laboratory tests[g]	X	X	X	X	X	X	X
Sampling for plasma donepezil levels[h]	X	X		X	X	X	X
Sampling for genotyping[i]		X					
Cranial MRI or CT[j]	X						
Dispense study medication		X[k]		X	X	X	

Assessments and Activities[a]	Screening (–4 weeks to Day 0)	Base-line visit	3 week visit (Safety only)	6 week visit	12 week visit	18 week visit	Final Visit (24 weeks) or Early Termination
Retrieve unused study medication				X	X	X	X
Study medication compliance				X	X	X	X
Discharge from study							X
Prior and concomitant medications	←----------	----------	----------	----------	----------	----------	----------→
AEs[l]		←----------	----------	----------	----------	----------	----------→

a - Unless otherwise indicated, procedures pertain to, and are performed only on, the patient.
b - If the patient is unable to provide written informed consent, written consent must be obtained from the patient's representative and verbal assent must be obtained from the patient. Separate consent will be required for genotyping.
c - At Screening, caregivers will be administered the MMSE, then the CES-D, to confirm their eligibility.
d - The MMSE, CSDD, and SIB test instruments will be administered to patients after informed consent/assent has been obtained from caregivers and patients and after caregiver eligibility has been established, but before clinical laboratory tests are drawn, so as to avoid performing venipuncture on patients whose psychometric assessment scores disqualify them from entry into the study (Revised per Amendment 02).
e - Blood pressure recordings should be the average of three separate recordings performed during the same visit (see Section 11.2.3).
f - At Baseline, ECG is to be obtained before study drug is administered.
g - All clinical laboratory tests will include hematology, clinical chemistry and urinalysis. Additionally, at the Screening visit only, assessments of serum vitamin B_{12}, folate levels, thyroid profile and hepatitis B and C titers will be obtained.
h - During Screening, blood samples will be drawn from every patient at every study site for determination of plasma donepezil levels. At subsequent visits, additional samples for pharmacokinetic evaluations will be collected at selected study sites. (Revised as per Amendment 02)
i - Separate informed consent for genotype determinations will also be requested from the patient or (where applicable) legal representative. Refusal will have no bearing on participation in any other aspect of the study.
j - If neither a cranial MRI nor CT was conducted on the patient during the last 12 months, an MRI or CT will be performed before the Baseline visit to rule out other causes of dementia (Revised per Amendment 02).
k - Patients and their caregivers will be instructed that patients must discontinue use of previous donepezil prescription(s).
l - All AEs should be collected from the time of consent.

6.1.9 Outcome Measures

6.1.9.1 Primary Efficacy Measures

- Severe Impairment Battery (SIB)
- Clinician Interview-Based Impression of Change-Plus (CIBIC-Plus)

6.1.9.2 Secondary Efficacy Measures

- Mini-Mental Status Examination (MMSE)
- Alzheimer's Disease Cooperative Study Activities (ADCS-ADL) scale (this will be considered a co-primary measure for registration in Europe in lieu of the Severe Impairment Battery)

6.1.9.3 Exploratory Efficacy Measures

- Quality of Life-Alzheimer's Disease Scale
- EuroQoL-5 Dimensions Scale

- Screen for Caregiver Burden
- Treatment Expectation Scale
- Treatment Outcome Scale
- Goal Attainment Scale

6.1.9.4 Safety Measures

Adverse events, vital signs, physical examinations, basic neurological examinations, safety laboratory tests and electrocardiograms.

6.1.9.5 Pharmacokinetic Measures

Plasma concentrations of donepezil.

6.1.10 Description Of Primary Efficacy Measures

6.1.10.1 Severe Impairment Battery (SIB)

The Severe Impairment Battery is the primary cognitive outcome measure for this study. The Severe Impairment Battery has been used as a primary (cognitive) efficacy measure in key pre-approval randomized, double-blind, placebo-controlled trials of memantine in moderate to severe Alzheimer's Disease (baseline Mini-Mental Status Examination score ranging from 3 - 14) and donepezil (immediate-release tablets) in severe Alzheimer's Disease (baseline Mini-Mental Status Examination score ranging from 1 - 12).

A further description of this measure is as follows.

This instrument has been developed to assess cognitive function more comprehensively than traditional cognitive tests in patients with moderate to severe Alzheimer's Disease. It is divided into 9 subscales assessing attention, orientation, language, memory, praxis, visuospatial perception, construction, social skills and orientation to name. Non-verbal responses are permitted. A total of 40 questions are asked. Total scores range from 0 to 100 points with lower scores indicating greater cognitive impairment.

6.1.10.2 Clinician Interview-Based Impression Of Change – Plus (CIBIC-Plus)

The CIBIC-Plus is a global rating that is intended to measure the following domains of patient function: general, mental/cognitive state, behavior, and activities of daily living. The rating, which is semi-structured is based on a comprehensive interview with the patient and caregiver by an independent rater.

The rater is to have access to source data and psychometric scores at baseline (only) for purposes of rating the Clinician Interview-Based Impression of Severity-Plus (CIBIS-Plus). The CIBIS-Plus is to rate disease severity on a 7-point scale extending from 1 = normal to 7 = extremely ill.

The independent rater is then to refer to the CIBIS-Plus in rating the CIBIC-Plus at each post-baseline visit.

The CIBIC-Plus is to be scored as follows.

1: Markedly improved
2: Moderately improved
3: Mildly improved
4: No change
5: Mildly worse
6: Moderately worse
7: Markedly worse

6.1.11 Description Of Alzheimer's Disease Cooperative Study – Activities of Daily Living Scale (ADCS-ADL)

As already noted, the ADCS-ADL, although designated as a secondary efficacy measure for US regulatory purposes, was designated as a co-primary efficacy measure for registration of the proposed new product in Europe.

This is a rating scale used to assess basic and instrumental activities of daily living. In the full version of the scale, 45 items are rated by the investigator using information supplied by the caregiver. Each item has a score range varying from 0-3 to 0-7. Higher scores indicate better function.

In Study 326, a modified version of the ADCS-ADL is to be used consisting of a subset of 19 of the above 45 items. These 19 items, selected to fit the expected activities of daily living profile of patients with moderate-to-severe dementia, consist of the following:

Eating	Ability to watch TV	Ability to be left alone
Walking	Making conversation	Ability to turn a faucet on
Toileting	Clearing a table	Ability to turn a faucet off
Bathing	Locating belongings	Ability to turn a light on
Grooming	Obtaining a beverage	Ability to turn a light off
Dressing	Litter disposal	
Use of a telephone	Traveling outside the home	

For the modified ADCS-ADL, a sum score is calculated by adding the scores for the individual items, and used as a primary efficacy measure. The sum score can range from 0 to 54, with higher scores indicating better function.

The modified ADCS-ADL has been used in a number of studies in moderate to severe Alzheimer's Disease.

6.1.12 Safety Monitoring

Adverse events, vital signs, physical examinations, basic neurological examinations, safety laboratory tests and electrocardiograms, are to be assessed according to the above Study Schedule.

6.1.13 Analysis Plan

The analysis plan summarized below is that intended to secure the registration of the proposed new formulation of Aricept® in the United States. The final statistical analysis plan is dated March 31, 2009.

6.1.13.1 General

Unless otherwise specified, all statistical tests will be conducted at the 0.05 level of significance (two-sided), and the treatment effect will be analyzed using Type III sums of squares.

All efficacy analyses will be conducted on the intent-to-treat population (see below for the intent-to-treat sub-categories).

Definitions and conventions for handling efficacy and safety data are specified in the analysis plan.

6.1.13.2 Study Populations

2 study populations are to be analyzed and are further described below

6.1.13.2.1 Safety Population

This population will consist of all those who were randomized and took at least one dose of study medication.

6.1.13.2.2 Intent-To-Treat Population

This will consist of all randomized patients who took at least one dose of study medication and for whom:

> EITHER
>
> Severe Impairment Battery scores are available both at baseline and at least one post-baseline timepoint while on double-blind treatment,
>
> OR
>
> A CIBIS-Plus (Clinician Interview-Based Impression of Severity-Plus) score is available at baseline, and a CIBIC-Plus rating available for at least one timepoint while receiving double-blind treatment.

The intent-to-treat population is to be further classified as:

- Observed Cases: Those who complete a visit will be considered Observed Cases at that visit

- Last-Observation-Carried-Forward: If a patient is missing a Week 24 observation, then the last observed value will be carried forward and used as the endpoint observation for the change from baseline analysis of primary and secondary efficacy measures.

(Efficacy analyses are to be conducted on both populations, although the latter will be primary).

6.1.13.3 Disposition

The disposition of all study subjects is to be summarized in tables indicating the number and percentage for the following in each treatment group.

- Randomized
- In each analysis population
- Prematurely discontinued.

6.1.13.4 Demographic And Baseline Characteristics

These will be summarized by treatment group, using descriptive statistics for continuous variables, and the number and percentage (in each category) for categorical variables.

6.1.13.5 Treatment Compliance

Treatment compliance is to be summarized using descriptive statistics and additional methods described in the submission.

6.1.13.6 Extent Of Exposure

The extent of exposure to study drug is to be calculated as the number of days between the date of the first dose of study drug and the date of the last dose of study drug for each pill type, and overall.

The extent of exposure will be summarized using descriptive statistics.

6.1.13.7 Prior And Concomitant Medications

Prior and concomitant medications (each defined separately in the submission) will be summarized by treatment group, using numbers and percentages of subjects with each WHO Drug Term class.

6.1.13.8 Primary Efficacy Parameters

The primary efficacy analysis is to be conducted on the intent-to-treat last-observation-carried-forward dataset, with Week 24 as the endpoint.

The purpose of the primary efficacy analysis is to establish the efficacy of the 23 mg sustained-release formulation of donepezil with the 10 mg immediate-release

formulation. The primary efficacy analysis is therefore to compare these 2 treatment groups.

The primary efficacy parameters are the following:

- Change from baseline to Week 24 in Severe Impairment Battery score
- CIBIC-Plus score at Week 24

The analysis of the Severe Impairment Battery data will be performed using an analysis of covariance model with terms for baseline, country, and treatment.

The CIBIC-Plus is to be analyzed using a non-parametric analysis of covariance with a Cochran-Mantel-Haenszel test component. The analysis is to adjust for CIBIS-Plus score at baseline with a stratification adjustment for country.

The superiority of the 23 mg/day sustained-release group over the 10 mg/day donepezil immediate-release group must be demonstrated on the Severe Impairment Battery and CIBIC-Plus for the study to be considered positive. Superiority will be demonstrated at a significance level of 0.05 (2-sided)

For each primary efficacy parameter, the p-value from the between-treatment difference will be provided; summary statistics will also be presented. Where appropriate, change scores, between treatment differences in adjusted means, and 95% confidence intervals for the difference will also be summarized.

6.1.13.9 Secondary Efficacy Parameters

The change from baseline to endpoint in the Mini-Mental Status Examination and ADCS-ADL are to be analyzed using the same model as that used for the Severe Impairment Battery and using the intent-to-treat last-observation-carried-forward dataset.

These analyses are intended to support the primary efficacy analysis.

Additional analyses on all the efficacy parameters are to be performed on the Observed Cases population.

6.1.13.10 Exploratory Efficacy Parameters

Exploratory efficacy parameters include the change from baseline to, or absolute scores when appropriate, at each of the post-baseline timepoints in each of the exploratory efficacy measures listed above as well as the SIB, CIBIC-Plus and ADCS-ADL. Both the last-observation-carried-forward and observed cases approaches are to be used.

Each of the continuous exploratory efficacy parameters are to be analyzed in a manner similar to the primary efficacy analysis for the SIB, except for the Goal

Attainment Scale which is to be analyzed using an analysis of variance model with terms for treatment and country.

The categorical endpoint, Treatment Outcome Evaluation Scale, is to be analyzed using a Cochran-Mantel-Haenszel test stratified by country, with a uniformly distributed function of the rank score.

6.1.13.11 Subgroup Analyses

The efficacy of the 23 mg/day dose of the sustained-release formulation of donepezil will be compared with that of the 10 mg/day immediate-release formulation on each of the primary efficacy parameters separately for subgroup sets defined by the following:

- Baseline memantine use (yes or no)
- APOE ε4 status
- CYP2D6 metabolizer status.

For each set above, summary statistics will be presented by visit for each subgroup by treatment group, for both the last-observation-carried-forward and observed cases populations.

Other subgroup analyses may be conducted, if considered appropriate, such as analyses based on demographic or other baseline characteristics.

6.1.13.12 Pooling Of Study Centers

This will be a multi-center study to be conducted in a number of countries, who are likely to vary considerably in regard to the number of subjects enrolled.

The following will be the strategy used sequentially for pooling data from study centers.

- Data from each country will be pooled.
- Individual countries will then be sorted in descending order of the number of subjects randomized.
- The largest country without an intent-to-treat subject in at least one treatment will be identified. If that country is not the smallest on the list, in regard to patient enrollment, it will be pooled with other countries lower on the same list, and, if necessary, with countries above it on the list so that the pooled group of countries has at least one intent-to-treat subject per treatment group.
- The above process will continue until all pooled country groups have at least one intent-to-treat subject per treatment group.

6.1.13.13 Safety Parameters

Safety analyses are to be conducted on the safety population for the following outcome measures: adverse events, laboratory data, vital signs and weight, electrocardiograms, and physical and neurological examinations.

6.1.13.13.1 Adverse Events

A treatment-emergent adverse event, also referred to as a treatment-emergent sign or symptom, is defined as an adverse event that either begins on or after the first day of study drug dosing and up to 30 days following dosing, or begins before the first day of study drug dosing, and increases in severity during the treatment phase.

The number and percentage of subjects in each treatment group with at least one adverse event, at least one treatment-emergent adverse event, at least one serious adverse event, and at least one adverse event leading to treatment discontinuation will also be summarized.

Other adverse event summary tables specified in the analysis plan will also be provided.

6.1.13.13.2 Laboratory Data

The change from baseline to each post-baseline visit in individual quantitative laboratory parameters will be summarized by treatment group, using descriptive statistics. Shift tables will be used to display the number and percentage of subjects with values within, above, or below the normal range comparing baseline assessment with each post-baseline assessment.

Qualitative laboratory parameters will be summarized using frequencies at each visit.

The incidence of treatment-emergent abnormal laboratory values will be summarized for those parameters that have a notable range defined.

6.1.13.13.3 Vital Signs And Weight

The change from baseline to each post-baseline visit in individual vital sign parameters and weight will be summarized by treatment group, using descriptive statistics.

Orthostatic changes in both systolic and diastolic blood pressure will be summarized both as actual values and change from baseline by visit for each treatment group.

6.1.13.13.4 Electrocardiograms

Electrocardiogram findings will be summarized. The numbers and percentages of subjects with electrocardiograms within normal limits will be tabulated using shift tables. Individual electrocardiogram results will also be listed.

6.1.13.13.5 Physical And Neurological Examinations

Physical and neurological examination findings will be summarized.

6.1.13.14 Pharmacokinetic Parameters

Donepezil concentrations at each visit will be presented in tabular and graphic format. Possible relationships between donepezil levels and the efficacy parameters for each of the pharmacodynamic measures will be explored using an E_{max} model.

In addition, exploratory pharmacokinetic-pharmacodynamic analysis using the most appropriate models will be applied to these data to assess potential. relationships between donepezil concentrations and clinical efficacy and safety findings.

6.1.13.15 Sample Size Rationale

The sample size estimate is based a Type I error of 0.05 (two-sided t test), using the pooled standard deviations from the intent-to-treat last-observation-carried-forward Week 24 analysis, using the primary efficacy measures, the SIB and CIBIC-Plus.

Additional aspects of the sample size estimate are summarized in the next table, taken from the submission. On that basis, an estimated sample size of 981 completing patients is needed (654 patients in the 23 mg/day sustained-release group and 327 patients in the 10 mg/day immediate-release group). Assuming an 80% rate of completion, about 1200 patients (800 patients in the 23 mg/day sustained-release group and 400 patients in the 10 mg/day immediate-release group) will need to be enrolled in the study.

Variable	Improvement	SD	Power
CIBIC+	0.2	1.053	80%
SIB	3.0	9.544	>99%
ADCS-ADL	1.37	7.18	80%

6.1.13.16 Interim Analysis (For Safety Only)

A single interim analysis is to be conducted after the first 400 randomized patients with efficacy and safety data have completed the study (Week 24 or early termination).

The object of the interim analysis is to evaluate safety, including any unexpected toxicity. If the results of the analysis indicate serious safety concerns, the sponsor is to consult with regulatory health authorities regarding stopping the trial.

Safety assessments are to include summaries of the incidence rate for adverse events; changes in vital signs, weight, and laboratory parameters; and the incidence rates of abnormal overall electrocardiogram interpretations, concomitant medication use, and premature termination.

[Note that an interim analysis of efficacy was originally planned].

6.2 Results

This study was conducted at 220 sites in 23 countries, between June 6, 2008 and March 27, 2009.

6.2.1 Patient Disposition

A total of 2186 patients were screened, of who 1467 patients were randomized.

The disposition of randomized patients by treatment group is summarized in the following table, which I have created from data included in the submission.

Category	Treatment Group		Total N (%)
	Donepezil SR 23 mg/day N (%)	Donepezil IR 10 mg/day N (%)	
Randomized	981 (100.0)	486 (100.0)	1467 (100.0)
Completed	685 (69.8)	399 (82.1)	1084 (73.9)
Discontinued	296 (30.2)	87 (17.9)	383 (26.1)

The reasons for treatment discontinuation in each group is further summarized in the next table, which I have again created from data included in the submission.

Category	Treatment Group	
	Donepezil SR 23 mg/day N (%)	Donepezil IR 10 mg/day N (%)
Discontinued (total)	296 (100.0)	87 (100.0)
Adverse event	182 (61.5)	39 (44.8)
Non-compliance	9 (3.0)	4 (4.6)
Protocol violation	15 (5.1)	5 (5.7)
Investigator or sponsor request	4 (1.4)	5 (5.7)
Withdrawal of consent	61 (20.6)	22 (25.3)
Lack of efficacy	24 (8.1)	12 (13.8)
Other	7 (2.4)	5 (5.7)

As the above table indicates, adverse events were the most common reason for discontinuation in both groups; the incidence of discontinuations due to adverse events was higher in the donepezil group than in the placebo group.

The distribution of patients in each treatment group by analysis population is in the next table, which is based on the sponsor's data.

Analysis Population	Treatment Group	
	Donepezil SR 23 mg/day N (%)	Donepezil IR 10 mg/day N (%)
Randomized	981 (100.0)	486 (100.0)
Safety	963 (98.2)	471 (96.9)
Intent-to-Treat	909 (92.7)	462 (95.1)

The distribution of patients by country and site is in the following sponsor table which is self-explanatory.

