CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022568

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

PRODUCT (Generic Name):	Donepezil
PRODUCT (Brand Name):	ARICEPT®
NDA:	22-568
DOSAGE FORM:	Tablets
DOSAGE STRENGTH:	23 mg
INDICATION:	Moderate to severe dementia of the Alzheimer's type
NDA TYPE:	Standard NME
SUBMISSION DATE:	9/24/2009
SPONSOR:	Eisai Medical Research Inc.
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1.0 EXECUTIVE SUMMARY

The sponsor is seeking the approval of ARICEPT 23-mg tablets for the treatment of moderate to severe dementia of the Alzheimer's type.

Donepezil hydrochloride is a reversible inhibitor of the enzyme acetylcholinesterase. Its immediate-release formulations, Aricept® and Acricept® ODT tablets, have been approved in US to treat mild-to-moderate and severe Alzheimer's disease (AD) patients. 5 mg or 10 mg Aricept® once a day was shown to be effective for mild-to-moderate AD, while 10 mg Aricept® once per day was demonstrated with efficacy for severe AD in controlled clinical trials.

A higher strength (23 mg) of Aricept is proposed to be marketed as film-coated tablet, a sustained-release formulation, to be orally administered once a day to patients who have been established on 10 mg donepezil with good tolerability for at least 4 to 6 weeks.

The clinical development program for Aricept 23-mg tablet included four Phase I studies in healthy subjects (formulation selection study, single- and multiple-dose pharmacokinetic studies, food effect study), one pivotal Phase III study in patients and one *in vitro* dissolution study.

The Overall Clinical Pharmacology Summary is provided in Section 1.3.

1.1   RECOMMENDATION

The NDA is acceptable from a Clinical Pharmacology perspective. The Labeling recommendations and Phase IV commitments should be conveyed to the sponsor.

1.2   PHASE IV COMMITMENT

1. To characterize the inhibition potential of donepezil for CYP2B6, 2C8 and 2C19 *in vitro*. If significant inhibition is observed, further *in vivo* study may be necessary.

2. To evaluate whether donepezil is a substrate of P-gp.

1.3 OVERALL SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

The findings from overall clinical pharmacology and biopharmaceutics section are as follows:

<u>Exposure-Response for Effectiveness:</u>
In the ITT (intent-to-treat) population and OC (observed cases) population, donepezil 23 mg was statistically superior to donepezil 10 mg in improvement of cognitive function as measured by the severe impairment battery (SIB) total score.

Donepezil 23 mg was slightly better than 10 mg in the improvement of global performance as measured by clinician's interview-based impression of change plus caregiver input (CIBIC+) score. The difference was not statistically significant for the ITT population but approached the statistical criteria for OC population.

There was no difference between donepezil 23 mg and 10 mg in the secondary endpoints of ADCS-ADL (Alzheimer's Disease Cooperative Study-Activities of Daily Living) and MMSE (Mini-Mental State Examination).

Exposure-Response for Safety:
There appears to be dose related increase in adverse events (AEs). Most common AEs were nausea, diarrhea, vomiting, anorexia. More patients in donepezil 23 mg were reported with AEs including weight loss compared to 10 mg group. After 3 weeks of continued use, the differences in AE frequency were inappreciable between the two treatment groups.

General Pharmacokinetics (ADME characteristics) of Donepezil:
Absorption:
- Peak plasma concentrations (C_{max}) of donepezil sustained-release formulation 14 or 23 mg are attained in approximately 5-6 hours post-dose, longer than the C_{max} of donepezil immediate-release formulation 10 mg (3-4 hrs).
- Absolute bioavailability of donepezil is unknown. Donepezil is assumed well absorbed.

Distribution:
- Tissue distribution of donepezil is extensive, as evidenced by a high apparent volume of distribution (V_{ss}/F), 12-16 L/kg.

Metabolism and Excretion:
- Donepezil is metabolized by CYP450 isoenzymes 2D6 and 3A4, and undergoes glucuronidation.
- The elimination half-life ($t_{1/2}$) of donepezil is about 70 hours. The mean apparent plasma clearance (CL/F) is 0.13-0.19 L/hr/kg.

Multiple dose pharmacokinetics:
- Following multiple dose administration, donepezil accumulates in plasma by 4-7 folds and steady state is attained after 15 days of once-daily dosing.

Dose proportionality:
The pharmacokinetics of donepezil is linear and dose-proportional.

Pharmacokinetics in patients:
The steady-state exposure (AUC_{ss}) of donepezil was about 35% higher in patients than that in healthy subjects. This difference may be largely due to the effect of age on apparent clearance of donepezil. Population PK analysis revealed that clearance of donepezil decreases when age increases. Compared with patients of 65-year old, younger

patients of 40-year old may have a 33% increase in clearance, consistent with the observed difference in donepezil exposure between healthy younger subjects and patients who are mostly elderly people.

Intrinsic Factors:
Age:
Population PK analysis suggested that the clearance of donepezil in patients decreases with increase of age. Compared with patients of 65-year old, subjects of 90-year old have a 17% decrease in clearance, while patients of 40-year old have a 33% increase in clearance.

Gender:
Population PK analysis indicated that there was a 13.5% decrease of donepezil clearance in female patients compared to male subjects.

Body weight:
There was a relationship noted between body weight and clearance based on population PK analysis. Over the range of weights from 50 kg to 110 kg, clearance of donepezil increased from 7.77 L/hr to 14.04 L/hr, with a value of 10 L/hr for 70-kg individuals.

CYP2D6 polymorphisms:
Examination of the effect of CYP2D6 genotype in AD patients showed differences in clearance among CYP2D6 genotype subgroups. Population PK analysis revealed that, compared to the extensive metabolizes (EMs), poor metabolizes (PMs) had a 31.5% lower clearance and ultra-metabolizes (UMs) had a 24% higher clearance.

Extrinsic Factors:
Drug-Drug Interactions:
Population PK analysis revealed that donepezil clearance was reduced by 17% in patients receiving concomitant CYP2D6 inhibitors compared to patients taking donepezil alone.

Biopharmaceutics:
BCS Class:
BCS Class has not been established. Donepezil is assumed well absorbed. Its aqueous solubility is pH dependent.

Bioequivalence/Relative Bioavailability:
- The dose-normalized C_{max} of donepezil after a single dose of 23 mg sustained-release tablet was 62% of the C_{max} following a single dose of 10 mg immediate-release tablet (currently approved Aricept®).
- After dose normalization, the exposure (AUC_{0-inf}) of donepezil following a single dose of 23 mg sustained-release tablet was 81% of the donepezil exposure after a single dose of 10 mg immediate-release tablet.
- No formal PK study has been conducted to directly compare the steady-state pharmacokinetic of donepezil between the 23 mg sustained-release and 10 mg immediate-release tablets. Based on the PK data and simulation results provided

by the sponsor, donepezil 23 mg appears to have similar fluctuation ratio [defined as $(C_{max}-C_{min})/C_{ave}$] as 10 mg (23mg vs. 10mg: 0.39 vs. 0.51). After dose-normalization, donepezil 23 mg seems to have similar AUC, C_{max} and C_{min} as IR 10 mg at steady state.

Food Effect:
Food has no significant effect on the pharmacokinetics of donepezil.

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2.0   QUESTION BASED REVIEW

2.1   GENERAL ATTRIBUTES

2.1.1   Drug/Drug Product Information:

Dosage Form/Strengths/Route: Film-coated Tablets, 23 mg, Oral

Indication: Moderate to severe dementia of the Alzheimer's type

Dosage and administration (Sponsor's Proposed):

Aricept 23 mg can be administered one tablet per day. Patients have to be already established on 10 mg donepezil hydrochloride with good tolerability. Aricept 23 mg should not be administered until patients have been on a daily dose of 10 mg donepezil hydrochloride for 4 to 6 weeks.

Pharmacologic Class: Reversible cholinesterase inhibitor

Chemical Name: (±)-2, 3-dihydro-5, 6-dimethoxy-2-[[1-(phenylmethyl)-4-piperidinyl]methyl]-1H-inden-1-one hydrochloride, Mol Wt: 415.96
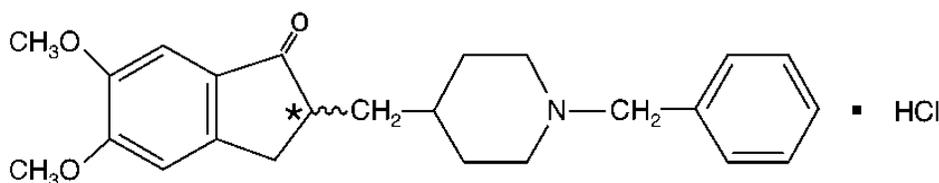
Other Names: E2020

Physical Characteristics: White crystalline powder.

Solubility: Freely soluble in chloroform, soluble in water and in glacial acetic acid, slightly soluble in ethanol and in acetonitrile and practically insoluble in ethyl acetate and in n-hexane

Mechanism of action: It is generally recognized that cognitive signs and symptoms of Alzheimer's disease may be due to a deficiency of cholinergic neurotransmission.

Donepezil hydrochloride is assumed to exert its therapeutic effect by enhancing cholinergic

function. It is a reversible inhibitor of cholinesterase, and thus can inhibit the hydrolysis of acetylcholine. The resulted increase in concentration of acetylcholine may be able to compensate the deficiency of cholinergic function in AD patients. There is no evidence showing that donepezil alters the progression of the disease.

Formulation: Sustained release formulation

2.2   GENERAL CLINICAL PHARMACOLOGY

2.2.1   What are the clinical studies used to support dosing or claims and what are their design features?

The sponsor's hypothesis of developing Aricept 23-mg tablet is that systemic exposure of donepezil is associated with inhibition of cholinesterase activity. Therefore, an increase in the currently approved dose (5-10mg) may produce greater inhibition of acetylcholinesterase activity that may enhance the cognitive benefit, and eventually achieve clinically meaningful improvement. However, simply increasing the dose of donepezil will increase $C_{max,}$ which may lead to more side-effects. Sustained-release formulation was therefore developed in aim to reduce the C_{max} at higher dose while maintaining adequate systemic exposure of donepezil.

The Aricept 23-mg tablet clinical development program included 4 Phase I studies in healthy subjects, one Phase III study and one *in vitro* dissolution study. (b) (4)

Table 1. Enumeration of Subjects in All Studies (Safety Population)				
Study Type	Placebo (N)	SR (N)	IR (10 mg) (N)	Total (N)
Overall Unique Subjects	15	1243	580	1756
Phase I study (020)	0	82	82	82
Phase I study (021)	0	57	27	84
Phase I study (022)	15	62	0	77
Phase I study (023)	0	79	0	79
Phase III study (326)	0	963	471	1434

Clinical Pharmacology Studies:

Three SR formulations were compared with the IR tablet at 10-mg dose level in a two-period, two-sequence, cross-over study (020). Based on the extent of decrease in C_{max} and AUC of donepezil compared to the IR tablet,   (b) (4)

Single-dose PK of donepezil SR   (b) (4)) 14 and 23 mg was then investigated along with IR 10 mg in a parallel-group study (021). Multiple-dose PK of donepezil SR 14 and 23 mg was further examined in a parallel-group, placebo-controlled study (022). Finally, the food effect on donepezil SR 14 and 23 mg was evaluated in a two-period, two- sequence, cross-over study (023).

Pivotal Clinical Study:
One Phase III study (326) was designed as a randomized, double-blind, parallel-group study to compare the efficacy/safety between donepezil IR10 mg and SR 23 mg. Patients with MMSE (Mini-Mental State Examination) baseline score of 0-20 and having been on treatment with 10 mg donepezil for at least three months were enrolled in the study and randomized at 2:1 ratio (SR 23 mg vs. IR10 mg, oral dose, once daily). The study was composed of visits at screening, baseline (at which time study medications were dispensed), 3 weeks (safety only), and 6, 12, 18 and 24 weeks or early termination.

2.2.2   What are the clinical end points and how are they measured in clinical pharmacology and clinical studies?

Primary efficacy endpoints in the Phase III study were the change of the severe impairment battery (SIB) total score from baseline to week 24, and the clinician's interview-based impression of change plus caregiver input (CIBIC+) score at week 24. These two endpoints reflect improvement of patients in cognitive function and global performance, respectively, and were used to determine whether donepezil 23 mg is superior to donepezil 10 mg in the ITT (intent-to-treat) population. SIB and CIBIC+ tests were performed in patients during the 6-, 12-, 18- and 24-week visits of study 326.

SIB change from Baseline to Week 24 is a continuous endpoint. The data in the ITT population were analyzed using an analysis of covariance (ANCOVA) model with terms for baseline, treatment, and country to estimate the treatment effects. For the categorical endpoint of CIBIC+ score at Week 24, a non-parametric ANCOVA combined with a Cochran-Mantel-Haenszel (CMH) test component was conducted. The analysis was adjusted for the Clinician's Interview-Based Impression of Severity plus caregiver input (CIBIS+) at baseline with a stratification adjustment for country.

Analysis of the primary endpoints was also conducted in OC (observed cases) population, and patient subgroups categorized based on concomitant use of memantine or not and MMSE baseline scores (3-14, 5-14, 0-16).

Secondary efficacy endpoints were the ADCS-ADL (Alzheimer's Disease Cooperative Study-Activities of Daily Living) total score change from Baseline to Week 24 and the MMSE total score change from Baseline to Week 24. ADCS-ADL and MMSE scores

represent the functional capabilities and cognitive function of a patient, respectively. These endpoints were also measured during the 6-, 12-, 18- and 24-week visits of study 326. A similar ANCOVA model to that used for the primary endpoints was used to analyze these secondary endpoints.

2.2.3 What are the characteristics of exposure/effectiveness relationships?

In the ITT population and OC population, donepezil SR 23 mg was statistically superior to IR 10 mg in improvement of cognitive function as measured by the change of SIB total score from baseline. Statistically significant difference favoring donepezil SR 23 mg was also observed for the sub-populations of patients.

Donepezil SR 23 mg was slightly better than donepezil IR 10 mg in the improvement of global performance as measured by CIBIC+ score. Such difference was not statistically significant for the ITT population but approached the statistical criteria (p=0.059) for OC population. With stratification of ITT population using MMSE baseline score, donepezil SR 23 mg was found statistically superior to IR 10 mg in terms of CIBIC+ score in sub-populations with MMSE baseline score of 0-16 and 5-14, while the difference approached significance in favor of SR 23 mg in sub-group with MMSE baseline score of 3-14. MMSE 0-16 subgroup represents the more severely impaired patients among the moderate-to-severe AD population. MMSE 3-14 and 5-14 were the cutoffs used to identify moderate-to-severe patients in the previous trials. Statistically significant difference favoring donepezil SR 23 mg was also observed for the US population (ITT).

The Agency pharmacometric review (Appendix III) demonstrated that the relationships between efficacy endpoints (SIB total score change from baseline and CIBIC+) and donepezil exposure are U-shaped (or inverted U-shaped depending on endpoint). The results imply that even though donepezil exposure is correlated with the cognitive benefit, higher plasma exposure does not warrant better clinical outcomes. There seems to be an optimal exposure window to achieve the maximum efficacy benefit. This optimal exposure window appears to be around 60-120 ng/mL for CIBIC+ and 90-130 ng/mL for SIB. Since the median exposures for 10 mg and 23 mg are around 57 ng/mL and 120 ng/mL, the observed difference in primary analysis results for SIB (23 mg is significantly better than 10 mg) and CIBIC+ (23 mg and 10 mg are comparable) may be explained by the different optimal exposure windows. Overall, 23 mg provides more benefit in terms of primary efficacy endpoints than 10 mg for moderate-severe AD patients.

There was no difference between donepezil SR 23 mg and IR 10 mg in terms of the secondary endpoints of AADCS-ADL or MMSE.

2.2.4 What are the characteristics of exposure-safety relationships?

There appears to be dose related increase in adverse events (AEs). Both the incidence of TESS (treatment-emergent signs and symptoms) and incidence of TESS resulting in

discontinuation from the study were higher in patients receiving donepezil SR 23 mg than IR 10 mg. For both groups, most TESS were classified as mild to moderate in severity. Most common adverse events (AEs) were nausea, diarrhea, vomiting, anorexia. The rates of serious TESS, severe AEs and deaths were similar in both groups. The higher rates of TESS in SR 23 mg was expected, since the patients had been tolerating the treatment of donepezil IR 10 mg for at least 3 months. The higher rates of TESS in SR group may reflect the incremental effect of the dose increase, and the rates of these events decreased over time.

More patients (4.7%) in donepezil SR 23 mg were reported with weight loss compared to donepezil IR 10 mg group (2.5%).

2.2.5 Does donepezil prolong QT or QTc interval?

No QT study has been conducted.

2.2.7 What are the general ADME characteristics of Donepezil?

The key ADME characteristics of donepezil are summarized below:

Absorption:
- Peak plasma concentrations (C_{max}) of donepezil SR are attained in approximately 5-6 hours post-dose, longer than the C_{max} of donepezil IR (3-4 hrs).
  It is noted that T_{max} of 9.16 hrs for SR was only observed in one study (020). In the later studies (021, 022, 023), the T_{max} of SR was about 5-6 hrs.
- Absolute bioavailability of donepezil is unknown. Donepezil is assumed well absorbed.

Distribution:
- Tissue distribution of donepezil is extensive, as evidenced by a high apparent volume of distribution (V_{ss}/F), 12-16 L/kg.

Metabolism and Excretion:
- Donepezil is metabolized by CYP450 isoenzymes 2D6 and 3A4, and undergoes glucuronidation.
- The elimination half-life ($t_{1/2}$) of donepezil is about 70 hours. The mean apparent plasma clearance (CL/F) is 0.13-0.19 L/hr/kg.

2.2.8 What are the basic pharmacokinetic parameters of Donepezil after single and multiple doses?

Single Dose Pharmacokinetics:
Single dose pharmacokinetics was assessed for donepezil SR 14 mg and 23 mg and IR 10 mg in healthy subjects. The PK parameters for donepezil are summarized in the following table.

Table 2: Pharmacokinetic summary of donepezil SR 23 mg, SR 14 mg, and IR 10 mg after single-dose administration to healthy subjects — Study 021

PK Parameter	Treatment Group		
	E2020 SR 14 mg (Test Drug)	E2020 SR 23 mg (Test Drug)	E2020 IR 10 mg (Reference Drug)
	(N=23)	(N=33)	(N=26)
AUC_{0-t} (ng*h/mL)			
Arithmetic mean (SD)	1186.93 (218.175)	1561.46 (450.364)	809.23 (219.408)
CV (%)	18.4	28.8	27.1
Median	1149.21	1616.50	754.99
Range	848.0 – 1585.3	569.0 – 2147.5	413.1 – 1269.5
$AUC_{0-\infty}$ (ng*h/mL)			
Arithmetic mean (SD)	1270.17 (243.004)	1650.84 (468.513)	885.30 (249.100)
CV (%)	19.1	28.4	28.1
Median	1242.88	1646.27	825.65
Range	917.5 – 1684.3	697.0 – 2317.3	559.0 – 1518.0
C_{max} (ng/mL)			
Arithmetic mean (SD)	23.13 (6.798)	32.63 (8.637)	20.90 (5.001)
CV (%)	29.4	26.5	23.9
Median	21.60	31.50	20.75
Range	12.3 – 35.6	16.3 – 50.6	12.6 – 31.6
t_{max} (h)			
Arithmetic mean (SD)	6.13 (1.866)	6.15 (1.873)	3.19 (0.939)
CV (%)	30.4	30.4	29.4
Median	6.00	6.00	3.00
Range	4.0 – 12.0	3.0 – 10.0	2.0 – 5.0
λz (1/h)			
Arithmetic mean (SD)	0.01 (0.002)	0.01 (0.004)	0.01 (0.002)
CV (%)	22.8	32.3	26.8
Median	0.01	0.01	0.01
Range	0.0 – 0.0	0.0 – 0.0	0.0 – 0.0
$t_{1/2}$ (h)			
Arithmetic mean (SD)	80.77 (22.407)	67.10 (17.965)	83.14 (24.097)
CV (%)	27.7	26.8	29.0
Median	76.20	64.75	80.13
Range	51.4 – 138.0	27.1 – 102.3	46.0 – 151.8

After single dose of donepezil SR, on average, maximum plasma concentrations of donepezil were attained at 6.1 h post-dose. Thereafter, plasma concentrations declined in a multi-phasic manner with a mean apparent terminal half-life ($t_{1/2}$) of approximately 67 to 80 h.

Figure 1. Mean plasma concentration versus time profiles (Entire Study or the First 24 hrs) after oral administration of single doses of donepezil SR 23 mg, SR 14 mg and IR 10 mg—Study 021
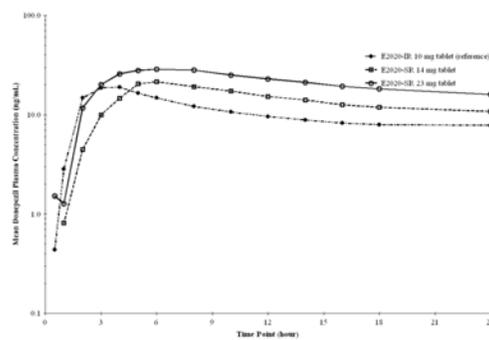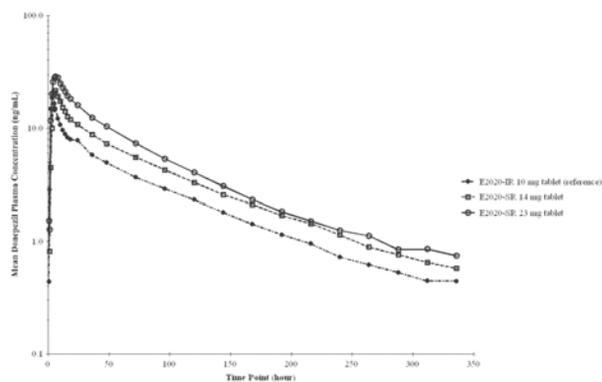
Multiple Dose Pharmacokinetics:

Multiple dose pharmacokinetics was assessed for donepezil SR 14 mg and 23 mg in healthy subjects.

Table 3. Study design of multiple-dose PK study (022)

| Group | Outpatient | | Inpatient | | |
	Period 1 (Days 1–7)		Period 2 (Days 8–21)		Period 3 (Days 22–35)
1	placebo 5 mg	→	donepezil SR 14 mg	→	donepezil SR 23 mg
2	placebo 5 mg	→	placebo 14 mg	→	placebo 23 mg
3	placebo 5 mg	→	donepezil SR 14 mg	→	placebo 14 mg
4	donepezil IR 5 mg	→	donepezil SR 14 mg	→	donepezil SR 23 mg
5	donepezil IR 5 mg	→	donepezil SR 14 mg	→	placebo 23 mg

Table 4: Summary of pharmacokinetic parameters of donepezil on day 35 after the last dose of 23 mg donepezil SR

| PK Parameter | Group | |
	Group 1 (n=9)	Group 4 (n=12)
C_{max} **(ng/mL)**		
Arithmetic mean (SD)	110.4 (27.84)	129.2 (38.52)
CV (%)	25.2	29.8
Median	105.0	124.5
Range	80 – 159	77 – 178
C_{avg} **(ng/mL)**		
Arithmetic mean (SD)	77.5 (18.63)	93.0 (25.51)
CV (%)	24.0	27.4
Median	70.4	91.8
Range	56 – 107	60 – 131
T_{max} **(h)**		
Arithmetic mean (SD)	4.6 (0.88)	5.2 (1.59)
CV (%)	19.4	30.7
Median	4.0	5.0
Range	4 – 6	3 – 8
AUC_{tau} **(ng*h/mL)**		
Arithmetic mean (SD)	1859.4 (447.16)	2232.5 (612.07)
CV (%)	24.0	27.4
Median	1688.7	2203.2
Range	1338 – 2558	1450 – 3154

AUC_{0-t} (ng*h/mL)		
Arithmetic mean (SD)	6329.6 (3197.22)	8368.5 (3298.50)
CV (%)	50.5	39.4
Median	5447.5	6994.1
Range	880 – 10927	4724 – 14241
$AUC_{0-\infty}$ (ng*h/mL)		
Arithmetic mean (SD)	7270.4 (2577.54)	8699.5 (3557.34)
CV (%)	35.5	40.9
Median	5767.5	7122.5
Range	4335 – 11399	4814 – 15113
$t_{1/2}$ (h)		
Arithmetic mean (SD)	62.9 (8.63)	64.5 (12.36)
CV (%)	13.7	19.2
Median	64.4	62.2
Range	47 – 73	46 – 87

After multiple doses of donepezil SR, on average, donepezil T_{max} was attained around 5 h post-dose, after which the plasma donepezil concentrations declined with a mean apparent $t_{1/2}$ of approximately 60-65 h.