	Number (%) of Patients[b]					
	Donepezil SR 23 mg			Donepezil IR 10 mg		
Country[a]	Randomized	Safety	ITT	Randomized	Safety	ITT
All countries	981	963	909 (94.4)	486	471	462 (98.1)
United States	313	308	292 (94.8)	152	146	141 (96.6)
India	75	72	62 (86.1)	38	35	34 (97.1)
Korea	59	59	52 (88.1)	33	33	32 (97.0)
Poland	58	58	54 (93.1)	28	28	28 (100.0)
Chile	54	52	51 (98.1)	23	23	23 (100.0)
South Africa	48	48	47 (97.9)	29	29	29 (100.0)
Germany	51	51	46 (90.2)	25	25	25 (100.0)
Argentina	44	44	42 (95.5)	23	22	22 (100.0)
Spain	39	37	37 (100.0)	23	23	23 (100.0)
Israel	31	30	28 (93.3)	13	13	13 (100.0)
Australia	24	21	20 (95.2)	13	13	13 (100.0)
Lithuania	26	26	25 (96.2)	10	10	10 (100.0)
Austria	26	26	26 (100.0)	9	8	8 (100.0)
Croatia	23	23	23 (100.0)	12	12	12 (100.0)
United Kingdom	22	22	22 (100.0)	10	10	10 (100.0)
Italy	23	22	21 (95.5)	8	8	8 (100.0)
Taiwan	19	19	18 (94.7)	12	11	11 (100.0)
France	17	17	17 (100.0)	9	7	5 (71.4)
Romania	13	12	11 (91.7)	6	5	5 (100.0)
Hong Kong	9	9	9 (100.0)	6	6	6 (100.0)
Sweden	5	5	4 (80.0)	2	2	2 (100.0)
Denmark	1	1	1 (100.0)	1	1	1 (100.0)
Singapore	1	1	1 (100.0)	1	1	1 (100.0)

a: Countries are listed in decreasing order of total number of randomized patients.
b: Percentages are based on Safety Population in each country at each treatment group.
Abbreviations: IR – immediate release; SR – sustained release; ITT – Intent-to-Treat.

As the above table indicates, the country with the largest proportion of randomized patients was the United States with 465 randomized patients (31.7% of all randomized patients); the country with the next largest proportion of randomized patients was India with 113 randomized patients (7.7% of all randomized patients).

6.2.2 Protocol Deviations

15 patients in the donepezil SR 23 mg QD group and 5 patients in the donepezil IR 10 mg QD group were withdrawn from the study on account of protocol violations; they represented 1.5% and 1.0% of those randomized to the 2 treatment groups, respectively. Most protocol deviations appear to have been minor and unlikely to have had a significant confounding effect on the study results.

The use of prohibited concomitant medications appears to have been a more common protocol violation. Individual prohibited concomitant medications used in each treatment group in the safety population are in the next sponsor table.

		Number (%) of Patients		
Anatomical Therapeutic Class	WHO Drug Term	Donepezil SR 23 mg (n=963)	Donepezil IR 10 mg (n=471)	Total (N=1434)
Number of patients with any prohibited concomitant medication		41	22	63
Analgesics	Pethidine	1 (0.1)	1 (0.2)	2 (0.1)
	Tramadol	1 (0.1)	3 (0.6)	4 (0.3)
Anti-Parkinson Drugs	Benzatropine	1 (0.1)	0 (0.0)	1 (0.1)
	Levodopa with Benserazide	1 (0.1)	0 (0.0)	1 (0.1)
Cough and Cold Preparations	Dextromethorphan	1 (0.1)	1 (0.2)	2 (0.1)
Drugs for Obstructive Airway Diseases	Salmeterol	0 (0.0)	1 (0.2)	1 (0.1)
	Theophylline	1 (0.1)	1 (0.2)	2 (0.1)
Nasal Preparations	Pseudoephedrine	1 (0.1)	0 (0.0)	1 (0.1)
Ophthalmologicals	Gentamicin	2 (0.2)	1 (0.2)	3 (0.2)
Psychoanaleptics	Doxepin	0 (0.0)	1 (0.2)	1 (0.1)
	Mirtazepine	5 (0.5)	2 (0.4)	7 (0.5)
	Protriptyline	1 (0.1)	0 (0.0)	1 (0.1)
	Trazodone	1 (0.1)	0 (0.0)	1 (0.1)
Psycholeptics	Alprazolam	9 (0.9)	1 (0.2)	10 (0.7)
	Buspirone	0 (0.0)	1 (0.2)	1 (0.1)
	Clonazepam	7 (0.7)	2 (0.4)	9 (0.6)
	Diazepam	2 (0.2)	1 (0.2)	3 (0.2)
	Lorazepam	10 (1.0)	8 (1.7)	18 (1.3)
	Meprobamate	2 (0.2)	0 (0.0)	2 (0.1)

Abbreviations: IR – immediate release; SR – sustained release; WHO – World Health Organization.

As the table above indicates, the use of individual prohibited concomitant medications was infrequent, relative to the number of patients enrolled in each treatment group.

6.2.3 Efficacy Analyses

6.2.3.1 Analysis Populations

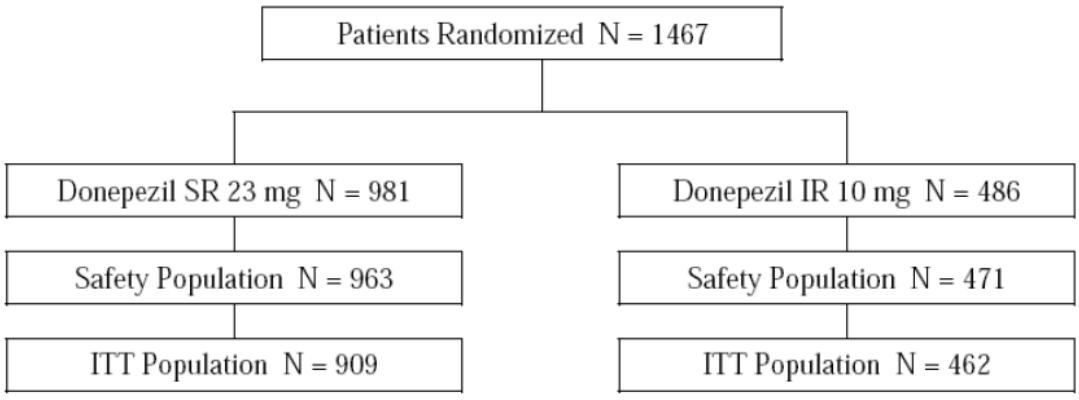
The number and proportion of patients in each analysis population is summarized in the following table, which I have extracted from a table contained in the submission.

	Number (%) of Patients		
	Donepezil SR 23 mg	**Donepezil IR 10 mg**	**Total**
Randomized patients	981	486	1467
Patients who received at least one dose of study medication[a]	972 (99.1)	479 (98.6)	1451 (98.9)
Patients who received study medication but were excluded from Safety Population[b]	9 (0.9)	8 (1.7)	17 (1.2)
Safety Population[c]	963 (100.0)	471 (100.0)	1434 (100.0)
ITT Population[c]	909 (94.4)	462 (98.1)	1371 (95.6)

a: Number of patients randomized was used as the denominator for calculating percentages.
b: Number of patients who received at least one dose of study medication was used as the denominator for calculating percentages.
c: Number of patients in the Safety Population was used as the denominator for calculating percentages.
Abbreviations: IR – immediate release; SR – sustained release; ITT – Intent-to-Treat.

As the table above indicates, the intent-to-treat population consisted of 909 patients in the donepezil 23 mg/day group and 462 patients in the donepezil 10 mg/day group.

These analysis populations are also depicted in the flowchart below, again extracted from a figure in the submission.



Abbreviations: IR – immediate release; SR – sustained release; ITT – Intent-to-Treat.

The number and percentage of patients in the above analysis groups who belonged to various sub-populations (that were a subject of additional analyses) are in the following table, which I have again extracted from a table included in the report of this study.

	Number (%) of Patients					
	Randomized Population		Safety Population		ITT Population	
	Donepezil SR 23 mg n=981	Donepezil IR 10 mg n=486	Donepezil SR 23 mg n=963	Donepezil IR 10 mg n=471	Donepezil SR 23 mg n=909	Donepezil IR 10 mg n=462
Concomitant memantine use						
Memantine	355 (36.2)	170 (35.0)	352 (36.6)	168 (35.7)	338 (37.2)	163 (35.3)
None	626 (63.8)	316 (65.0)	611 (63.4)	303 (64.3)	571 (62.8)	299 (64.7)
CYP2D6 phenotype[a]						
Analyzed (n)	549[b]	270	543[b]	266	513[b]	261
Extensive metabolizer	508 (92.5)	252 (93.3)	502 (92.4)	248 (93.2)	473 (92.2)	244 (93.5)
Poor metabolizer	30 (5.5)	12 (4.4)	30 (5.5)	12 (4.5)	29 (5.7)	11(4.2)
Ultra-rapid metabolizer	11 (2.0)	6 (2.2)	11 (2.0)	6 (2.3)	11 (2.1)	6 (2.3)
$APOE_4$ genotype[a]						
Analyzed (n)	550	270	544	266	514	261
No E_4[c]	233 (42.4)	109 (40.4)	230 (42.3)	107 (40.2)	217 (42.2)	104 (39.8)
Increased risk[c]	243 (44.2)	129 (47.8)	240 (44.1)	128 (48.1)	226 (44.0)	126 (48.3)
High risk[c]	74 (13.5)	32 (11.9)	74 (13.6)	31 (11.7)	71 (13.8)	31 (11.9)
MMSE score at Baseline						
3-14	505 (51.5)	265 (54.5)	499 (51.8)	260 (55.2)	478 (52.6)	256 (55.4)
5-14	464 (47.3)	251 (51.6)	458 (47.6)	247 (52.4)	438 (48.2)	244 (52.8)
0-16	684[d] (69.7)	345[d] (71.0)	676 (70.2)	338 (71.8)	643 (70.7)	331 (71.6)
17-20	287[d] (29.3)	134[d] (27.6)	286[e] (29.7)	133 (28.2)	265[e] (29.2)	131 (28.4)
US Population	313 (31.9)	152 (31.3)	308 (32.0)	146 (31.0)	292 (32.1)	141 (30.5)

a: Percentage is calculated based on the number of patients that had samples analyzed.
b: One patient in the donepezil SR 23 mg group did not have a phenotype that could be measured from the sample.
c: No E_4 = E2/E2, E2/E3, E3/E3; Increased risk = E2/E4, E3/E4; High risk = E4/E4.
d: Because Baseline was defined as the last assessment before the first dose date, for patients without any dose, these patients in the Randomized Population do not have any Baseline per SAP algorithm. Therefore, this category of patients cannot be accurately placed into the MMSE groups of 0-16 or 17-20. The values presented here represent those patients who had double-blind medication at Baseline.
e: One patient in the donepezil SR 23 mg group had a baseline MMSE score of 22 and was not included in the analyses.
Abbreviations: IR – immediate release; SR – sustained release; $APOE_4$ – apolipoprotein E_4; ITT – Intent-to-Treat; MMSE – Mini-Mental State Examination; US – United States.

Noteworthy among the data in the above table are the following:

- Only a minority of patients enrolled in the study were concomitantly using memantine
- The majority of patients enrolled in the study had a Mini-Mental Status Examination entry score in the 16 to 20 range.

6.2.3.2 Key Demographic And Other Baseline Characteristics

A summary of key demographic and other baseline characteristics in the 2 treatment groups are in the following table, to create which I have used summary data contained in the study report.

Category	Treatment Group	
	Donepezil SR 23 mg/day N (%)	Donepezil IR 10 mg/day N (%)
Females (%)	63.0	62.4
Body Mass Index	25.2 (4.39)	25.04 (4.30)
Age (mean ± standard deviation) (years)	73.9 (8.53)	73.8 (8.56)
Mini-Mental Status Examination score (mean ± standard deviation)*	13.1 (4.99)	13.0 (4.75)
Severe Impairment Battery score (mean ± standard deviation)	74.3 (17.55)	75.4 (16.47)
Clinician Interview-Based Impression of Severity-Plus (mean ± standard deviation)	4.41 (0.85)	4.39 (0.89)
Duration of treatment with donepezil IR prior to study entry ((mean ± standard deviation) (weeks)	112.17 (108.18)	104.76 (98.98)

*The range of Mini-Mental Status Examination scores at baseline extended from 0 to 22 in the donepezil 23 mg QD group and from 0 to 20 in the donepezil 10 mg QD group.

Both treatment groups appear to have been largely comparable on the above parameters.

6.2.3.3 Treatment Compliance

The extent of treatment compliance is summarized in the next table, which I have extracted from the submission.

	Donepezil SR 23 mg			Donepezil IR 10 mg		
	Donepezil SR 23 mg (n=963)	Placebo[a]	Overall	Donepezil IR 10 mg (n=471)	Placebo[b]	Overall
Compliance rate (%)						
N[c]	952	952	952	470	470	470
Mean (SD)	93.2 (81.03)	93.3 (80.98)	93.2 (80.98)	97.4 (31.09)	97.1 (31.48)	97.3 (31.17)
Median	99.0	99.0	99.0	99.0	99.0	99.0
Min, Max	5, 2500	5, 2500	5, 2500	9, 714	2, 714	9, 714

a: Placebo was identical in appearance to donepezil IR 10 mg tablets and was administered with donepezil SR 23 mg.
b: Placebo was identical in appearance to donepezil SR 23 mg tablets and was administered with donepezil IR 10 mg.
c: The number of tablets removed from the bottle could not be determined for several patients. As the consequence, the compliance could not be calculated for these patients.
Abbreviations: IR – immediate release; SR – sustained release; max – maximum; min – minimum; SD – standard deviation.

As the table above indicates, the extent of treatment compliance was slightly better in the donepezil 10 mg/day group than in the 23 mg/day group.

6.2.3.4 Primary Efficacy Analysis

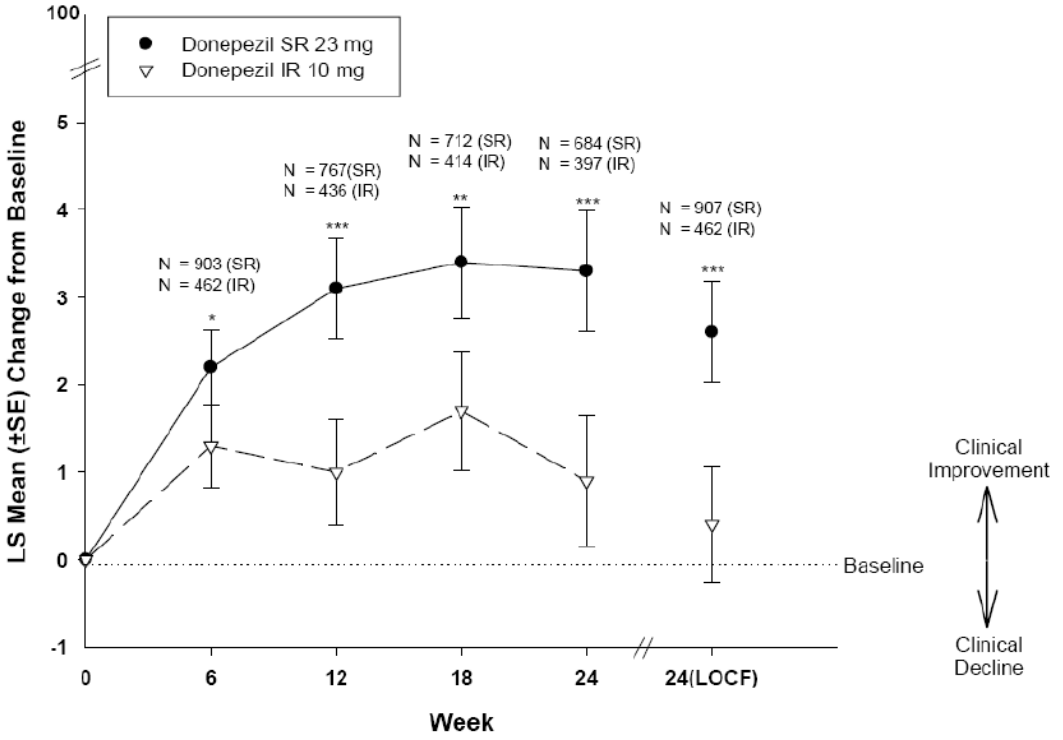
6.2.3.4.1 Primary Efficacy Analysis Of SIB

The results of the primary efficacy analysis of the SIB, performed on the intent-to-treat population, and using the last-observation-carried-forward method of imputation, and as presented by the sponsor, is summarized in the following table.

Treatment Group	N	SIB Change from baseline to Week 24 LS mean (SE)	Difference in LS mean change from baseline at Week 24	p-value (Donepezil SR 23 mg versus donepezil IR 10 mg)
Donepezil SR 23 mg	907	2.6 (0.58)	2.2	0.0001
Donepezil IR 10 mg	462	0.4 (0.66)		

LS: Least squares
SE: Standard error

The same results are graphically depicted in the following figure, which I have copied from the submission.



Note: * = p<0.05, ** = p<0.01, *** = p< 0.001.
Abbreviations: IR – immediate release; SR – sustained release; ITT – Intent-to-Treat; LOCF – last observation carried forward; LS – least squares; OC – observed cases; SE – standard error.

The above results indicate that donepezil 23 mg/day showed a small, but statistically significant superiority over donepezil 10 mg/day on the primary efficacy analysis of the SIB.

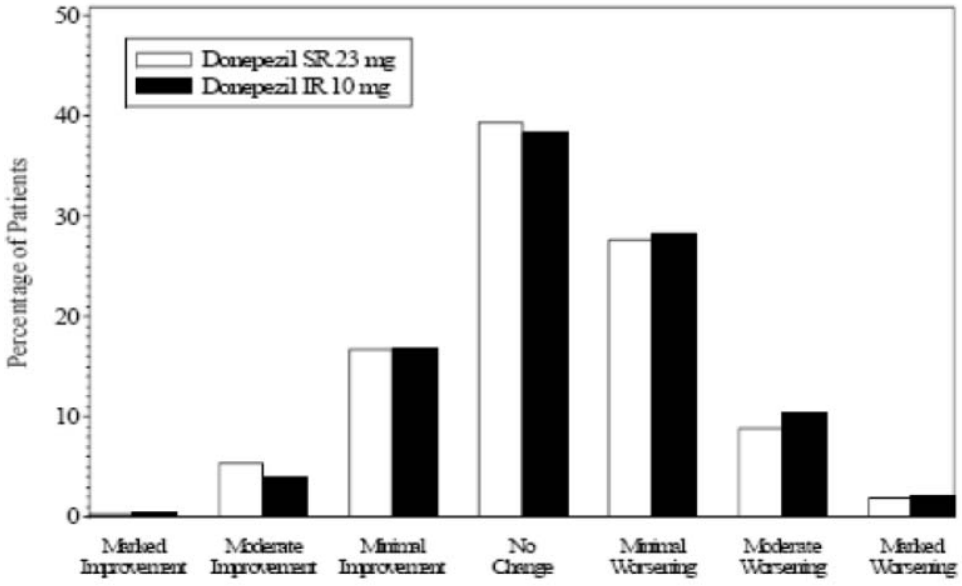
6.2.3.4.2 Primary Efficacy Analysis Of CIBIC-Plus

The results of the primary efficacy analysis of the CIBIC-Plus (using mean ratings), performed on the intent-to-treat population, using the last-observation-carried-forward method of imputation, and as presented by the sponsor, is summarized in the following table.

Treatment Group	N	CIBIC-Plus Mean (SE) at Week 24	Difference in mean score at Week 24	p-value (Donepezil SR 23 mg versus donepezil IR 10 mg)
Donepezil SR 23 mg	908	4.23 (1.07)	0.06	0.1789
Donepezil IR 10 mg	459	4.29 (1.07)		

SE: Standard error

The results of the categorical analysis of the CIBIC-Plus, again using the intent-to-treat population, and last-observation-carried-forward method of imputation is summarized in the next sponsor figure.



Abbreviations: IR – immediate release; SR – sustained release; ITT – Intent-to-Treat; LOCF – last observation carried forward.

As the above analyses indicate, there was only a miniscule difference in the effect of the two treatment groups on this parameter, albeit a difference that might be considered to trend in favor of the 23 mg QD dose. More importantly, the difference was clearly not statistically significant.

6.2.3.5 Additional Analyses Of Primary Efficacy Parameters

6.2.3.5.1 Additional Analyses Of SIB Alone

Other (i.e., non-primary) analyses of the change from baseline to Week 24 in SIB score (some of these analyses were post-hoc) are compared with the primary efficacy analysis in the following sponsor table, which I have copied from the submission. The table is self-explanatory, with the small beneficial effect of donepezil SR being maintained in these analyses.

Analysis	Donepezil SR 23 mg	Donepezil IR 10 mg
Primary: ITT population, LOCF		
SIB change from Baseline to Week 24	n = 907	n = 462
LS mean (SE)	2.6 (0.58)	0.4 (0.66)
p value compared to donepezil IR[a]	0.0001	
Exploratory: ITT population, OC		
SIB change from Baseline to Week 24	n = 684	n = 397
LS mean (SE)	3.3 (0.69)	0.9 (0.75)
p value compared to donepezil IR[a]	0.0001	
Concomitant Memantine Use, LOCF		
SIB change from Baseline to Week 24	n=338	n=163
LS mean (SE)	-0.2 (1.27)	-3.0 (1.36)
p value compared to donepezil IR[a]	0.0033	
No Concomitant Memantine Use, LOCF		
SIB change from Baseline to Week 24	n=569	n=299
LS mean (SE)	3.1 (0.61)	1.3 (0.72)
p value compared to donepezil IR[a]	0.0069	
Post Hoc : US Population, LOCF		
SIB change from Baseline to Week 24	n = 292	n = 141
LS mean (SE)	2.7 (0.59)	-1.2 (0.85)
p value compared to donepezil IR[a]	0.0002	
Post Hoc: MMSE Baseline Score of 3-14, LOCF		
SIB change from Baseline to Week 24	n=476	n=256
LS mean (SE)	1.1 (0.97)	-2.0 (1.08)
p value compared to donepezil IR[a]	0.0005	
Post Hoc: MMSE Baseline Score of 5-14, LOCF		
SIB change from Baseline to Week 24	n=436	n=244
LS mean (SE)	1.2 (0.96)	-1.4 (1.07)
p value compared to donepezil IR[a]	0.0034	
Post Hoc: MMSE Baseline Score of 0-16, LOCF		
SIB change from Baseline to Week 24	n=641	n=331
LS mean (SE)	1.6 (0.78)	-1.5 (0.88)
p value compared to donepezil IR[a]	<0.0001	

[a] Analysis method was ANCOVA model with terms for Baseline, country, and treatment.
Abbreviations: IR – immediate release; SR – sustained release; ANCOVA – analysis of covariance; ITT – intent-to-treat population; LOCF – last observation carried forward; LS – least squares; MMSE – Mini-Mental State Examination; SIB – Severe Impairment Battery.

6.2.3.5.2 Additional Analyses Of CIBIC-Plus Alone

Other (i.e., non-primary) analyses of the CIBIC-Plus score at Week 24 (some of these analyses are post-hoc) are compared with the primary efficacy analysis in the following sponsor table, which I have copied from the submission. The table

is self-explanatory and the additional analyses are identical to those of the SIB depicted earlier

Analysis	Donepezil SR 23 mg	Donepezil IR 10 mg
Primary: ITT population, LOCF		
CIBIC+ change in assessment at Week 24 overall change	n = 908	n = 459
Mean (SD)	4.23 (1.07)	4.29 (1.07)
p value compared to donepezil IR[a]	0.1789	
Exploratory: OC Population		
CIBIC+ change in assessment at Week 24 overall change	n = 682	n = 395
Mean (SD)	4.18 (1.11)	4.28 (1.09)
p value compared to donepezil IR[a]	0.0592	
Concomitant Memantine Use, ITT-LOCF		
CIBIC+ change in assessment at Week 24 overall change	n=338	n=161
Mean (SD)	4.40 (1.02)	4.52 (0.94)
p value compared to donepezil IR[a]	0.1372	
No Concomitant Memantine Use, ITT-LOCF		
CIBIC+ change in assessment at Week 24 overall change	n=570	n=298
Mean (SD)	4.12 (1.09)	4.16 (1.12)
p value compared to donepezil IR[a]	0.3795	
US Population, ITT-LOCF		
CIBIC+ change in assessment at Week 24 overall change	n = 292	n = 141
Mean (SD)	4.38 (0.97)	4.57 (0.89)
p value compared to donepezil IR[a]	0.0330	
MMSE Baseline Score of 3-14, ITT-LOCF		
CIBIC+ change in assessment at Week 24 overall change	n=478	n=254
Mean (SD)	4.37 (1.10)	4.47 (1.14)
p value compared to donepezil IR[a]	0.0508	
MMSE Baseline Score of 5-14, ITT-LOCF		
CIBIC+ change in assessment at Week 24 overall change	n=438	n=242
Mean (SD)	4.34 (1.11)	4.45 (1.16)
p value compared to donepezil IR[a]	0.0469	
MMSE Baseline Score of 0-16, ITT-LOCF		
CIBIC+ change in assessment at Week 24 overall change	n = 642	n = 329
Mean (SD)	4.31 (1.09)	4.42 (1.10)
p value compared to donepezil IR[a]	0.0279	

[a] Analysis method was non-parametric ANCOVA combined with a Cochran-Mantel-Haenszel test, adjusted for CIBIS+ at Baseline with a stratification adjustment for countries.
Abbreviations: IR – immediate release; SR – sustained release; ANCOVA – analysis of covariance; CIBIC+ – Clinician's Interview-Based Impression of Change (Plus Version); ITT – intent-to-treat population; LOCF – last observation carried forward; MMSE – Mini-Mental State Examination.

Among the effects depicted in the above table to which the sponsor has draw attention are nominally statistically significant or borderline statistically significant effects on this measure at Week 24, favoring the 23 mg QD dose over the 10 mg QD dose, in the following subsets:

- US population
- Mini-Mental Status Examination score of 3-14 at entry

- Mini-Mental Status Examination score of 5-14 at entry
- Mini-Mental Status Examination score of 0-16 at entry.

The sponsor also points out that there was a greater effect of the 23 mg QD dose over the 10 mg QD dose on the CIBIC-Plus in those concomitantly taking memantine than in those not concomitantly taking memantine. Those taking memantine had more severe disease, based on the CIBIS-Plus at entry, than those not taking memantine.

6.2.3.5.3 Responder Analyses

For purposes of these post-hoc analyses, a responder was defined as a patient with a CIBIC-Plus score ≤ 4 and a change in SIB score ≥ 0% from baseline to Week 24.

For the entire intent-to-treat dataset, using the last-observation-carried-forward method of imputation, the number and proportion of responders in each treatment group and the odds ratio and p-value derived from the comparison of the 2 treatment groups using a logistic model with treatment, country, and baseline Mini-Mental Status Examination scores as terms is in the following table which I have created from data provided by the sponsor.

Category	Treatment Group		Treatment Comparison	
	Donepezil 23 mg QD N (%)	Donepezil 10 mg QD N (%)	Odds Ratio	p-value
Analysis dataset	906 (100)	459 (100)	1.1678	0.2021
Responders	430 (47.5)	201 (43.8)		
Non-responders	476 (52.5)	258 (56.2)		

The same type of analysis performed for the subset with a Mini-Mental Status Examination score of 0-16 at entry is shown in the next table, which is again based on data provided by the sponsor. As the table indicates, the results of this analysis were nominally statistically significant.

Category	Treatment Group		Treatment Comparison	
	Donepezil 23 mg QD N (%)	Donepezil 10 mg QD N (%)	Odds Ratio	p-value
Analysis dataset	640 (100.0)	329 (100.0)	1.5752	0.0024
Responders	275 (43.0)	114 (34.7)		
Non-responders	365 (57.0)	215 (65.3)		

6.2.3.5.4 Summary Of Analysis Of SIB AND CIBIC-Plus By Entry Mini-Mental Status Examination Score Subset

The following sponsor table is intended to demonstrate that the superiority of the 23 mg QD dose of donepezil over the 10 mg QD dose was greatest on both the SIB and CIBIC-Plus for the subset with an entry Mini-Mental Status Examination score between 0 and 16. For each subset, the methods of analysis used are the same as those used for the primary efficacy analysis.

	SIB				CIBIC+			
MMSE Range	Donepezil SR 23 mg	Donepezil IR 10 mg	LS Mean Treatment Difference	p-value	Donepezil SR 23 mg	Donepezil IR 10 mg	Treatment Difference	p-value
0-16	1.14	-1.80	3.14	<0.0001	4.31	4.42	0.11	0.0279
0-17	1.35	-1.18	2.63	<0.0001	4.29	4.37	0.08	0.0706
0-18	1.69	-0.78	2.51	<0.0001	4.25	4.33	0.07	0.1008
0-19	2.02	-0.31	2.36	<0.0001	4.23	4.31	0.08	0.1033
0-20	2.23	0.09	2.15	0.0001	4.23	4.29	0.06	0.1847

Abbreviations: IR – immediate release; SR – sustained release; CIBIC+ – Clinician's Interview-Based Impression of Change Plus Caregiver Input; MMSE – Mini-Mental State Examination; SIB – Severe Impairment Battery.

6.2.3.5.5 Additional Sub-Group Analyses

Additional subgroup analyses of the primary efficacy parameters are summarized below.

6.2.3.5.5.1 Analyses Based On CYP2D6 Phenotype

Analyses of the primary efficacy parameters based on CYP2D6 phenotype (extensive metabolizer [wild type]; poor metabolizer; and ultra-rapid metabolizer) are summarized in the following sponsor table.

	Extensive Metabolizer			Poor Metabolizer			Ultra-rapid Metabolizer		
Assessment Time Point (Mean ± SD)	Donepezil SR 23 mg (n=473)	Donepezil IR 10 mg (n=244)	p-value	Donepezil SR 23 mg (n=29)	Donepezil IR 10 mg (n=11)	p-value	Donepezil SR 23 mg (n=11)	Donepezil IR 10 mg (n=6)	p-value
SIB (n)	471	244		29	11		11	6	
Baseline (LS Mean ± SE)	76.4 (1.60)	78.3 (1.73)	0.1507	80.4 (7.32)	73.9 (8.77)	0.5441	76.1 (9.89)	85.1 (10.27)	0.5446
Change from Baseline to Week 24 (ITT) (LS Mean ± SE)	3.2 (0.90)	0.5 (0.98)	0.0004	0.6 (2.28)	3.5 (2.68)	0.3733	3.3 (4.37)	7.3 (4.75)	0.5547
CIBIC+ overall change (n)	473	242		29	11		11	6	
Week 24 (ITT)	4.34 (0.99)	4.43 (1.03)	0.0794	4.69 (0.89)	4.18 (0.98)	0.0500	4.00 (1.10)	4.67 (0.82)	0.4920

Abbreviations: IR – immediate release; SR – sustained release; CIBIC+ – Clinician's Interview-Based Impression of Change Plus Caregiver Input; CYP2D6 – subtype of cytochrome P450 enzyme; ITT – Intent-to-Treat; LS – least squares; OC – observed cases; SD – standard deviation; SIB – Severe Impairment Battery.

As the sponsor points out, the small size of the poor metabolizer and ultra-rapid metabolizer, and the difference in baseline scores for the SIB between the treatment groups within each CYP2D6 metabolizer-designated subgroups, made interpretation of these analyses difficult.

6.2.3.5.5.2 Analyses Based On APOE ε4 Genotype

Analyses of the primary efficacy parameters based on APOE ε4 genotype are summarized in the next sponsor table, which I have also copied from the submission.

Assessment Time Point (Mean ± SD)	Average Risk (E2/E2, E2/E3, E3/E3) Donepezil SR 23 mg (n=217)	Donepezil IR 10 mg (n=104)	p-value	Increased Risk (E2/E4, E3/E4) Donepezil SR 23 mg (n=226)	Donepezil IR 10 mg (n=126)	p-value	High Risk (E4/E4) Donepezil SR 23 mg (n=71)	Donepezil IR 10 mg (n=31)	p-value
SIB, n	216	104		225	126		71	31	
Baseline (LS Mean ± SE)	77.0 (2.13)	76.7 (2.38)	0.9235	75.2 (1.97)	80.7 (2.27)	0.0043	79.3 (2.73)	77.9 (3.57)	0.7056
Change from Baseline to Week 24 (ITT) (LS Mean ± SE)	3.4 (1.02)	1.2 (1.14)	0.0280	2.4 (1.05)	0.9 (1.22)	0.1444	4.1 (2.01)	-4.6 (2.61)	0.0018
CIBIC+, n	217	103		226	125		71	31	
Week 24 (ITT)	4.26 (0.99)	4.28 (1.06)	0.3776	4.42 (0.93)	4.51 (0.97)	0.2049	4.39 (1.15)	4.55 (1.03)	0.8249

As the table indicates, the differences between treatment groups on both parameters were most prominent in the subgroup with the E4/E4 genotype.

6.2.3.5.5.3 Analyses Based On Age

Analyses were carried out comparing the effects of the two treatment groups on the primary efficacy parameters in 4 age-defined subgroups.

The results are as summarized in the following sponsor table.

Efficacy Assessment (Mean ± SD) Time point	45-64 Years Donepezil SR 23 mg (n=152)	Donepezil IR 10 mg (n=83)	65-74 Years Donepezil SR 23 mg (n=309)	Donepezil IR 10 mg (n=131)	75-84 Years Donepezil SR 23 mg (n=425)	Donepezil IR 10 mg (n=218)	85-90 Years Donepezil SR 23 mg (n=77)	Donepezil IR 10 mg (n=39)
SIB (n)	142	82	290	127	404	215	71	38
Baseline								
Mean (SD)	69.4 (19.09)	71.3 (19.20)	72.6 (18.56)	73.9 (17.51)	76.5 (16.08)	77.2 (14.72)	76.4 (16.22)	81.8 (9.60)
LS Mean (SE)	68.5 (2.16)	70.6 (2.67)	73.7 (1.56)	75.0 (2.00)	77.4 (1.19)	78.0 (1.37)	73.7 (2.21)	78.7 (2.75)
p-value	0.4618		0.4998		0.6440		0.1061	
Change from Baseline to Week 24 (ITT)								
Mean (SD)	1.8 (9.03)	-2.1 (10.19)	2.1 (10.78)	-0.6 (13.26)	2.6 (8.68)	1.1 (9.44)	1.7 (7.75)	1.6 (6.72)
Treatment Comparison								
LS Mean (SE)	1.6 (1.04)	-2.2 (1.29)	2.0 (0.98)	-0.3 (1.27)	2.8 (0.69)	1.2 (0.80)	1.6 (1.18)	1.0 (1.44)
p-value	0.0069		0.0583		0.0338		0.6882	
Change from Baseline to Week 24 (ITT)								
CIBIC+ Overall Change (n)	142	82	290	125	405	214	71	38
Week 24 (ITT)								
Mean (SD)	4.13 (1.03)	4.18 (1.35)	4.24 (1.19)	4.29 (1.20)	4.23 (0.97)	4.33 (0.91)	4.31 (1.18)	4.26 (0.76)
p-value	0.4133		0.7260		0.2082		0.8960	

Abbreviations: IR – immediate release; SR – sustained release; CI – confidence interval; CIBIC+ – Clinician's Interview-Based Impression of Change (Plus Caregiver Input Version); ITT – Intent-to-Treat; LOCF – last observation carried forward; LS – least squares; SD – standard deviation; SIB – Severe Impairment Battery

As the table suggests, the effect of the high-dose donepezil group relative to the low-dose group on the change in SIB score (from baseline to Week 24) was most pronounced in those aged 45-64 years.

6.2.3.5.5.4 Analyses Based On Race

There was a sufficient number of white and Asian/Pacific patients for analyses to be conducted in those subgroups comparing the two treatment groups on both primary efficacy parameters. These analyses are summarized in the following sponsor table, which is self-explanatory: differences favoring the high-dose donepezil group over the low-dose group on both the SIB and CIBIC-Plus were seen only in white patients.