Figure 2. Semi-log (Panel B) plots of mean plasma concentration versus time profile of donepezil on Day 35 after administration of the last Dose of donepezil SR 23 mg (study 022)

	Period 1 (Days 1-7)	Period 2 (Days 8 - 21)	Period 3 (Days 22-35)
Group 1:	5 mg Placebo	14 mg E2020 SR	23 mg E2020 SR
Group 3:	5 mg Placebo	14 mg E2020 SR	14 mg Placebo
Group 4:	5 mg E2020 IR	14 mg E2020 SR	23 mg E2020 SR
Group 5:	5 mg E2020 IR	14 mg E2020 SR	23 mg Placebo
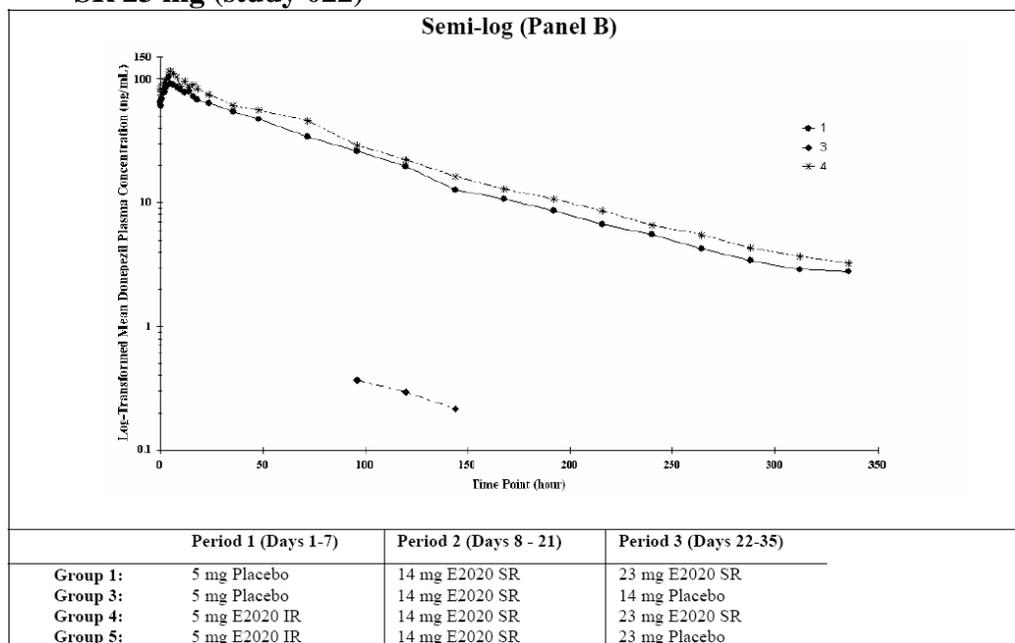
2.2.9   Do the pharmacokinetic parameters change with time following chronic dosing?

Donepezil accumulated in plasma following repeated administration. Compared to the a single dose of donepezil SR 23 mg, donepezil accumulates in plasma by 4- and 4.7-fold after multiple doses ($R_{A,Css(max)/C1(max)}$ and $R_{A,Css(min)/C1(min)}$, respectively). Steady-state plasma concentrations were reached after at least 14 days.

2.2.10 What is the variability in the PK data?

The CV% of C_{max} and AUC_{0-inf} of donepezil ranged from 19-30% in healthy subjects after a single dose of SR 14 mg or 23 mg. The CV% of general PK parameters (C_{max}, C_{ave}, AUC_{0-inf} and $AUC_{0-\tau}$) of donepezil in healthy subjects after multiple doses of SR was about 24-41%. Based on population PK analysis, the inter-subject variability (IIV) of apparent clearance of donepezil was 32.4% (expressed as CV%).

2.2.11 How do the pharmacokinetics of the drug in healthy volunteers compare to that in AD patients?

The steady-state exposure (AUC_{ss}) of donepezil SR 23 mg was about 35% higher in patients than in healthy subjects (3015 vs. 2232.5 ng*hr/ml). Consistently, the model-estimated apparent clearance of donepezil in patients and healthy subjects were 10 and 13.1 L/hr, respectively, based on population PK analysis. The difference in clearance of donepezil between patients and healthy volunteers may be largely due to the effect of age on clearance of donepezil. Population PK analysis revealed that clearance of donepezil decreases when age increases. Compared with patients of 65-year old, younger patients of 40-year old may have a 33% increase in clearance, consistent with the difference observed between healthy young subjects and patients who are largely elderly people.

2.2.12 Based on the pharmacokinetic parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

After single dose of donepezil SR 14 mg and 23 mg, the increase in exposure (AUC_{0-inf}) and concentrations (C_{max}) of donepezil in healthy volunteers was approximately dose proportional (study 021, 023).

After multiple doses of donepezil SR 14 mg and 23 mg, plasma concentrations and exposure of donepezil in healthy subjects also increased dose-proportionally (study 022).

Table 5. Comparisons of concentrations and exposure of donepezil after single- or multiple-dose administration of donepezil SR 14 mg and 23 mg.

Single-Dose	SR 14 mg	SR 23 mg	Ratio (23mg /14mg)
Cmax	23.13	32.63	1.41
AUC_{0-inf}	1270.17	1650.84	1.30
Multiple-Dose (Group 1)			
Cmax	61.5	110.4	1.80
AUC_{0-24hr}	1064	1859.4	1.75
Multiple-Dose (Group 4)			
Cmax	72.9	129.2	1.77
AUC_{0-24hr}	1296.4	2232.5	1.72

2.3   INTRINSIC FACTORS

2.3.1   What intrinsic factors influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics? Based on what is known about exposure response relationships and their variability, is dosage adjustment needed for any of the subgroups?

2.3.1.3   Effect of age:

No formal PK study has been performed to evaluate the effect of age on PK of donepezil. Population PK analysis suggested that the clearance of donepezil in patients decreases with increase of age. Compared with patients of 65-year old, subjects of 90-year old have a 17% decrease in clearance, while patients of 40-year old have a 33% increase in clearance. The effect of age on clearance of donepezil may be due to decreased metabolic functions of liver in elderly subjects. This change is not considered clinically meaningful.

Table 6. Effect of Age on Clearance – Final Phase III Pharmacokinetic Model

Age (y)	Clearance (L/h)	Percent of Reference*
40	13.26	132.59
50	11.65	116.47
60	10.48	104.76
65	10.00	100.00
70	9.58	95.79
80	8.86	88.64
90	8.28	82.77

Dosage adjustment: No

2.3.1.4   Effect of Gender:

No formal PK study has been conducted to evaluate the effect of gender on PK of donepezil. Population PK analysis indicated that there was a 13.5% decrease of donepezil clearance in female patients compared to male patients, which is not considered clinically meaningful.

Figure 3. Effect of Gender on Clearance of Donepezil
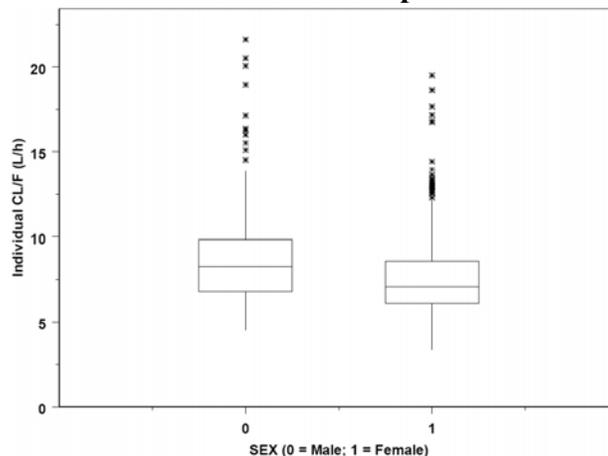
Dosage adjustment: No

2.3.1.6   CYP2D6 Polymorphism:
No specific pharmacokinetic study was performed to assess the effect of CYP2D6 polymorphisms on the PK of donepezil. Population PK analysis showed that compared to the extensive metabolizes (EMs, n=508), poor metabolizes (PMs, n=31) had a 31.5% slower clearance and ultra-metabolizes (UMs, n=13) had 24% faster clearance.

Table 7. Clearance Estimates and Associated Asymptotic 95% Confidence Intervals (CIs) by CYP2D6 Phenotype.

Parameter	Lower 95% Confidence Interval	Mean Parameter	Upper 95% Confidence Interval	Percent of Reference*
$CL/F_{2D6,EM}$ (L/h)	9.57	10	10.43	100
$CL/F_{2D6,PM}$ (L/h)	5.94	6.85	7.76	68.5
$CL/F_{2D6,URM}$ (L/h)	9.82	12.4	14.98	124

*- reference value is the clearance for an extensive metabolizer

Figure 4. Distribution of Clearance Values Based on Genotype for SR and IR Formulations
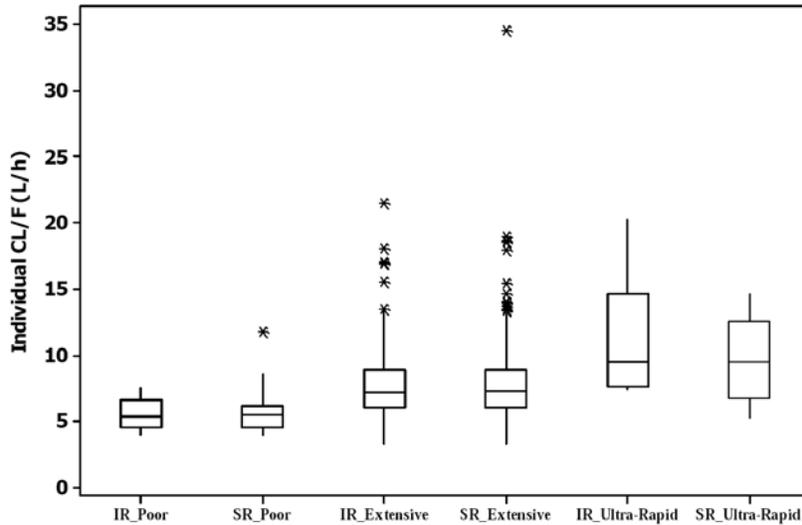
Overall, there was higher incidence of common TESS in the PM group than in the EM/UM groups for donepezil SR 23 mg treatment. In general, the incidence of gastrointestinal disorders was similar for the PM and EM groups for donepezil SR 23 mg treatment, and both groups had higher incidence than the UM group. It is noted that the numbers of patients in PM and UM groups were small, 42 and 17, respectively.

Dose adjustment: No dose adjustment was proposed by the sponsor.

Reviewer Comment: Caution is needed for concomitant use of donepezil SR 23 mg and strong CYP3A4 inhibitors (e.g., ketoconazole) in CYP2D6 PMs.

2.3.1.7 Body Weight:

There is no formal PK study to investigate the effect of body weight on PK of donepezil. A relationship between body weight and clearance of donepezil in patients was noted based on population PK analysis. Over the range of weights from 50 kg to 110 kg, clearance of donepezil increased from 7.77 L/hr to 14.04 L/hr.

Table 8. Effect of Weight on Clearance – Final Phase III Pharmacokinetic Model

Weight (kg)	Clearance (L/h)	Percent of Reference*
50	7.77	77.70
60	8.91	89.08
70	10.00	100.00
80	11.05	110.53
90	12.07	120.74
100	13.07	130.67
110	14.04	140.35

Dose adjustment: No dose adjustment based on body weight was proposed. (b) (4)

Such consideration appears more based on the concern about safety. Weight loss was known as an adverse event of donepezil. In the controlled clinical trial, among patients in 23 mg treatment group, those patients weighing < 55 kg reported more nausea, vomiting, and decreased weight than patients weighing 55 kg or more. There were more withdrawals due to adverse events as well.

2.4 EXTRINSIC FACTORS

2.4.1 Is donepezil a substrate, inhibitor or inducer of CYP enzymes?

The information below is obtained from the labeling of Aricept®

Substrate: Donepezil is metabolized by CYP450 isozymes and undergoes glucuronidation. CYP2D6 and 3A4 are primarily responsible for donepezil metabolism.

Inhibitor: Donepezil inhibits CYP2D6 and 3A4 with Ki about 50-130 μM. Considering its steady state C_{max} (0.36 μM), donepezil is a weak inhibitor of these enzymes.

Reviewer's Comment: The [I]/Ki ratio is much less than 0.1 for 2D6 or 3A4, based on the above values. According to the draft of DDI guidance currently under revisions, an alternative estimation of inhibitor concentration is maximum unbound blood concentration at the inlet to the liver. Using this formula, the [I] will be ~ 0.49 μM, still giving a [I]/Ki ratio << 0.1. Therefore, significant inhibition on 2D6 or 3A4 by donepezil *in vivo* is less likely.

There have been two DDI studies published in literature evaluating the effects of donepezil on warfarin and theophylline. AUC or Cmax of warfarin and theophylline were only increased up to 8.3% with co-administration of 5-mg or 10-mg multiple doses of donepezil, suggesting that donepezil does not significantly inhibit 1A2 or 2C9 *in vivo*.

So far there has been no report about *in vitro/in vivo* inhibition potency of donepezil on 2B6, 2C8 or 2C19. We consulted the medical officers about the possibility of concomitant usage of donepezil and drugs that are sensitive substrates of these enzymes. S-mephenytoin and efavirenz were ruled out because these are not likely to be prescribed to AD patients. Repaglinide is not commonly used, since there are many drugs currently marketed for non-insulin dependent diabetes. Though bupropion is prescribed to some AD patients, it is more used as second-line medication or add-on therapy for SSRIs. Considering the fact that donepezil has been approved in US since 1996 and used widely over the world, we recommend the evaluation of inhibition potential of donepezil on 2B6, 2C8 and 2C19 as PMC.

Inducer: Induction potential of donepezil is unknown.

2.4.2   Is donepezil a substrate and/or inhibitor of P-glycoprotein transport processes or any other transporter system?

This has not been evaluated. However, a drug interaction study has been conducted with digoxin. The AUC of digoxin after a single dose was only increased by 3.2% with co-administration of a single-dose donepezil, while digoxin C_{max} was not altered. These findings suggest that donepezil is less likely to be an inhibitor of P-gp.

The sponsor has not conducted any *in vitro/in vivo* study to evaluate donepezil as a substrate of P-gp.

Reviewer's Comment: In a literature study, the efflux ratio (ER) of donepezil across MDR1-MDCK monolayer was measured as 2.3, while only compounds with ER ≥ 3.0 were considered as P-gp substrates according to the authors (Summerfield SG, et al. *J Pharmacol Exp Ther.* 2007 Jul;322(1):205-13). In another study using MDR1-MDCK cells, the P-gp efflux ratio of donepezil was determined as 1.6 ± 0.4, also lower than the threshold (2.5) set by the authors for P-gp substrates (Wager TT, et al. *ACS Chem Neurosci.* 2010, 1, 420-434). In the other study, P-gp-expressing brain cell monolayers were utilized to perform the transcellular transport study and showed that the flux of donepezil from apical to basal and basal to apical sides of the cells were the same, indicating that donepezil is not human P-gp substrate (Yoshihiro O, *Drug Metab Rev.* 2005 Nov; 37 (suppl 2): 177-178).

According to the current DDI guidance, a net efflux ratio ($R=R_T/R_W$) over 2 is considered as a positive result if R_T is measured using MDCK-MDR1 cells. However, for the above studies, the net flux ratio can not be calculated, since there was no information about the ratio of donepezil across the non-transfected MDCK cells (R_W).

There is only one report suggesting that the transport of donepezil may be modulated by P-gp. In a study using mice, cyclosporin A was found to increase both the uptake into brain and brain-to-blood ratio of ^{11}C-donepezil (Ishiwata K, et al. J Nucl Med. 2007 Jan;48(1):81-7). However, caution needs to be taken to interpret the data. First, CsA was intravenously administered at a high dose (50 mg/kg) in this study. Such high dose can not be reached in clinical setting and the finding seems not likely to be clinically relevant. Secondly, the extents of increase for donepezil were much lower than the extents for verapermil which is a positive control.

Based on the above information, also considering the fact that donepezil has been approved in US since 1996 and used world widely, we recommend the *in vitro* evaluation of the potential of donepezil of P-gp substrate as PMC.

2.4.4 What extrinsic factors (such as herbal products, diet, smoking and alcohol) influence exposure and or response and what is the impact of any differences in exposure on pharmacodynamics?

In vitro dissolution study demonstrated that the release of donepezil from SR formulation was greatly reduced by alcohol (up to ~50% decrease). The results indicated that extensive consumption of alcohol may decrease the exposure of donepezil SR 23 mg. However, such effect may not lead to clinical concerns. First, the lower exposure will actually reduce the incidence of AEs. Secondly, 10-mg IR tablet has been approved for treatment of moderate-to-severe AD and 23-mg SR tablet was overall just slightly better than 10-mg IR tablet. So, even if the exposure of donepezil after SR 23mg is reduced with consumption of large amount of alcohol, acceptable efficacy may still be achieved. Lastly, alcohol abuse is less likely in the target population which is mainly composed with elderly patients.

Figure 5. *In Vitro* dissolution profile of donepezil SR in varying concentrations of ethanol
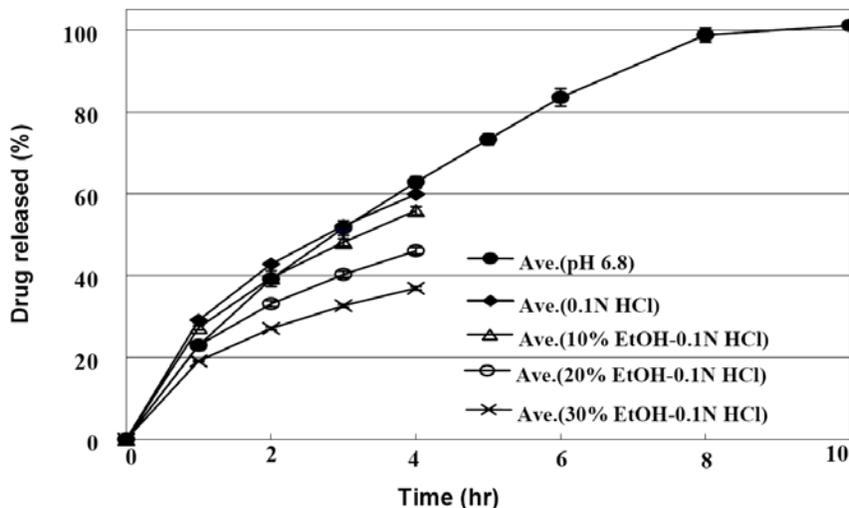
2.4.5   Are there any in-vivo drug-drug interaction studies that indicate the exposure alone and/or exposure response relationships are different when drugs are coadministered? If yes, is there a need for dosage adjustment?

2.4.5.1   Influence of donepezil on other drugs:

According to the labeling of Aricept®, formal pharmacokinetic studies evaluated the potential of donepezil for interaction with theophylline, cimetidine, warfarin, digoxin and ketoconazole. No effects of donepezil on the pharmacokinetics of these drugs were observed.

2.4.5.2   Influence of other drugs on donepezil:

Effects of CYP2D6 inhibitors on donepezil clearance were evaluated by population PK analysis based on the data from the phase 3 study. There were 763 subjects taking no CYP2D6 inhibitors, 48 taking weak inhibitors, 3 taking moderate inhibitors and 36 taking strong inhibitors. Donepezil clearance was reduced by approximately 17% (95% CI: 11% to 23%) with co-administration of CYP2D6 inhibitors.

Table 9. CYP2D6 Inhibitor Classification

Strong Inhibitors	Moderate Inhibitors	Weak Inhibitors
bupropion	duloxetine	cimetidine
fluoxetine	terbinafine	amiodarone
paroxetine		sertraline
quinidine		

Figure 6. Effect of CYP2D6 Inhibitor on Clearance

(0 = Not on CYP2D6 drugs; 1 = Weak Inhibitor; 2 = Moderate Inhibitor; 3 = Extreme Inhibitor)
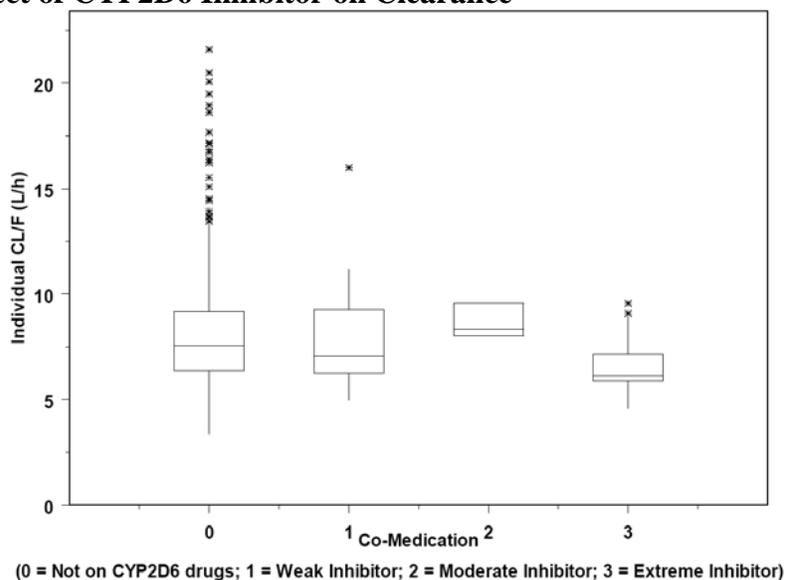
Consistently, the incidence of specific TESS that occurred in >0.5% of patients was higher in patients concurrently taking a CYP2D6 inhibitor than in patients not receiving CYP2D6 inhibitor. In the donepezil SR 23 mg treatment group, patients receiving concomitant CYP2D6 inhibitors were more likely to have at least one TESS (45.8%) than patients receiving donepezil alone (40.3%). Similarly, in the donepezil IR 10 mg treatment group, patients receiving concomitant CYP2D6 inhibitors also were more likely to have at least one TESS (37.5%) than those patients receiving concomitant donepezil alone (23.0%).

Dose adjustment: No dosing adjustment recommendation has been proposed in the labeling.

2.5   GENERAL BIOPHARMACEUTICS

2.5.1   Based on the BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

BCS Class has not been established. Donepezil is assumed well absorbed. Its aqueous solubility is highly pH dependent. The equilibrium solubility of donepezil HCl in aqueous solutions is high (11 to 16 mg/mL) in the acidic range and < 0.01 mg/mL in the basic range. Donepezil may be a BCS I or II class drug, which still needs to be justified.

2.5.2   Is the proposed to-be-marketed formulation of Donepezil bioequivalent to the formulation used in the clinical trials and pharmacokinetic studies?

(b) (4)

2.5.2.1   What data support or do not support a waiver for in vivo BE data?

BE study is not relevant, since donepezil SR 23 mg is not developed as an alternative to the currently approved Aricept dosing regimen.

2.5.3   Has relative bioavailability been established with any other formulation? If yes, are they bioequivalent?

In the original submission, the sponsor proposed Aricept $^{(b)\,(4)}$ as the name for the SR 23-mg tablet, which was designated to reflect the sustained release characteristics. However, during the review process, the reviewers found that the SR 23 mg formulation behaves similarly with IR 10 mg in humans in terms of dose normalized C_{max}, C_{24hr}, AUC and fluctuation index. $^{(b)\,(4)}$. Based on

these findings, the agency required the sponsor change the name during a tele-conference. The sponsor accordingly removed the name of Aricept (b) (4) and just proposed SR 23 mg as a higher strength of currently approved Aricept®. The details of data analysis performed by the reviewers were summarized as following.

First, the pharmacokinetic parameters of donepezil SR 10 mg and IR 10 mg were compared in the formulation selection study (020).

Table 10. Comparisons between donepezil IR 10 mg and SR 10 mg (b) (4) (b) (4) **after single-dose administration in healthy subjects (study 020)**

PK Endpoint	Mean Test[1,2]	Mean Ref.[1,2]	Test/Ref Ratio	Lower 90% CL	Upper 90% CL	Intra-subject CV/%
C_{max} (ng/mL)	8.29	19.8	0.419	0.383	0.457	18.28
AUC_{0-inf} (ng*h/mL)	565.65	710.95	0.796	0.735	0.862	16.53
CL=confidence Level	intra-subject CV/% = 100*[exp(error mean square)-1]					
1. Mean in the antilog of the Least square mean of the log-transformed data for the test and reference treatments.						
2. Ref. is donepezil IR 10 mg. Test is donepezil SR (b) (4) 10 mg.						

The exposure of donepezil after a single dose of SR 10 mg (b) (4) was reduced by about 20% compared to IR 10 mg, while the C_{max} was reduced more than 50%. The development of donepezil SR formulation was based on such a hypothesis that more advanced AD patients can benefit from an increased dose of already established AChE inhibitor therapy. (b) (4)

The pharmacokinetic parameters of donepezil were then compared between SR 23 mg (b) (4) and IR 10 mg in single-dose PK study in healthy subjects (study 021).

Table 11. Pharmacokinetic Analyses After Dose-normalization of Donepezil SR 23 mg to Donepezil IR 10 mg (Study 021)

PK Parameter	Summary Statistics	Donepezil SR 23 mg (test drug) n=14
C_{max} (ng/mL)	geometric mean test/reference ratio[a]	0.622
	90% confidence interval	0.532 – 0.728
	percent change as compared to reference	37.77
AUC_{0-t} (ng*h/mL)	geometric mean test/reference ratio[a]	0.821
	90% confidence interval	0.706 – 0.955
	percent change as compared to reference	17.90
$AUC_{0-\infty}$ (ng*h/mL)	geometric mean test/reference ratio[a]	0.812
	90% confidence interval	0.694 – 0.950
	percent change as compared to reference	18.82

Consistent with the results from study 020, AUC after a single dose of donepezil SR 23 mg was about 80% of that following IR 10 mg. However, the C_{max} after SR 23 mg was only reduced by 38% compared to IR 10 mg, not as much as the extent observed in study 020 (58% decrease).

Since IR 10 mg was not administered in the multiple-dose PK study (022), it is impossible to directly compare steady-state PK parameters of donepezil after SR 23 mg and IR 10 mg within this study. The sponsor conducted population PK analysis using the data from all the phase 1 studies (020, 021, 022 and 023), and then performed simulation using the developed model (Phase I model) to simulate the steady-state concentration profiles of SR 23 mg and IR 10 mg in healthy subjects as shown in the following figure.

Figure 7. 95% Prediction Intervals for Steady State Concentration versus Time Profiles for 23 mg Daily SR and 10 mg IR Formulation Using Phase I Model
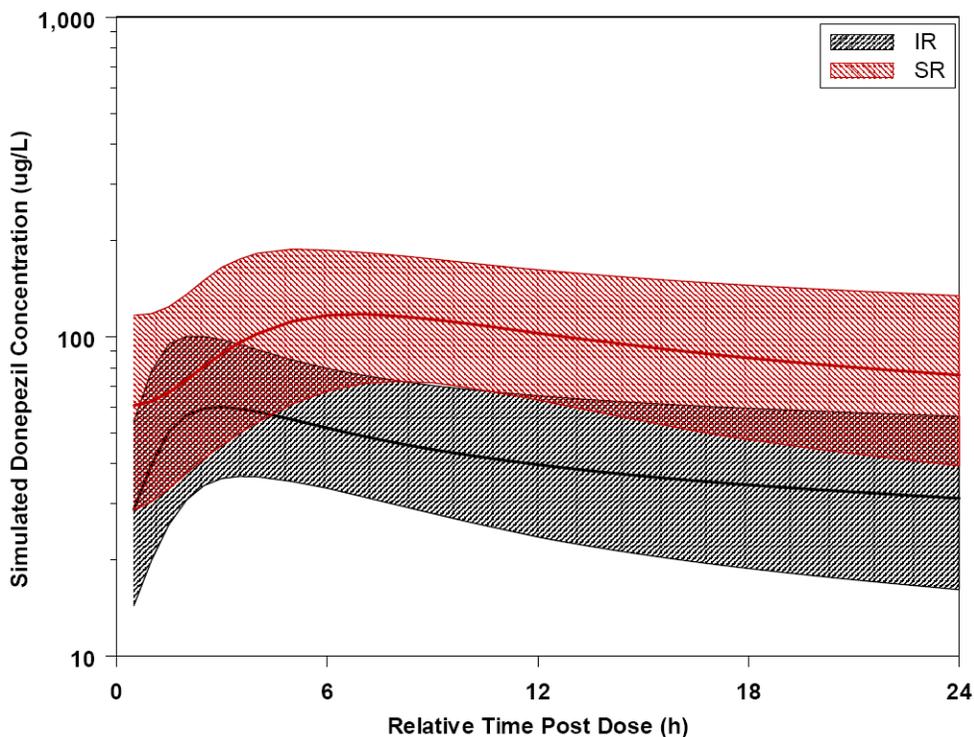
Based on the simulation results, the exposure of donepezil after multiple doses of SR 23 mg was 2.2-fold of that following IR 10 mg (2281.84 and 1025.91 ng*hr/mL for SR and IR, respectively). After dose-normalization, the exposure of donepezil was the same between SR 23 mg and IR 10 mg (SR/IR: 0.97), indicating that the relative bioavailability of SR after multiple doses is about 100%. Dose-normalized C_{max} after SR 23 mg and IR 10 mg was also similar (SR/IR: 0.84), suggesting that the difference observed between SR 23 mg and IR 10 mg after single-dose administration (38% decrease, study 021) was reduced following multiple dosing (16% decrease). It is speculated that the high accumulation ratio (at least 4-fold) of donepezil after multiple dose administration may mask the difference observed between SR and IR after a single dose.

The sponsor also conducted population PK analysis based on the data obtained from patients in the phase 3 study (326). The average exposure of donepezil after multiple doses of SR 23 mg was estimated to be 2.17-fold of the exposure following IR 10 mg, and thus the relative bioavailability of SR 23 mg was 92%. The result is similar with the observation in healthy subjects as mentioned above (97%). Due to sparse PK sampling in study 326, it is difficult to accurately determine the C_{max} for SR 23 mg or IR 10 mg in these patients. The sponsor assumed that concentrations measured at 3±1 hr post-dose of IR 10 mg represented C_{max} for IR, while the concentrations measured at 7±2 hr post-dose of SR 23 mg were used to calculate the C_{max} for SR. Based on these assumptions, the C_{max} after multiple doses of SR 23 mg was 2.09-fold of that following IR 10 mg. After dose-normalization, the C_{max} of SR 23 mg (6.03 ng/mL) was only 9% lower than the one of IR 10 mg (6.64 ng/mL), suggesting that there was little difference between the two formulations in patients.

The sponsor did not compare the C_{trough} (C_{24hr} in this case) between SR 23 mg and IR 10 mg. Using the datasets and the phase I population PK model provided by the sponsor, the reviewer performed the analysis and the results were presented in the following table. Overall, the C_{24hr} of SR 23 mg was around 2-fold of that of IR 10 mg. After dose normalization, the C_{24hr} of SR 23 mg was 84%-103% of the C_{24hr} of IR 10 mg. The ratio of C_{max}/C_{24hr} was smaller for SR 10 mg compared to IR 10 mg (1.63 vs. 3.43), which was expected for SR formulation (study 020). However, such difference was reduced when SR 23 mg was compared to IR 10 mg (2.24 vs. 2.95, study 021), and further reduced after multiple dose administration. Similar trend was also observed for T_{max}, where a much more delayed absorption for donepezil SR compared to IR only occurred in study 020 (SR: 9.16 hr; IR: 2.67 hr) but not in the other studies (SR: 5-7 hr; IR: 2-4 hr).

Table 12. Comparisons of pharmacokinetic parameters of donepezil between SR 10 or 23 mg and IR 10 mg.

	Study	Subject	Dose of SR	AUC_{SR}/AUC_{IR}	$C_{max,SR}/C_{max,IR}$	$C_{24hr,SR}/C_{24hr,IR}$	C_{max}/C_{24hr} SR vs. IR	T_{max} SR vs. IR
Single Dose	-020	Healthy	*10 mg*	0.78	0.42	0.91	1.63 vs. 3.43	9.16 vs. 2.67
	-021	Healthy	23 mg	1.86	1.56	2.06	2.24 vs. 2.95	6.15 vs. 3.19

Multiple Dose	-022, literature[1]	Healthy	23 mg	1.98	2.14	1.94	1.79 vs. 1.57	5.2 vs. 3.9
	Simulation[2]	Healthy	23 mg	2.30	2.13	2.36	1.48 vs. 1.64	6.83 vs. 2.83
	-326	patients	23 mg	2.17	2.09[3]	1.99[4]	1.57 vs. 1.50	6.36 vs. 3.0[5]
	(After Dose Normalization)							
Single Dose	-020	Healthy	*__10 mg__*	0.78	0.42	0.91	1.63 vs. 3.43	9.16 vs. 2.67
	-021	Healthy	23 mg	0.81	0.68	0.89	2.24 vs. 2.95	6.15 vs. 3.19
Multiple Dose	-022, literature[1]	Healthy	23 mg	0.86	0.93	0.84	1.79 vs. 1.57	5.2 vs. 3.9
	Simulation[2]	Healthy	23 mg	1.00	0.92	1.03	1.48 vs. 1.64	6.83 vs. 2.83
	-326	patients	23 mg	0.92	0.91[3]	0.87[4]	1.57 vs. 1.50	6.36 vs. 3.0[5]

1. Cross study comparison. There was no PK information for donepezil IR in study 022. Therefore, it is impossible to compare stead-state PK of donepezil between SR 23 mg and 10 mg within this study. There was one literature report published by the sponsor having PK parameters of donepezil IR 10 mg at steady state (Tiseo PJ, *Br J Clin Pharmacol.* 1998 Nov;46 Suppl 1:13-8). Hence, a cross-study comparison was made based on the data in study 022 (SR 23 mg) and the information in the literature (IR 10 mg). It should be noted that the dosing regimens were different. In study 022, 7-day once daily dose of IR 5 mg was administered first as titration. Then, 2-week treatment of SR 14 mg was initiated followed by another 14-day once daily dosing of SR 23 mg. The concentrations measured after the last dose of donepezil were used for the analysis. In the literature, 7-day IR 5 mg q.d. dosing of donepezil was followed by 21-day once daily dosing of IR 10 mg. The concentrations measured after the last doses of donepezil were used for the analysis.
2. The sponsor developed a population PK model based on the data from the phase 1 studies (020, 021, 022 and 023). Using the model, the pharmacometric reviewer simulated the steady-state plasma concentration profiles of donepezil SR 23 mg and IR 10 mg. The derived C_{max}, C_{24hr} and AUC values were used to calculate the ratios between SR and IR for these PK parameters. The calculated AUC and C_{max} ratios (2.30 and 2.13) are very close to the values (2.22 and 1.98) provided by the sponsor.
3. Only limited data available. For IR, 26 concentrations at 3±1 hr post-dose were included. For SR, 39 concentrations at 7±2 hr post-dose were used. Hence, the estimation may be affected by the pre-specified windows for T_{max}.
4. Only limited data available. C_{24hr} refer to the concentrations measured at relative-to-last-dose (RLTD) time between 23 and 24 hrs during visit weeks of 6, 12, 18 or 24. There were only 21 and 39 observations for IR 10 mg and SR 23 mg, respectively.
5. Sponsor stated that the T_{max} of SR 23 mg was 8 hrs. However, the value calculated by the reviewer was 6.36 hrs.

Besides the ratio of C_{max}/C_{24hr}, the reviewer also calculated the fluctuation index (defined as $(C_{max}-C_{24hr})/C_{ave}$, where C_{ave} is $AUC_{0-24hr}/24$) for SR 23 mg and IR 10 mg based on steady-state concentrations of donepezil in study 022, the literature report and the results of simulation conducted by the pharmacometric reviewer. The fluctuation index was similar between SR 23 mg and IR 10 mg (0.39 vs. 0.51 or 0.59 vs. 0.47, depending on the source of the data).

Table 13. Fluctuation Index of donepezil SR 23 mg and IR 10 mg.

Simulation[1]	C_{max}	C_{24hr}	$C_{max}-C_{24hr}$	AUC_{0-24hr}	C_{ave}	$(C_{max}-C_{24hr})/C_{ave}$
10mg IR	41.7	25.4	16.3	762.40	31.8	0.51
23mg SR	88.7	60.0	28.6	1753.97	73.1	0.39
Study 022, literature	C_{max}	C_{24hr}	$C_{max}-C_{24hr}$	AUC_{0-24hr}	C_{ave}	$(C_{max}-C_{24hr})/C_{ave}$
10 mg IR[2]	60.50	38.5	22.0	1127.8	47.0	0.47
23 mg SR[3]	129.2	74.6	54.6	2232.5	93.0	0.59

1. The sponsor developed a population PK model based on the data from the phase 1 studies (020, 021, 022 and 023). Using the model, the pharmacometric reviewer simulated the steady-state plasma concentration profiles of donepezil SR 23 mg and IR 10 mg. The derived C_{max}, C_{24hr} and AUC values were used to calculate the fluctuation index ratio.
2. Reference: Tiseo PJ, *Br J Clin Pharmacol.* 1998 Nov;46 Suppl 1:13-8. A literature published by the sponsor.
3. Data for SR 23 mg were extracted from study 022.

In conclusion, the steady-state PK parameters (AUC_{ss}, C_{max} and C_{24hr}) of donepezil SR 23 mg were similar to IR 10 mg after dose normalization. The fluctuation index was also similar between SR 23 mg and IR 10 mg. The SR 23 mg behaves like IR 20 mg, assuming linear PK for IR in the range of 10-20 mg (Doody RS, et al. *Drugs Aging.* 2008;25(2):163-74). The desired large decrease in C_{max} after donepezil SR compared to IR was only observed in study 020. Such difference appeared to be less in the later single-dose studies (021, 023) and became even smaller after multiple-dose administration.

2.5.4   Has dosage strength equivalence been established between different strengths of the to-be marketed formulation? If yes, are they bioequivalent?

Not applicable. Only donepezil 23 mg will be marketed.

2.5.5   What is the effect of food on the bioavailability of the drug from the dosage form? What dosing recommendations need to be made regarding the administration of donepezil in relation to meals or meal types?

The effect of food on pharmacokinetic of donepezil SR were investigated for single-dose SR 14 mg (panel 1), single-dose SR 23 mg (panel 2) and single-dose SR 23 mg preceded by a titration of 7-day once daily SR 14 mg (panel 3).

Figure 8. Study design of Food-effect study (023)

Panel 1 and 2:

Panel 3:

| 14 mg E2020 SR x 7 days* | → | Fasting: 23 mg E2020 SR x 1 day | → | 14 mg E2020 SR x 7 days* | → | Fasting: 23 mg E2020 SR x 1 day |

(flow diagram: 14 mg E2020 SR x 7 days* → Fasting: 23 mg E2020 SR x 1 day / Fed: 23 mg E2020 SR x 1 day → 14 mg E2020 SR x 7 days* → Fasting: 23 mg E2020 SR x 1 day / Fed: 23 mg E2020 SR x 1 day)

| DAYS 1-7 | DAY 8---------Washout---------DAYS 22-28 | DAY 29 |
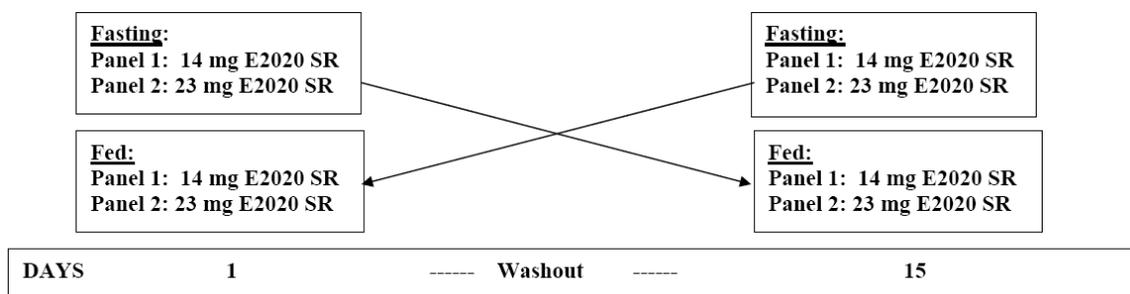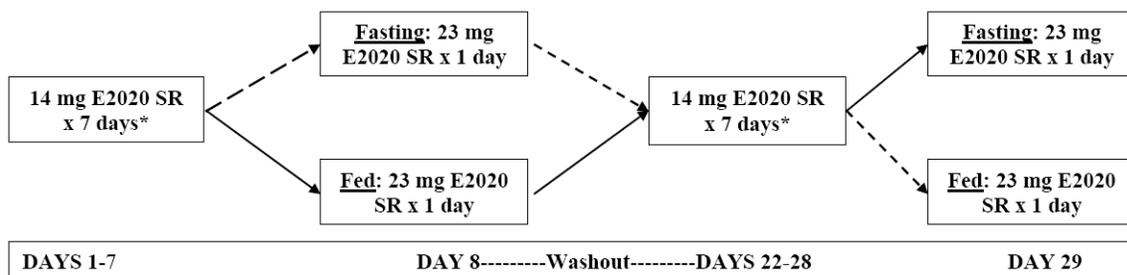
Table 14. Food Effect Bioavailability Analysis of Donepezil SR

PK Parameter	Panel		
	1	2	3
	14 mg E2020 SR (n=15)	23 mg E2020 SR (n=17)	14 mg/23 mg E2020 SR (n=13)
C_{max} (ng/mL)			
Ratio of Geometric Means (Fed/Fasted)	100.7	122.7	116.1
90% Confidence Interval (lower, upper)	84.2, 120.5	98.6, 152.8	108.1, 124.6
AUC_{0-t} (ng*h/mL)			
Ratio of Geometric Means (Fed/Fasted)	95.7	108.2	-
90% Confidence Interval (lower, upper)	84.0, 108.9	96.9, 120.7	-
AUC_{0-24h} (ng*h/mL)			
Ratio of Geometric Means (Fed/Fasted)	-	-	105.3
90% Confidence Interval (lower, upper)	-	-	101.4, 109.4
$AUC_{0-\infty}$ (ng*h/mL)			
Ratio of Geometric Means (Fed/Fasted)	96.4	109.4	-
90% Confidence Interval (lower, upper)	84.9, 109.4	98.2, 121.9	-

The AUC of donepezil in all the panels were similar between fed and fasted states. Difference in C_{max} was only observed for SR 23 mg but not SR 14 mg. There was a slight increase (22.7%) of C_{max} after a single dose of SR 23 mg under fed conditions. No food effect was observed when the single dose of SR 23 mg was administered after multiple doses of SR 14 mg. The small food effect noted after single-dose administration may be masked by the elevated baseline plasma concentration of donepezil after multiple-dose administration, which is due to the high accumulation ratio. In conclusion, donepezil SR 23 mg can be taken without regard to meals.

2.6 ANALYTICAL

2.6.1 What bioanalytical method is used to assess concentrations of active moieties and is the validation complete and acceptable?

A LC/MS/MS assay was developed to quantitate donepezil and 6-OH donepezil in heparinized plasma and used to measure the samples from study 020. The method used solid phase extraction and a cyano amine reversed-chromatography column. A modified LC/MS/MS method using donepezil-d_4 as internal standard was further developed and used to determine the concentrations of donepezil in plasma samples of study 021, 022, 023 and 326. The assay validation for the method is acceptable.

Table 15. Validation Assay Performance Summary for Donepezil

Report Title	Determination of Donepezil and 6-OH Donepezil in Human Plasma by LC/MS/MS[a]	Quantitation of Donepezil in Human Plasma via HPLC with MS/MS Detection[b]
Used In Clinical Study	020	021, 022, 023, and 326
Lab/Project Code (year)	PPD/ABIS (2000)	PPD/ADZT (2007)
Analyte Names	Donepezil[c], 6-OH Donepezil	Donepezil
		(b) (4)
Analytical Method Type	LC/MS/MS	LC/MS/MS
Extraction Method	Solid/liquid	Liquid/liquid
QC Concentrations	0.2, 0.6, 4.0, and 40.0 ng/mL	0.2, 0.5, 1.0, 3.5, 10.0 and 45.0 ng/mL
Standard Curve Concentrations	0.2, 0.4, 0.8, 2.0, 4.0, 8.0, 20.0 40.0 and 60.0 ng/mL	0.200, 0.350, 0.600, 2.00, 6.00, 20.0, 50.0 and 60.0 ng/mL
Lower Limit Of Quantitation (ng/mL)	0.2 ng/mL	0.200 ng/mL
Upper Limit Of Quantitation (ng/mL)	60.0 ng/mL	60.0 ng/mL
Range Recovery of Donepezil (%)	95.4 to 100%	89.7 to 99.7%
Average Recovery of IS (%)	103%	98%
QC Intra-assay Precision Range (%CV) for Donepezil	1.38 to 5.42%	2.61 to 13.8%
QC Intra-assay Accuracy Range (%Diff) for Donepezil	-8.3 to -4.0%	-2.42 to 9.05%
QC Inter-assay Precision Range (%CV) for Donepezil	3.17 to 4.56%	3.12 to 7.52%
QC Inter-assay Accuracy Range (%Diff) for Donepezil	-4.2 to 2.0%	-0.232 to 2.90%
Stock Solution Solvent for Donepezil and IS	methanol	methanol
Master Stock Solution Stability in Methanol for Donepezil and IS	2 years and 3 months at -20°C	831 days at -20ºC and 29 hours at room temperature
Benchtop Stability of Donepezil in thaw human sodium heparinized plasma	3 cycles of 4 hours	114 hours
Freeze/thaw Stability of Donepezil in human sodium heparinized plasma	3 cycles at -20°C	5 cycles at -20°C
Long-term Storage Stability in human sodium heparinized plasma	11.5 months at -20°C	Not done
Autosampler Stability in Reconstitution Solvent	72 hours at room temperature	365 hours at room temperature
Specificity for low QC (0.5 ng/mL) (%Diff) for donepezil	No major interfering peaks	-5.06 to 0.242%

a. Determination of Donepezil and 6-OH Donepezil in Human Plasma by LC/MS/MS.
b. Quantitation of Donepezil in Human Plasma via HPLC with MS/MS Detection,
c. Only assay performance for donepezil is provided in this table.

3.0 LABELING RECOMMENDATIONS

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in blue color.

12. CLINICAL PHARMACOLOGY
12.2 Pharmacokinetics
Pharmacokinetics of donepezil are linear over a dose range of 1-10 mg given once daily. (b) (4)
The rate and extent of absorption of ARICEPT (b) (4) tablets are not influenced by food. (b) (4)

Following oral dosing, peak plasma concentration is achieved for ARICEPT 23 mg tablets in approximately (b) (4) hours, compared with 3 (b) (4) hours for ARICEPT 10 mg tablets. (b) (4)

The elimination half life of donepezil is about 70 hours, and the mean apparent plasma clearance (Cl/F) is 0.13-0.19 L/hr/kg. Following multiple dose administration, donepezil accumulates in plasma by 4-7 fold, and steady state is reached within 15 days. The steady state volume of distribution is 12-16 L/kg. Donepezil is approximately 96% bound to human plasma proteins, mainly to albumins (about 75%) and alpha1 - acid glycoprotein (about 21%) over the concentration range of 2-1000 ng/mL.

Age: No formal pharmacokinetic study was conducted to examine age-related differences in the pharmacokinetics of ARICEPT. (b) (4)

Population PK analysis suggested that the clearance of donepezil in patients decreases with increase of age. Compared with patients of 65-year old, subjects of 90-year old have a 17% decrease in clearance, while patients of 40-year old have a 33% increase in clearance. The effect of age on donepezil clearance may not be clinically significant.

Body weight: There was a relationship noted between body weight and clearance. Over the range of weights from 50 kg to 110 kg, clearance increased from 7.77 L/h to 14.04 L/h, with a value of 10 L/hr for 70kg-individuals.

4.0 APPENDIX I

4.1 INDIVIDUAL STUDIES REVIEW

<u>**4.1.1 PK in HEALTHY SUBJECTS:**</u>

Study 020: **A Bioavailability Study of E2020 (Aricept®) Sustained Release Tablet Following Oral Administration to Healthy Subjects**

<u>**Objectives:**</u>

- *Primary objective:* To evaluate the relative bioavailability of a single dose of each of the three sustained release formulations of donepezil hydrochloride (E2020-SR) following oral administration to healthy subjects.
- *Secondary objective:* To evaluate the safety of the E2020-SR tablets after oral administration to healthy subjects.

The study design is as follows:

Study Design	Phase 1, randomized, open-label, two-period, two-sequence crossover study.
Study Population	N=82/73 (Enrolled/Completed) Healthy subjects <u>Age:</u> 19-46 years <u>Gender:</u> 36/46 (Males/Females) <u>Weight:</u> 47.6-97.0 kg <u>Race:</u> All Hispanics (except 1 Black)
Treatment Group	Cohorts I-III
Dosage and Administration	Cohort I: dosed with formulation E2020-SR dissolution 4-hour type (E2020-SR-4H) and E2020 regular release formulation (E2020-RR) Cohort II: dosed with formulation E2020-SR dissolution 8-hour type (E2020-SR-8H) and E2020-RR Cohort I: dosed with formulation E2020-SR dissolution 12-hour type (E2020-SR-12H) and E2020-RR Subjects in each cohort were administered a single dose of 10 mg E2020-SR or 10 mg E2020-RR in the morning during each period. So the total dose of E2020 for each subject during the study was 20 mg. <u>Diet:</u> Overnight fast <u>Washout:</u> Approximately 3 weeks between two periods
Sampling: Blood	<u>For plasma E2020 and its major metabolite (6-O-desmethyl donepezil):</u> At pre-dose, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, 288, 312 and 336 hours post dose.
Analysis	Lower Limits of Quantitation and Linear range of calibration curve Donepezil 0.2 ng/ml 0.2-60 ng/ml 6-O-desmethyl donepezil 0.2 ng/ml 0.2-60 ng/ml
PK Assessment	AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, $t_{1/2}$, λz
Safety Assessment	Incidence of AEs and severe AEs (SAEs); changes from baseline in clinical laboratory evaluations; vital signs; physical examinations and ECGs

Pharmacokinetic Results:

The mean pharmacokinetic parameters of donepezil are shown in the following table:

Table 1. Pharmacokinetic summary of E2020-SR formulations by cohort with pooled reference (PK population)

PK Parameter	Cohort I (E2020-SR-4H)	Cohort II (E2020-SR-8H)	Cohort III (E2020-SR-12H)	Pooled Reference (E2020-RR)
AUC_{0-t} (ng*h/mL)				
N	24	25	24	73
Arithmetic mean	708.02	561.49	544.86	732.44
Geometric mean	685.88	525.49	511.35	704.11
CV	62.75	65.53	65.38	63.66
Median	706.3	530.88	542.6	714.4
Range	374.2 – 1207	154.6 – 988.0	191.2 – 858.2	127.9 – 1382
AUC_{0-inf} (ng*h/mL)				
N	23	25	24	72
Arithmetic mean	756.47	608.11	588.35	778.96
Geometric mean	734.99	566.86	551.29	746.27
CV	62.48	65.78	65.40	63.89
Median	746.8	558.0	577.56	740.71
Range	470.3 – 1309	165.5 – 1066	214.5 – 965.8	133.9 – 1469
C_{max} (ng/mL)				
N	24	25	24	73
Arithmetic mean	17.42	8.74	6.80	20.89
Geometric mean	16.64	8.30	6.34	20.30
CV	63.93	63.97	65.64	62.40
Median	18.0	7.9	6.7	19.8
Range	6.70 – 27.70	4.70 – 15.70	2.50 – 10.90	13.10 – 36.90
T_{max} (h)				
N	24	25	24	73
Arithmetic mean	4.83	9.16	16.25	2.67
Geometric mean	4.69	8.42	13.31	2.57
SD	1.20	3.92	10.19	0.74
Median	5	8	14	3
Range	3.00 – 7.00	4.00 – 18.00	5.00 – 36.00	1.00 – 5.00
λz (1/h)				
N	23	25	24	72
Arithmetic mean	0.01	0.01	0.01	0.01
Geometric mean	0.01	0.01	0.01	0.01
CV	61.34	62.23	62.06	62.35
Median	0.01	0.01	0.01	0.01
Range	0.01 – 0.01	0.01 – 0.02	0.01 – 0.01	0.01 – 0.03
$t_{1/2}$ (h)				
N	23	25	24	72
Arithmetic mean	75.04	75.52	75.85	76.64
Geometric mean	74.16	73.91	74.12	74.94
CV	61.41	62.21	62.20	62.32
Median	74.58	76.49	76.83	78.02
Range	52.13 – 105.4	33.11 – 100.5	47.95 – 102.9	20.39 – 102.9

CV (coefficient of variation) = 100*SQRT[exp(VAR)-1]; where VAR is the variance on the logarithmic scale.
ng/mL = nanogram per milliliter   h=hour   1/h = per hour
NOTE: Reference group was pooled across the three cohorts.

Overall, the AUC and C_{max} of donepezil were decreased with different extents following SR formulations compared to IR formulation and T_{max} was delayed, while $t_{1/2}$ of donepezil was not altered.