Efficacy Assessment (Mean ± SD) Time point	White		Asian/Pacific	
	Donepezil SR 23 mg (n=708)	Donepezil IR 10 mg (n=346)	Donepezil SR 23 mg (n=161)	Donepezil IR 10 mg (n=87)
SIB (n)	677	339	143	85
Baseline				
Mean (SD)	74.6 (17.18)	76.3 (15.97)	72.3 (18.02)	73.1 (18.06)
LS Mean (95% CI)	75.7 (1.05)	77.3 (1.22)	76.8 (4.16)	77.3 (4.25)
p-value	0.1473		0.8398	
Change from Baseline to Week 24 (ITT)				
Mean (SD)	2.2 (9.42)	0.5 (10.30)	1.9 (9.42)	-0.4 (11.18)
Treatment Comparison				
LS Mean (95% CI)	2.6 (0.60)	0.8 (0.70)	1.4 (2.42)	-0.8 (2.47)
p-value	0.0047		0.1177	
CIBIC+ Overall Change (n)	677	338	143	84
Week 24 (ITT)				
Mean (SD)	4.31 (1.04)	4.37 (1.01)	3.92 (1.13)	3.93 (1.14)
p-value	0.2794		0.7925	

Abbreviations: IR – immediate release; SR – sustained release; CI – confidence interval; CIBIC+ – Clinician's Interview-Based Impression of Change (Plus Caregiver Input Version); ITT – Intent-to-Treat; LS – least squares; SD – standard deviation; SIB – Severe Impairment Battery

6.2.3.5.5.5 Analyses Based On Gender

Nominally statistically significant treatment differences between the two treatment groups, favoring the high-dose donepezil group over the low-dose group, on both primary efficacy parameters were seen only in men and not in women, as indicated by the following sponsor table.

Efficacy Assessment (Mean ± SD) Time point	Male		Female	
	Donepezil SR 23 mg (n=356)	Donepezil IR 10 mg (n=177)	Donepezil SR 23 mg (n=607)	Donepezil IR 10 mg (n=294)
SIB (n)	335	175	572	287
Baseline				
Mean (SD)	74.2 (16.91)	76.0 (15.11)	74.2 (17.98)	75.3 (16.97)
LS Mean (95% CI)	75.4 (1.39)	77.4 (1.64)	74.7 (1.30)	76.0 (1.46)
p-value	0.1903		0.2872	
Change from Baseline to Week 24 (ITT)				
Mean (SD)	2.7 (9.37)	0.5 (10.46)	1.9 (9.38)	-0.1 (10.74)
Treatment Comparison				
LS Mean (95% CI)	3.0 (0.83)	1.1 (0.98)	2.5 (0.73)	0.2 (0.82)
p-value	0.0430		0.0018	
CIBIC+ Overall Change (n)	334	172	574	287
Week 24 (ITT)				
Mean (SD)	4.11 (1.12)	4.34 (1.07)	4.30 (1.04)	4.25 (1.08)
p-value	0.0079		0.7956	

Abbreviations: IR – immediate release; SR – sustained release; CI – confidence interval; CIBIC+ – Clinician's Interview-Based Impression of Change (Plus Caregiver Input Version); ITT – Intent-to-Treat; LS – least squares; SD – standard deviation; SIB – Severe Impairment Battery

6.2.3.6 Analysis Of Secondary Efficacy Measures

6.2.3.6.1 ADCS-ADL

The results of the analysis of the change from baseline to Week 24 in modified ADCS-ADL score in the intent-to-treat population, using the last-observation-carried-forward method of imputation, is summarized in the following table, which I have created using the sponsor's data.

Treatment Group	N	ADCS-ADL Change from baseline to Week 24 LS mean (SE)	p-value (Donepezil 23 mg QD versus donepezil 10 mg QD)
Donepezil 23 mg QD	908	-1.2 (0.40)	0.4758
Donepezil 10 mg QD	461	-1.2 (0.45)	

LS: Least Squares
SE: Standard error

As the above table indicates, there was no difference between treatment groups in the effect of donepezil on this measure.

Similar results were seen in the observed cases population.

6.2.3.6.2 MMSE

The results of the analysis of the change from baseline to Week 24 in MMSE score in the intent-to-treat population, using the last-observation-carried-forward method of imputation, is summarized in the following table, which is based on the sponsor's data.

The table confirms that there was no difference in the effect of the two treatment groups on this measure.

Treatment Group	N	MMSE Change from baseline to Week 24 LS mean (SE)	p-value (Donepezil 23 mg QD versus donepezil 10 mg QD)
Donepezil 23 mg QD	908	0.4 (0.18)	0.2443
Donepezil 10 mg QD	462	0.2 (0.20)	

LS: Least Squares
SE: Standard error

The results were similar in the observed cases population.

6.2.3.7 Analysis Of Exploratory Efficacy Measures

No statistically significant differences between treatment groups were seen for any of the exploratory efficacy measures.

6.2.4 Safety Analyses

6.2.4.1 Exposure

Study drug exposure is summarized in the following table, taken from the submission. As the table indicates, the duration of exposure to study drug appears to have been slightly longer in the donepezil 10 mg QD group than in the donepezil 23 mg QD group.

	Donepezil SR 23 mg			Donepezil IR 10 mg		
	Donepezil SR 23 mg	Placebo[a]	Overall	Donepezil IR 10 mg	Placebo[b]	Overall
Treatment duration: weeks						
N	963	963	963	471	471	471
Mean (SD)	19.18 (8.48)	19.18 (8.48)	19.18 (8.48)	21.98 (5.67)	21.96 (5.72)	21.98 (5.67)
Median	24.00	24.00	24.00	24.00	24.00	24.00
Min, Max	0.1, 28.0	0.1, 28.0	0.1, 28.0	0.3, 26.6	0.1, 26.6	0.3, 26.6
Treatment duration in months: n (%)[c]						
< 3	221 (22.9)	221 (22.9)	221 (22.9)	43 (9.1)	43 (9.1)	43 (9.1)
3 to <6	730 (75.8)	730 (75.8)	730 (75.8)	419 (89.0)	419 (89.0)	419 (89.0)
≥ 6	12 (1.2)	12 (1.2)	12 (1.2)	9 (1.9)	9 (1.9)	9 (1.9)

Note: The treatment duration is defined as the total number of dosing days from first to last day (inclusive) of study treatment.
a: Placebo was identical in appearance to donepezil IR 10 mg tablets and was administered with donepezil SR 23 mg.
b: Placebo was identical in appearance to donepezil SR 23 mg tablets and was administered with donepezil IR 10 mg.
c: Number of patients in the Safety Population was used as the denominator for computing percentages.
Abbreviations: IR – immediate release; SR – sustained release; Max – maximum; Min – minimum; SD – standard deviation.

6.2.4.2 Adverse Events

6.2.4.2.1 Summary Of All Adverse Events

As the following sponsor table indicates, the incidence of all treatment-emergent adverse events and of discontinuations due to treatment-emergent adverse events was higher in the donepezil 23 mg QD group than in the donepezil 10 mg QD group; the incidence of discontinuations due to treatment-emergent adverse events was notably so.

	Number (%) of Patients[b]					
	Donepezil SR 23 mg (n=963)		Donepezil IR 10 mg (n=471)		Total (N=1434)	
Patients who experienced TESS[a]	710	(73.7)	300	(63.7)	1010	(70.4)
Patients who experienced serious TESS	80	(8.3)	45	(9.6)	125	(8.7)
Patients who experienced severe TESS	81	(8.4)	34	(7.2)	115	(8.0)
Patients who discontinued due to TESS	179	(18.6)	37	(7.9)	216	(15.1)
Patients who died during the study	8	(0.8)	5	(1.1)	13	(0.9)

a: A TESS is an AE that either begins on or after the date of first study drug dose and up to 30 days after date of last study drug dose or begins before the date of first study drug dose and increased in severity during the treatment period.
b: The Safety Population (total or by treatment group) was used as the denominator for computing percentages.
Abbreviations: IR – immediate release; SR – sustained release; AE – adverse event; SAE – serious adverse event; TESS – treatment-emergent signs or symptoms.

6.2.4.2.2 Deaths

As noted earlier 0.8% of patients in the donepezil 23 mg QD group and 1.1% of patients in the donepezil 10 mg QD died during the study, either on or after

administration of the first dose of study drug or within 30 days of study drug discontinuation. These patients are listed in the following sponsor table.

Total number of deaths among patients in the donepezil SR 23 mg group	**8**
Total number of deaths among patients in the donepezil IR 10 mg group	**5**

Patient Number	Treatment Group	Day of Death (Study Day)	Cause of Death (Preferred Term)	Related to Treatment[b]
60181017	SR 23 mg	(b) (6)	cardiorespiratory arrest (cardio-respiratory arrest)	Not related
60491003	SR 23 mg		drowning (drowning)	Not related
70271017	SR 23 mg		AE pneumonia (pneumonia aspiration)	Not related
70351010	SR 23 mg		internal bleeding from digestive tract due to gastric ulcer (gastric ulcer hemorrhage)	Not related
70901035	SR 23 mg		cardiovascular disease (cardiovascular disorder)	Not related
71071013	SR 23 mg		bilateral pneumonia (pneumonia aspiration)	Not related
71091002	SR 23 mg		sequelae of stroke (cerebrovascular accident)	Not related
71291012[c]	SR 23 mg		not provided (cardiopulmonary failure)	Not related
60021020	IR 10 mg		septic shock (septic shock)	Not related
60211007	IR 10 mg		natural causes (ischemic heart disease) (myocardial ischemia)	Not related
61011005	IR 10 mg		due to progression of Alzheimer's disease, patient ran away and died of heart failure due to hypothermia (hypothermia)	Not related
70141008	IR 10 mg		myocardial infarction (myocardial infarction)	Not related
70351011	IR 10 mg		exposure to excessive natural cold (hypothermia)	Not related

a: Patients who died prior to receiving double-blind study medication are not included in this table.
b: Investigator's assessment.
c: Patient 71291012 withdrew consent and discontinued from the study on 30 January 2009. The patient died during the 30-day follow-up period; therefore, study day of death was not applicable.
Abbreviations: IR – immediate release; SR – sustained release; N/A – not applicable.

On reading the detailed narratives for each death in the table above, it appears unlikely that any was attributable to donepezil. All deaths seem likely to have been due to intercurrent illnesses common in the elderly.

6.2.4.2.3 Non-Fatal Serious Adverse Events

Non-fatal serious adverse events that occurred in > 0.2% of patients in either treatment group are summarized in the following sponsor table.

Body System Preferred Term	Number (%) of Patients[a,b] Donepezil SR 23 mg (n=963)	Donepezil IR 10 mg (n=471)	Total (N=1434)
Number of patients with at least one serious TESS	80 (8.3)	45 (9.6)	125 (8.7)
Cardiac disorders			
Atrial fibrillation	4 (0.4)	1 (0.2)	5 (0.3)
Bradycardia	4 (0.4)	0 (0.0)	4 (0.3)
Gastrointestinal disorders			
Diarrhea	4 (0.4)	0 (0.0)	4 (0.3)
Vomiting	3 (0.3)	0 (0.0)	3 (0.2)
General disorders and administration site conditions			
Hypothermia	1 (0.1)	2 (0.4)	3 (0.2)
Infections and infestations			
Pneumonia	3 (0.3)	3 (0.6)	6 (0.4)
Urinary tract infection	6 (0.6)	2 (0.4)	8 (0.6)
Injury, poisoning and procedural complications			
Fall	6 (0.6)	2 (0.4)	8 (0.6)
Femur fracture	4 (0.4)	1 (0.2)	5 (0.3)
Metabolism and nutrition disorders			
Dehydration	3 (0.3)	0 (0.0)	3 (0.2)
Nervous system			
Convulsion	0 (0.0)	2 (0.4)	2 (0.1)
Dizziness	4 (0.4)	1 (0.2)	5 (0.3)
Presyncope	3 (0.3)	0 (0.0)	3 (0.2)
Syncope	2 (0.2)	5 (1.1)	7 (0.5)
Psychiatric disorders			
Aggression	2 (0.2)	4 (0.8)	6 (0.4)
Confusional state	1 (0.1)	3 (0.6)	4 (0.3)
Renal and urinary disorders			
Renal failure acute	3 (0.3)	0 (0.0)	3 (0.2)
Respiratory, thoracic and mediastinal disorders			
Pneumonia aspiration	3 (0.3)	0 (0.0)	3 (0.2)

a: Patients are counted only once per treatment in each row.
b: The Safety Population (total or by treatment group) was used as the denominator for computing percentages.
Abbreviations: IR – immediate release; SR – sustained release; TESS – treatment-emergent signs or symptoms.

As the table indicates, while the incidence of all non-fatal serious adverse events was comparable between treatment groups, that of several events attributable to the cholinomimetic effects of donepezil (e.g., bradycardia, diarrhea, and vomiting) was slightly higher in the 23 mg QD group than in the 10 mg QD group.

6.2.4.2.4 Discontinuations Due To Adverse Events

The incidence of all discontinuations due to treatment-emergent adverse events was clearly higher with donepezil 23 mg QD than with donepezil 10 mg QD.

The next table copied from the submission displays treatment-emergent adverse events that led to discontinuation and occurred in ≥ 0.3% of patients in either treatment group.

Body System Preferred Term	Number (%) of Patients[a,b] Donepezil SR 23 mg (n=963)	 Donepezil IR 10 mg (n=471)	 Total (N=1434)
TESS leading to discontinuation	179 (18.6)	37 (7.9)	216 (15.1)
Cardiac disorders			
Bradycardia	7 (0.7)	0 (0.0)	7 (0.5)
Gastrointestinal disorders			
Diarrhea	16 (1.7)	2 (0.4)	18 (1.3)
Nausea	18 (1.9)	2 (0.4)	20 (1.4)
Vomiting	28 (2.9)	2 (0.4)	30 (2.1)
Investigations			
Electrocardiogram QT prolonged	4 (0.4)	0 (0.0)	4 (0.3)
Metabolism and nutrition disorders			
Anorexia	3 (0.3)	1 (0.2)	4 (0.3)
Nervous system disorders			
Dizziness	11 (1.1)	0 (0.0)	11 (0.8)
Headache	4 (0.4)	0 (0.0)	4 (0.3)
Somnolence	6 (0.6)	0 (0.0)	6 (0.4)
Syncope	2 (0.2)	2 (0.4)	4 (0.3)
Psychiatric disorders			
Aggression	5 (0.5)	2 (0.4)	7 (0.5)
Agitation	8 (0.8)	1 (0.2)	9 (0.6)
Confusional state	7 (0.7)	0 (0.0)	7 (0.5)

a: Patients are counted only once per treatment in each row.
b: The Safety Population (total or by treatment group) was used as the denominator for computing percentages.
Abbreviations: IR – immediate release; SR – sustained release; TESS – treatment-emergent signs or symptoms.

Note that the incidence of discontinuations due to vomiting, diarrhea, nausea, and dizziness was notably higher with donepezil 23 mg QD than with donepezil 10 mg QD; in particular, 2.9% of patients in the donepezil 23 mg QD group discontinued on account of vomiting, versus 0.4% of those in the donepezil 10 mg QD group.

108 (60.3%) out of 179 patients who discontinued treatment on account of treatment-emergent adverse events in the donepezil 23 mg QD group did so during the first month of treatment.

6.2.4.2.5 Most Common Adverse Events

The following table taken from the submission displays treatment-emergent adverse events that occurred in ≥ 2% of patients and at a higher frequency in the donepezil 23 mg QD than in the donepezil 10 mg QD group.

Body System Preferred Term	Number (%) of Patients[a,b] Donepezil SR 23 mg (n=963)	Donepezil IR 10 mg (n=471)	Total (N=1434)
Number of patients with at least one TESS	710 (73.7)	300 (63.7)	1010 (70.4)
Gastrointestinal disorders			
Nausea	114 (11.8)	16 (3.4)	130 (9.1)
Vomiting	89 (9.2)	12 (2.5)	101 (7.0)
Diarrhea	80 (8.3)	25 (5.3)	105 (7.3)
General disorders and administration site conditions			
Fatigue	23 (2.4)	4 (0.8)	27 (1.9)
Asthenia	20 (2.1)	3 (0.6)	23 (1.6)
Infections and infestations			
Urinary tract infection	42 (4.4)	19 (4.0)	61 (4.3)
Injury, poisoning and procedural complications			
Fall	39 (4.0)	18 (3.8)	57 (4.0)
Contusion	20 (2.1)	1 (0.2)	21 (1.5)
Investigations			
Weight decreased	45 (4.7)	12 (2.5)	57 (4.0)
Metabolism and nutrition disorders			
Anorexia	51 (5.3)	8 (1.7)	59 (4.1)
Nervous system disorders			
Dizziness	47 (4.9)	16 (3.4)	63 (4.4)
Headache	41 (4.3)	15 (3.2)	56 (3.9)
Somnolence	20 (2.1)	5 (1.1)	25 (1.7)
Psychiatric disorders			
Agitation	38 (3.9)	18 (3.8)	56 (3.9)
Insomnia	33 (3.4)	11 (2.3)	44 (3.1)
Aggression	26 (2.7)	12 (2.5)	38 (2.6)
Renal and urinary disorders			
Urinary incontinence	24 (2.5)	6 (1.3)	30 (2.1)

a: Patients were counted only once per treatment in each row.
b: The Safety Population (total or by treatment group) was used as the denominator for computing percentages.
Abbreviations: IR – immediate release; SR – sustained release; TESS – treatment-emergent signs or symptoms.

Note that the incidence of nausea, vomiting, and anorexia was considerably higher in the donepezil 23 mg QD group than in the donepezil 10 mg QD group. The difference in incidence of gastrointestinal adverse events was most readily apparent during the first month of treatment. The mean duration of vomiting was stated to be 5.61 days in the donepezil 23 mg QD group and 1.25 days in the donepezil 10 mg QD group (based on additional data included in the 120-Day Safety Update).

The majority of treatment-emergent adverse events, including nausea, vomiting and anorexia were classed as “mild” or “moderate” in severity. Most vomiting was considered “moderate” in severity.

There was no correlation between age, gender, or race, and the overall incidence of adverse events.

The incidence of all adverse events at a donepezil dose of 23 mg QD was highest in patients with a weight < 55 kg at entry, as indicated in the following table, which is based on data provided by the sponsor.

Weight Group	Treatment Group	Total number of patients	Number (%) of patients with at least one adverse event
< 55 kg	Donepezil 23 mg QD	218	178 (81.7)
	Donepezil 10 mg QD	111	74 (66.7)
55 to < 65 kg	Donepezil 23 mg QD	245	175 (71.4)
	Donepezil 10 mg QD	129	85 (65.9)
65 to < 75 kg	Donepezil 23 mg QD	240	172 (71.7)
	Donepezil 10 mg QD	110	72 (65.5)
≥ 75 kg	Donepezil 23 mg QD	259	184 (71.0)
	Donepezil 10 mg QD	121	69 (57.0)

Nausea, vomiting, and weight loss were also most common at a dose of 23 mg QD in those with a weight < 55 kg at entry.

6.2.4.2.6 Laboratory Data

There were no differences of note between the two treatment groups in the incidence of treatment-emergent abnormal laboratory values, or of changes from baseline in laboratory data.