The mean plasma concentration profiles for donepezil are shown in the following figures.

Figure 1. Cohort I - Semi-log plot of mean donepezil plasma concentration versus time profile of E2020-SR-4H and E2020-RR
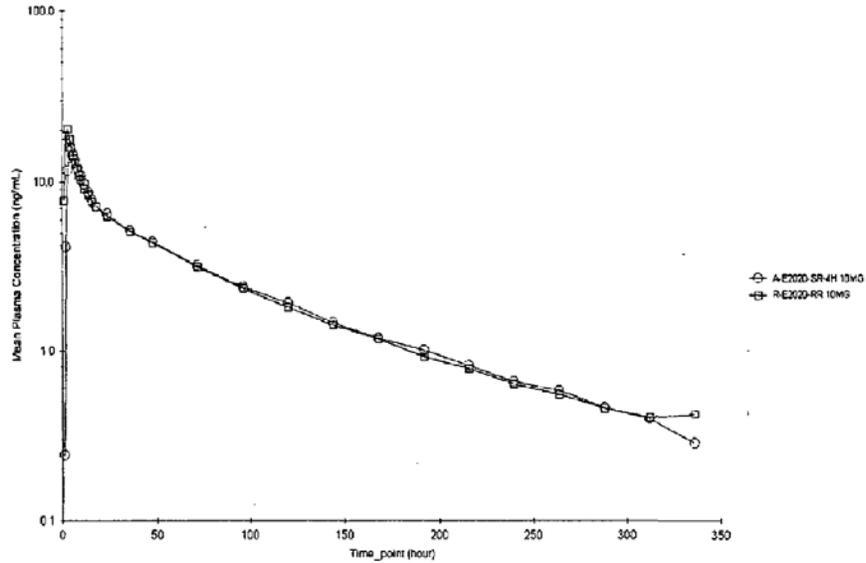
Figure 2. Cohort II - Semi-log plot of mean donepezil plasma concentration versus Time profile of E2020-SR-8H and E2020-RR
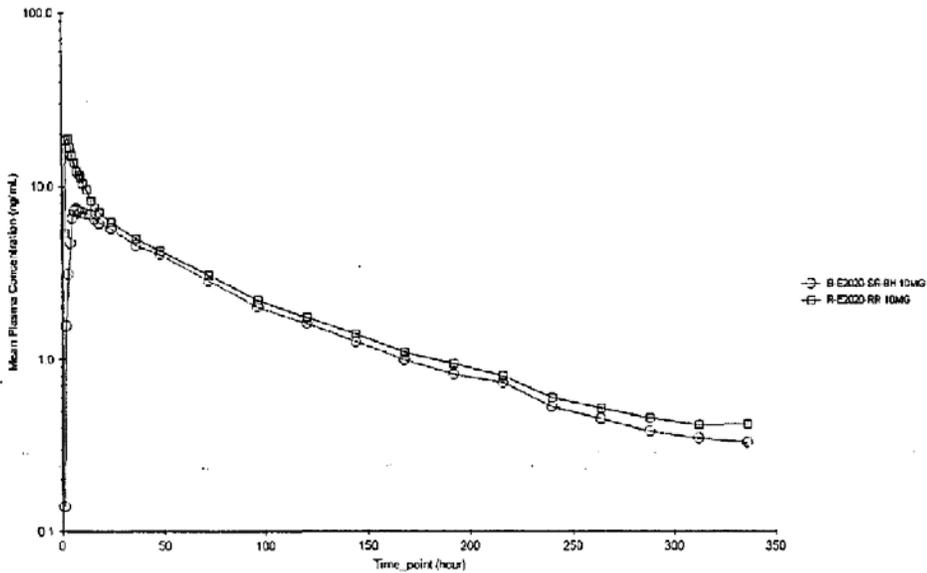
Figure 3. Cohort III - Semi-log plot of mean donepezil plasma concentration versus time profile of E2020-SR-12H and E2020-RR
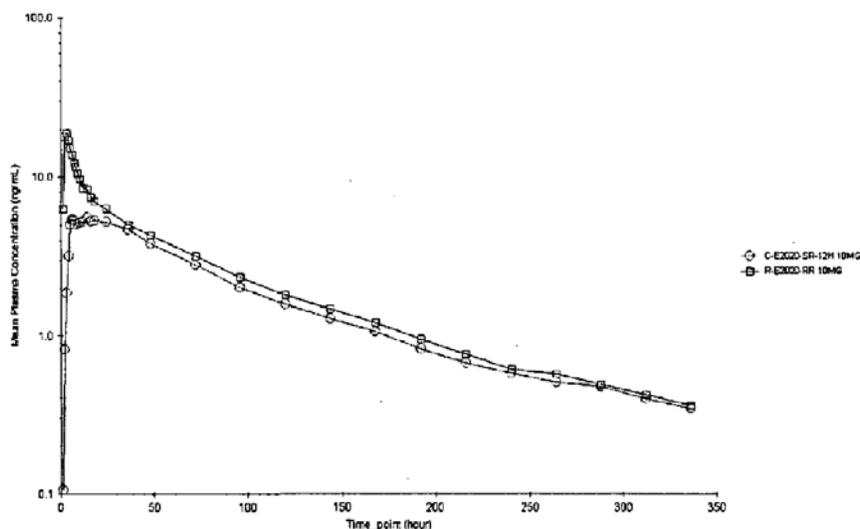
- The PK profile of donepezil after the administration of the E2020-SR-4H formulation seems to be similar with the one following the regular release formulation (donepezil IR), while the PK profiles of donepezil for the E2020-SR-8H and -12H formulations appears to be different from that of the donepezil IR and have much lower peaks.

The relative bioavailability of the three SR formulations using IR as the reference is summarized in the following table:

Table 2. Bioavailability Summary - Ordinary least squares-GLM analysis of PK endpoints of E2020-SR formulations -All Cohorts (PK Population)

| PK Endpoint	Mean Test[1]	Mean Ref.[1]	Lower 90% CL	T/R Ratio	Upper 90% CL	Intra-subject CV/%
Cohort I (E2020-SR-4H)						
AUC_{0-t} (ng*h/mL)	685.88	731.55	0.899	0.938	0.977	8.39
C_{max} (ng/mL)	16.64	21.51	0.719	0.773	0.832	14.85
AUC_{0-inf} (ng*h/mL)	735.55	776.57	0.918	0.947	0.977	6.11
Az (1/h)	0.0093	0.0090	1.002	1.039	1.077	7.09
Cohort II (E2020-SR-8H)						
AUC_{0-t} (ng*h/mL)	524.22	668.70	0.720	0.784	0.854	17.68
C_{max} (ng/mL)	8.29	19.80	0.383	0.419	0.457	18.28
AUC_{0-inf} (ng*h/mL)	565.65	710.95	0.735	0.796	0.862	16.53
Az (1/h)	0.0094	0.0093	0.945	1.002	1.062	12.01
Cohort III (E2020-SR-12H)						
AUC_{0-t} (ng*h/mL)	509.17	709.73	0.641	0.717	0.803	23.05
C_{max} (ng/mL)	6.33	19.55	0.279	0.324	0.376	30.96
AUC_{0-inf} (ng*h/mL)	549.07	752.09	0.655	0.730	0.814	22.16
Az (1/h)	0.0094	0.0094	0.957	0.995	1.034	7.80

CL=confidence level
Note: Intra-Subject CV%=100*[exp(error mean square)-1)]
1. Mean is the anti-log of the Least square mean of the log-transformed data for the test and reference treatments.

The sponsor's hypothesis of developing Aricept (b) (4) is that systemic exposure of donepezil is associated with appreciable inhibition of cholinesterase activity. Therefore,

an increase of dose in the currently approved dose (5-10mg) may produce greater inhibition of AChE activity that may enhance the cognitive benefit, and eventually achieve clinically meaningful improvement. However, simply increasing the dose of donepezil IR will increase C_{max} which may lead to more side-effects.

(b) (4)

Reviewer's Comment: There were no pre-specified criteria about the extent of decrease in C_{max} and AUC to be achieved following SR formulation compared to IR. Hence, the decision about which formulation to be chosen for further development was more or less arbitrary.

(b) (4)

As to the metabolite, 6-O-desmethyl donepezil, the concentrations in the majority of the samples were below the lower limit of Quantitation (LOQ) of 0.2 ng/ml with the exception of a few samples.

Safety:
The reference group (donepezil IR) had the highest percentage (~38%) of subjects reporting at least one treatment-emergent symptoms and signs (TESS), while 31% of subjects given E2020-SR-4H reported at least one TESS and much lower percentages occurred in E2020-SR-8H and -12H (~11%). Such difference may be related with lower C_{max} in E2020-SR-8H and -12H groups. No deaths or other SAEs happened during the study, and the majority of the AEs were mild in severity. The most common AEs are: dizziness, nausea, vomiting and headache.

Overall Conclusions:
All the E2020 formulations were well tolerated when administered as a single oral 10 mg dose.

(b) (4)

Study 021:   A Randomized, Double-Blind, Single-Dose Pharmacokinetic and Pharmacodynamic Study of E2020 (Aricept®) Sustained Release Tablet Following Oral Administration To Healthy Subjects

Objectives:

- *Primary objective:* To evaluate the PK of a single dose of E2020-SR-8H (from now on called Donepezil SR) tablets (14 mg and 23 mg) following oral administration to healthy subjects.
- *Secondary objective:*
    1) To determine the safety and tolerability of donepezil SR;
    2) To evaluate the relationship between plasma concentration of donepezil and inhibition of peripheral acetylcholinesterase in red blood cells RBC-AChE inhibition (*i.e.*, PD evaluation)

Study Design	Phase I, randomized, double-blind, single-dose PK/PD study
Study Population	N=82 Healthy subjects Age: 19-43 years Gender: 34/50 Males/Females Weight: 43.7- 105.0 kg (mean 68.7 kg) Race: 51 Caucasian/ 21 Hispanic / 10 Black
Treatment Group	Group 1: SR 14 mg (N=23) Group 2: SR 23 mg (N=33) Group 3: IR 10 mg (N=26)
Dosage and Administration	Subjects were randomized to receive one of the following treatments: donepezil SR 14 mg, SR 23 mg or IR 10 mg tablet. Subjects were administered a single dose in the morning after overnight fasting.
Sampling: Blood	For plasma donepezil: At pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, 288, 312 and 336 hours post dose. For RBC-AChE levels: Collected at 60-minute intervals for up to 6 hours post-dose and thereafter during each PK blood sample collection.
Analysis	LOQ: 0.2 ng/ml; Linear range of calibration curve: 0.2-60 ng/ml
PK Assessment	AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, $t_{1/2}$, Tlag, MRT, ka, λz
PD Assessment	E_{max}, , $AUE_{0-\infty}$ (the area under the effect curve)
Safety Assessment	Vital signs, physical examination, ECG , Clinical laboratory, AEs and SAEs

Pharmacokinetic Results:

The mean pharmacokinetic parameters of donepezil are shown in the following table:

Table 3. Pharmacokinetic summary of Donepezil SR 23 mg, Donepezil SR 14 mg, and Donepezil IR 10 mg After Single-dose Administration to Healthy Subjects—Study 021

PK Parameter	Treatment Group		
	Donepezil SR 14 mg (Test Drug) (N=23)	Donepezil SR 23 mg (Test Drug) (N=33)	Donepezil IR 10 mg (Reference Drug) (N=26)
AUC_{0-t} (ng*h/mL)			
Arithmetic mean (SD)	1186.93 (218.175)	1561.46 (450.364)	809.23 (219.408)
CV (%)	18.4	28.8	27.1
Median	1149.21	1616.50	754.99
Range	848.0 – 1585.3	569.0 – 2147.5	413.1 – 1269.5
$AUC_{0-\infty}$ (ng*h/mL)			
Arithmetic mean (SD)	1270.17 (243.004)	1650.84 (468.513)	885.30 (249.100)
CV (%)	19.1	28.4	28.1
Median	1242.88	1646.27	825.65
Range	917.5 – 1684.3	697.0 – 2317.3	559.0 – 1518.0
C_{max} (ng/mL)			
Arithmetic mean (SD)	23.13 (6.798)	32.63 (8.637)	20.90 (5.001)
CV (%)	29.4	26.5	23.9
Median	21.60	31.50	20.75
Range	12.3 – 35.6	16.3 – 50.6	12.6 – 31.6
T_{max} (h)			
Arithmetic mean (SD)	6.13 (1.866)	6.15 (1.873)	3.19 (0.939)
CV (%)	30.4	30.4	29.4
Median	6.00	6.00	3.00
Range	4.0 – 12.0	3.0 – 10.0	2.0 – 5.0
λz (1/h)			
Arithmetic mean (SD)	0.01 (0.002)	0.01 (0.004)	0.01 (0.002)
CV (%)	22.8	32.3	26.8
Median	0.01	0.01	0.01
Range	0.0 – 0.0	0.0 – 0.0	0.0 – 0.0
$t_{\frac{1}{2}}$ (h)			
Arithmetic mean (SD)	80.77 (22.407)	67.10 (17.965)	83.14 (24.097)
CV (%)	27.7	26.8	29.0
Median	76.20	64.75	80.13
Range	51.4 – 138.0	27.1 – 102.3	46.0 – 151.8
T_{lag} (h)			
Arithmetic mean (SD)	0.70 (0.249)	0.48 (0.177)	0.45 (0.299)
CV (%)	35.6	37.0	66.1
Median	0.52	0.50	0.50
Range	0.5 – 1.0	0.0 – 1.0	0.0 – 1.0
MRT (h)			
Arithmetic mean (SD)	103.23 (19.296)	84.71 (22.871)	100.24 (21.805)
CV (%)	18.7	27.0	21.8
Median	101.27	79.62	100.74
Range	67.2 - 142.8	41.8 - 135.7	58.7 - 166.2
K_a (1/h)			
Arithmetic mean (SD)	3.58 (4.384)	4.63 (4.757)	6.89 (3.044)
CV (%)	122.5	102.7	44.2
Median	1.18	1.70	6.61
Range	0.3 – 11.9	0.3 – 13.4	1.8 – 13.1

The exposure and C_{max} of donepezil following single-dose administration of SR appeared increasing in a dose proportional manner. The T_{max} of donepezil was delayed after SR 14 mg or 23 mg compared to IR 10 mg (6 hr vs. 3 hr). The exposure and C_{max} of donepezil after SR 23 mg and IR 10 mg were further compared after dose-normalization as shown in the following table:

Table 4. Pharmacokinetic Analyses After Dose-normalization of Donepezil SR 23 mg to Dnepezil IR 10 mg—Study 021

PK Parameter	Summary Statistics	Donepezil SR 23 mg (test drug) n=14
C_{max} (ng/mL)	geometric mean test/reference ratio[a]	0.622
	90% confidence interval	0.532 – 0.728
	percent change as compared to reference	37.77
AUC_{0-t} (ng*h/mL)	geometric mean test/reference ratio[a]	0.821
	90% confidence interval	0.706 – 0.955
	percent change as compared to reference	17.90
$AUC_{0-\infty}$ (ng*h/mL)	geometric mean test/reference ratio[a]	0.812
	90% confidence interval	0.694 –0.950
	percent change as compared to reference	18.82

a Reference treatment was donepezil IR 10 mg

Dose-normalized AUC of donepezil after SR 23 mg was about 80% of that after IR 10 mg. The extent of decrease was similar to that observed for SR 10 mg and IR 10 mg (study 020). Dose-normalized C_{max} after SR 23 mg was also decreased with a geometric mean ratio of 0.62 (SR/IR). However, such decrease in C_{max} is less than that observed for SR 10 mg and IR 10 mg in the previous study (SR/IR: 0.42). In addition, T_{max} of donepezil was less delayed after SR 23 mg (~ 6 hr) compared to SR 10 mg (~9 hr), while T_{max} of IR 10 mg from the two studies were similar (~ 3 hr). These findings indicate that the extent of sustained release observed with SR formulation was less following administration of SR 23 mg compared to SR 10 mg.

The mean plasma concentration profiles for donepezil are shown in the following figure.

Figure 4. Mean plasma concentration versus time profiles (Entire Study ro the first 24 hours) after oral administration of single doses of donepezil SR 23 mg, donepezil SR 14 mg, and donepezil IR 10 mg—Study 021
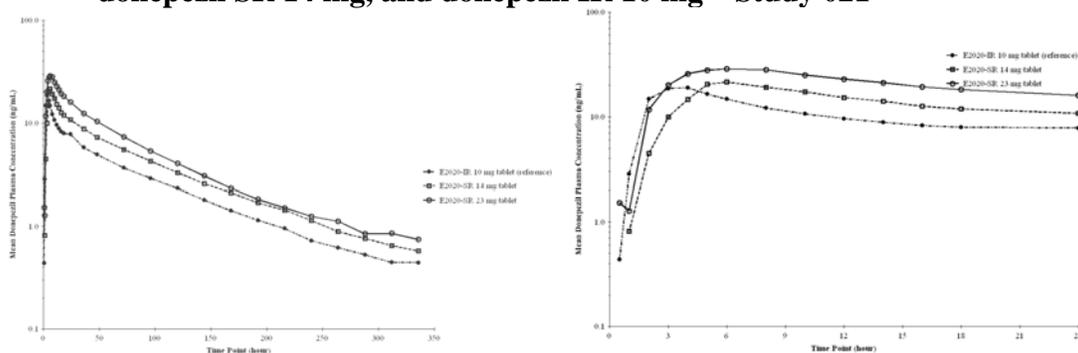
Pharmacodynamic Results:
Due to analytical problems at the laboratory (faulty sample probe) and inability to retest samples due to specimen stability issues, the PD data from this study were considered equivocal and therefore not reported.

Safety:
The most common AEs were: nausea, vomiting, dizziness, abdominal pain, headache, and fatigue. No deaths or other SAEs occurred during the study. The majority of reported AEs were moderate in severity. Nearly all of the AEs reported were considered either possibly or probably related to study treatment. The highest percentage (approximately 91%) of subjects reporting at least one AE occurred in the highest sustained-release dose group (SR 23 mg), while 61% of subjects receiving SR 14 mg and 63% of subjects receiving IR 10 mg reported at least one AE.

Conclusions:
The C_{max} of the donepezil SR formulation was slightly blunted compared to that of the IR formulation. Though dose-normalized C_{max} of donepezil was decreased by about 40% after SR 23 mg compared to IR 10 mg, the extent of decrease was less than that observed for SR 10 mg in the previous study. Consistently, the T_{max} of donepezil was less delayed after SR 23 mg compared to SR 10 mg, indicating that the effect of sustained release was less following administration of SR 23 mg. The exposure and C_{max} of donepezil after SR formulation increased roughly in a dose proportional manner. SR 14 mg had an adverse event profile similar to that of IR 10 mg, while more AEs were reported after SR 23 mg.

Study 022: **A Randomized, Placebo-controlled, Multiple-dose Pharmacokinetic and Pharmacodynamic Study of E2020 (Aricept®) Sustained Release Tablet After Oral Administration to Healthy Subjects**

Objectives:
- *Primary objective:* To evaluate the PK of multiple doses of donepezil SR tablets following oral administration to healthy subjects.
- *Secondary objective:*
  1) To evaluate the safety and tolerability of donepezil SR;
  2) To evaluate the relationship between plasma concentration of donepezil and inhibition of peripheral acetylcholinesterase in red blood cells RBC-AChE inhibition (*i.e.*, PD evaluation)

The study design is as follows:

Study Design	Phase I, double-blind, placebo-controlled, repeated-dose study
Study Population	N=77 Healthy subjects (~15 per group) Age: 19-45 years (mean 36.5 years) Gender: Males (57.1%) Weight: 52-105 kg (mean 73.5 kg) Race: Hispanic (96.1%)
Treatment Group	Subjects were randomly assigned in a blinded fashion to one of five different groups.
Dosage and Administration	(table below)
Sampling: Blood	For plasma donepezil: Blood samples were collected for PK assessment at pre-dose on Day 1. On Days 8, 21 and 22, samples were collected at pre-dose and at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 16 and 24 hours post-dose. Samples were also collected at pre-dose (trough blood levels of drug) daily from Days 23 to 34. On Day 35, samples were collected at pre-dose and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, 288, 312 and 336 hours after administration of the last dose of study medication. For RBC-AChE levels: same as PK sampling
Analysis	LOQ: 0.2 ng/ml; Linear range of calibration curve: 0.2-60 ng/ml
PK Assessment	AUC_{0-t}, $AUC_{0-\tau}$, $AUC_{0-\infty}$, C_{max}, C_{avg}, T_{max}, $t_{1/2}$, MRT, CLss/F, Vz/F
PD Assessment	E_{max}, , $AUE_{0-\infty}$ (the area under the effect curve)
Safety Assessment	Vital signs, physical examination, ECG , Clinical laboratory, AEs and SAEs

Within "Dosage and Administration":

		Outpatient		Inpatient		
Group		Period 1 (Days 1–7)		Period 2 (Days 8–21)		Period 3 (Days 22–35)
1		placebo 5 mg	→	donepezil SR 14 mg	→	donepezil SR 23 mg
2		placebo 5 mg	→	placebo 14 mg	→	placebo 23 mg
3		placebo 5 mg	→	donepezil SR 14 mg	→	placebo 14 mg
4		donepezil IR 5 mg	→	donepezil SR 14 mg	→	donepezil SR 23 mg
5		donepezil IR 5 mg	→	donepezil SR 14 mg	→	placebo 23 mg

Doses were administered orally, once daily in the morning.

On Days 1, 8, 21, 22, and 35, study drug was administered after an overnight fast (no food or beverages except water for at least 10 hours prior to drug administration). Food was to be provided at 4 hours post administration.

Pharmacokinetic Results:

The mean plasma concentration profiles for donepezil are shown in the following figures.

Figure 5. Linear Plots of Mean Plasma Concentration versus Time Profile of Donepezil of Group 1 and 4 During the Entire Study Period (Days 1–49) — Study 022
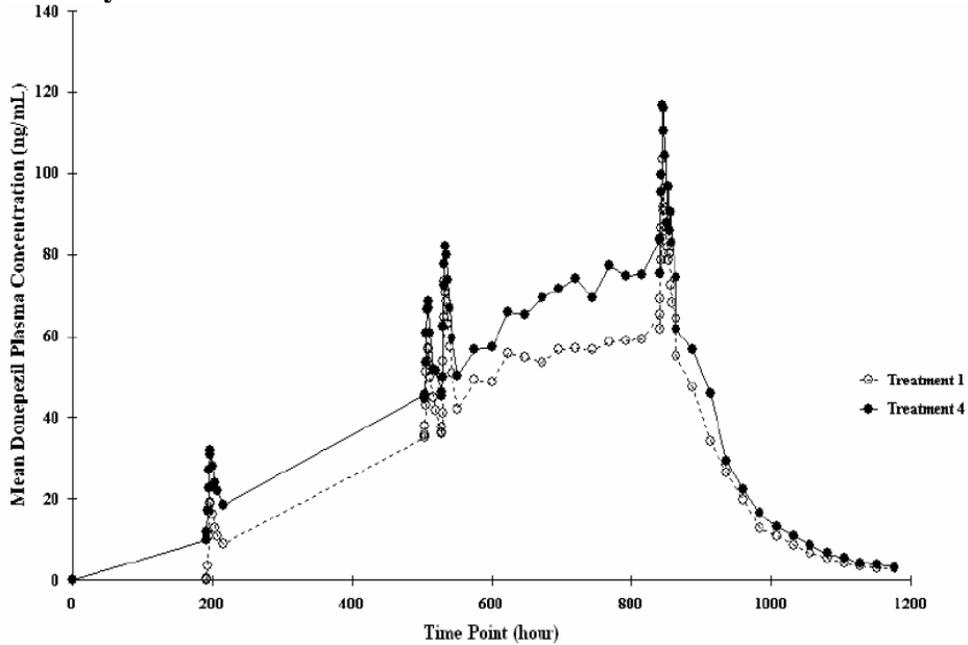
Figure 6. Semi-log (Panel B) plots of mean plasma concentration versus time profile of donepezil on Day 35 after administration of the last Dose of donepezil SR 23 mg (study 022)

	Period 1 (Days 1-7)	Period 2 (Days 8 - 21)	Period 3 (Days 22-35)
Group 1:	5 mg Placebo	14 mg E2020 SR	23 mg E2020 SR
Group 3:	5 mg Placebo	14 mg E2020 SR	14 mg Placebo
Group 4:	5 mg E2020 IR	14 mg E2020 SR	23 mg E2020 SR
Group 5:	5 mg E2020 IR	14 mg E2020 SR	23 mg Placebo

44
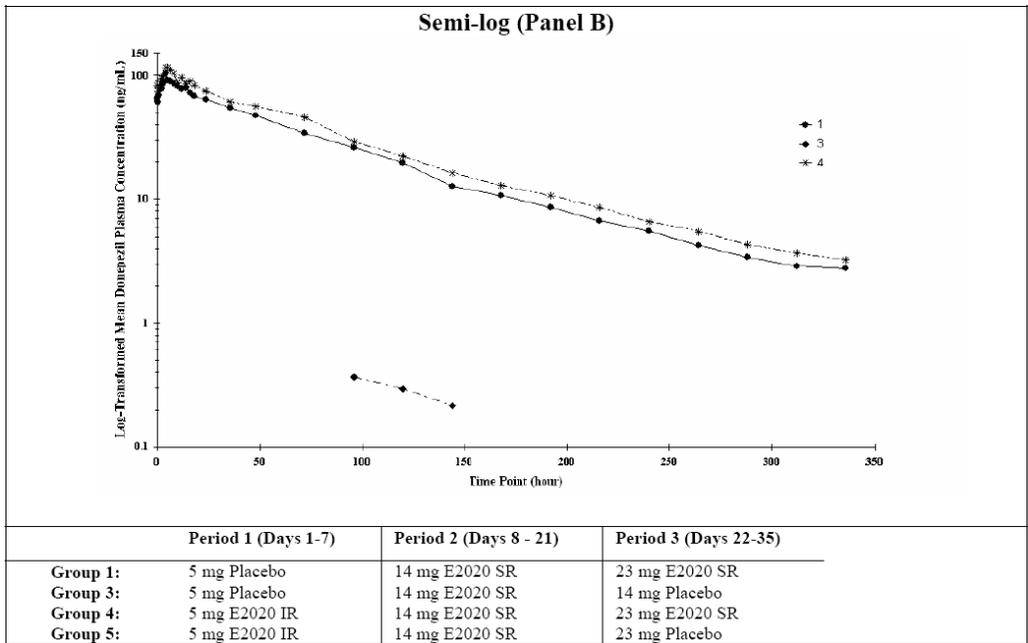
The mean pharmacokinetic parameters of donepezil are shown in the following table:

Table 5. Summary of Pharmacokinetic Parameters of Donepezil on Day 8 After the First Dose of 14 mg donepezil SR

PK Parameter	Groups			
	Group 1 (n=15)	Group 3 (n=16)	Group 4 (n=14)	Group 5 (n=15)
C_{max} (ng/mL)				
Arithmetic mean (SD)	21.3 (7.08)	20.5 (6.64)	33.6 (8.93)	35.6 (10.49)
CV (%)	33.2	32.3	26.6	29.4
Median	19.0	19.0	34.0	34.5
Range	12 – 37	12 – 36	19 – 51	20 – 56
T_{max} (h)				
Arithmetic mean (SD)	5.3 (1.35)	5.5 (2.16)	5.9 (2.11)	5.9 (2.36)
CV (%)	25.2	39.3	35.9	40.2
Median	5.0	5.0	5.5	5.0
Range	3 – 8	4 – 12	3 – 12	3 – 12
AUC_{0-t} (ng*h/mL)				
Arithmetic mean (SD)	278.4 (85.97)	248.4 (69.24)	514.4 (168.55)	537.2 (99.30)
CV (%)	30.9	27.9	32.8	18.5
Median	265.7	242.7	481.8	536.9
Range	185 – 509	107 – 357	231 – 806	371 – 731

Table 6. Summary of Pharmacokinetic Parameters of Donepezil on Day 21 After 14 Days of 14 mg donepezil SR

PK Parameter	Groups			
	Group 1 (n=13)	Group 3 (n=14)	Group 4 (n=12)	Group 5 (n=12)
C_{max} (ng/mL)				
Arithmetic mean (SD)	61.5 (22.95)	64.4 (23.57)	72.9 (23.99)	72.3 (16.36)
CV (%)	37.3	36.6	32.9	22.6
Median	55.0	67.7	65.1	70.2
Range	37 – 114	15 – 92	41 – 117	49 - 98
T_{max} (h)				
Arithmetic mean (SD)	5.3 (1.38)	4.6 (1.01)	4.8 (1.12)	5.2 (1.12)
CV (%)	26.0	21.7	23.1	21.6
Median	6.0	5.0	4.5	5.0
Range	3 – 8	3 – 6	3 – 6	4 - 8
AUC_{0-t} (ng*h/mL)				
Arithmetic mean (SD)	1064.0 (352.75)	1050.8 (403.96)	1296.4 (420.46)	1195.9 (246.86)
CV (%)	33.2	38.4	32.4	20.6
Median	926.3	1119.3	1169.7	1177.2
Range	664 – 1840	191 – 1609	791 – 2173	905 - 1664

Table 7. Summary of the Pharmacokinetic Parameters of Donepezil on Day 22 After the First Dose of 23 mg donepezil SR or Placebo

PK Parameter	Groups			
	Group 1 (n=13)	Group 3 (n=6)	Group 4 (n=12)	Group 5 (n=5)
C_{max} (ng/mL)				
Arithmetic mean (SD)	79.3 (21.47)	39.8 (18.37)	85.3 (25.50)	47.4 (13.52)
CV (%)	27.1	46.2	29.9	28.5
Median	72.7	43.5	82.1	46.9
Range	50 – 129	4 – 59	49 – 124	29 – 65
T_{max} (h)				
Arithmetic mean (SD)	4.9 (1.55)	NA	5.3 (1.50)	NA
CV (%)	31.5		28.1	
Median	4.0		5.0	
Range	3 – 8		3 – 8	
AUC_{0-t} (ng*h/mL)				
Arithmetic mean (SD)	1319.8 (368.10)	732.3 (363.97)	1526.3 (463.32)	818.1 (242.89)
CV (%)	27.9	49.7	30.4	29.7
Median	1222.6	772.3	1401.4	752.5
Range	790 – 2270	73 – 1184	980 – 2429	495 – 1141

Table 8. Summary of Pharmacokinetic Parameters of Donepezil on Day 35 After the Last Dose of 23 mg donepezil SR

PK Parameter	Group	
	Group 1 (n=9)	Group 4 (n=12)
C_{max} (ng/mL)		
Arithmetic mean (SD)	110.4 (27.84)	129.2 (38.52)
CV (%)	25.2	29.8
Median	105.0	124.5
Range	80 – 159	77 – 178
C_{avg} (ng/mL)		
Arithmetic mean (SD)	77.5 (18.63)	93.0 (25.51)
CV (%)	24.0	27.4
Median	70.4	91.8
Range	56 – 107	60 – 131
T_{max} (h)		
Arithmetic mean (SD)	4.6 (0.88)	5.2 (1.59)
CV (%)	19.4	30.7
Median	4.0	5.0
Range	4 – 6	3 – 8
AUC_{tau} (ng*h/mL)		
Arithmetic mean (SD)	1859.4 (447.16)	2232.5 (612.07)
CV (%)	24.0	27.4
Median	1688.7	2203.2
Range	1338 – 2558	1450 – 3154
AUC_{0-t} (ng*h/mL)		
Arithmetic mean (SD)	6329.6 (3197.22)	8368.5 (3298.50)
CV (%)	50.5	39.4
Median	5447.5	6994.1
Range	880 – 10927	4724 – 14241
$AUC_{0-\infty}$ (ng*h/mL)		
Arithmetic mean (SD)	7270.4 (2577.54)	8699.5 (3557.34)
CV (%)	35.5	40.9
Median	5767.5	7122.5
Range	4335 – 11399	4814 – 15113

PK Parameter	Group	
	Group 1 (n = 9)	Group 4 (n = 12)
$t_{1/2}$ (h)		
Arithmetic mean (SD)	62.9 (8.63)	64.5 (12.36)
CV (%)	13.7	19.2
Median	64.4	62.2
Range	47 – 73	46 – 87
CL_{ss}/F (mL/h)		
Arithmetic mean (SD)	12968.3 (2838.69)	11084.7 (3163.95)
CV (%)	21.9	28.5
Median	13620.1	10556.3
Range	8992 – 17194	7292 – 15863
V_z/F (mL)		
Arithmetic mean (SD)	1170270.1 (288697.15)	1026856.4 (377644.60)
CV (%)	24.7	36.8
Median	1084807.0	875540.7
Range	825436 – 1655214	723347 – 1993342
MRT_{inf} (h)		
Arithmetic mean (SD)	79.4 (13.11)	78.7 (16.46)
CV (%)	16.5	20.9
Median	84.5	79.9
Range	55 – 94	56 – 113

Note: n = number of subjects with PK assessment on Day 35. Day 35 is the last day of Period 3; PK parameter values were calculated for subjects who received 23 mg E2020 SR (Group 1 and 4).

CV (%) (coefficient of variation) = 100*(SD/Arithmetic Mean), SD=Standard Deviation, ng/mL = nanogram per milliliter, h = hour, mL/h = milliliters per hour.

	Period 1	Period 2	Period 3
Group 1:	5 mg Placebo	14 mg E2020 SR	23 mg E2020 SR
Group 4:	5 mg E2020 IR	14 mg E2020 SR	23 mg E2020 SR

- Concentrations of donepezil approached steady-state after 14 days of daily treatment of SR 14 mg or 23 mg.
- Compared to the a single dose of SR 23 mg, donepezil accumulates in plasma by 3.96- and 4.66-fold after multiple doses ($R_{A,Css(max)/C1(max)}$ and $R_{A,Css(min)/C1(min)}$, respectively*), similar to that reported for donepezil IR (4-7 fold accumulation)

*The C_{max} of donepezil SR 23 mg on Day 35 in group 4 (129.2 ng/mL) was compared with the C_{max} of a single dose of SR 23 mg (32.63 mg/mL in study 021). The C_{24hr} of donepezil after single- and multiple-dose administration of SR 23 mg were extracted from the original datasets provided by the sponsor and calculated as 16.01 and 74.6 ng/mL, respectively.

- The exposure and C_{max} of donepezil after SR 14 mg and 23 mg increased roughly in a dose proportional manner.
- The $AUC_{0-\tau}$ of donepezil after multiple doses of SR were similar to the AUC_{0-inf} of donepezil after a single dose, suggesting that there is no auto-inhibition or induction.
- A lead-in dose of IR 5 mg slightly increased the initial concentrations of donepezil achieved after administration of SR 14 mg on Day 8, but the effect seemed to be negligible upon repeated administration.

Since IR 10 mg was not administered in this study, it is impossible to directly compare steady-state PK parameters of donepezil after administration of SR 23 mg and IR 10 mg within the study. One published literature report by the sponsor had PK parameters of donepezil IR 10 mg at steady state (Tiseo PJ, Br J Clin Pharmacol. 1998 Nov;46 Suppl 1:13-8). A cross-study comparison was made by the reviewer based on the data in study 022 (SR 23 mg) and the information from the literature (IR 10 mg). It should be noted that the dosing regimens were different. In study 022, 7-day once daily dose of IR 5 mg was administered first as titration. Then, 2-week treatment of SR 14 mg was initiated followed by another 14-day once daily dosing of SR 23 mg. In the literature, 7-day IR 5 mg q.d. dosing of donepezil was followed by 21-day once daily dosing of IR 10 mg. The concentrations measured after the last doses of donepezil were used for the analysis.

Table 9. Comparisons of steady-state PK parameters of donepezil between SR 23 mg and IR 10 mg.

AUC_{SR}/AUC_{IR}	$C_{max,SR}/C_{max,IR}$	$C_{24hr,SR}/C_{24hr,IR}$	C_{max}/C_{24hr} (SR vs. IR)	T_{max} (SR vs. IR)
1.98	2.14	1.94	1.79 vs. 1.57	5.2 vs. 3.9
(After Dose Normalization)				
0.86	0.93	0.84	1.79 vs. 1.57	5.2 vs. 3.9

The dose-normalized $AUC_{0-\tau}$ of donepezil after SR 23 mg was about 86% of that after IR 10 mg, similar to the value (~80%) observed in study 021. However, the dose-normalized steady-state C_{max} of donepezil was only decreased by 7% after SR 23 mg compared to IR 10 mg. The extent of decrease in C_{max} was much less than that achieved after a single dose of SR 23 mg (~40%, study 021). Following single-dose administration, the C_{max}/C_{24hr} ratio of donepezil after SR 23 mg was smaller than that after IR 10 mg (2.24 vs. 2.95), as expected for sustained-release formulation. However, following multiple-dose administration, the ratio became similar between SR 23 mg and IR 10 mg (1.79 vs. 1.57). These findings suggested that the effect of sustained release becomes minimal following multiple dosing of donepezil. The reduced sustained-release effect may be related with the high accumulation of donepezil after multiple doses, which gradually masks the difference between SR and IR observed after single-dose administration. Overall, it appears that SR 23 mg has similar exposure and C_{max} as IR 20 mg, assuming linear PK for IR formulation over the dose range of 10-20 mg. Dose proportional increase of C_{trough} in patients receiving IR 10 mg and 20 mg has been observed (Doody RS, et al. Drugs Aging. 2008;25(2):163-74).

Pharmacodynamic Results:
The assay method used to measure cholinesterase activity failed to detect measurable alteration of binding by donepezil. Thus, the sponsor concluded that the method used was inappropriate for the purposes of this evaluation. Thus, the PD data collected were not analyzed further.

Safety:
The most common AEs were: nausea, vomiting, diarrhea, abdominal pain, headache, dizziness, and asthenia. No deaths or other SAEs occurred during the study. Overall, Group 3 had the highest percentage of subjects reporting at least one AE (93.8%)

followed by Group 1 and 4. There was no apparent relationship between AEs and cumulative exposure to donepezil. In a separate analysis, the incidence of vomiting was found significantly higher in subjects treated with SR 14 mg that were pretreated with placebo when compared with subjects treated with SR 14 mg that were pre-treated with IR 5 mg, suggesting that titration may be necessary.

<u>Overall Conclusions:</u>
Steady state of donepezil was approximately achieved after 14-day daily oral dose of SR 14 or 23 mg, with accumulation ratio of 4- to 4.7-fold. It seems that there was linear PK for SR 14 and 23 mg after multiple dosing. Compared to single-dose administration, the difference between SR and IR appears to be smaller following multiple-dose treatment. The reduced sustained-release effect for SR 23 mg may be due to the high accumulation of donepezil after multiple dosing which gradually masks the difference observed between SR and IR after single-dose administration. Overall, SR 23 mg seems to have similar exposure and C_{max} as IR 20 mg at steady state.

4.1.2. PK in PATIENTS:

Study 326:   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

Objectives:

- *Primary objective:* To compare the efficacy of donepezil SR 23 mg with donepezil IR 10 mg in the treatment of patients with moderate to severe Alzheimer's disease (AD).
- *Secondary objective:* To assess secondary efficacy parameters in support of the co-primary efficacy parameters, and to assess the safety and tolerability of donepezil SR 23 mg.
- *Exploratory objective:* To evaluate quality-of-life in patients administered donepezil SR 23 mg and in their caregivers for comparison with donepezil IR 10 mg, and to evaluate whether treatment response was related to rate of drug metabolism as modified by cytochrome P450 2D6 (CYP2D6) alleles and to the presence of AD risk factor apolipoprotein E_4 ($APOE_4$).

Study Design	Phase III, randomized, double-blind, double-dummy, parallel-group study
Study Population	N= 1467 Patients (1084 completed the study) Patients had to be taking donepezil IR 10 mg for a minimum of 3 months to be eligible for the study. Age: 47-90 years (mean 73.8 years) Gender: 533 males and 901 females Weight: 329, <55kg; 374, 55kg to < 65kg; 350, 65kg to < 75kg; 380, ≥ 75kg. Race: 1054 White, 93 Hispanic, 31 Black, 248 Asian/Pacific
Treatment Group	Two groups
Dosage and Administration	The study was composed of a screening period, a baseline visit and a 24-week treatment period with visits to the clinic 3, 6, 12, 18 and 24 weeks after the baseline visit. Patients were randomized to receive either donepezil SR 23 mg concurrently with placebo (identical in appearance to donepezil IR 10 mg) or donepezil IR 10 mg concurrently with placebo (identical in appearance to donepezil SR 23 mg).
Sampling: Blood	For plasma donepezil: During Screening, blood samples were drawn from every patient at every study site for determination of plasma donepezil levels. At subsequent visits, additional samples for PK evaluations were collected at selected study sites.
Analysis	LOQ: 0.2 ng/ml; Linear range of calibration curve: 0.2-60 ng/ml
PK Assessment	Population PK analysis
Efficacy Assessment	Co-primary efficacy assessments included the Severe Impairment Battery (SIB) score and the Clinician's Interview-Based Impression of Change Plus Caregiver

	Input (CIBIC+).
	Secondary efficacy assessments included the Mini-Mental State Examination (MMSE) and the modified Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL).
	Exploratory efficacy assessments included the Quality of Life-Alzheimer's Disease (QoL-AD) Scale, EuroQoL-5 Dimensions Scale (EQ-5D), Screen for Caregiver Burden (SCB), Treatment Outcome Scale (TOS), and the Goal Attainment Scale (GAtS).
Safety Assessment	Vital signs, ECG , weight, Physical Examination, neurological examination, Clinical laboratory, AEs

Pharmacokinetic Results:

A population PK model was developed and validated based on the phase III data. The AUC_{ss} was derived from the model-estimated apparent clearance (CL/F) for each individual.

Table 10. Derived AUC_{ss} Values

	IR Formulation	SR Formulation
Summary Statistic	AUC_{ss} (µg*hr/L)	AUC_{ss} (µg*hr/L)
N	361	696
Mean (SD)	1388 (397.2)	3015 (926)
Min	464.3	314.1
Median	1371.5	2970
Max	3026	6440

As shown in the table, the steady-state AUC after SR 23 mg was 2.17 fold of that after IR 10 mg. Dose-normalized AUC_{ss} of SR 23 mg was 94% of that after IR 10 mg.

$C_{max,ss}$ was not derived for the Phase III subjects from population PK analysis because of the substantial shrinkage in all parameters except for CL/F. Alternatively, the sponsor performed some preliminary analysis based on limited data. The sponsor assumed that concentrations measured at 3±1 hr post-dose of IR 10 mg during the treatment period represented C_{max} for IR, while the concentrations measured at 7±2 hr post-dose of SR 23 mg were used to calculate the C_{max} for SR. Based on such assumption, the C_{max} after multiple doses of SR 23 mg was 2.09-fold of that following IR 10 mg. After dose-normalization, the C_{max} of SR 23 mg (6.03 ng/mL) was only 9% lower than the one of IR 10 mg (6.64 ng/mL), indicating that there was little difference between the two formulations in patients. It is recognized that due to sparse PK sampling it is difficult to accurately determine the C_{max} for SR 23 mg or IR 10 mg in the patients and the pre-specified windows for T_{max} may have impact on the estimation of C_{max}.

Besides AUC_{ss} and C_{max}, the C_{24hr} of donepezil after SR 23 mg was also about 2 fold of that after IR 10 mg (78.1 and 40.3 ng/mL for SR and IR, respectively), similar to the results observed in healthy subjects in study 022. The ratio of C_{max}/C_{24hr} of SR 23 mg was almost the same as that of IR 10 mg (1.57 vs. 1.50).

Overall, SR 23 mg seemed having similar steady-state exposure and concentrations of donepezil as IR 20 mg, assuming linear PK for IR over the dose range of 10-20 mg. The anticipated decrease of C_{max} resulted from the sustained-release formulation was nearly diminished.

Please refer to the pharmacometric reviewer's review (Appendix III) for the details of the population PK analysis and the effects of covariates (*e.g*, weight, age, gender, CYP2D6 status, concurrent administration of 2D6 inhibitors, etc.) on PK of donepezil.

Efficacy Results:
Cognition Function
Table 11. Analysis of Severe Impairment Battery (SIB) Total Score – Change from Baseline to Week 24

Analysis[a]	Donepezil SR 23 mg	Donepezil IR 10 mg
Primary: ITT population, LOCF		
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	0.0001	
Exploratory: OC population		
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	0.0001	
Concomitant Memantine Use, ITT		
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	0.0033	
No Concomitant Memantine Use, ITT		
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	0.0069	
US Population, ITT		
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	0.0002	
MMSE Baseline Score of 3-14 , ITT		
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	0.0005	
MMSE Baseline Score of 5-14 , ITT		
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	0.0034	
MMSE Baseline Score of 0-16 , ITT		
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	<0.0001	

As shown in the above table, donepezil SR 23 mg is superior to IR 10 mg in terms of improvement of patients' cognitive performance in the total ITT (intent-to-treat) population and also sub-populations.

Global Function

Table 12. Analysis of Clinician's Interview-Based Impression of Change Plus Caregivers Input (CIBIC+) Score at Week 24

Analysis[a]	Donepezil SR 23 mg	Donepezil IR 10 mg
Primary: ITT population, LOCF		
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	0.1789	
Exploratory: OC population		
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	0.0592	
Concomitant Memantine Use, ITT		
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	0.1372	
No Concomitant Memantine Use, ITT		
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	0.3795	
US Population, ITT		
Change in assessment at Week 24 overall change	n = 292	n = 140
Mean (SD)	4.38 (0.97)	4.57 (0.89)
p-value compared to donepezil IR	0.0330	
MMSE Baseline Score of 3-14 , ITT		
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	0.0508	
MMSE Baseline Score of 5-14, ITT		
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	0.0469	
MMSE Baseline Score of 0-16 , ITT		
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	0.0279	

The difference between SR 23 mg and IR 10 mg in improvement of the global performance of patients measured as CIBIC+ scores was not statistically significant in ITT population. Such difference approached statistical significance favoring SR 23 mg in the OC (observed cases) population. After stratification of the total population with baseline MMSE scores, SR 23 mg was found statistically superior to IR 10 mg in sub-groups with MMSE baseline scores of 0-16 or 5-14, while the difference was on the margin of significance for sub-group with MMSE baseline score of 3-14. Population with baseline MMSE scores from 0 to 16 represents the more severely impaired patients among the moderate-to-severe AD population. In addition, the difference between SR 23 mg and IR 10 mg was statistically significant for US ITT population.

Safety Results:
Most common adverse events (AEs) were nausea, diarrhea, vomiting, anorexia. The cholinergic adverse effects were generally transient, occurring most frequently upon introduction of the drug and during dose escalation. More AEs were reported in SR 23 mg group compared to IR 10 mg group in the first couple of weeks. After 3 weeks of continued use, the difference in AE frequency was inappreciable between the two treatment groups.
More patients in donepezil SR 23 mg were reported with weight loss compared to donepezil IR 10 mg group.

Conclusions:
It appears that SR 23 mg has a similar PK profile as IR 20 mg, assuming linear PK for IR formulation over the range from 10 to 20 mg. A population PK model has been developed and validated based on the data of this study and used to identify the effects of several covariates (*e.g*, weight, age, gender, CYP2D6 status and co-administration of CYP2D6 inhibitors) on PK of donepezil.

4.1.3. FOOD EFFECT

Study 023: **A Randomized, Open-label, Single and Repeated Dose Study to Evaluate the Effect of Food on the Bioavailability of E2020 (Aricept®) Sustained Release Tablet Following Oral Administration to Healthy Subjects**

Objectives:

- *Primary objective:* To evaluate the effect of food on bioavailability of donepezil SR tablets following single and repeated oral administration to healthy subjects.
- *Secondary objective:* To determine the safety and tolerability of donepezil SR.

Study Design	Phase I, randomized, open-label, two-period, two-sequence, crossover, multiple-cohort study
Study Population	N=79 Healthy subjects (45 included in PK population) Age: 19-45 years (mean 29 years) Gender: 44 males and 35 females Weight: 52-107 kg (mean 74.3 kg) Race: 43 White, 25 Hispanic, 10 Black, 1 Asian/Pacific
Treatment Group	Panel 1: Single dose donepezil SR 14 mg (N=17) Panel 2: Single dose donepezil SR 23 mg (N=35) Panel 3: Donepezil SR 14 mg daily for 7 days, followed by a single dose of donepezil SR 23 mg (N=27)
Dosage and Administration	Panel 1 and 2: Panel 3: * 14 mg donepezil 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 donepezil SR was administered after breakfast.
Sampling: Blood	For plasma donepezil: Blood samples for the measurement of donepezil levels were collected at pre-dose and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, 288, 312, and 336 hours post-dose.
Analysis	LOQ: 0.2 ng/ml; Linear range of calibration curve: 0.2-60 ng/ml
PK Assessment	AUC_{0-t}, AUC_{0-24hr}, $AUC_{0-\infty}$, C_{max}, T_{max}, $t_{1/2}$, λz
Safety Assessment	Vital signs, ECG , Physical Examination, Clinical laboratory, AEs and SAEs

Pharmacokinetic Results:

The mean plasma concentration profiles for donepezil are shown in the following figure.

Figure 7. Mean Plasma Concentration versus Time Profiles After Oral Administration of Donepezil SR 23 mg Single Doses Under Fasted or Fed Conditions With (Right Panel) or Without (Left Panel) Titration with Donepezil SR 14 mg for 7 Days
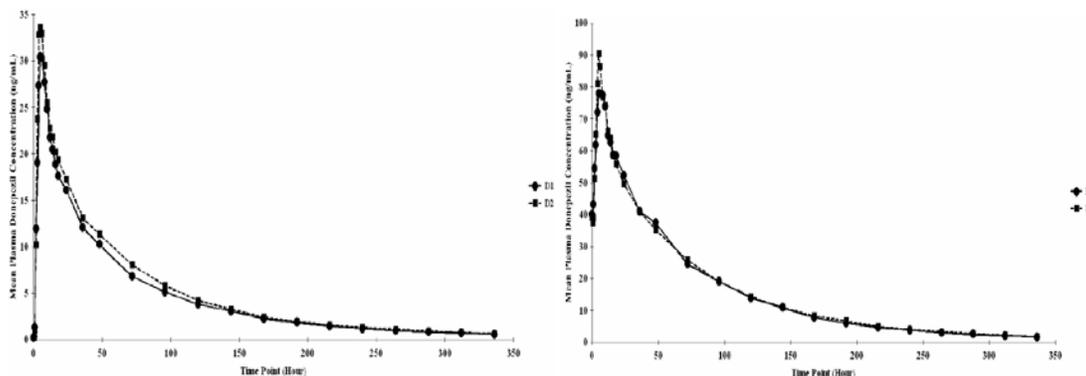
D1, E1 = Fasted; D2, E2= Fed

The effects of food on the rate and extent of absorption of donepezil SR were summarized in the following table:

Table 13. Food Effect Bioavailability Analysis of Donepezil SR

PK Parameter	Panel		
	1	2	3
	14 mg E2020 SR (n=15)	23 mg E2020 SR (n=17)	14 mg/23 mg E2020 SR (n=13)
C_{max} (ng/mL)			
Ratio of Geometric Means (Fed/Fasted)	100.7	122.7	116.1
90% Confidence Interval (lower, upper)	84.2, 120.5	98.6, 152.8	108.1, 124.6
AUC_{0-t} (ng*h/mL)			
Ratio of Geometric Means (Fed/Fasted)	95.7	108.2	-
90% Confidence Interval (lower, upper)	84.0, 108.9	96.9, 120.7	-
AUC_{0-24h} (ng*h/mL)			
Ratio of Geometric Means (Fed/Fasted)	-	-	105.3
90% Confidence Interval (lower, upper)	-	-	101.4, 109.4
$AUC_{0-\infty}$ (ng*h/mL)			
Ratio of Geometric Means (Fed/Fasted)	96.4	109.4	-
90% Confidence Interval (lower, upper)	84.9, 109.4	98.2, 121.9	-

NOTE: 90% confidence interval calculations are based on the mixed model with sequence, period, and treatment (fed/fasted) as fixed effects, subject nested in sequences as random effects.