6.2.4.2.7 Vital Signs

As noted earlier, there was an increased incidence of discontinuations due to bradycardia in the group receiving donepezil in a dose of 23 mg QD as compared with the group receiving donepezil in a dose or 10 mg QD. With that exception, there were no differences of note between the treatment groups in the incidence of vital sign-related adverse events, or in the mean change from baseline to endpoint in vital sign parameters.

6.2.4.2.8 Weight

As already noted, there was an increased incidence of weight loss (as a treatment-emergent adverse event) in the group that received donepezil 23 mg QD as compared with the group that received 10 mg QD.

The mean change from baseline to Week 24 in weight was -0.85 kg (standard deviation ± 2.95 kg) in the 23 mg QD group and 0.05 kg (standard deviation ± 2.67 kg).

6.2.4.2.9 Electrocardiograms

10 patients (1.0%) in the donepezil 23 mg QD group and 1 patient (0.2%) in the donepezil 10 mg QD group were recorded as having a prolonged QT interval as an adverse event; 4 of the 10 patients in the donepezil 23 mg QD group who had a prolonged QT interval discontinued study drug as opposed to none in the

donepezil 10 mg QD group. The difference in the incidence of this adverse event in the two treatment groups was attributed by the sponsor to a slow heart rate (of less than 60 beats per minute) in out of the 10 patients in the donepezil 23 mg QD group. There were apparently no instances of tachyarrhythmia or hypotension associated with the prolongation in QT interval; in 2 patients, symptoms were associated with the prolongation in QT interval. I have reviewed the narratives and (where available) Case Report Forms for all 11 patients who were recorded as having a prolonged QT interval in this study; while in no instance was there a strong reason to believe that the apparent prolongation in QT interval was related to the use of donepezil, the actual numerical QT and QT_c data at each study visit have not been provided for these patients in either the body of the study report, additional tables or listings, or in statistical datasets.

The sponsor was therefore requested to provide individual QT/QT_c data and heart rate data for the above 11 patients on July 1, 2010. The sponsor responded on July 8, 2010 with a detailed analysis of the above phenomenon, including the requested data. I have reviewed the sponsor's response in detail. The adverse event in question (i.e., the prolonged QT interval) was confounded in each instance by one or more of the following: bradycardia (with the QT_c then being with an acceptable range), QT prolongation prior to entering the study, concomitant medications that might predispose to the same phenomenon, other pertinent electrocardiogram abnormalities at baseline, and a return of the QT interval to within an acceptable range despite continuation of the same dose of study medication.

There were no clinically notable differences between the 2 treatment groups in the change from baseline to Week 24 in individual electrocardiogram parameters. The proportion of patients in each treatment group who had normal electrocardiographic recordings at baseline and abnormal recordings at Week 24 was similar, namely, 14.2% and 14.1% in the 23 mg QD and 10 mg QD groups, respectively; in only one instance, however, was the recording considered clinically significant with a patient in the 23 mg QD being recorded as having sinus tachycardia at the Week 24 visit.

6.3 Sponsor's Conclusions

6.3.1 Efficacy

The sponsor has concluded the following:

- The results of Study 326 did show a statistically significant superiority of the 23 mg QD dose of donepezil (over the 10 mg QD dose of donepezil) on the Severe Impairment Battery

- The results of Study 326 showed a numerical superiority of the 23 mg QD dose of donepezil (over the lower dose) on the Clinician Interview-Based Impression of Change-Plus. While this effect was not statistically significant in the pre-specified dataset used for the primary efficacy analysis, a number of sensitivity analyses

showed that this effect was statistically significant in patients who were more severely ill at baseline, and in particular, in those with a Mini-Mental Status Examination score of 0-16 at entry which was more representative of moderate to severe Alzheimer's Disease than a Mini-Mental Status Examination range of 0-20 at entry.

6.3.2 Safety

The sponsor has drawn the following conclusions from the analysis of safety data for this study.

The overall incidence of treatment-emergent signs and symptoms was higher in the donepezil 23 mg QD group than in the donepezil 10 mg QD group, with nausea, vomiting, diarrhea and anorexia occurring more often in the former than in the latter group. The majority of adverse events in both treatment groups were mild to moderate in severity. The difference between treatment groups in the incidence of adverse events attributable to the cholinomimetic effects of donepezil was most apparent early during treatment, as might have been expected given that the donepezil 23 mg QD group had an escalation in dose at the commencement of the study

6.4 Agency Biometrics Reviewer's Comments

The Agency Biometrics reviewer for this application was Dr Tristan Massie, who has performed independent analyses of the primary efficacy measures using datasets supplied by the sponsor.

He has concluded that while the proposed higher dose of donepezil (i.e., 23 mg QD) did demonstrate a statistically significant superiority to the lower dose (i.e., 10 mg QD) on the co-primary cognitive efficacy measure (i.e., the SIB) in Study 326, the difference between doses on the other co-primary efficacy measure, the CIBIC-Plus, was not statistically significant.

He further concludes that "the data from this trial does not seem to provide enough support for the efficacy" of the 23 mg QD dose of donepezil.

The following is a summary of some of the other observations that Dr Massie has made regarding the effect of the 23 mg QD dose relative to the 10 mg QD dose on the CIBIC-Plus and SIB:

- Earlier randomized clinical trials in severe Alzheimer's Disease in which the efficacy of the 10 mg QD dose of donepezil has been compared with placebo on the CIBIC-Plus have not yielded an effect that was consistently statistically significant. Thus, it would be <u>not</u> be reasonable to assume that the 23 mg QD dose of donepezil had efficacy based on its non-inferiority to the 10 mg QD dose, unless there was an *a priori* belief that the treatment effect must increase as a function of dose.

- While the sponsor has demonstrated a nominal statistically significant treatment difference on the CIBIC-Plus on a post-hoc subset analysis of those with an entry Mini-Mental Status Examination score ranging from 0-16, now considered by the sponsor to be more representative of moderate to severe Alzheimer's Disease, the use of those results to support the efficacy of the 23 mg QD dose was problematical not only because the analysis was post-hoc, but also because the same analysis performed for other subsets within or otherwise close to the same range of entry Mini-Mental Status Examination scores did not even yield nominally statistically significant results (the other subgroups were those with entry scores of 3-14, 0-14, 0-15, and 0-17).

- It was unclear whether the study had assay sensitivity, not only because previous donepezil trials did not consistently show a beneficial effect on the CIBIC-Plus, but also because the baseline SIB score range for patients in this study was about 10 to 20 points higher than in previous clinical trials of donepezil in (severe) Alzheimer's Disease in whom the SIB was an efficacy measure. A further reason for believing that the study may not have assay sensitivity is derived from additional sensitivity analyses that were performed on the SIB on account of a higher discontinuation rate in the 23 mg QD dose group (30%) than in the 10 mg QD dose group (18%): while both the primary efficacy analysis and a secondary observed cases (at Week 24) analysis of the SIB did show a nominally statistically significant treatment difference favoring the higher dose of donepezil, even a nominally statistically significant treatment difference was not observed on other sensitivity analyses of the SIB, including a Wilcoxon rank sum test analysis in which the worst rank for change in SIB at Week 24 was assigned to dropouts, and other similar analyses (the implication here is that a higher discontinuation rate in the 23 mg QD group may have influenced the analysis of the SIB and contributed to a lack of assay sensitivity).

Dr Massie also has questions about the basis by which the sponsor cancelled plans for an interim analysis of efficacy; the sponsor stated that the interim analysis of efficacy was cancelled because of more rapid than expected enrollment.

Please see Dr Massie's review for further details of the analyses that he has performed as well as additional discussion of the data from Study 326.

6.5 Reviewer's Summary Of Study And Comments

6.5.1 Summary Of Study 326

6.5.1.1 Design

The primary objective of Study 326 was to compare the efficacy of the 23 mg QD dose of donepezil with that of the 10 mg QD dose in the treatment of moderate to

severe Alzheimer's Disease. Among the secondary objectives of the study was to evaluate the safety and tolerability of the 23 mg QD dose of donepezil in Alzheimer's Disease.

This was a randomized, double-blind, double-dummy, active-controlled, parallel-arm study of 24 weeks duration

The key inclusion criteria for this study were a diagnosis of Probable Alzheimer's Disease, using the National Institute for Neurological and Communicative Diseases and Stroke – Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria, an entry Mini-Mental Status Examination (MMSE) score of 0-20, a Severe Impairment Battery score ≤ 90 at entry, and use of donepezil at a stable daily dose of 10 mg QD for at least 3 months prior to study entry.

Patients enrolled in this study were randomized to the following treatment groups for the 24-week duration of the study.

- Donepezil 23 mg QD
- Donepezil 10 mg QD

(Patients assigned to the 23 mg QD dose received that dose without titration).

The primary efficacy measures for the study were:

- A measure of cognition, the Severe Impairment Battery (SIB)
- A measure of global function, the Clinician Interview-Based Impression of Change-Plus (CIBIC-Plus).

The secondary efficacy measures for this study consisted of a 19-item version of the Alzheimer's Disease Cooperative Study – Activities of Daily Living Scale (ADCS-ADL) specially designed for patients with moderate to severe dementia, and the MMSE.

Safety measures included adverse events, vital signs, physical and basic neurological examinations, safety laboratory tests, and electrocardiograms.

The primary efficacy parameters were the change from baseline in the total SIB score at Week 24 and the CIBIC-Plus score at Week 24. The primary efficacy analysis was performed on the intent-to-treat dataset at Week 24, using the last-observation-carried-forward method of imputation. The intent-to-treat dataset consisted of all randomized patients who received at least one dose of study medication and had at least one post-baseline evaluation of the SIB or CIBIC-Plus.

The analysis of the Severe Impairment Battery data was to be performed using an analysis of covariance model with terms for baseline, country, and treatment.

The CIBIC-Plus was to be analyzed using a non-parametric analysis of covariance with a Cochran-Mantel-Haenszel test component. The analysis was to adjust for Clinician Interview-Based Impression of Severity-Plus (CIBIS-Plus) score at baseline with a stratification adjustment for country.

The superiority of the 23 mg/day sustained-release group over the 10 mg/day donepezil immediate-release group must to have been demonstrated on the Severe Impairment Battery and CIBIC-Plus, during the primary efficacy analysis, for the study to be considered positive. Superiority was to have been demonstrated at a significance level of 0.05 (2-sided) for each primary efficacy measure.

6.5.1.2 Results

A total of 1467 patients were enrolled in this study. The number randomized to the 2 treatment groups and the number completing the study in each group is in the following table.

Category	Treatment Group	
	Donepezil SR 23 mg/day N (%)	Donepezil IR 10 mg/day N (%)
Randomized	981 (100.0)	486 (100.0)
Completed	685 (69.8)	399 (82.1)

The actual MMSE scores for patients enrolled in the study ranged from 0-22 with a mean score of 13.1 (standard deviation ± 4.91).

The results of the primary efficacy analysis revealed the following:

- A least squares mean change from baseline of 2.6 points in the donepezil 23 mg QD group and 0.4 points in the donepezil 10 mg QD group, on the SIB, with the difference between groups being statistically significant (p = 0.0001)

- A mean score of 4.23 points in the donepezil 23 mg QD group and 4.29 points in the donepezil 10 mg QD group, on the CIBIC-Plus, with the difference between groups not being statistically significant (p = 0.1789).

Sensitivity and other analyses of the SIB, including post-hoc analyses confined to subsets with and within an entry Mini-Mental Status Examination score range of 0 to 16, were all consistent with the primary efficacy analysis. Additional analyses of the CIBIC-Plus showed a nominally statistically significant treatment difference favoring the 23 mg QD group over the 10 mg QD group for the subset with an entry MMSE score of 0-16, but not consistently for subsets either close to or within that range.

No statistically significant treatment difference was seen between the treatment groups on the 2 secondary efficacy measures, the ADCS-ADL and the MMSE.

Indeed, there was no difference at all between the treatment groups on the mean change from baseline to Week 24 in the ADCS-ADL

The incidence of deaths and of all serious adverse events was similar in the 2 treatment groups, while the incidence of all adverse events and of adverse events leading to treatment discontinuation was clearly higher in the donepezil 23 mg QD group than in the donepezil 10 mg QD group. The individual adverse events that were substantially more common in the higher dose donepezil group were nausea, vomiting, and anorexia; vomiting, notably, had an incidence of 9.2% in the 23 mg QD group and only 2.5 % in the 10 mg QD group, with the difference in incidence of gastrointestinal adverse events between the 2 treatment groups being particularly apparent during the first 2 months of the study. The sponsor-provided descriptions of deaths and serious adverse events that occurred in this study suggested that they were most unlikely to be attributable to donepezil. The same applies to adverse events that led to treatment discontinuation, with the exception of nausea, vomiting, diarrhea, and dizziness the incidence of which was notably higher in the donepezil 23 mg QD group than in the 10 mg QD group. Other safety data analyzed, including vital signs, safety laboratory tests, and electrocardiograms showed no areas of concern when comparing the two treatment groups.

6.5.2 Comments

It is a long-established requirement of this Agency that the efficacy of a drug intended for the treatment of Alzheimer's Disease should be demonstrated on both a cognitive instrument and on a global or functional measure: on a cognitive measure, because the core symptoms of Alzheimer's Disease are cognitive; and on a global or functional measure to confirm that the effect on the cognitive measure is clinically meaningful. So far, the efficacy of drugs approved for the treatment of Alzheimer's Disease has been demonstrated in comparison with placebo in either a monotherapy study or in a study of "add-on" design.

In communications with the sponsor prior to the submission of the current application, it was agreed that Study 326 would suffice in its design to demonstrate the efficacy of the new higher-dose formulation of donepezil (23 mg, taken once daily). Although the efficacy of the proposed higher dose of donepezil was to be demonstrated in comparison with the currently-approved maximum dose of 10 mg QD, it was also agreed that for the results of Study 326 to be considered sufficient to support the efficacy of the new formulation, the 23 mg QD dose of donepezil must have been demonstrated to have a statistically significant superiority to the 10 mg QD dose on both the cognitive primary efficacy measure, the SIB, and the global primary efficacy measure, the CIBIC-Plus.

(Note that this Division did have at least some reservations, as noted in several of the above communications, as to whether the SIB was an appropriate cognitive efficacy measure to use in those with an entry MMSE score in the 16-

20 range, since its use was better-established and better-supported by the medical literature in those with a MMSE score in the 0-15 range).

As is evident from the above summary, the results of Study 326 did not satisfy the pre-specified criteria for demonstrating the efficacy of the higher dose of donepezil (23 mg QD).

Although the primary efficacy analysis showed a small, but clearly statistically significant, effect of donepezil (23 mg QD) on the SIB, that was maintained on at least some sensitivity analyses, and in a post-hoc analysis of the subset with an entry MMSE score in the 0-16 range, the primary efficacy analysis of the CIBIC-Plus did not show a statistically significant benefit, thus failing to provide confirmation that the small effect on the SIB was clinically meaningful. While the sponsor has through a set of post-hoc subset analyses sought to draw attention to a nominally statistically significant superiority of the 23 mg QD dose of donepezil on the CIBIC-Plus for the subset with an entry MMSE score in the 0-16 range, arguing that the 0-16 range is more representative of moderate to severe Alzheimer's Disease, such an effect is not only questionable based as it is on a post-hoc analysis, but is not even consistent within that subset as the Agency Biometrics reviewer has pointed out.

While it may be argued that since the efficacy of the 10 mg QD dose of donepezil as a treatment for moderate to severe Alzheimer's Disease has already been established, the efficacy of the 23 mg QD dose can be assumed, especially since that dose was not demonstrated to be inferior to the 10 mg QD dose on the CIBIC-Plus in Study 326, a statistically significant beneficial effect of the 10 mg QD dose on the CIBIC-Plus has not been consistently demonstrated in previous trials in severe Alzheimer's Disease (as the Agency Biometrics reviewer has also pointed).

Further evidence that the effect of the 23 mg QD dose of donepezil on the SIB may not be clinically meaningful is provided by the apparent lack of any effect on the modified ADCS-ADL, a secondary efficacy measure. (Note that the CIBIC-Plus and ADCS-ADL were the co-primary efficacy measures designated for purposes of registration of the 23 mg QD formulation in the European Union).

While evidence is lacking that the 23 mg QD dose of donepezil has a clinically meaningful benefit (and firm evidence is thus lacking that the same dose had efficacy) in Alzheimer's Disease, an additional, and very significant, concern about that dose is that its introduction in Study 326 was associated with an incidence of vomiting of 9.2%, as compared with several-fold lower incidence of only 2.5% in those continuing to receive donepezil in a dose of 10 mg QD; the occurrence of vomiting can lead to even greater morbidity in patients with Alzheimer's Disease, that includes pneumonia, massive gastrointestinal bleeding, esophageal rupture, or death. Thus, in addition to lacking any evidence of a clinically meaningful benefit, at least in comparison with the 10 mg QD dose

of donepezil, the use of a 23 mg QD dose (i.e., an escalation in dose from 10 mg QD to 23 mg QD) is also associated with a significant risk to patient safety.

The results of Study 326 therefore do not support the approval of Aricept® in a dose of 23 mg QD for the treatment of moderate to severe Alzheimer's Disease.

7. Integrated Summary Of Safety (Summary Of Clinical Safety)

The contents of the Summary of Clinical Safety are outlined under the following headings.

7.1 Sources Of Safety Data

As already outlined, the sources of safety data included in this submission are as follows:

- Study E2020-G000-326, a randomized, double-blind, active-controlled, parallel-arm study of 26 weeks duration. This is the main source of safety data in this submission.

- Study E2020-G000-328, a 12-month open-label uncontrolled extension to Study E2020-G000-326, which is currently ongoing.

- Clinical pharmacology studies, listed below

  - Study E2020-A001-020, in which 4-hour, 8-hour, and 12-hour sustained-release formulations of donepezil (different from the current sustained-release formulation) were compared with the approved immediate-release formulation, using a 10 mg dose single-dose for both formulations.

  - 3 pharmacokinetic studies that have been conducted by the sponsor using the sustained-release formulation of donepezil (b) (4) in strengths of 14 mg and 23 mg. They include:

    - Study E2020-A001-021, which compared the pharmacokinetics of single doses of 14 mg and 23 mg of sustained-release Aricept® with single doses of 10 mg of immediate-release Aricept® in healthy men and women, aged 19 to 45 years

    - Study E2020-A001-022, which compared the pharmacokinetics of multiple doses of 14 mg and 23 mg of sustained-release Aricept® with multiple doses of 5 mg of immediate-release Aricept® and placebo in healthy men and women, aged 19 to 45 years (each tablet strength was administered for up to 2 weeks)

    - Study E2020-A001-023, which evaluated the effect of food on the bioavailability of single and multiple doses of the 14 mg sustained-release formulation of Aricept® and of single doses of the 23 mg immediate-release formulation.

7.2 Safety Data From Study E2020-G000-326

These data have already been summarized in Section 6.2.4.

7.3 Safety Data From Study E2020-G000-328

7.3.1 Outline Of Study

Patients completing Study E2020-G000-326 were eligible to enter an open-label uncontrolled extension study (E2020-G000-328) in which all patients were to receive the donepezil in a dose of 23 mg/day for 12 months.

Safety assessments in Study E2020-G000-328, to be performed every 3 months, were to include adverse events, vital signs, physical examinations, basic neurological examinations, safety laboratory tests, and electrocardiograms.

This study is currently ongoing and is also referred to as “Study 328” in this review.

7.3.2 Summary Of Safety Data

The cut-off date for safety data from Study 328 included in the original NDA submission was June 30, 2009, except for discontinuations due to adverse events for which the cut-off date was April 1, 2009.

Council for International Organizations of Medical Sciences (CIOMS) forms were provided for each of the above deaths and serious adverse events (through the cut-off date of June 30, 2009), with written narratives being provided for discontinuations due to adverse events through the cut-off date of April 1, 2009.

7.3.2.1 Enrollment

915 patients had been enrolled in Study 328 as of the cut-off date.

7.3.2.2 Deaths

7 deaths had occurred in Study 328 as of the cut-off date above. These deaths are listed in the following table which I have copied from the submission.

Patient Number	Dose	Day of Death (Study Day)	Cause of Death (Investigator's Assessment)
60391005	Donepezil SR 23 mg	(b) (6)	death, natural causes (death from natural causes)
61081027[a]	Donepezil SR 23 mg		lung cancer (lung cancer)
70851008	Donepezil SR 23 mg		sudden death (sudden death)
70271021	Donepezil SR 23 mg		pancreatic mass (pancreatic mass)
70791010	Donepezil SR 23 mg		bronchitis (bronchitis), multiple organ failure (multiple organ failure), and global heart decompensation (decompensation cardiac)
71291008	Donepezil SR 23 mg		found dead (found dead)
70951003	Donepezil SR 23 mg		B/L pneumonia (bilateral pneumonia), septicemia (septicemia), and acute renal failure (acute renal failure)

[a] Patient 61081027 had an SAE with an outcome of not recovered at the time of the data cut-off date; follow-up CIOMS information received on 13 July 2009, amended the outcome for the event of lung cancer from not recovered to death.
Abbreviations: SR – sustained-release.

The clinical descriptions contained in the CIOMS forms for each of the above deaths do not suggest that donepezil was very likely to be responsible for those events.

7.3.2.3 Non-Fatal Serious Adverse Events

69 patients experienced a non-fatal serious adverse event in Study 328, as of the above cut-off date.

A review of the listing for those patients (which I have not reproduced here), supplemented by clinical descriptions contained in CIOMS forms when needed, does not indicate a high probability of donepezil being responsible for those events.

7.3.2.4 Discontinuations Due To Adverse Events

64 patients discontinued from Study 328 on account of adverse events through April 1, 2009. I have read the narratives for the adverse events that occurred in all these patients. Except for a few instances where the cholinomimetic effects of donepezil may have been responsible for causing the adverse events (such as nausea, vomiting, diarrhea, and bradycardia) that lead to treatment discontinuation, the narrative reports provided do not suggest a strong likelihood of donepezil being responsible for the events described; the majority of such events appear likely to have intercurrent illnesses common in this population, as were the deaths and non-fatal serious adverse events described earlier.

7.4 Safety Data From Clinical Pharmacology Studies E2020-A001-020, -021, 022, And 0-23

Adverse event data for each of these studies conducted in healthy subjects is summarized below. Each of these studies has already been outlined in the table contained in Section 5, and the design of each is further described below.

7.4.1 Study E2020-A001-020

7.4.1.1 Outline

This was a randomized, open-label, two-period, two-sequence crossover study in which three separate 10 mg dissolution formulations of donepezil SR (4-hour type, 8-hour type, and 12-hour type) distinct from the currently-proposed formulation were compared, in regard to their bioavailability, with the approved 10 mg formulation.

A total of 82 men and women, ranging in age from 19 to 46 years, were enrolled in the study.

7.4.1.2 Safety Data

There were no deaths or serious adverse events in this study. 3 subjects discontinued on account of vomiting (two of these subjects had concomitant nausea).

Treatment-emergent adverse events seen in ≥ 5% of those in any treatment group are summarized in the following table, which I have copied from the submission. The majority of adverse events were mild in severity.

	Number (%) of Subjects			
Preferred Term	**Donepezil IR 10 mg (n=82)**	**Donepezil SR-4H 10 mg (n=29)**	**Donepezil SR-8H 10 mg (n=26)**	**Donepezil SR-12H 10 mg (n=27)**
Subjects with at least one AE	31 (37.8)	9 (31.0)	3 (11.5)	3 (11.1)
Dizziness	18 (22.0)	5 (17.2)	0	0
Nausea	8 (9.8)	5 (17.2)	0	0
Headache	3 (3.7)	3 (10.3)	1 (3.8)	1 (3.7)

Abbreviations: IR – immediate release; SR – sustained release; AE – adverse event.

7.4.2 Study E2020-A001-021

7.4.2.1 Outline

This was a randomized, double-blind, single-dose study that compared the pharmacokinetics of donepezil SR 14 mg, donepezil SR 23 mg (the formulation chosen for development in Alzheimer's Disease), and donepezil immediate-release 10 mg in healthy men and women, aged 19 to 45 years. 84 subjects were enrolled in the study.

7.4.2.2 Safety Data

There were no deaths or serious adverse events in this study. 17 patients discontinued from this study on account of vomiting, with 10 patients discontinuing at the 23 mg dose.

Adverse events that occurred in ≥ 5% of subjects in any dose group are summarized in the following sponsor table, which is self-explanatory.

	Number (%) of Subjects		
Preferred Term	**Donepezil SR 14 mg (n=23)**	**Donepezil SR 23 mg (n=34)**	**Donepezil IR 10 mg (n=27)**
Subjects with at least one AE	14 (60.9)	31 (91.2)	17 (63.0)
Nausea	12 (52.2)	24 (70.6)	8 (29.6)
Vomiting	7 (30.4)	22 (64.7)	7 (25.9)
Dizziness	6 (26.1)	11 (32.4)	8 (29.6)
Abdominal pain	0	6 (17.6)	1 (3.7)
Headache	0	3 (8.8)	4 (14.8)
Hiccups	1 (4.3)	2 (5.9)	1 (3.7)
Diarrhea	2 (8.7)	2 (5.9)	0
Feeling hot	0	2 (5.9)	0
Fatigue	3 (13.0)	0	0
Nasopharyngitis	1 (4.3)	0	2 (7.4)

Abbreviations: IR – immediate release; SR – sustained release; AE – adverse event.

7.4.3 Study E2020-A001-022

7.4.3.1 Outline

This was a randomized, double-blind, placebo-controlled, parallel-arm, multiple-dose study.

77 healthy men and women, ranging in age from 19 to 45 years, were enrolled in the study.

Subjects enrolled in this study were assigned to one of 5 dosing regimes, summarized in the following sponsor table.

Group	Outpatient (Days 2-6)	Inpatient	
	Period 1 (Days 1-7)	Period 2 (Days 8-21)	Period 3 (Days 22-35)
1	5 mg Placebo tablet	14 mg E2020 SR tablet	23 mg E2020 SR tablet
2	5 mg Placebo tablet	14 mg Placebo tablet	23 mg Placebo tablet
3	5 mg Placebo tablet	14 mg E2020 SR tablet	14 mg Placebo tablet
4	5 mg E2020 IR tablet	14 mg E2020 SR tablet	23 mg E2020 SR tablet
5	5 mg E2020 IR tablet	14 mg E2020 SR tablet	23 mg Placebo tablet
E2020 IR = Donepezil hydrochloride immediate release; E2020 SR = Donepezil hydrochloride sustained release Note: Doses were administered orally, once daily in the morning.			

7.4.3.2 Safety Data

There were no deaths or serious adverse events in this study.

3 subjects discontinued on account of treatment-emergent adverse events: 2 of these subjects discontinued on account of abnormal liver function tests (apparently not considered clinically significant), and the remaining subject discontinued on account of abdominal pain.

Adverse events that occurred in ≥ 5% of subjects in any treatment group are summarized in the following sponsor table, which is self-explanatory. Most adverse events were mild.

Preferred Term	Number (%) of Subjects				
	Group 1 (n=15)	Group 2 (n=15)	Group 3 (n=16)	Group 4 (n=15)	Group 5 (n=16)
Subjects with at least one AE	13 (86.7)	9 (60.0)	15 (93.8)	13 (86.7)	12 (75.0)
Dizziness	11 (73.3)	1 (6.7)	11 (68.8)	10 (66.7)	8 (50.0)
Headache	6 (40.0)	2 (13.3)	10 (62.5)	8 (53.3)	7 (43.8)
Nausea	10 (66.7)	1 (6.7)	10 (62.5)	8 (53.3)	4 (25.0)
Vomiting	9 (60.0)	0	10 (62.5)	6 (40.0)	3 (18.8)
Abdominal pain	3 (20.0)	2 (13.3)	1 (6.3)	5 (33.3)	4 (25.0)
Constipation	1 (6.7)	2 (13.3)	2 (12.5)	4 (26.7)	0
Diarrhea	4 (26.7)	1 (6.7)	5 (31.3)	4 (26.7)	3 (18.8)
Insomnia	3 (20.0)	0	4 (25.0)	4 (26.7)	2 (12.5)
Asthenia	5 (33.3)	1 (6.7)	1 (6.3)	3 (20.0)	2 (12.5)
Chills	1 (6.7)	0	4 (25.0)	3 (20.0)	0
Paresthesia	2 (13.3)	0	4 (25.0)	3 (20.0)	1 (6.3)
Dyspepsia	3 (20.0)	0	2 (12.5)	2 (13.3)	2 (12.5)
Musculoskeletal chest pain	0	0	0	2 (13.3)	0
Nightmare	1 (6.7)	0	0	2 (13.3)	2 (12.5)
Palpitations	0	0	0	2 (13.3)	0
Back pain	2 (13.3)	0	0	1 (6.7)	0
Flatulence	1 (6.7)	0	2 (12.5)	1 (6.7)	2 (12.5)
Hallucination	1 (6.7)	0	3 (18.8)	1 (6.7)	0
Abdominal distention	0	0	2 (12.5)	0	0
Anorexia	0	0	2 (12.5)	0	0
Anxiety	2 (13.3)	0	1 (6.3)	0	0
Nasopharyngitis	0	0	1 (6.3)	0	2 (12.5)
Paresthesia oral	0	0	2 (12.5)	0	0
Somnolence	0	0	2 (12.5)	0	1 (6.3)
Syncope vasovagal	2 (13.3)	0	0	0	0

Abbreviations: IR – immediate release; SR – sustained release; AE – adverse event.

7.4.4 Study E2020-A001-023

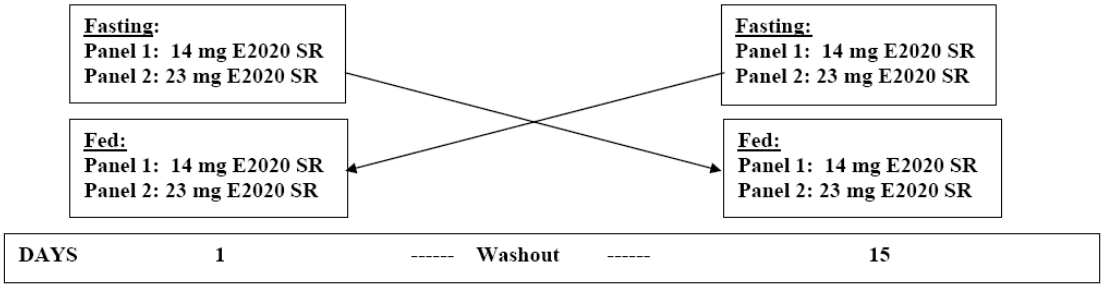
7.4.4.1 Outline

This was a randomized, open-label, open-label, two-period, two-sequence crossover, single and repeated-dose study that was intended to evaluate the effect of food on the bioavailability of the donepezil SR tablet.

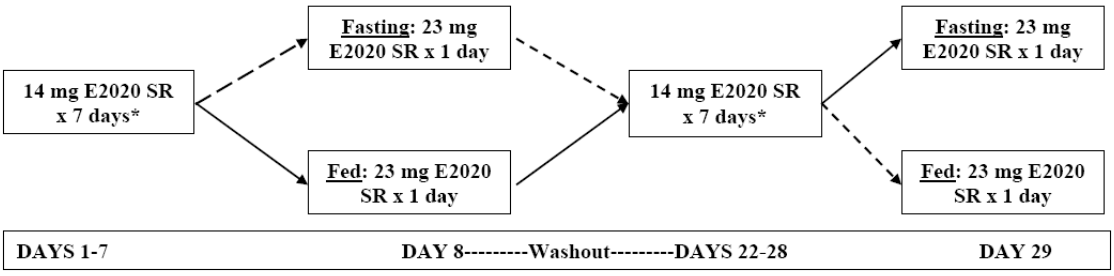
Subjects enrolled in this study were to be assigned to one of 3 dosing panels

Panel	Dose
1	Donepezil SR 14 mg as a single dose
2	Donepezil SR 23 mg as a single dose
3	Donepezil SR 14 mg QD for 7 days followed by donepezil SR 23 mg as a single dose

The cross-over dosing schema for Panels 1 and 2 is in the following sponsor figure.



The cross-over dosing schema for Panel 3 is in the next sponsor figure.



* 14 mg E2020 SR was administered as a single dose in the morning of Days 1 and 22 under fasting conditions. On Days 2-7 and Days 23-28, 14 mg E2020 SR was administered after breakfast.

79 healthy men and women ranging in age from 19 to 45 years were enrolled in the study.

7.4.4.2 Safety Data

There were no deaths or serious adverse events in this study.

20 subjects discontinued from the study because of adverse events; in 18 of these subjects, the adverse event responsible for discontinuation was vomiting. 15/20 subjects who discontinued were in Panel 2.

Any adverse event that occurred in Panel 1, either in the fed or fasted state, are summarized in the next table, copied from part of a sponsor table. The table indicates the number of subjects with adverse events.

System Organ Class And Preferred Term	1	
	14 mg E2020 SR	
	Fasted (n=15)	Fed (n=17)
Psychiatric Disorders		
Abnormal Dreams	4 (26.7%)	0 (0.0%)
Confusional state	0 (0.0%)	0 (0.0%)
Euphoric mood	0 (0.0%)	0 (0.0%)
Insomnia	0 (0.0%)	1 (5.9%)
Nervousness	0 (0.0%)	0 (0.0%)
Respiratory, Thoracic, and Mediastinal Disorders		
Pharyngolaryngial pain	1 (6.7%)	0 (0.0%)
Skin and Subcutaneous Tissue Disorders		
Hyperhidrosis	1 (6.7%)	1 (5.9%)
Vascular Disorders		
Flushing	0 (0.0%)	0 (0.0%)

Treatment-emergent adverse events that occurred in ≥ 5% of subjects who received single doses of 23 mg of donepezil SR (Panel 2) in this study, either in the fed or fasted state, are displayed in the following sponsor table.

Preferred Term	Number (%) of Subjects		
	Donepezil SR 23 mg		
	Fasted (n=22)	Fed (n=30)	Entire Study (n=35)
Subjects with at least one AE	18 (81.8)	27 (90.0)	35 (100.0)
Nausea	15 (68.2)	23 (76.7)	31 (88.6)
Vomiting	10 (45.5)	22 (73.3)	29 (82.9)
Dizziness	9 (40.9)	10 (33.3)	18 (51.4)
Headache	5 (22.7)	3 (10.0)	8 (22.9)
Hyperhidrosis	2 (9.1)	4 (13.3)	6 (17.1)
Flushing	0 (0.0)	4 (13.3)	4 (11.4)
Tremor	2 (9.1)	2 (6.7)	4 (11.4)
Abdominal pain	2 (9.1)	1 (3.3)	3 (8.6)
Euphoric mood	3 (13.6)	0	3 (8.6)
Fatigue	1 (4.5)	3 (10.0)	3 (8.6)
Hypomagnesaemia	1 (4.5)	2 (6.7)	3 (8.6)
Diarrhea	2 (9.1)	0	2 (5.7)
Muscle spasms	1 (4.5)	1 (3.3)	2 (5.7)
Nervousness	0	2 (6.7)	2 (5.7)

Abbreviations: AE – adverse event; SR – sustained release.

Treatment-emergent adverse events that occurred in ≥ 5% of subjects who received the dosing regimen for Panel 3, either in the fed or fasted state, are displayed in the next sponsor table.

Preferred Term	Number (%) of Subjects		
	Donepezil SR 14 mg/23 mg		
	Fasted (n=21)	Fed (n=22)	Entire Study (n=27)
Subjects with at least one AE	19 (90.5)	21 (95.5)	25 (92.6)
Nausea	15 (71.4)	17 (77.3)	22 (81.5)
Dizziness	11 (52.4)	14 (63.6)	19 (70.4)
Vomiting	8 (38.1)	13 (59.1)	17 (63.0)
Headache	9 (42.9)	10 (45.5)	13 (48.1)
Fatigue	6 (28.6)	9 (40.9)	11 (40.7)
Diarrhea	6 (28.6)	5 (22.7)	9 (33.3)
Insomnia	5 (23.8)	4 (18.2)	8 (29.6)
Abdominal pain	5 (23.8)	5 (22.7)	7 (25.9)
Flushing	3 (14.3)	3 (13.6)	5 (18.5)
Somnolence	4 (19.0)	2 (9.1)	5 (18.5)
Anorexia	2 (9.5)	2 (9.1)	4 (14.8)
Hyperhidrosis	1 (4.8)	3 (13.6)	4 (14.8)
Muscle spasms	1 (4.8)	4 (18.2)	4 (14.8)
Abnormal dreams	2 (9.5)	2 (9.1)	3 (11.1)
Confusional state	1 (4.8)	2 (9.1)	3 (11.1)
Irritability	1 (4.8)	2 (9.1)	3 (11.1)
Nervousness	2 (9.5)	2 (9.1)	3 (11.1)
Pharyngolaryngeal pain	0	3 (13.6)	3 (11.1)
Tremor	1 (4.8)	2 (9.1)	3 (11.1)
Vision blurred	1 (4.8)	2 (9.1)	3 (11.1)
Chest discomfort	2 (9.5)	1 (4.5)	2 (7.4)
Cold sweat	0	2 (9.1)	2 (7.4)
Disorientation	0	2 (9.1)	2 (7.4)
Dysarthria	0	2 (9.1)	2 (7.4)
Dyspepsia	0	2 (9.1)	2 (7.4)
Dyspnea	1 (4.8)	1 (4.5)	2 (7.4)
Eructation	2 (9.5)	1 (4.5)	2 (7.4)
Euphoric mood	1 (4.8)	2 (9.1)	2 (7.4)
Flatulence	2 (9.5)	0	2 (7.4)
Palpitations	1 (4.8)	1 (4.5)	2 (7.4)
Photophobia	1 (4.8)	1 (4.5)	2 (7.4)
Pollakiuria	1 (4.8)	1 (4.5)	2 (7.4)
Skin irritation	1 (4.8)	1 (4.5)	2 (7.4)

Abbreviations: AE – adverse event; SR – sustained release.