The AUC of donepezil in all the panels were similar between fed and fasted states. Difference in C_{max} was only observed for SR 23 mg but not SR 14 mg. There was a slight increase (22.7%) of C_{max} after a single dose of SR 23 mg under fed conditions. No food effect was observed when the single dose of SR 23 mg was administered after multiple doses of SR 14 mg. The small food effect noted after single-dose administration may be

masked by the elevated baseline plasma concentration of donepezil after multiple-dose administration, which is due to the high accumulation ratio. In conclusion, donepezil SR 23 mg can be taken without regard to meals.

Safety:
The most common AEs were: nausea, vomiting, dizziness, and headache. All AEs were mild to moderate in severity; there were no death or severe AEs. Approximately 75% of the subjects (15/20 subjects) who discontinued from the study prematurely were in Panel 2 (23 mg single dose of donepezil SR), and most of them discontinued during the fed period. The higher rate of discontinuation may be related with higher C_{max} of donepezil under fed state in panel 2. In all panels, the incidence of vomiting was greater during the fed period versus the fasted period. The incidence of vomiting in subjects dosed with 23 mg donepezil SR was lower when they were pre-treated with 14 mg donepezil SR for 7 days (Panel 2 versus Panel 3), suggesting that titration may be needed.

Conclusions:
In most cases, both C_{max} and AUC_{0-24h} values for the fasted and fed periods were bioequivalent, suggesting that food has no effect on the rate and extent of absorption of donepezil SR. Only 23% increase in C_{max} of donepezil was observed following single-dose of SR 23 mg, which disappeared when the single dose of SR 23 mg was administered after a 7-day titrated treatment of SR 14 mg. In conclusion, donepezil SR can be taken without regard to meals.

4.1.4. Alcohol Dumping
Study W-20080032:   Effect of Ethanol concentration in the acidic medium on the dissolution profile of E2020SR-FT23mg

Objective: To investigate the effect of ethanol concentration in the medium (0.1N hydrochloric acid) on dissolution profile of donepezil SR 23 tablets.

Methods:
The dissolution rate of donepezil SR 23mg tablet was determined using Apparatus 2 of USP <711>, with 900 mL each of 0.1N HCI, 0.1N HCI containing 10% ethanol, 0.1N HCI containing 20% ethanol and 0.1N HCI containing 30% ethanol as dissolution medium and a paddle rotation speed of 50 rpm. It was performed for 4 hours considering that gastric emptying time is generally 2 hours. A HPLC method was employed for the determination of donepezil dissolved.

Results:
Figure 8. In Vitro Dissolution Profile of Donepezil SR in Varying Concentrations of Ethanol
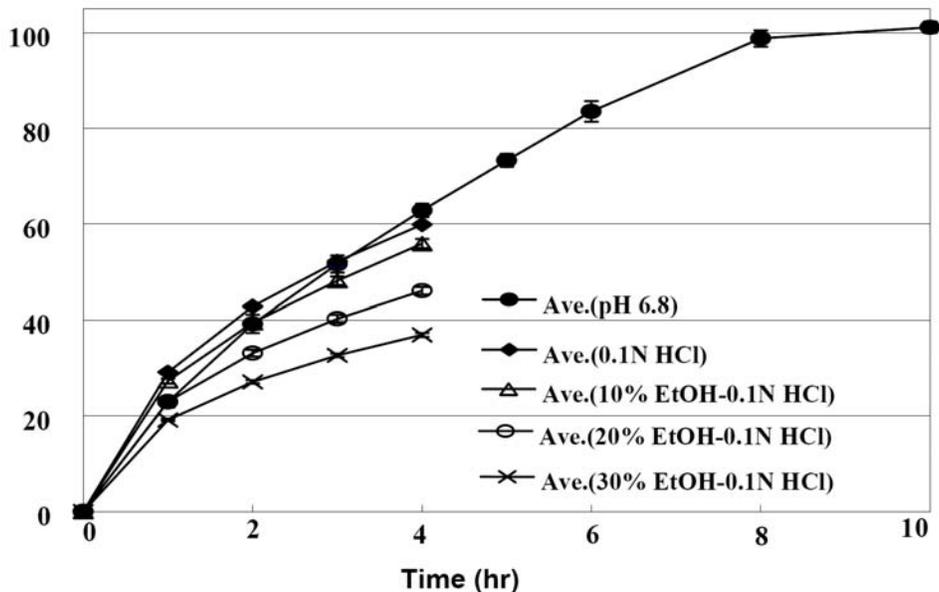
In vitro dissolution study demonstrated that the release of donepezil from SR formulation was greatly reduced by alcohol (up to ~50% decrease).

(b) (4)

The dissolution results indicated that extensive consumption of alcohol may decrease the exposure of donepezil SR 23 mg *in vivo*. However, such effect may not lead to clinical

concerns. First, the lower exposure will actually reduce the incidence of AEs. Secondly, 10-mg IR tablet has been approved for treatment of moderate-to-severe AD and 23-mg SR tablet was overall just slightly better than 10-mg IR tablet. So, even if the exposure of donepezil after SR 23mg is reduced with consumption of large amount of alcohol, acceptable efficacy may still be achieved. Lastly, alcohol abuse is less likely in the target population which is mainly composed with elderly patients.

Conclusions:
Decreased dissolution of donepezil was observed in the presence of ethanol rather than dissolution dumping. The decreased dissolution may reduce the exposure of donepezil. But such effect may not lead to clinical concerns.

5.0 APPENDIX II

OCPB FILING REVIEW

Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	N 22-568	**Brand Name**	▓▓▓▓ (b) (4)
OCP Division (I, II, III)	DCP-I	**Generic Name**	Donepezil hydrochloride (E2020-SR)
Medical Division	HFD-120	**Drug Class**	acetylcholinesterase inhibitor
OCP Reviewer	Ju-Ping Lai	**Indication(s)**	Moderate to severe Alzheimer's Disease (AD)
OCPB Team Leader	Angela Men	**Dosage Form**	Extended Release Tablets (23 mg)
		Dosing Regimen	**Initiation:** Patients established with 10 mg can be administered ▓▓▓▓ (b) (4) 23 mg, QD **Maintainance:** ▓▓▓▓ (b) (4) 23 mg, QD
Date of Submission	9/24/2009	**Route of Administration**	Oral
Estimated Due Date of OCP Review	5/24/2010	**Sponsor**	Eisai Medical Research Inc.
Division Due Date	6/24/2010	**Priority Classification**	Standard
PDUFA Due Date	7/24/2010		

Clin. Pharm. and Biopharm. Information

This application for Aricept ^{(b) (4)} (Donepezil hydrochloride) Extended Release ^{(b) (4)} Tablets is being submitted as a 505(b)(1) submission for the treatment for moderate-to-severe dementia of the Alzheimer's type.

Oral donepezil hydrochloride (Aricept®), a selective, reversible inhibitor of acetylcholinesterase, has been first approved in the US as a treatment for mild to moderate Alzheimer's Disease (AD) in November 1996. Expanded indication to include patients with severe AD has also been approved in US to date. Donepezil is currently marketed as immediate-release (IR) (Aricept®) and orally disintegrating (ODT) (Aricept® ODT) 5 mg and 10 mg tablet formulations for once daily administration in the US.

As the recommended dose for Aricept® is 5 or 10 mg QD, the symptomatic benefits usually gradually lost over time despite continued treatment, the sponsor therefore attempted to produce a higher dose (23 mg) donepezil tablet ^{(b) (4)}

The clinical development program for Aricept ^{(b) (4)} consists of 4 Phase I studies under IND 35,974. The Phase I studies (E2020-A001-020, -021, -022 and -023) consist of a relative bioavailability study for 3 SR formulation evaluation, single dose and multiple dose pharmacokinetic studies and one food effect study. Efficacy and safety of Aricept ^{(b) (4)} was evaluated in a single pivotal Phase III (E2020-G000-326) study to establish the superiority of Aricept ^{(b) (4)} over the currently-marketed donepezil 10 mg IR tablets in the treatment of patients with moderate to severe AD. One population pharmacokinetic (PK) study was also generated utilizing sparse sampling from study 326. In addition, an *in vitro* dissolution study (W20080032) was conducted to evaluate the potential of dose dumping for the Aricept ^{(b) (4)}. A second Phase III open-labeled trial (E2020-G000-328) is currently ongoing.

The formulation of donepezil SR 23 mg tablets was not changed from the clinical trials through commercial production.

This NDA consists of

- **4 Phase I studies:**
  1. Bioavailability study: relative BA for three 10 mg SR formulations
     E2020-A00 1-020:

     (b) (4)

     - Mean Cmax ↓ more than 50% and AUC were ~ 80% for the E2020-SR-8H formulation compared to regular release formulation.
     - Tmax were 2.7, 4.8, 9.2, and 16.3 hours for the E2020-RR, E2020-SR-4H, E2020-SR-8H, and E2020-SR-12H formulations, respectively.
     - T1/2 remained unchanged of approximately 75 to 78 hours.

  2. Single dose pharmacokinetic study
     E2020-A00 1-021:
     - SD, 10 mg IR vs 14 mg SR vs 23 mg SR
     - 14 mg SR vs 23mg SR exposure showed approximately proportion
     - C_{max} of the SR formulation was blunted compared to IR formulation
     - $AUC_{0-\infty}$ of the 14 mg SR was slightly more than proportionately higher than that of the 10 mg IR.
     - 14 mg SR had a similar adverse event profile to the 10 mg IR.

  3. Multiple dose pharmacokinetic study
     E2020-A00 1-022:
     - MD, 5 mg IR x 7 days vs 14 mg SR x 14 days vs 23 mg SR x 14 days
     - similar Tmax and T1/2 for 14 mg SR and 23 mg SR
     - 23 mg SR (AUC & Cmax) showed greater than proportion than 14 mg SR.
     - steady-state achieved during 14 days of daily administration of SR formulation

  4. Food effect study:
     E2020-A00 1-023:
     - no food effect on the PK of SR after a single- or multiple-dosing regimen.
     - a greater percentage of subjects reporting vomiting when study drug was administered in the fed condition (why?)

- **1 Population PK study:**
  E2020-G000-326: to be reviewed by Pharmacometrics reviewer

- **1 *In vitro* dissolution study:** alcohol interaction (dumping) study
  W20080032: dissolution ↓ when alcohol ↑ from 0 to 30%

- **1 Phase III study:**
  E2020-G000-326: a single pivotal efficacy and safety trial

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	2		
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1		
multiple dose:	X	1		
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
Renal impairment:				
Hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -	X	1		
Data rich:	X			
Data sparse:	X			
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X	1		
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1		
Dissolution:	X	1		
(IVIVC):				
Bio-waiver request based on BCS				

BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	66			
Total Number of Studies				
	4 PK + 1 Pop PK + 1 in vitro+ 2 Assay+ Literature			

Filability and QBR comments

I.	"X" if yes	Comments
II. Application filable?	X	
III. Comments sent to firm? **IV.**	**X**	Please provide all datasets (NONMEM format) for population PK analyses along with programs and outputs.
QBR questions (key issues to be considered)	- Is dose proportionality established in the therapeutic range? - Is there any food effect? - Is dose adjustment necessary for concomitant use of other drugs (e.g. CYP2D6 inhibitors)? - Is dose adjustment necessary for CYP2D6 poor metabolizers? - Is the exposure of 23 mg SR comparable to the 10 mg IR?	
Other comments or information not included above		
Primary reviewer Signature and Date	Ju-Ping Lai	
Secondary reviewer Signature and Date	Angela Men	

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	To-be-marketed formulation used.
2	Has the applicant provided metabolism and drug-drug	x			

#	Question				
	interaction information?				
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			

Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)

#	**Data**				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	x			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?		x		
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?		x		
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?		x		
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? ___Yes_____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Ju-ping Lai, Ph.D.	12/18/2009
Reviewing Clinical Pharmacologist	Date
Angela Men, M.D., Ph.D.	12/18/2009
Team Leader/Supervisor	Date

			5.2 Tabular Listing of Clinical Studies					
Study Type	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product (s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Completed; Final CSR
BA	E2020-A001-020	5.3.1.1.1	Primary objective: to evaluate the relative bioavailability of a single dose of each of the three sustained-release formulations Secondary objective: to evaluate safety	Open-label, Phase I BA study	Donepezil HCl 10 mg oral tablets: 4-hour dissolution type, 8-hour dissolution type, and 12-hour dissolution type	82 subjects	Healthy subjects	Single dose study	Completed; Final Report
BA	E2020-A001-023	5.3.1.1.2	Primary objective: to evaluate the effect of food on bioavailabilty of tablets following single and repeated oral administration Secondary objective: to determine the safety and tolerability	Open-label, Phase I BA study	Donepezil HCl sustained-release (E2020 SR) 14 mg and 23 mg oral tablets	79 subjects	Healthy subjects	Up to 16 Days	Completed; Final Report
BA	W-20080032	5.3.1.3.1	To evaluate the effect of ethanol concentration in the acidic medium on the dissolution profile of E2020SR-FT 23 mg	In vitro dissolution study	NA	NA	NA	NA	Completed; Final Report

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					5.2 Tabular Listing of Clinical Studies					

Study Type	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product (s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Completed; Final CSR
BA	(b) (4)	5.3.1.4.1	Determination of Donepezil and 6-OH Donepezil in Human Plasma by LC/MS/MS	Method validation	NA	NA	NA	NA	Completed; Final Report
BA	P561.02	5.3.1.4.2	Determination of Donepezil and 6-OH Donepezil in Human Plasma by LC/MS/MS	Method development	NA	NA	NA	NA	Completed; Final Report
BA	P840.00	5.3.1.4.3	Determination of Donepezil in Human Plasma by LC/MS/MS	Method development	NA	NA	NA	NA	Completed; Final Report
BA	ADZT	5.3.5.1.1 Section 16.1.15	Quantitation of Donepezil in Human Plasma via HPLC with MS/MS Detection	Method validation	NA	NA	NA	NA	Completed; Final Report

5.2 Tabular Listing of Clinical Studies									
Study Type	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product (s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Completed; Final CSR
PK	E2020-A001-021	5.3.3.1.1	Primary objective: to evaluate the PK of a single dose of 14 mg and 23 mg sustained-release formulations following oral administration Secondary objective: to evaluate safety and tolerability and to evaluate the relationship between plasma concentrations of donepezil and RBC-AChE inhibition.	Double-blind, single dose PK/PD Study	Single dose of donepezil HCl 14 mg and 23 mg sustained-release oral tablets or donepezil HCl immediate release 10 mg oral tablets	84 subjects	Healthy subjects	Single dose study	Completed; Final Report
PK	E2020-A001-022	5.3.3.1.2	Primary objective: to evaluate the PK of mutiple doses of the tablets following oral administration to healthy subjects. Secondary objective: evaluate the safety and tolerability and to evaluate the relationship between plasma concentrations and inhibition of peripheral acetylcholinesterase in red blood cells	Double-blind, placebo-controlled, repeated-dose PK/PD Study	Donepezil HCl; 5mg immediate release oral tablets or matching placebo once daily for 7 days; then 14 mg oral tablets or matching placebo once daily for 14 days; then 23 mg oral tablets or matching placebo once daily for 14 days	77 subjects	Healthy subjects	5 weeks	Completed; Final Report

				5.2 Tabular Listing of Clinical Studies					

Study Type	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product (s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Completed; Final CSR
Phase III	E2020-G000-326	5.3.5.1.1	Primary objective: to compare 23 mg donepezil SR with 10 mg donepezil IR. Secondary objective: to assess secondary effficacy parameters, to perform exploratory quality-of-life assessments in patients administered 23 mg donepezil SR and in the caregivers for comparsion with 10 mg donepezil IR, to assess the safety and tolerability of 23 mg donepezil SR during administration, to determine whether treatment response is related to rate of drug metabolism and whether treatment response is related to the presence of AD risk factor APOE4.	Double-blind, double-dummy, parallel-group comparison	Donepezil HCl sustained-release 23 mg oral tablets once daily + placebo; or donepezil HCl immediate release 10 mg oral tablets once daily + placebo	1200 patients planned; 1467 patients randomized	Patients with moderate to severe Alzheimer's Disease	24 wks	Completed; Final Report

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6.0 APPENDIX III

PHARMACOMETRIC REVIEW

OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRIC REVIEW

Summary of Findings

<u>Key Review Questions</u>

The purpose of this review is to address the following key questions.

Is there any evidence of dose-efficacy relationship in support of the new donepezil SR 23 mg formulation?

The sponsor's hypothesis is that systemic exposure of donepezil is associated with appreciable inhibition of acetylcholinesterase (AChE) activity. Therefore, an increase in the currently approved dose may produce greater inhibition of AChE activity that may enhance the cognitive benefit, and eventually achieve clinically meaningful improvement.

Donepezil hydrochloride (Aricept®) is currently marketed as immediate release (IR) and oral dispersible formulations at daily doses of 5 mg and 10 mg. There have been over 4.8 billion patient-days of exposure to donepezil globally since its first introduction, with no substantial amendments to the safety profile. In a 31-patient study (E2020-A001-409), donepezil IR 15 mg and 20 mg was assessed and demonstrated reasonable degree of safety and tolerability. (b) (4) Given 92% bioavailability relative to IR formulation, the SR 23 mg should be considered similar as the IR formulation with doubled strength. To diminish the untoward side effects, patients recruited in this trial were required to be on a stable dose of donepezil IR 10 mg for at least 3 months. Therefore, the sponsor's dose justification appears acceptable.

Two co-primary efficacy endpoints were evaluated in the pivotal trial (E2020-G000-326): Severe Impairment Battery (SIB) total score change from baseline to Week 24; and the Clinician's Interview-Based Impression of Change Plus version (CIBIC+) score at Week 24.

Fig 1. shows the least square (LS) mean difference between treatments was statistically significant for the change of SIB total score from baseline as early as Week 6 and then throughout the study duration at Weeks 12, 18, and 24, is favor of the treatment with donepezil SR 23 mg.

Figure 1. Severe Impairment Battery (SIB) Total Score Change from Baseline by Visit (OC) and at Endpoint (ITT: LOCF)
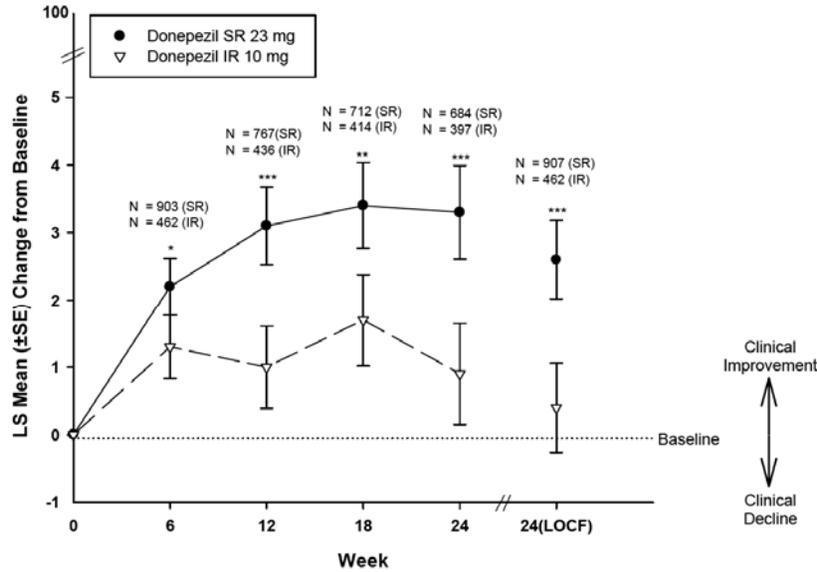
Note: * = p<0.05, ** = p<0.01, *** = p<0.001

Source: Sponsor's CSR Figure 3 on page 99 of 2503.

As presented in Figure 2, patients assigned to donepezil SR 23 mg failed to show statistically significant superior CIBIC+ scores compared to patients assigned to the donepezil IR 10 mg group.

Figure 2. Frequency Distribution of Modified Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC+) Scores at Week 24 (ITT: LOCF)
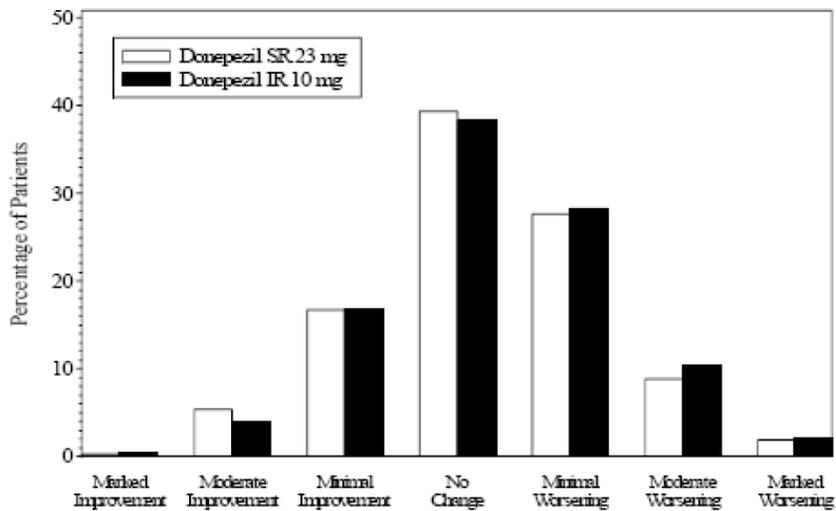
Source: Sponsor's CSR Figure 7 on page 108 of 2503.

Are there any covariates that influence pharmacokinetics of donepezil?

The population pharmacokinetic analysis conducted by the sponsor identified age, weight, CYP2D6 genotype as predictors that influence PK of donepezil (Figure 3), but none explained enough inter-subject variability to warrant dose adjustment.

Figure 3. Relationships between Covariates of Interest and Donepezil Clearance
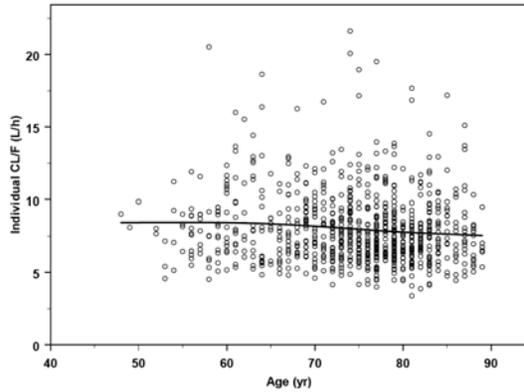
Figure 35 on page 83 Sponsor's population PK report
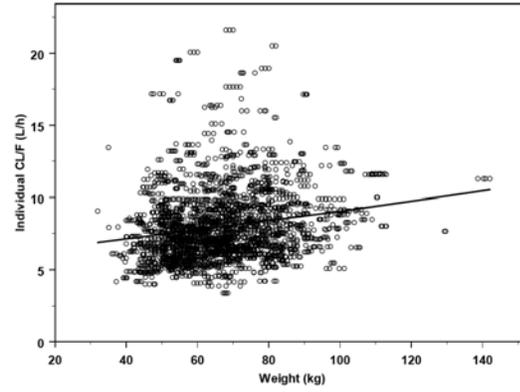
*Figure 38 on page 86 Sponsor's population PK report*
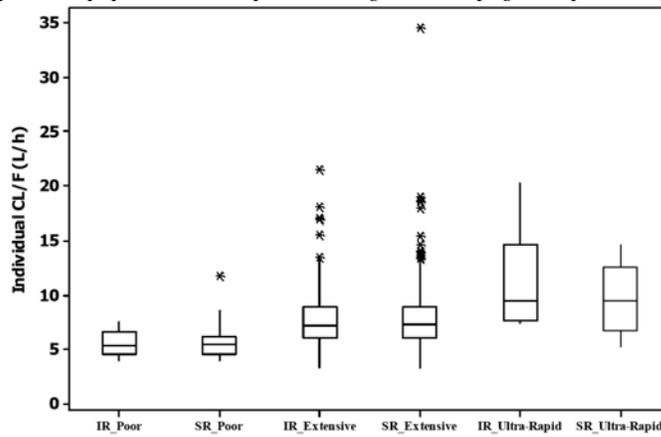
Figure 41 on page 89 of Sponsor's population PK report

No discernable relationships between gender, dose, formulation and clearance were observed (Figure 4). The effect of gender may be partially attributable to the differences in weight, but there was no indication of collinearity in these parameters estimates.