7.5 Sponsor's Conclusions

The sponsor points out that the main source of safety data in the Summary of Clinical Safety is Study 326, with limited additional data being obtained from Study 328 and from the 4 clinical pharmacology studies.

The sponsor's conclusions regarding the safety results of Study 326 are repeated below.

The overall incidence of treatment-emergent signs and symptoms was higher in the donepezil 23 mg QD group than in the donepezil 10 mg QD group, with nausea, vomiting, diarrhea and anorexia occurring more often in the former than in the latter group. The majority of adverse events in both treatment groups were mild to moderate in severity. The difference between treatment groups in the incidence of adverse events attributable to the cholinomimetic effects of donepezil was most apparent early during treatment, as might have been expected given that the donepezil 23 mg QD group had an escalation in dose at the commencement of the study

The sponsor has not identified any additional safety concerns in the available data for Study 328 or in the safety data for the clinical pharmacology studies.

7.6 Reviewer's Comments

I had commented earlier about the safety results of Study 326, and noted, with concern, the high incidence of vomiting in the 23 mg QD dose of donepezil relative to the other dose group.

I concur that the available data for Study 328 and the safety data for the clinical pharmacology studies do not raise any additional clinically significant safety concerns.

8. 120-Day Safety Update

The 120-Day Safety Update report for this application was submitted on January 21, 2010, in electronic format.

This update consists not only of new safety data that was not included in the original submission of this application, but of a full summary of clinical safety data for all the following studies.

- Study E2020-G000-326
- Study E2020-G000-328 (an ongoing study)
- Clinical pharmacology studies, listed below
    - E2020-A001-020
    - E2020-A001-021
    - E2020-A001-022
    - E2020-A001-023.

The full safety data for the randomized, double-blind, placebo-controlled, parallel-arm study E2020-G000-326, and for the 4 clinical pharmacology studies listed

above were already included in the original submission for this application. For the ongoing open-label extension study E2020-G000-328 (also referred to as Study 328), the cut-off date for safety data from Study 328 included in the original NDA submission was June 30, 2009, except for discontinuations due to adverse events for which the cut-off date was April 1, 2009.

In the 120-Day Safety Update, the new safety data provided are exclusively for Study 328 and data for deaths, serious adverse events, and discontinuations due to adverse events in Study 328 include the following:

- Council for International Organizations of Medical Sciences (CIOMS) forms for deaths and serious adverse events that occurred through a cut-off date of November 25, 2009
- Listings of deaths and serious adverse events that occurred through a cut-off date of July 25, 2009
- Narratives for discontinuations due to non-serious adverse events that occurred through a cut-off date of July 25, 2009.

Note that in the 120-Day Safety Update, the available data for Study 328 are presented in a cumulative manner so as to include a combination of data originally submitted with this application as well as new data contained in the Safety Update. They are therefore also summarized in the same manner below.

8.1 Patient Disposition In Study 328

A total of 915 patients have been enrolled in Study 328, of whom the participation of 589 patients remains ongoing. The disposition of these patients, based on their treatment assignment in the preceding Study 326, is the sponsor table below: patients who received donepezil 23 mg QD in Study 326 are in the SR/SR group whereas those who received donepezil 10 mg QD in Study 326 are listed in the IR/SR group (the same nomenclature is used for other sponsor tables in this Update).

	Number (%) of Patients[a]		
	SR/SR[ab]	IR/SR[ab]	Total
Enrolled	579	336	915
Safety Population	570	332	902
Completed	89 (15.6)	46 (13.9)	135 (15.0)
Discontinued	99 (17.4)	79 (23.8)	178 (19.7)
Ongoing	382 (67.0)	207 (62.3)	589 (65.3)
Reason for discontinuation			
AE[c]	48 (8.4)	42 (12.7)	90 (10.0)
Medication noncompliance	3 (0.5)	0 (0.0)	3 (0.3)
Protocol violation	1 (0.2)	1 (0.3)	2 (0.2)
Request of sponsor or investigator	5 (0.9)	5 (1.5)	10 (1.1)
Patient withdrew consent	17 (3.0)	17 (5.1)	34 (3.8)
Lack of efficacy	7 (1.2)	1 (0.3)	8 (0.9)
Other	18 (3.2)	13 (3.9)	31 (3.4)
Death	4 (0.7)[d]	3 (0.9)	7 (0.8)

[a] Number of patients in the Safety Population was used as the denominator for calculating percentages.

[b] SR/SR refers to patients in Study 328 who received donepezil SR 23 mg treatment in Study 326. IR/SR refers to patients in Study 328 who received donepezil IR 10 mg treatment in Study 326.

[c] Includes SAEs.

[d] One SR/SR patient died within 30 days after the last dose of study medication, and therefore, is not included in this table.

Abbreviations: SR – sustained release; IR – immediate release; AE – adverse event; SAE – serious adverse event.

Note that there has already been a higher incidence of discontinuations due to adverse events in those who received donepezil in a dose of 10 mg QD in Study 326, a finding that is not unexpected.

8.2 Duration Of Exposure To Study Drug In Study 328

The duration of exposure to donepezil 23 mg QD in Study 328, for patients who completed or discontinued, is summarized based on treatment assignment in Study 326 in the following sponsor table.

Duration in months:	SR/SR[a] (n=570)	IR/SR[a] (n=332)	Total (N=902)
	n (%)[b]	n (%)[b]	n (%)[b]
Number of Patients who completed or discontinued from the study	188	125	313
< 3	34 (18.1)	38 (30.4)	72 (23.0)
3 to < 6	26 (13.8)	18 (14.4)	44 (14.1)
≥ 6	27 (14.4)	19 (15.2)	46 (14.7)
9 to <12	47 (25.0)	20 (16.0)	67 (21.4)
≥ 12	54 (28.7)	30 (24.0)	84 (26.8)

Note: The treatment duration was defined as the total number of dosing days from first to last day (inclusive) of study treatment.

[a] *SR/SR refers to patients in Study 328 who received donepezil SR 23 mg in Study 326. IR/SR refers to patients in Study 328 who received donepezil IR 10 mg in Study 326.*

[b] *Number of patients who completed/ discontinued from the study was used as the denominator for computing percentages.*

Abbreviations: IR – immediate release; SR – sustained release; Max – maximum; Min – minimum; SD – standard deviation.

8.3 Adverse Events In Study 328

8.3.1 All Adverse Events

The following sponsor table provides an overview of the incidence of treatment-emergent signs and symptoms, based on their prior treatment assignment in Study 326. As the table indicates, the incidence of specific categories of adverse events was higher, as might be expected, in those who received donepezil 10 mg QD in the preceding double-blind study, Study 326.

	Number (%) of Patients[a]					
	SR/SR[b] (n=570)		IR/SR[b] (n=332)		Total N=902)	
Patients who experienced TESS[c,d]	335	(58.8)	224	(67.5)	559	(62.0)
Patients who experienced serious TESS	50	(8.8)	35	(10.5)	85	(9.4)
Patients who experienced severe TESS	40	(7.0)	41	(12.3)	81	(9.0)
Patients who discontinued due to TESS	49	(8.6)	45	(13.6)	94	(10.4)
Patients who died[e]	5	(0.9)	3	(0.9)	8	(0.9)

Note: Data are provided through 25 July 2009; study is ongoing.

[a] *Number of patients in the Safety Population was used as the denominator for computing percentages.*

[b] *SR/SR refers to patients in Study 328 who received donepezil SR 23 mg in Study 326. IR/SR refers to patients in Study 328 who received donepezil IR 10 mg in Study 326.*

[c] *TESS was defined as an AE that either 1) began on or after the date of the first dose of study drug (up to 30 days after date of last dose of study drug or 2) increased in severity during the treatment period.*

[d] *Patients were counted only once per treatment in each row.*

[e] *Includes patients who died during the study or within 30 days of discontinuing study medication.*

Abbreviations: IR – immediate release; SR – sustained release; AE – adverse event; TESS – treatment-emergent signs or symptoms.

Also note that the incidence of discontinuations due to adverse events in the above table in both groups is minimally different from that in the earlier sponsor table depicting patient disposition; the reason for that inconsistency is not entirely clear, but the inconsistency is of little import.

8.3.2 Most Common Adverse Events

The incidence of the most common treatment-emergent signs and symptoms so far is in the following sponsor table, which depicts those events that occurred in at least 2% of those who were in either of the two treatment groups in the preceding double-blind study.

As the table indicates, the incidence of nausea and vomiting was more than 2-fold higher in those who received donepezil in a dose of 10 mg QD in the preceding double-blind trial than in those who received donepezil in a dose of 23 mg QD in Study 326; the incidence of diarrhea, weight loss, anorexia, and dizziness was also higher in the IR/SR group. The difference between the 2 groups in the incidence of gastrointestinal adverse events was most apparent during the first month of treatment.

Body System Preferred Term	Number (%) of Patients[a,b]					
	SR/SR[c] (n=570)		IR/SR[c] (n=332)		Total (N=902)	
Patients with at least one TESS	335	(58.8)	224	(67.5)	559	(62.0)
Gastrointestinal disorders						
Nausea	8	(1.4)	18	(5.4)	26	(2.9)
Vomiting	7	(1.2)	12	(3.6)	19	(2.1)
Diarrhea	16	(2.8)	15	(4.5)	31	(3.4)
General disorders and administration site conditions						
Irritability	11	(1.9)	7	(2.1)	18	(2.0)
Asthenia	4	(0.7)	9	(2.7)	13	(1.4)
Infections and infestations						
Urinary tract infection	20	(3.5)	14	(4.2)	34	(3.8)
Nasopharyngitis	10	(1.8)	7	(2.1)	17	(1.9)
Injury, poisoning, and procedural complications						
Fall	35	(6.1)	14	(4.2)	49	(5.4)
Investigations						
Weight decreased	28	(4.9)	27	(8.1)	55	(6.1)
Metabolism and nutrition disorders						
Anorexia	6	(1.1)	8	(2.4)	14	(1.6)
Hypercholesterolemia	9	(1.6)	7	(2.1)	16	(1.8)
Musculoskeletal and connective tissue disorders						
Arthralgia	4	(0.7)	8	(2.4)	12	(1.3)
Nervous system disorders						
Syncope	13	(2.3)	6	(1.8)	19	(2.1)
Dizziness	4	(0.7)	9	(2.7)	13	(1.4)
Psychiatric disorders						
Agitation	25	(4.4)	20	(6.0)	45	(5.0)
Aggression	22	(3.9)	19	(5.7)	41	(4.5)
Depression	15	(2.6)	7	(2.1)	22	(2.4)
Insomnia	13	(2.3)	14	(4.2)	27	(3.0)
Renal and urinary disorders						
Urinary incontinence	6	(1.1)	8	(2.4)	14	(1.6)

Note: Data are provided through 25 July 2009; study is ongoing.

[a] *Patients were counted only once per treatment in each row..*

[b] *The Safety Population was used as the denominator for computing percentages.*

[c] *SR/SR refers to patients in Study 328 who received donepezil SR 23 mg in Study 326. IR/SR refers to patients in Study 328 who received donepezil IR 10 mg in Study 326.*

Abbreviations: IR – immediate release; SR – sustained release; TESS – treatment-emergent signs or symptoms.

8.3.3 Deaths

Deaths that have occurred in Study 328 are summarized in the following sponsor table by treatment assignment in Study 326. As the table indicates, a total of 8 deaths have occurred so far in this study; the individual clinical summaries (in CIOMS forms) do not suggest that any of these events were clearly attributable

to the use of donepezil; most could have been due to incidental illnesses common in this population.

	Number (%) of Patients[a,b]		
Body System Preferred Term	SR/SR[c] (n=570)	IR/SR[c] (n=332)	Total (N=902)
Patients with AEs associated with fatal outcome[d]	5 (0.9)	3 (0.9)	8 (0.9)
Cardiac disorders			
Cardiac failure	0 (0.0)	1 (0.3)	1 (0.1)
Gastrointestinal disorders			
Hematemesis	0 (0.0)	1 (0.3)	1 (0.1)
Pancreatic mass	1 (0.2)	0 (0.0)	1 (0.1)
General disorders and administration site conditions			
Death	2 (0.4)	0 (0.0)	2 (0.2)
Sudden death	0 (0.0)	1 (0.3)	1 (0.1)
Infections and infestations			
Pneumonia	1 (0.2)	0 (0.0)	1 (0.1)
Sepsis	1 (0.2)	0 (0.0)	1 (0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung neoplasm malignant	1 (0.2)	0 (0.0)	1 (0.1)
Renal and urinary disorders			
Renal failure acute	1 (0.2)	0 (0.0)	1 (0.1)

Note: Data are provided through 25 July 2009; study is ongoing.

[a] Patients are only counted once per treatment in each row.

[b] The Safety Population was used as the denominator for computing percentages.

[c] SR/SR refers to patients in Study 328 who received donepezil SR 23 mg in Study 326. IR/SR refers to patients in Study 328 who received donepezil IR 10 mg in Study 326.

[d] Refers to any deaths that occurred during the study or within 30 days after the last dose of study medication.

Abbreviations: IR – immediate release; SR – sustained release; AE – adverse event.

8.3.4 Serious Adverse Events

A total of 85 patients have experienced serious adverse events, both fatal and non-fatal, in Study 328; 50 (8.8%) have been in the SR/SR group and 35 (10.5%) in the IR/SR group. Individual types of event have been very infrequent. Again, the individual clinical summaries (in CIOMS forms) do not strongly suggest that any of these events were clearly linked to the use of donepezil; most were equally likely have been due to incidental illnesses common in this population.

8.3.5 Discontinuations Due To Adverse Events

Treatment-emergent signs and symptoms that led to treatment discontinuation were seen in a total of 94 patients enrolled in this currently-ongoing study. Their incidence based on treatment assignment in the preceding double-blind study is in the following table, which I have copied from the submission.

Note that the overall incidence of such events was higher in those who received donepezil in a dose of 10 mg QD in the previous double-blind trial than in those who received 23 mg QD; so was the incidence of several individual events including nausea, vomiting, and bradycardia.

Body System Preferred Term	Number (%) of Patients[a,b] SR/SR[c] (n=570)	 IR/SR[c] (n=332)	 Total (N=902)
TESS leading to discontinuation	49 (8.6)	45 (13.6)	94 (10.4)
Cardiac disorders			
Bradycardia	0 (0.0)	3 (0.9)	3 (0.3)
Cardiac failure	0 (0.0)	1 (0.3)	1 (0.1)
Congenital, familial and genetic disorders	0 (0.0)	1 (0.3)	1 (0.1)
Encephalocele	0 (0.0)	1 (0.3)	1 (0.1)
Gastrointestinal disorders			
Abdominal discomfort	0 (0.0)	1 (0.3)	1 (0.1)
Diarrhea	3 (0.5)	1 (0.3)	4 (0.4)
Fecal incontinence	1 (0.2)	1 (0.3)	2 (0.2)
Hematemesis	0 (0.0)	1 (0.3)	1 (0.1)
Nausea	0 (0.0)	4 (1.2)	4 (0.4)
Vomiting	0 (0.0)	4 (1.2)	4 (0.4)
General disorders and administration site conditions			
Asthenia	0 (0.0)	2 (0.6)	2 (0.2)
Death	2 (0.4)	0 (0.0)	2 (0.2)
Edema peripheral	0 (0.0)	1 (0.3)	1 (0.1)
Sudden death	0 (0.0)	1 (0.3)	1 (0.1)
Hepatobiliary disorders			
Liver disorder	0 (0.0)	1 (0.3)	1 (0.1)
Injury, poisoning and procedural complications			
Fall	0 (0.0)	1 (0.3)	1 (0.1)
Subdural hematoma	0 (0.0)	2 (0.6)	2 (0.2)
Metabolism and nutrition disorders			
Anorexia	0 (0.0)	1 (0.3)	1 (0.1)
Increased appetite	0 (0.0)	1 (0.3)	1 (0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.2)	2 (0.6)	3 (0.3)
Lung neoplasm malignant	1 (0.2)	1 (0.3)	2 (0.2)
Malignant melanoma	0 (0.0)	1 (0.3)	1 (0.1)
Nervous system disorders			
Bradykinesia	0 (0.0)	1 (0.3)	1 (0.1)
Cerebral hemorrhage	1 (0.2)	1 (0.3)	2 (0.2)
Dementia	0 (0.0)	1 (0.3)	1 (0.1)
Dementia Alzheimer's type	0 (0.0)	1 (0.3)	1 (0.1)
Dizziness	2 (0.4)	1 (0.3)	3 (0.3)
Ischemic cerebral infarction	0 (0.0)	1 (0.3)	1 (0.1)

Body System Preferred Term	Number (%) of Patients[a,b] SR/SR[c] (n=570)	 IR/SR[c] (n=332)	 Total (N=902)
Syncope	2 (0.4)	1 (0.3)	3 (0.3)
Psychiatric disorders			
Aggression	4 (0.7)	1 (0.3)	5 (0.6)
Agitation	6 (1.1)	4 (1.2)	10 (1.1)
Major depression	1 (0.2)	1 (0.3)	2 (0.2)
Renal and urinary disorders			
Urinary incontinence	0 (0.0)	1 (0.3)	1 (0.1)
Uncoded Body System			
Uncoded Preferred Term	0 (0.0)	2 (0.6)	2 (0.2)

Note: Data are provided through 25 July 2009; study is ongoing

[a] Patients were counted only once per treatment in each row.

[b] The Safety Population was used as the denominator for computing percentages.

[c] SR/SR refers to patients in Study 328 who received donepezil SR 23 mg in Study 326. IR/SR refers to patients in Study 328 who received donepezil IR 10 mg in Study 326.

Abbreviations: IR – immediate release; SR – sustained release; TESS – treatment-emergent signs or symptoms.

8.4 Laboratory Data In Study 328

There were no differences of note in the incidence of treatment-emergent abnormal laboratory values, or of changes from baseline in laboratory data, based on treatment assignment in the preceding double-blind trial, Study 326.

8.5 Vital Sign And Weight Data In Study 328

There were no differences of note in mean changes from baseline in vital sign parameters, between those who received donepezil 23 mg QD in the preceding double-blind trial, Study 326, and those who received donepezil in a dose of 10 mg QD in that study.

There were no differences of note in mean changes from baseline in weight, between those who received donepezil 23 mg QD in the preceding double-blind trial, Study 326, and those who received donepezil in a dose of 10 mg QD in that study.

8.6 Electrocardiograms In Study 328

There were no differences of note in electrocardiographic parameters between those who received . Neither were there any individual electrocardiographic data of particular concern that were seen during this study.

8.7 Sponsor's Conclusions

The sponsor has concluded that the data presented in the 120-Day Safety Update do not raise new safety concerns for, and support the approval, of the 23 mg QD dose of donepezil.

8.8 Reviewer's Comment

I concur that the safety data presented by the sponsor in the 120-Day Safety Update for donepezil do not raise any new concerns about the safety and tolerability of the 23 mg QD dose of donepezil.

9. Sponsor's Summary Of Clinical Pharmacokinetics Of New Formulation

The sponsor's summary of the clinical pharmacokinetics of the 23 mg tablet formulation (referred to as the sustained-release formulation in the submission) is based on the 4 Phase 1 clinical pharmacology studies (E2020-A001-020, E2020-A001-021, E2020-A001-022, and E2020-A001-023) and the results of a population pharmacokinetic analysis for Study E2020-G000-326.

The sponsor has drawn the following conclusions from the results of the Phase 1 studies, regarding the 23 mg tablet formulation of Aricept® proposed for approval:

- The selected formulation for the 23 mg tablet had a longer T_{max}, a lower dose-normalized C_{max}, and a slightly lower dose-normalized AUC than the approved immediate-release formulation
- With the 23 mg tablet, plasma concentrations of donepezil reached steady state over 14 days. After cessation of treatment, plasma concentrations of donepezil declined exponentially reaching asymptote within 2 weeks
- There was no clinically significant effect of food on the bioavailability of the selected 23 mg formulation.

The sponsor has summarized the key findings from the population pharmacokinetic analysis for Study E2020-G000-326 as follows:

- The pharmacokinetics of donepezil are well described using a two compartment linear model that includes transit input function and first-order elimination from the central compartment.
- The AUC at steady-state was about two-fold higher for the 23 mg donepezil formulation than for the 10 mg tablets (as might be expected)
- The T_{max} following the administration of the 23 mg formulation was about twice as long as for the 10 mg tablet
- A small difference in relative bioavailability was seen between the 23 mg and 10 mg formulations

- CYP2D6 phenotype, age, and weight were predictive of donepezil clearance, although those effects were small relative to the total variability in donepezil clearance. Gender and the co-administration of CYP2D6 inhibitors also had an effect on donepezil clearance.

10. Description Of New Drug Product Formulation

The 23 mg Aricept® tablet is described by the sponsor as a reddish, film-coated (b) (4) tablet containing 23 mg of donepezil.

Inactive ingredients in the 23 mg tablet are stated to include ethylcellulose, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate and methacrylic acid copolymer, Type C. The film coating includes ferric oxide, hypromellose 2910, polyethylene glycol 8000, talc and titanium dioxide.

11. Summary Of Additional Agency Reviews Of Submission

11.1 Chemistry, Manufacturing, And Controls Review

The Chemistry, Manufacturing, and Controls review of this submission has been completed by Akm Khairuzzaman, PhD. He has concluded that the data submitted in the application itself are sufficient to support the approval of this application.

He has recommended the deletion of any reference to (b) (4) (in reference to the 23 mg tablet) from the Package Insert.

Please see his review for further details.

11.2 Office Of Clinical Pharmacology Review

The Office of Clinical Pharmacology review of this submission has been completed by Xinning Yang, PhD. He has concluded that the application is acceptable from a Clinical Pharmacology perspective. He has made a number of recommendations pertaining to labeling. In addition he has recommended the following Phase 4 Commitments (these were eventually considered Phase 4 Requirements by the Agency):

- Characterization of the potential for donepezil to inhibit the following isoenzymes *in vitro*: CYP2B6, CYP2C8, and CYP2C19. If significant inhibition of one of more of these pathways is noted *in vitro*, an *in vivo* study might be required.

- Evaluation of whether donepezil is a substrate for p-glycoprotein

Dr Yang has made a number of observations in his review about the pharmacokinetic data submitted with this application. Among the more significant of his observations is that no formal study has been conducted to directly

compare the steady-state pharmacokinetics of the new 23 mg formulation and the earlier-approved 10 mg standard tablet formulation. The actual pharmacokinetic data and simulation results provided by the sponsor indicate that the 23 mg and 10 mg tablets have a similar fluctuation ratio and that after dose-normalization, the 23 mg and 10 mg tablets had a similar C_{max}, C_{min} and AUC at steady-state. Thus it could not be concluded that the 23 mg tablet was in fact a controlled (or extended)-release formulation.

Other findings that Dr Yang has noted include, but are not limited to, the following:

- A population pharmacokinetic analysis using Study 326 data showed differences in clearance between CYP2D6 genotypes indicating that poor metabolizers had a 31.5% lower clearance of donepezil than extensive metabolizers, whereas ultra-metabolizers had a 24% higher clearance than extensive metabolizers

- A population pharmacokinetic analysis again using Study 326 data showed that donepezil clearance was reduced by 17% in those concomitantly taking CYP2D6 inhibitors

- There was no effect of food on the pharmacokinetics of donepezil.

(b) (4)

A review by Houda Mahayni, PhD, Biopharmaceutics Reviewer in the Office of New Drug Quality Assessment, was completed on February 4, 2010 and concluded that the sponsor's dissolution specifications for the proposed new formulation were acceptable.

11.3 Proprietary Name Review

The originally-proposed proprietary name for the 23 mg formulation of donepezil (b) (4) was judged by the Agency not to be acceptable and was withdrawn by the sponsor in a letter dated December 11, 2009

A review of the (b) (4) proprietary name subsequently proposed for the 23 mg tablet of donepezil was then completed by Irene Chan, PharmD, of the Division of Medical Error Prevention and Analysis (DMEPA) on April 1, 2010. The (b) (4) proprietary name was found to be acceptable at that time.

However, a subsequent letter to the sponsor from Carol Holquist, RPh, Director of DMEPA, dated May 24, 2010, stated that the proprietary name (b) (4) was no longer considered acceptable for the 23 mg tablet of donepezil, as that product no longer met the criteria for an extended-release formulation. The letter

further recommended that the 23 mg tablet of donepezil continued to be subsumed under the existing name, Aricept®. The same conclusion had been conveyed to the sponsor during a teleconference on May 14, 2010, in which both this Division and DMEPA participated.

11.4 Label And Labeling Review

A label and labeling review of this application was also completed by Irene Chan, PharmD, of DMEPA on July 14, 2010.

Dr Chan had comments for both the Division and applicant, which are further summarized or detailed below.

11.4.1 Comments For The Division

Her comments are copied below.

1. The Applicant has utilized the abbreviations "IV" and "µg" within the insert labeling to represent intravenous and micrograms. The abbreviation I.V can be misinterpreted to mean I.U or I.N. The abbreviation "µg" can be misinterpreted to mean "mg." As part of a national campaign to decrease the use of dangerous abbreviations, FDA agreed to not use such abbreviations in the approved labeling of products because these abbreviations can be carried over to prescribing. Therefore we recommend that "IV" be replaced with the text *intravenous* and "µg" be replaced with the text *micrograms* or *mcg*.
2. The Applicant has utilized trailing zeros within the insert labeling. Trailing zeros can lead to 10-fold errors in dosing. DMEPA recommends removing all trailing zeros with the exception of when it is required to demonstrate the level of precision of the value being reported, such as for laboratory results, imaging studies that report size of lesions, or catheter/tube sizes

(Note that the product label has been modified by me in accordance with the above).

11.4.2 Comments For The Applicant

In addition to general comments pertaining to labels and labeling, she also had comments pertaining to retail container labels, the professional sample blister foil label, and the professional sample carton label. Please see her review for further details. These comments were conveyed to the applicant (sponsor).

11.5 Biometrics Review

The contents of the Agency Biometrics review have already been summarized in Section 6.4

11.6 Pharmacology-Toxicology Review

The Pharmacology-Toxicology review of this submission was completed by David Hawver, PhD.

Dr Hawver considers the application approvable. He notes that no non-clinical studies were included in this application

Dr Hawver further notes that donepezil is often used in combination with memantine. Since donepezil can potentiate the neurodegeneration induced by memantine in the rat (Creeley et al. *Neurobiology of Aging* 29: 153-167, 2008), Dr Hawver has recommended that the sponsor conduct a single-dose oral neurotoxicity study with donepezil and memantine, alone, and in combination, in female rats, as a Post-Marketing Requirement. Details of how that study should be conducted are in his review.

Dr Hawver recommends changes to the product labeling that include conversion to the Physicians Labeling Rule format and modifications to the text describing reproductive and developmental toxicity studies in Section 8.1 and to the text describing carcinogenicity, mutagenesis, and fertility studies in Section 13.1. Please see his review for full details.

A memorandum from Dr Lois Freed, Pharmacology-Toxicology Team Leader additionally recommends changes to the text of the following sections of the product label: Section 8.3 (Nursing Mothers); Section 8.4 (Pediatric Usage); and Section 13.2 (Animal Toxicology). The last of these is a brief description of the results of the study conducted by Creeley et al and cited above. Please see Dr Freed's memorandum for further information.

12. Review Of Labeling

My review of the sponsor's proposed labeling (the version submitted on June 3, 2010) is below.

The draft labeling submitted by the sponsor is in Physician's Labeling Rule (PLR) format. The sub-headings in this section of my review are the same as in the label itself.

By agreement with the Agency and as documented in the sponsor's cover letter accompanying the submission of June 3, 2010, the proposed labeling combines that for all currently approved and marketed formulations of Aricept® (standard and orally-disintegrating 5 mg and 10 mg tablets) with the proposed labeling for the 23 mg formulation.

The currently-labeling for Aricept® is in standard format. For purposes of this submission, the approved labeling in standard format has been converted to PLR format by the sponsor, with a "Highlights" section added; it is this file that has

been used as the base document by me for editing labeling. Note that in a submission (Prior Approval Labeling Supplement) submitted on November 25, 2008, under NDA 20690, the sponsor had already proposed the conversion of the current approved labeling for Aricept® from standard to PLR format.

My review is confined to listing changes that have been made to the sponsor's proposed labeling by me and during the course of discussions with the sponsor; with some more significant changes, the reasons for making those changes have also been explained. The actual final label is in a separate document that has been filed by me as a component of this review.

Throughout product labeling, I have eliminated the "®" after ARICEPT. "Micrograms" has been substituted for "µg" at the recommendation of the Division of Medication Error Prevention and Analysis.

Note that the sponsor's proposed labeling has been both reviewed and edited, despite my overall recommendation that the application not be approved.

12.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

I have incorporated most changes proposed by the sponsor, but a number of editorial and other changes have been made including the addition of a statement that the 23 mg dose of Aricept® should not be administered until a patient has received the 10 mg dose for at least 3 months. A statement that Aricept® is an acetylcholinesterase inhibitor has been deleted.

12.2 FULL PRESCRIBING INFORMATION: CONTENTS

12.2.1 INDICATIONS AND USAGE

(b) (4)

The labeling as edited by me makes it clear that the 10 mg dose of Aricept® is effective for moderate to severe Alzheimer's Disease as well as mild to moderate Alzheimer's Disease.

12.2.2 DOSAGE AND ADMINISTRATION.

I have added a statement that the 23 mg dose of Aricept® should not be administered until a patient has received the 10 mg dose for at least 3 months.

The labeling for this section as edited by me makes it clear that the 10 mg dose of Aricept® is effective for moderate to severe Alzheimer's Disease as well as mild to moderate Alzheimer's Disease.

I have made a number of other editorial changes to the sponsor's proposed labeling for this section, including altering the sequence in which statements have been made and the headings without changing the substance of what the sponsor has stated.

12.2.3 DOSAGE FORMS AND STRENGTHS

The sponsor's proposed changes to this section have been accepted, with modifications proposed by the Agency Chemistry reviewer also included.

12.2.4 CONTRAINDICATIONS

No changes have been made to the labeling for this section.

12.2.5 WARNINGS AND PRECAUTIONS

The sponsor's proposed changes to this section have been incorporated with minor editorial changes. Other changes have been made including the addition of a new heading pertaining to nausea and vomiting.

12.2.6 ADVERSE REACTIONS

The adverse event tables for discontinuations due to adverse events occurring at a frequency of > 1% and all adverse events occurring at a frequency of > 2% for Study 326 (comparing the 23 mg QD dose with the 10 mg QD dose) have been modified as follows:

- The incidence rates have been corrected to the nearest whole number (or 0) as indicated.

- The second of the above tables has also been modified so as to include only those adverse events that were more frequent in those receiving the dose of 23 mg QD

- Corrections have been made to the incidence of diarrhea and vomiting in the sponsor's table displaying the incidence of discontinuations due to adverse events.

Other, mainly editorial, changes have been made to the product label.

12.2.7 DRUG INTERACTIONS

Changes recommended by the Clinical Pharmacology reviewer to this section of the product labeling have been concurred with by this reviewer, although minor editorial alterations to that text have been made.

(b) (4)

(b) (4)

12.2.8 USE IN SPECIFIC POPULATIONS

No changes have been made by me to this section of the sponsor's proposed labeling.

Changes recommended by the Pharmacology-Toxicology reviewer to the Pregnancy, Nursing Mothers, and Pediatric Use subsections have been incorporated into the labeling text.

12.2.9 OVERDOSAGE

No changes have been made to this section, except for using "intravenous" instead of "i.v." and eliminating trailing zeros, both as per the advice of the Division of Medication Error Prevention and Analysis.

12.2.10 DESCRIPTION

The sponsor's proposed changes to this section have been accepted, with modifications proposed by the Agency Chemistry reviewer also included.

12.2.11 CLINICAL PHARMACOLOGY

Changes recommended by the Clinical Pharmacology reviewer to this section of the product labeling have been concurred with by this reviewer, although minor editorial alterations to that text have been made.

12.2.12 NON-CLINICAL TOXICOLOGY

No changes have been made by me to this section of the sponsor's proposed labeling. Changes recommended by the Pharmacology-Toxicology reviewer to this section have been incorporated into the labeling text.

12.2.13 CLINICAL STUDIES

I have included a description of Study E2020-G000-326 (comparing the 23 mg QD dose with the 10 mg QD dose) in the product label. This description corresponds largely to that proposed by the sponsor. (b) (4)

A number of editorial changes have also been made to this section of the product label.

12.2.14 HOW SUPPLIED/STORAGE AND HANDLING

The sponsor's proposed changes to this section have been accepted, with modifications proposed by the Agency Chemistry reviewer also included.

12.2.15 PATIENT COUNSELING INFORMATION

The sponsor-supplied Patient Counseling Information section has designated as a Patient Package Insert. An abbreviated Patient Counseling Information section directed at the healthcare provider has been created by the sponsor to which minor editorial changes were made.

13. Financial Disclosure Certification

Financial disclosure information has been collected only for the single clinical efficacy trial, E2020-G000-326, included in this submission.

13.1 Components Of Certification

13.1.1 Certification Pertinent To Investigators/Sub-Investigators Who Declared That They Did Not Have Any Relevant Financial Interests (FDA Form 3454)

The sponsor has supplied a list of all such investigators and sub-investigators who were involved in these studies. In regard to this list the sponsor has:

- Certified that it has not entered into any financial agreement with the clinical investigators listed in the application, whereby the compensation to the investigator could be affected by the outcome of the study in which the investigator was a participant, as defined by 21 CFR 54.2 (a)

- Certified that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2 (b) did not disclose any such arrangements

- Certified that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2 (f).

13.1.2 Certification Pertinent To Investigators/Sub-Investigators From Whom Financial Information Could Not Be Obtained (FDA Form 3454)

The sponsor has listed a number of investigators and sub-investigators who were involved in these studies for whom financial information could not be obtained. For these individuals, the sponsor states that it acted with due diligence to obtain the requisite information, but was unsuccessful after repeated attempts.

13.1.3 Certification Pertinent To Investigators/Sub-Investigators With Disclosable Financial Interests (FDA Form 3455)

There were no investigators or sub-investigators to whom such certification applied.

13.2 Reviewer's Comments

It appears unlikely that the financial arrangements disclosed above introduced significant bias into the results of the single efficacy study (E2020-G000-326) submitted with this application.

14. Study Site Inspection Report

Two large sites (#s 6108 and 7069) for Study E2020-G000-326 were inspected by the Agency.

These sites are listed in the table below.

Site #, Name of Investigator, and Address	Number of Subjects Enrolled
Site #6108 Reinaldo D Verson, MD Columbus Research and Wellness 3645 Gentian Boulevard, #3B Columbus, GA 31907 USA	29
Site # 7069 Manuel Lavados Montes, MD Especialidades Medicas L y S (Consulta Privada) Kennedy 5757 Of. 608 Torre Oriente Edificio Marriott Las Condes Santiago 7560356 Chile	37

A Clinical Inspection Summary, dated May 17, 2010, for the above sites has been provided by Antoine El-Hage, PhD, of the Division of Scientific Investigations, Office of Compliance, Center for Drug Evaluation and Research. The summary indicates that data from both sites were considered reliable and acceptable in support of this application.

15. Overall Conclusions

The sponsor has failed to provide substantial evidence for the efficacy or safety of Aricept® administered in a dose of 23 mg QD to patients with moderate to severe Alzheimer's Disease.

16. Recommendation

I recommend that this application, which seeks the approval of Aricept® in a new dose strength of 23 mg, administered once daily, for the treatment of moderate to severe dementia of the Alzheimer's type not be approved.

Ranjit B. Mani, M.D.
Medical Reviewer

rbm 7/23/10
cc:
HFD-120
NDA 22568

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22568	ORIG-1	EISAI MEDICAL RESEARCH INC	DONEPEZIL HYDROCHLORIDE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RANJIT B MANI
07/23/2010