Figure 4. Effects of Sex, Dose and Formulation on Clearance
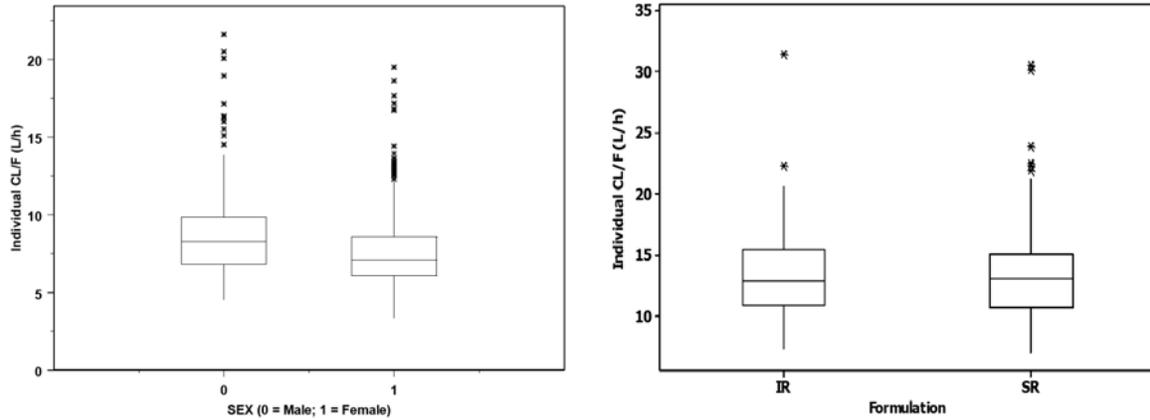
Figure 39 on page 87 Sponsor's population PK report

Figure 15 on page 60 Sponsor's population PK report
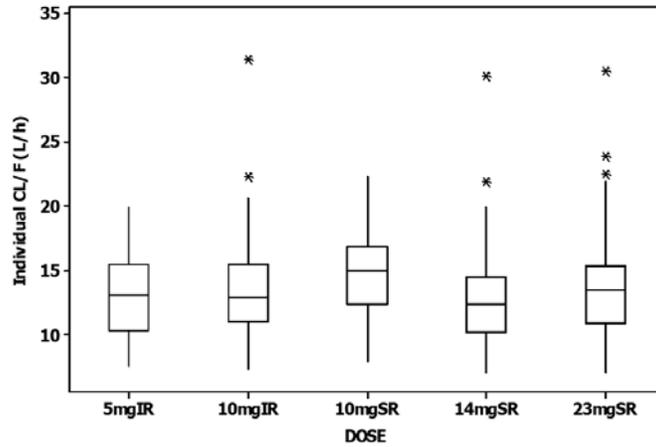
Figure 5 shows the trough concentrations of donepezil in patients with different renal status, which was defined by creatinine clearance at baseline (E2020-G000-326). Concentrations from the SR 23 mg group were normalized to 10 mg and adjusted with relative bioavailability (92%). Majority of the patients in Phase III trial had mild to moderate renal impairment, with incidence of 39% and 49%, respectively. Only 4% of the patients were severely impaired in renal function. As compared to patients with normal renal function, trough concentration at steady state increased 50% in patients with severe renal impairment; whereas they had similar safety profile as compared to rest of patient population in this Phase III trial. Therefore, dose adjustment is not needed in patients with renal impairment.

Figure 5. Donepezil Trough Concentration versus Renal Status
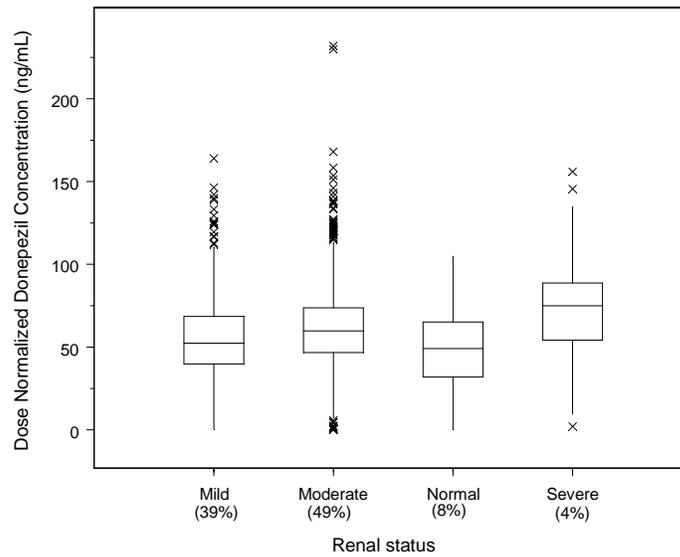
Source data: p3dt.xpt from sponsor's dataset.

Is there any evidence of dose/exposure-safety relationship observed in the pivotal trial?

There appears to be dose related increase in adverse events (AEs). A total of 216 (15.1%) patients discontinued from the study because of treatment-emergent signs and symptoms (TESS): 179 (18.6%) patients in the donepezil SR 23 mg group and 37 (7.9%) patients in the donepezil IR 10 mg group. The sponsor did not perform the concentration-safety analyses.

Previous studies with donepezil have found that cholinergic adverse effects were generally transient, occurring most frequently upon introduction of the drug and during dose escalation. Figure 6 displayed the percentage of AE occurred over the duration of study 326, which is consistent with the findings in previous studies. The most common adverse events included vomiting, nausea, and diarrhea. After 3 weeks of continued use, the differences in AE frequency were inappreciable between the two treatment groups.

Figure 6. Adverse Event Time Course
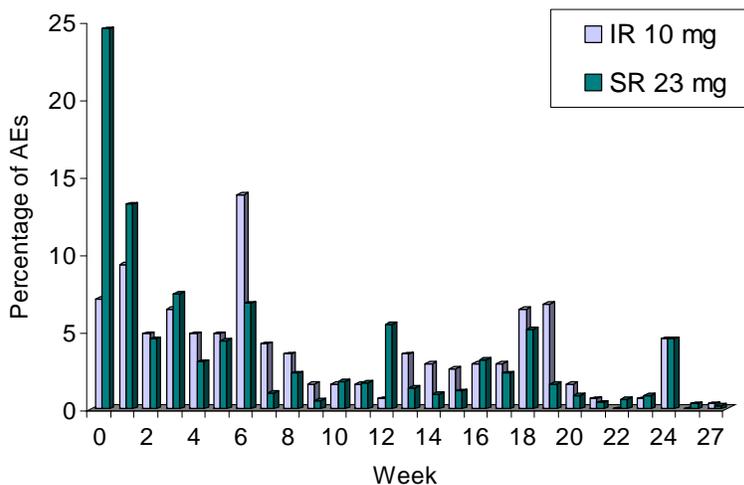
Recommendations

NDA 22568 is acceptable from pharmacometric perspective based on reviewer's exposure-efficacy analysis.

Label Statements

Please refer to the review by Dr Xinning Yang for labeling language.

Pertinent regulatory background

Donepezil was first approved in the US in November 1996 for the treatment of mild-to-moderate Alzheimer's disease (AD) and was later approved for the treatment of severe AD in October 2006. The clinical development of donepezil SR has been conducted under Investigational New Drug Application 35,974 since April 2005. It was granted by the agency that a single pivotal study was sufficient to demonstrate the safety and efficacy of the donepezil SR 23 mg formulation. No additional non-clinical studies would be needed to support an NDA for donepezil SR. The clinical development program of donepezil SR consists of four Phase I studies in healthy subjects, and one randomized, double-blind Phase III study (E2020-G000-326).

Results of Sponsor's Analysis

Population Pharmacokinetic Analysis

The objectives of this population PK analysis are:
- To characterize the PK and PK variability of donepezil in subjects with moderate-to-severe AD.
- To compare the PK of donepezil when administered as an SR versus IR formulation.

- To determine if CYP2D6 genotype or concomitant administration of moderate/strong CYP2D6 inhibitors, influences the PK of donepezil.
- To identify and characterize demographic factors, such as age, weight and gender as well as other factors such as hepatic and renal function which may influence the PK and PK variability of donepezil.

Two databases were constructed for the population PK analysis: a Phase I PK database (E2020-A001-020, E2020-A001-021, E2020-A001-022, and E2020-A001-023) and a Phase III PK database (E2020-G000-326). From the study E2020-A001-020, only data from E2020-SR dissolution 8-hour type formulation were included in the Phase I database. The number of BLQ values comprised 5.7% of the total observations and were treated as missing values. Plasma donepezil concentration time data were evaluated using NONMEM version VI level 2.0. The evaluation of the Phase I data was done to obtain a structural model and then this model was used as a frequentist prior for the evaluation of the Phase III data.

Pharmacokinetic Structural Model

The pharmacokinetics of donepezil were described using a two compartment linear model with transit input function and first order elimination from the central compartment. Several input functions were evaluated for the Phase I data. No further exploration on absorption models was done after Phase I model was established, because of the sparseness of Phase III data.
The inter-subject variability was described using an exponential error model:

$$P_j = TVP \cdot e^{\eta_j}$$

The residual variability for the PK model was described as a composite of an additive error in combination with a CCV error:

$$Ln(Cp_{ij}) = Ln(\hat{C}p_{ij}) + \sqrt{\varepsilon_{ij_1}^2 + \frac{\varepsilon_{ij_2}^2}{\hat{C}p_{ij}^2}}$$

First order conditional estimation (FOCE) was the primary method used for the PK evaluation of Phase I data. However the first order (FO) estimation method was used for the Phase III data evaluation.

Covariate Model

Covariates assessed in the population PK model include age, weight, height, BSA, BMI, creatinine clearance, ALT, AST, total bilirubin, albumin, sex, race, formulation, CYP2D6 genotype, and concomitant medications. The covariate models in this analysis were defined to represent covariate influences as shifts in the parameters of interest from the values observed in a hypothetical reference subject. The reference subject was defined in the analysis as a 65 year old, male, Caucasian weighing 70 kg, with a creatinine clearance of 70 mL/min, with normal hepatic function (ALT of 50 IU/L, AST of 50 IU/L), not taking any CYP inhibitors, and a CYP2D6 extensive metabolizer genotype.
Continuous covariates such as age or weight were modeled using a general power function:

$$TVP_{Clearance} = P_{pop} * \left(\frac{Wt}{Median} \right)^{0.75}$$

$$TVP_{Volume} = P_{pop} * \left(\frac{Wt}{Median} \right)$$

Categorical covariates (e.g. race, gender) were modeled using the following equation:

$$TVP = P_{pop} \cdot \theta_i^{cov_i}$$

In this equation, cov_i is either 0 (for the standard or reference subject), or 1 for the comparative subject.

A nominal decrease in the objective function of 7.8 points (p<0.005) was used as a criteria for nested single covariate models. The full model then underwent backward deletion to assess the impact of removal of a covariate. The covariate was retained in the final model if its removal resulted in at least 10.84 points (p<0.001) increase in the objective function from the full model. In addition, covariate factors had to have clinical or physiological relevance. If the magnitude of the change of the parameter due to a covariate influence resulted in less than a 20% variation of the parameter, the covariate factor was not considered clinically relevant.

MAP Bayesian analysis, bootstrap methods were used in model qualification. The percentile bootstrap confidence intervals were constructed by taking the lower 2.5% and the upper 97.5% value of the number of estimates for each parameter.

Results

The final model included variance terms for CL/F, VC/F, VP/F and Ktr. The model fitted log transformed data and used a constant coefficient of variation residual error (CCV) model (additive on the log scale). The FO estimation method was used. The equations for the parameters describing the final model are shown below.

$$IF \; (CYP2D6 = EM) \;\; TVCL = \theta_8$$

$$IF \; (CYP2D6 = PM) \;\; TVCL = \theta_1$$

$$IF \; (CYP2D6 = URM) \;\; TVCL = \theta_9$$

$$\frac{CL}{F} = \left(TVCL \bullet \left(\frac{Weight}{70} \right)^{0.75} \bullet \theta_{10}^{SEX} \bullet \left(\frac{Age}{65} \right)^{\theta_{11}} \bullet \theta_{13}^{CYPINH} \right) \bullet \exp(\eta_1)$$

$$\frac{VC}{F} = \left(\theta_2 \bullet \frac{Weight}{70} \right) \bullet \exp(\eta_2)$$

$$\frac{Q}{F} = \theta_3$$

$$\frac{VP}{F} = \theta_4 \exp(\eta_4)$$

$$IF \ \left(Formulation = IR\right) \ TVKtr = \theta_5$$

$$IF \ \left(Formulation = SR\right) \ TVKtr = \theta_6$$

$$Ktr = TVKtr \bullet \exp\left(\eta_3\right)$$

$$IF \ \left(Formulation = IR\right) \ F1 = 1$$

$$IF \ \left(Formulation = SR\right) \ F1 = \theta_{12}$$

$$K20 = \frac{CL}{VC}$$

$$K23 = \frac{VC}{Q}$$

$$K32 = \frac{VP}{Q}$$

Source: page 76 on sponsor's population PK report.

Table 1. Summary of Baseline Demographics for the Phase III Pharmacokinetic Model Database (n=850)

Demographic (units)	Mean (SD)	Median	Range
Age (y)	74.3 (8.29)	76	48-89
Height (cm)	162 (10.1)	161	135-191
Weight (kg)	66.8 (14.3)	76	32-139
CrCL (mL/min)*	60.6 (20.1)	58	16.3-180
ALB (g/dL)	4.26 (0.30)	4.3	2.8-5.5
ALT (IU)	19.0 (10.3)	17	4-108
AST (IU)	22.1 (7.78)	21	8-112
BILI (mg/dL)	0.50 (0.25)	0.4	0.1-1.6
Formulation	SR=557; IR=293		
Sex	Male=308; Female=542		
Race	Caucasian=655; Non Caucasian=195		
CYP2D6 Genotype	Poor Metabolizer=31; Extensive Metabolizer=508; Ultra-rapid Metabolizer=13; Not Classified**=298		
Co-administered CYP2D6 Inhibitor	No Inhibitors=763; Weak Inhibitors=48; Moderate inhibitors=3; Strong Inhibitors=36		

* - Creatinine Clearance capped at 150 mL/min in the control stream as a reasonable upper limit; this means that individuals whose creatinine clearance was higher than 150 mL/min was set to 150 mL/min in the model control stream

** - Individuals who did not have an associated genotype were assumed to be extensive metabolizers as the predominant genotype.

Source: Table 6 on page 34 of Sponsor's population PK report.

Table 2. Parameters Estimates for Final Pharmacokinetic Model using Phase III Data

Parameter (Units)		Population Mean (SE*)	%CV Inter-Individual Variance (SE*)
CL/F$_{2D6,EM}$ (L/h)	Θ_1	10 (2.2)	32.4 (5.2)
CL/F$_{2D6,PM}$ (L/h)	Θ_8	6.85 (6.8)	
CL/F$_{2D6,URM}$ (L/h)	Θ_9	12.4 (10.6)	
Effect of Weight	_	0.75 FIX	
Effect of Gender	Θ_{10}	0.865 (2.5)	
Effect of Age	Θ_{11}	-0.581 (18.2)	
Effect of CYP2D6 Inhibitor	Θ_{13}	0.829 (3.9)	
VC/F (L)	Θ_2	556 (3.5)	47.6 (8.4)
Effect of Weight	_	1 FIX	
Q/F (L/h)	Θ_3	35.8 (1.7)	NE
VP/F (L)	Θ_4	624 (0.7)	679 (18.9)
Ktr (1/h)	Θ_5	2.77 (2.2)	33.9 (8.3)
KtrSR (1/h)	Θ_6	0.89 (2.2)	
Relative Bioavailability SR	Θ_{12}	0.919 (1.5)	NE
CCV Residual Error (as %CV)		29.7 (1.5)	

* - SE given as %CV (parameter SE/parameter estimate); NE - Not Estimated

Eta	PPVCL	PPVVC	PPVVP	PPVKTR
Shrinkage	0.122	0.711	0.880	0.768

Source: Table 15 and Table 16 on page 474 of Sponsor's population PK report.

Table 3. 95% Bootstrap Confidence Intervals

Parameter (Units)		Population Mean (SE*)	Bootstrap Median [95% Confidence Interval]
CL/F EM (L/h)	Θ_1	10 (2.2)	10 [9.56-11]
CL/F PM (L/h)	Θ_8	6.85 (6.8)	6.85 [6.12-7.81]
CL/F URM (L/h)	Θ_9	12.4 (10.6)	12.65 [10.3-15.3]
Effect of Weight	_	0.75 FIX	---
Effect of Gender	Θ_{10}	0.865 (2.5)	0.860 [0.811-0.906]
Effect of Age	Θ_{11}	-0.581 (18.2)	-0.564 [-0.767- -0.328]
Effect of CYPINH	Θ_{13}	0.829 (3.9)	0.831 [0.778-0.893]
VC/F (L)	Θ_2	556 (3.5)	562 [527-629]
Effect of Weight	_	1 FIX	---
Q/F (L/h)	Θ_3	35.8 (1.7)	35.5 [34.6-36.1]
VP/F (L)	Θ_4	624 (0.7)	623 [620-628]
Ktr (1/h)	Θ_5	2.77 (2.2)	2.76 [0.201-2.79]
KtrSR (1/h)	Θ_6	0.89 (2.2)	0.887 [0.0841-0.897]
Relative Bioavailability SR	Θ_{12}	0.919 (1.5)	0.922 [0.882-1.05]
CCV Residual Error (as %CV)	Θ_7	29.7 (1.5)	0.297 [0.275-0.327]

*SE – standard error as %CV

Source: Table 19 on page 90 of Sponsor's population PK report.

Figure 7. Goodness of Fit – Final Pharmacokinetic Model Phase III Database

A) Observed versus Typical Predicted Concentrations – Final Pharmacokinetic Model Phase III Database (*Source: Figure 33 on page 81 of Sponsor's population PK report*)
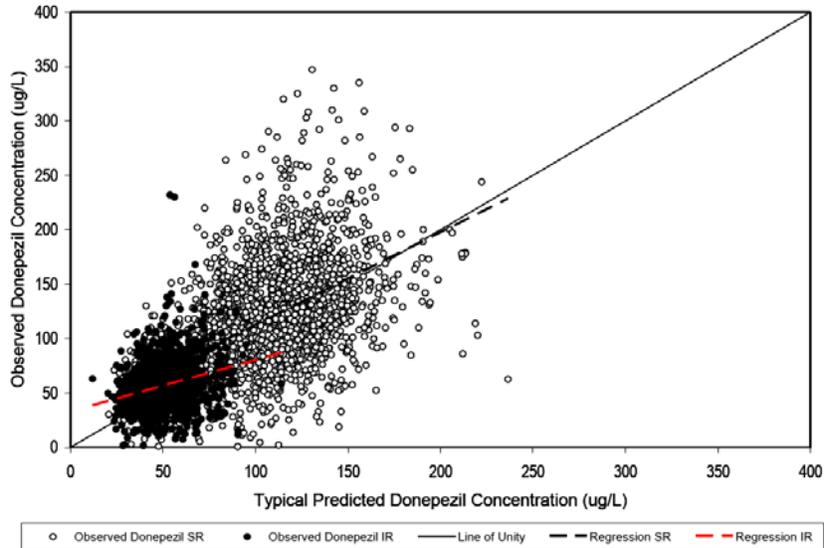
B) Observed and Typical Predicted Concentrations versus Time for 23 mg Dose SR Formulation – Final Pharmacokinetic Model Phase III database (*Source: Figure 32 on page 79 of Sponsor's population PK report*)
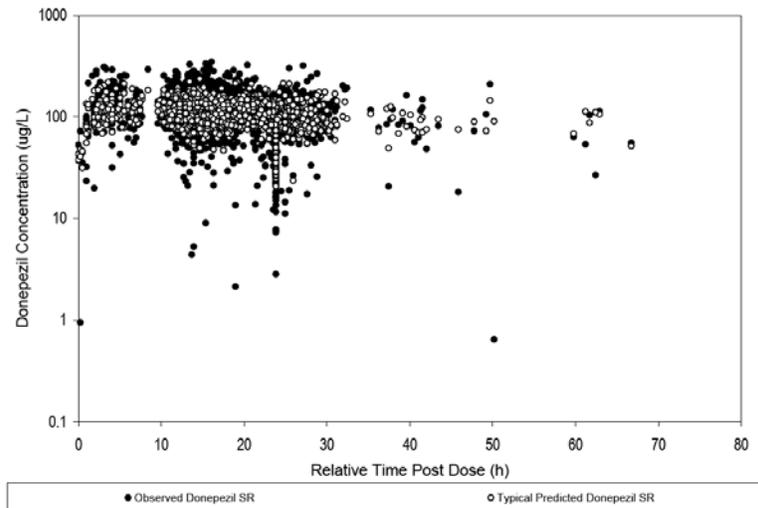
Donepezil clearance was found to be significantly influenced by age, weight, CYP2D6 genotype irrespective of the formulation administered. Donepezil clearance decreased with increase in patient age, and increased with increase in patient body weight. Over the range of ages from 40 years to 90 years, clearance decreased from 13.26 L/h to 8.28 L/h, and over the range of weights from 50 kg to 110 kg, clearance increased from 7.77 L/h to 14.04 L/h. The age effect most likely reflects the normal age-related loss of hepatic function. By comparing Phase I and Phase III data, differences in donepezil concentrations were observed, which is likely due to the fact that the subjects in Phase I (median age at 32 year) were younger than those in Phase III database (median age at 74.3 year).

Figure 8. Steady State Donepezil Concentrations versus Time for Phase I and Phase III Data – 23 mg SR Formulation
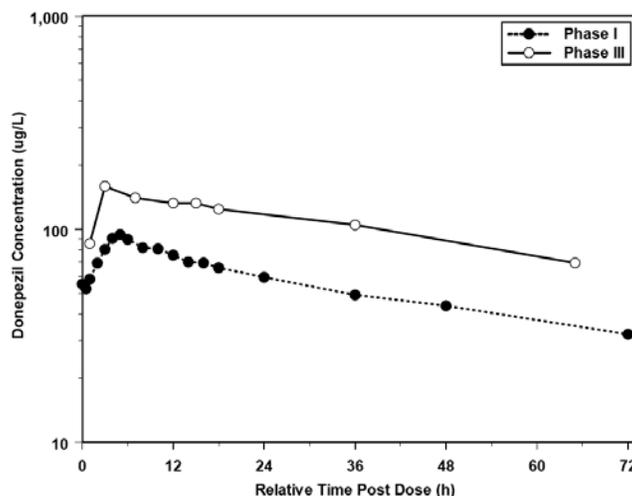
Source: Figure 37 on page 85 of Sponsor's population PK report

Differences in clearance values were observed among the CYP2D6 subgroups with a clear trend towards increasing clearance from poor to ultra-rapid metabolizer phenotype. When compared to the extensive metabolizers, the poor metabolizer group had a 31.5% lower clearance and the ultra-rapid metabolizer group had a 24% higher clearance. While significant, the overall effect of CYP2D6 status and co-administration of CYP2D6 inhibitors was comparable or small relative to the overall variability observed in donepezil clearance.

Table 4. Clearance Estimates by CYP2D6 Genotype Status

Parameter	Lower 95% Confidence Interval	Mean Parameter	Upper 95% Confidence Interval	Percent of Reference*
$CL/F_{2D6,EM}$ (L/h)	9.57	10	10.43	100
$CL/F_{2D6,PM}$ (L/h)	5.94	6.85	7.76	68.5
$CL/F_{2D6,URM}$ (L/h)	9.82	12.4	14.98	124

*- reference value is the clearance for an extensive metabolizer

Source: Table 18 on page 89 of Sponsor's population PK report.

Other Pertinent Clinical Pharmacology Facts

- Drug-drug interaction study was not performed for donepezil SR 23 mg. Formal pharmacokinetic studies evaluated the potential of donepezil IR formulation with theophylline, cimetidine, warfarin, digoxin and ketoconazole. In a 7-day crossover study in 18 healthy volunteers, ketoconazole (200 mg q.d.) increased mean donepezil (5 mg q.d.) concentrations (AUC_{0-24} and C_{max}) by 36%. The clinical relevance of this increase in concentration is unknown. (Source: Aricept® IR 10 mg labeling).
- In a study of 10 patients with stable alcoholic cirrhosis, the clearance of donepezil was decreased by 20%, relative to that observed in 10 healthy age- and gender-matched subjects following a single dose of 5 mg donepezil IR. Pharmacokinetics

of donepezil SR 23 mg after multiple doses was not investigated in patients with hepatic impairment.

- Fed/fasted status was not evaluated as a covariate in the population PK analysis. Food effect on pharmacokinetics of donepezil was investigated in a Phase I study E2020-A001-023. Overall the values of key PK parameters (T_{max}, half-life, AUC) were similar between fed and fasted states. Donepezil SR 23 mg can be taken without regard to meals or time of day.
- Concentration-efficacy analyses and concentration-safety analyses were not performed by the sponsor.

Reviewer's comments:

- *The sponsor's pharmacokinetic model provides an adequate description of donepezil concentrations. The covariate analysis did not identify any clinically relevant effects.*
- *Pharmacokinetics of donepezil SR 23 mg after multiple doses were not investigated in patients with hepatic impairment. This treatment should be used with caution in the hepatic impaired patients.*
- *Previous study showed increased exposure of donepezil (IR 5 mg q.d.) at the presence of ketoconazole. Drug-drug interaction was not investigated for donepezil SR 23 mg formulation. Caution should be used if a patient has concomitant medication including ketoconazole.*

Reviewer's Analysis

Introduction

The sponsor's analysis indicated only one of the co-primary endpoints; the Severe Impairment Battery (SIB) reached statistical significance with donepezil SR 23 mg demonstrating superiority over the current 10 mg donepezil IR formulation. However, the global co-primary endpoint, the Clinician's Interview-Based Impression of Change Plus version (CIBIC+), showed numerically but not statistically significance with SR 23 mg demonstrating non-inferiority to the 10 mg IR formulation. The sponsor did not perform the dose/exposure-response analysis.

At steady state, the mean value of AUC after repeated administrations of 23 mg SR formulation was approximately two-fold as compared to that of 10 mg IR formulation. The population PK analyses performed by the sponsor further confirmed that formulation has minimal effect on pharmacokinetics of donepezil. Based on this information, reviewer explored the exposure-response relationship using Phase III data regardless of the formulation.

Objectives

The objective of this analysis is to explore the relationships between the trough concentrations of donepezil at steady state and the two co-primary clinical endpoints.

Methods

No formal statistical analysis was conducted. The aim was to graphically evaluate whether there was an evidence of exposure-response to support the donepezil SR 23 mg formulation.

Data Sets

Data sets used are summarized in Table 5.

Table 5. Analysis Data Sets

Study Number	Name	Link to EDR
E2020-G000-326	adcibic.xpt adsib.xpt adpc.xpt	\\Cdsesub1\evsprod\NDA022568\0000\m5\datasets\e2020-g000-326\analyses

Software

SAS version 9.2 and R 2.9.2

Results

Plasma Concentrations of Donepezil

The data of PK concentrations and efficacy endpoints (SIB total score and CIBIC+) were merged by subject ID, visit number. Only observations with both concentrations and efficacy outcomes were retained.

The trough concentrations of donepezil from two treatment groups were summarized in the Table 6 below. The median values of donepezil concentrations were approximately 55 ng/mL for IR 10 mg, and 120 ng/mL for SR 23 mg. Then the pooled concentrations were ranked evenly into five groups.

Table 6. Summary Statistics of Donepezil Concentrations (ng/mL)

Treatment		Visit Number			
		6	12	18	24
Donepezil IR 10 mg	N	323	330	311	304
	Mean	57.52	57.37	56.46	57.39
	Median	56.60	54.80	55.20	55.45
	Range	0.2 - 232	0.2 - 230	0.2 - 140	0.2 - 127
Donepezil SR 23 mg	N	585	582	547	525
	Mean	127	124.94	127.06	123.18
	Median	125	121.5	121	120
	Range	0.2 - 347	0.2 - 308	0.2 - 330	0.2 – 335

Source: Sponsor's CSR Table 14.1.3.16 on page 482 of 2503.

SIB total score change from baseline versus donepezil concentration

An inverted U-shaped exposure-response relationship was observed, which is reported in a number of animal studies and early-phase clinical trials as a feature for Alzheimer's disease drugs, mainly acetylcholinesterase (AChE)-inhibitors. The mechanistic explanation of the U-shaped relationship is unknown. It might be possible that the

adverse events interfere with the assessment of cognition; or higher-than-optimal exposure down-regulates the receptors.[1-3]

As presented in Figure 9a, if missing SIB values were imputed using the Last Observation Carried Forward (LOCF) method, an inverted U-shaped relationship was observed for visits 6, 12 and 18, but not visit 24. The dashed vertical reference lines represented the median concentrations of donepezil of two treatment groups.

Figure 9. Relationship between SIB Total Score Change and Donepezil Concentration

a) LOCF method was used to account for missing data
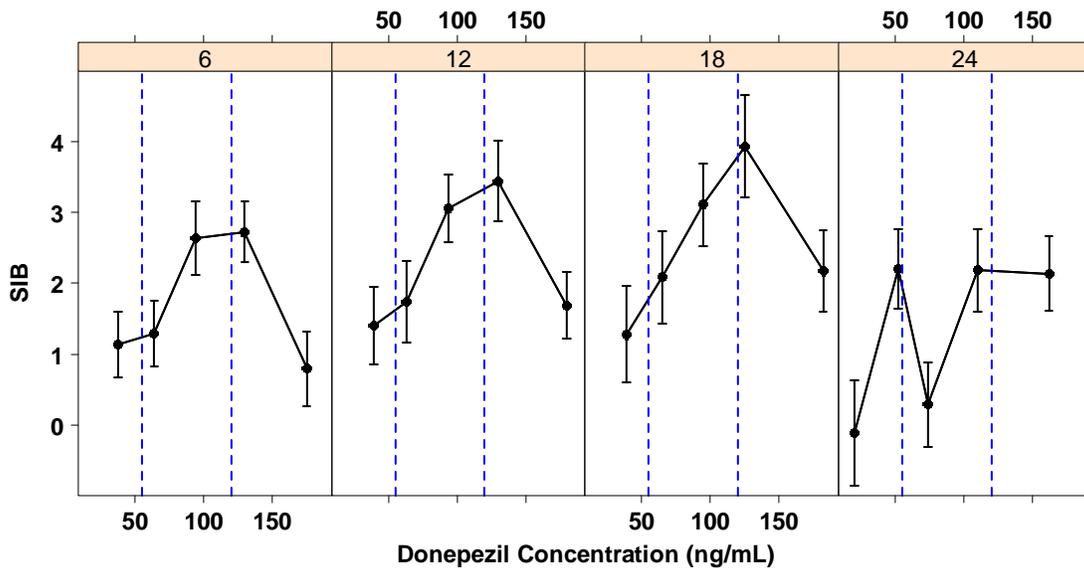
If only observed values were plotted as in Figure 9b, the inverted U-shaped was preserved at visit 24, indicating LOCF method could modify the shape of exposure-response relationship.

b) LOCF was removed; analysis was performed using the observed values
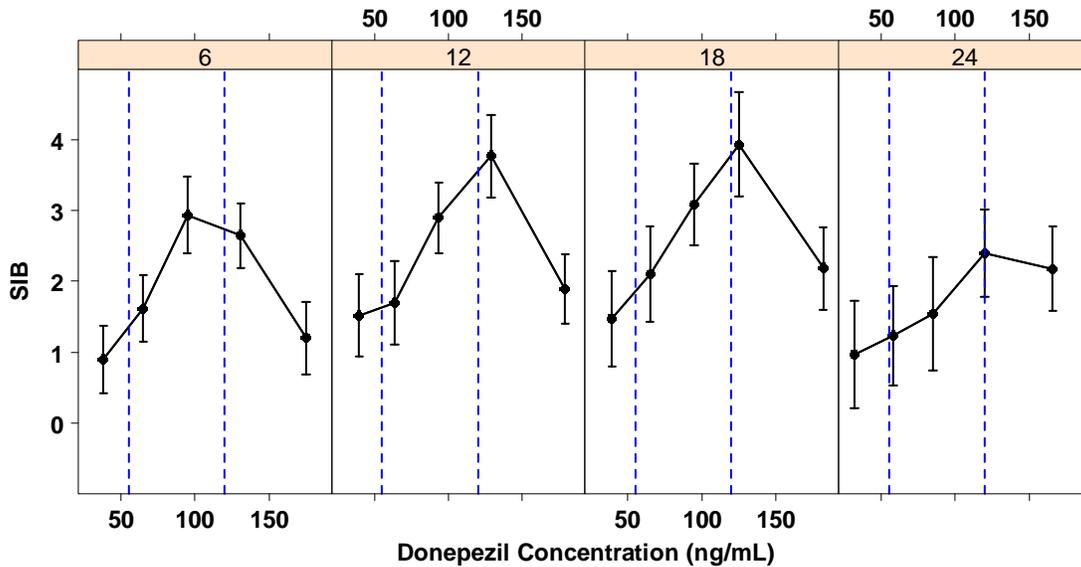
Global CIBIC+ score versus donepezil concentration

In sponsor's analysis, the CIBIC+ score was treated as a categorical variable (1=marked improvement, 2=moderate improvement, 3=minimal improvement, 4=no change, 5=minimal worsening, 6=moderate worsening, 7=marked worsening).
In reviewer's analysis, summary statistics were calculated for the CIBIC+ as it is a continuous variable, and plotted against the donepezil concentration. As shown in Figure 10, the exposure-response relationship appears to be U-shaped. The optimal exposure range seems to be lower for CIBIC+ response than for SIB response.

Figure 10. Relationship between CIBIC+ Score and Donepezil Concentration

a) LOCF method was used to account for missing data
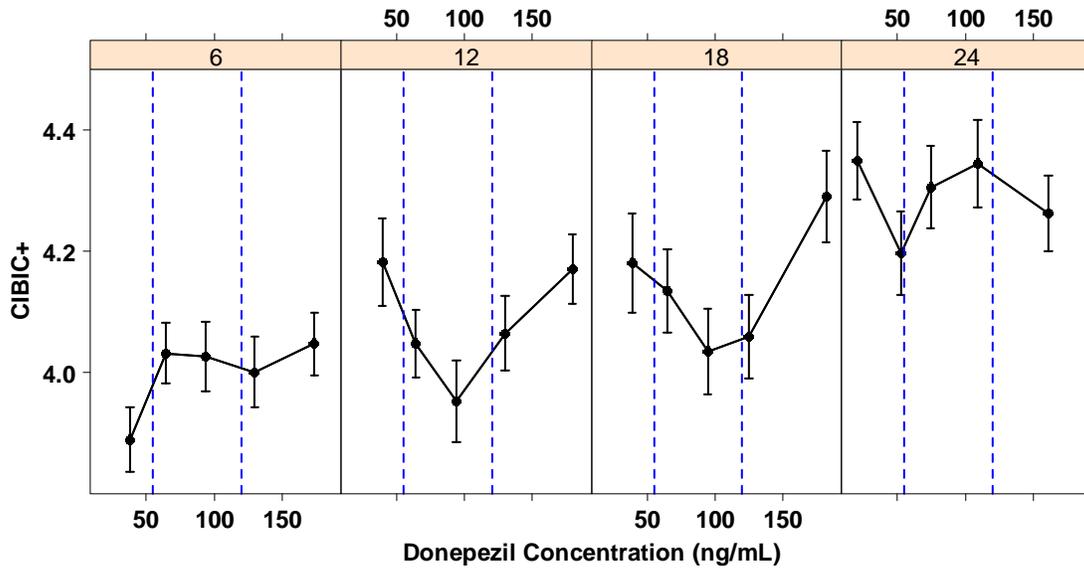
b) LOCF was removed; analysis was performed using the observed values
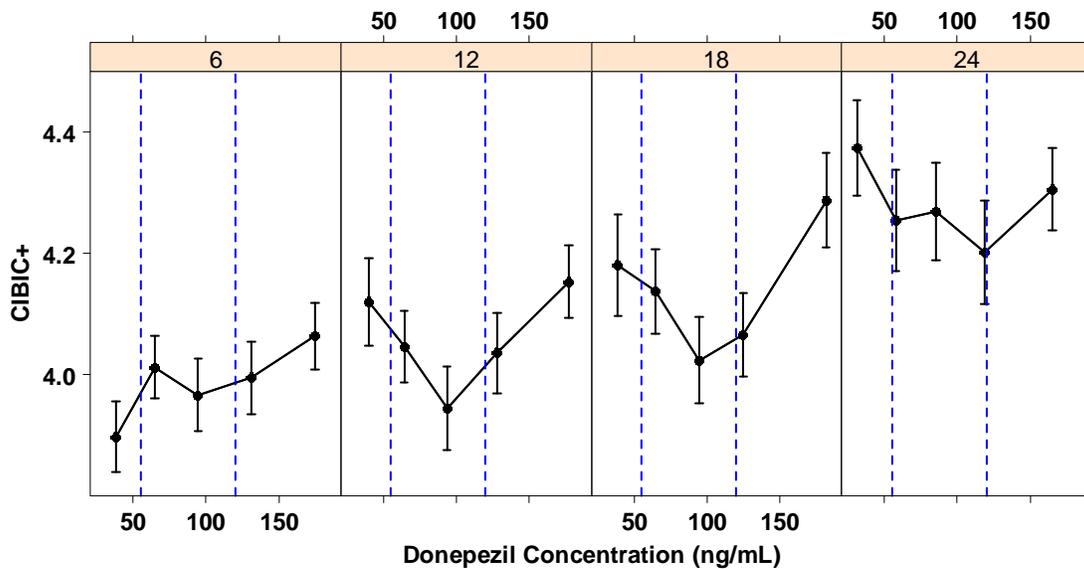
In summary, the relationships of efficacy endpoints (SIB total score change from baseline and global CIBIC+) and donepezil exposure are U-shaped (or inverted U-shaped depending on endpoint). The results imply that even though donepezil exposure is correlated with the cognitive benefit, higher plasma exposure does not warrant better clinical outcomes. There seems to be an optimal exposure window to achieve the maximum efficacy benefit. This optimal exposure window appears to be around 60-120 ng/mL for CIBIC+ and 90-130 ng/mL for SIB. Since the median exposures for 10 mg and 23 mg are 55 ng/mL and 120 ng/mL, the observed difference in primary analysis results for SIB (23 mg is significantly better than 10 mg) and CIBIC+ (23 mg and 10 mg are comparable) may be explained by the different optimal exposure windows. Overall, 23 mg provides more benefit on efficacy than 10 mg for moderate-severe AD patients.

However, further significantly higher exposure of donepezil due to intrinsic or extrinsic factors could lead to suboptimal efficacy in addition to potential safety concern.

Listing of Analyses Codes and Output Files

File Name	Description	Location in \\cdsnas\pharmacometrics\
pksib.sas pkcibic.sas ERplot.R	Inverted U-shaped relationship between SIB total score change from baseline and donepezil concentration. U-shaped relationship between CIBIC+ score and donepezil concentration. R script for exposure-response plot	\\cdsnas\PHARMACOMETRICS \Reviews\Ongoing PM Reviews\AriceptHD_NDA22568 _HHZ\ER Analyses

References
1. Calabrese E (2008) Alzheimer's Disease Drugs: An Application of the Hormetic Dose-Response Model. *Critical Reviews in Toxicology,* 38:419–451
2. Soncrant T, Raffaele K, Asthana S (1993) Memory Improvement without Toxicity During Chronic, Low Dose Intravenous Arecoline in Alzheimer's Disease. *Psychopharmacology*, 112:421-427
3. Lockwood P, Ewy W, Hermann D, Holford N (2006) Clinical Trial Simulation to Compare Proof-of-Concept Trial Designs. *Pharmaceutical Research,* 23(9):2050-2059

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

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/s/

XINNING YANG
07/21/2010

YANING WANG
07/21/2010

YUXIN MEN
07/21/2010

MEHUL U MEHTA
08/04/2010

BIOPHARMACEUTICS REVIEW

NDA#	22568
Drug	Donepezil, Aricept (b) (4)
Formulation	23 mg tablets
Type	Original NDA
Sponsor	Esai Pharmaceuticals
Letter Date	September 24, 2009
Reviewer/Team Leader	Patrick Marroum, Ph.D.

Background:

Esai Pharmaceuticals is submitting this NDA for the approval of a new (b) (4) formulation of donepezil for the treatment of moderate to severe dementia of the Alzheimer type. During the review a question was raised as to whether it is a truly controlled release as it is giving a similar plasma concentration time profile as the immediate release formulation without reduction of the dosing rate as both the IR and ER formulations are to be dosed as once a day. Unfortunately the sponsor did not conduct a multiple dose relative bioavailability to determine whether the steady state performance is equivalent to a currently marketed non extended release formulation that contains the same active drug ingredient or therapeutic moiety that is subject to an approved full new drug application as per CFR 320.25 (f)(iii). Moreover, there are no studies included in the NDA that will allow the determination of the fluctuation index (the peak to trough ratio) which will help in establishing the controlled release nature of the formulation.

Recommendation:

This NDA is deficient in that it did not conduct the necessary studies required by the CFR to establish the controlled release nature of the formulation and should have never been filed Moreover, there was insufficient data included in the NDA to characterize the release characteristics of the formulation and determine that the fluctuation index is smaller than what is seen with the immediate release formulation specially in view of the fact that no dosing interval reduction is achieved with the proposed ER formulation.

_____   Date_____
Patrick Marroum, Ph. D.
Office of New Drug Quality Assessment

cc: Sood, Khairuzaman, Men

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

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PATRICK J MARROUM
04/02/2010

Biopharmaceutics Review

NDA:	**22-568**
Submission Date:	**September 24, 2009**
Type of Submission:	**Original New Drug Application**
Product name	**Aricept** (b) (4) **(donepezil hydrochloride)**
Dosage Form:	(b) (4)
Dosage Strengths:	**23 mg**
Sponsor:	**Eisai Medical Research Inc.**

Recommendations

The dissolution test parameters are as follows:

Dissolution Test Parameters

Apparatus	Paddle apparatus (Apparatus 2) in accordance with USP <711>
Dissolution medium	0.05 mol/L phosphate buffer (at pH 6.8)
Volume of dissolution medium	900 mL
Number of tablet per vessel	1 tablet
Temperature of the dissolution medium	37 ± 0.5 °C
Paddle rotation speed	50 rpm
Sampling time	1 hour, 3 hours and 8 hours

The sponsor proposed the following specifications for Aricept SR 23 mg tablet:

(b) (4)

The dissolution method and specifications are acceptable.

Alcohol did not increase the dissolution rate of Aricept. Therefore, the potential of dose dumping from this   (b) (4) dosage form is unlikely.

The different debossment utilized for Aricept tablets used in clinical trials and final market image did not have an effect on the dissolution profiles of Aricept SR tablets.

Background

Donepezil hydrochloride, a selective, reversible inhibitor of acetylcholinestrase, was first approved in the US in November 1996, as a treatment for mild to moderate Alzheimer Disease (AD). Donepezil is currently marketed in the US as immediate-release (IR), and orally disintegrating tablet (ODT) formulations (5 mg and 10 mg) for once daily administration.

Aricept SR 23 mg tablets are film-coated, [(b) (4)] tablets. The [(b) (4)] tablet is composed of donepezil hydrochloride, lactose monohydrate, ethylcellulose (EC), methacrylic acid copolymer Type C (MAC), hydroxypropyl cellulose (HPC) and magnesium stearate. [(b) (4)]

Aricept SR tablet will be manufactured at the Eisai (Kawashima) manufacturing facility in Japan.

Aricept SR 10 mg tablets, Aricept SR 14 mg tablets, and Aricept SR 23 mg tablets were used in clinical trials. However, only Aricept SR 23 mg tablets were used for the pivotal study and will be commercialized.

Table 1 below provides the qualitative and quantitative composition of Aricept SR 23 mg tablet.

Table 1: Composition of Aricept SR 23 mg Tablet

Ingredient	Function	Amount (mg)
E2020 Drug Substance	Active Ingredient	23.0
Lactose Monohydrate		
Ethylcellulose		
Methacrylic Acid Copolymer, Type C		
Hydroxypropylcellulose		
[(b) (4)]		
Magnesium Stearate		
[(b) (4)]		
[(b) (4)]		

The sponsor developed a dissolution method and specifications for Aricept SR 23 mg tablet, and examined the effect of alcohol and debossing on dissolution.

This review will assess the dissolution method and specifications, and the effect of alcohol and debossing on the dissolution of Aricept.

Assessment of the Dissolution Method

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(b) (4)

Houda Mahayni, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Patrick Marroum, Ph.D.
Biopharmaceutics Expert
Office of New Drug Quality Assessment

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

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/s/

HOUDA MAHAYNI
02/04/2010

PATRICK J MARROUM
02/04/2010

Office of Clinical Pharmacology			
New Drug Application Filing and Review Form			
General Information About the Submission			
	Information		Information
NDA Number	N 22-568	**Brand Name**	Aricept ^{(b) (4)}
OCP Division (I, II, III)	DCP-I	**Generic Name**	Donepezil hydrochloride (E2020-SR)
Medical Division	HFD-120	**Drug Class**	acetylcholinesterase inhibitor
OCP Reviewer	Ju-Ping Lai	**Indication(s)**	Moderate to severe Alzheimer's Disease (AD)
OCPB Team Leader	Angela Men	**Dosage Form**	^{(b) (4)} Tablets (23 mg)
		Dosing Regimen	**Initiation:** Patients established with 10 mg can be administered Aricept ^{(b) (4)} 23 mg, QD **Maintainance:** Aricept ^{(b) (4)} 23 mg, QD
Date of Submission	9/24/2009	**Route of Administration**	Oral
Estimated Due Date of OCP Review	5/24/2010	**Sponsor**	Eisai Medical Research Inc.
Division Due Date	6/24/2010	**Priority Classification**	Standard
PDUFA Due Date	7/24/2010		

1

Clin. Pharm. and Biopharm. Information

This application for Aricept [(b) (4)] (Donepezil hydrochloride) Extended Release [(b) (4)] Tablets is being submitted as a 505(b)(1) submission for the treatment for moderate-to-severe dementia of the Alzheimer's type.

Oral donepezil hydrochloride (Aricept®), a selective, reversible inhibitor of acetylcholinesterase, has been first approved in the US as a treatment for mild to moderate Alzheimer's Disease (AD) in November 1996. Expanded indication to include patients with severe AD has also been approved in US to date. Donepezil is currently marketed as immediate-release (IR) (Aricept®) and orally disintegrating (ODT) (Aricept® ODT) 5 mg and 10 mg tablet formulations for once daily administration in the US.

As the recommended dose for Aricept® is 5 or 10 mg QD, the symptomatic benefits usually gradually lost over time despite continued treatment, the sponsor therefore attempted to produce a higher dose (23 mg) donepezil [(b) (4)]

The clinical development program for Aricept [(b) (4)] consists of 4 Phase I studies under IND 35,974. The Phase I studies (E2020-A001-020, -021, -022 and -023) consist of a relative bioavailability study for 3 SR formulation evaluation, single dose and multiple dose pharmacokinetic studies and one food effect study. Efficacy and safety of Aricept [(b) (4)] was evaluated in a single pivotal Phase III (E2020-G000-326) study to establish the superiority of Aricept [(b) (4)] over the currently-marketed donepezil 10 mg IR tablets in the treatment of patients with moderate to severe AD. One population pharmacokinetic (PK) study was also generated utilizing sparse sampling from study 326. In addition, an *in vitro* dissolution study (W20080032) was conducted to evaluate the potential of dose dumping for the Aricept [(b) (4)]. A second Phase III open-labeled trial (E2020-G000-328) is currently ongoing.

The formulation of donepezil SR 23 mg tablets was not changed from the clinical trials through commercial production.

This NDA consists of

- **4 Phase I studies:**
  1. Bioavailability study: relative BA for three 10 mg SR formulations
     E2020-A00 1-020:
     -                               (b) (4)
     - Mean C_{max} ↓ more than 50% and AUC were ~ 80% for the E2020-SR-8H formulation compared to regular release formulation.
     - Tmax were 2.7, 4.8, 9.2, and 16.3 hours for the E2020-RR, E2020-SR-4H, E2020-SR-8H, and E2020-SR-12H formulations, respectively.
     - T1/2 remained unchanged of approximately 75 to 78 hours.

  2. Single dose pharmacokinetic study
     E2020-A00 1-021:
     - SD, 10 mg IR vs 14 mg SR vs 23 mg SR
     - 14 mg SR vs 23mg SR exposure showed approximately proportion
     - C_{max} of the SR formulation was blunted compared to IR formulation
     - $AUC_{0-\infty}$ of the 14 mg SR was slightly more than proportionately higher than that of the 10 mg IR.
     - 14 mg SR had a similar adverse event profile to the 10 mg IR.

  3. Multiple dose pharmacokinetic study
     E2020-A00 1-022:
     - MD, 5 mg IR x 7 days vs 14 mg SR x 14 days vs 23 mg SR x 14 days
     - similar Tmax and T1/2 for 14 mg SR and 23 mg SR
     - 23 mg SR (AUC & C_{max}) showed greater than proportion than 14 mg SR.
     - steady-state achieved during 14 days of daily administration of SR formulation

  4. Food effect study:
     E2020-A00 1-023:
     - no food effect on the PK of SR after a single- or multiple-dosing regimen.
     - a greater percentage of subjects reporting vomiting when study drug was administered in the fed condition (why?)

- **1 Population PK study:**
  E2020-G000-326: to be reviewed by Pharmacometrics reviewer

- **1 *In vitro* dissolution study:** alcohol interaction (dumping) study
  W20080032: dissolution ↓ when alcohol ↑ from 0 to 30%

- **1 Phase III study:**
  E2020-G000-326: a single pivotal efficacy and safety trial

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	2		
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1		
multiple dose:	X	1		
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
Renal impairment:				
Hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -	X	1		
Data rich:	X			
Data sparse:	X			
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				

	"X" if yes	Comments		
solution as reference:				
alternate formulation as reference:	X	1		
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1		
Dissolution:	X	1		
(IVIVC):				
Bio-waiver request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	66			
Total Number of Studies				
	4 PK + **1 Pop PK +** **1 in vitro+** **2 Assay+** **Literature**			

Filability and QBR comments

	"X" if yes	Comments
Application filable?	X	
Comments sent to firm?	X	Please provide all datasets (NONMEM format) for population PK analyses along with programs and outputs.
QBR questions (key issues to be considered)		• Is dose proportionality established in the therapeutic range? • Is there any food effect? • Is dose adjustment necessary for concomitant use of other drugs (e.g. CYP2D6 inhibitors)? • Is dose adjustment necessary for CYP2D6 poor metabolizers? • Is the exposure of 23 mg SR comparable to the 10 mg IR?
Other comments or information not included above		
Primary reviewer Signature and Date	Ju-Ping Lai	
Secondary reviewer Signature and Date	Angela Men	

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	To-be-marketed formulation used.
2	Has the applicant provided metabolism and drug-drug interaction information?	x			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	x			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?		x		
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?		x		
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	

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16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?		x		
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
___**Yes**_____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Reviewing Clinical Pharmacologist   Date

Team Leader/Supervisor   Date

	**5.2 Tabular Listing of Clinical Studies**
Study Type	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product (s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Completed; Final CSR
BA	E2020-A001-020	5.3.1.1.1	Primary objective: to evaluate the relative bioavailability of a single dose of each of the three sustained-release formulations Secondary objective: to evaluate safety	Open-label, Phase I BA study	Donepezil HCl 10 mg oral tablets: 4-hour dissolution type, 8-hour dissolution type, and 12-hour dissolution type	82 subjects	Healthy subjects	Single dose study	Completed; Final Report
BA	E2020-A001-023	5.3.1.1.2	Primary objective: to evaluate the effect of food on bioavailabilty of tablets following single and repeated oral administration Secondary objective: to determine the safety and tolerability	Open-label, Phase I BA study	Donepezil HCl sustained-release (E2020 SR) 14 mg and 23 mg oral tablets	79 subjects	Healthy subjects	Up to 16 Days	Completed; Final Report
BA	W-20080032	5.3.1.3.1	To evaluate the effect of ethanol concentration in the acidic medium on the dissolution profile of E2020SR-FT 23 mg	In vitro dissolution study	NA	NA	NA	NA	Completed; Final Report

5.2 Tabular Listing of Clinical Studies

Study Type	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product (s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Completed; Final CSR
BA	(b) (4)	5.3.1.4.1	Determination of Donepezil and 6-OH Donepezil in Human Plasma by LC/MS/MS	Method validation	NA	NA	NA	NA	Completed; Final Report
BA	P561.02	5.3.1.4.2	Determination of Donepezil and 6-OH Donepezil in Human Plasma by LC/MS/MS	Method development	NA	NA	NA	NA	Completed; Final Report
BA	P840.00	5.3.1.4.3	Determination of Donepezil in Human Plasma by LC/MS/MS	Method development	NA	NA	NA	NA	Completed; Final Report
BA	ADZT	5.3.5.1.1 Section 16.1.15	Quantitation of Donepezil in Human Plasma via HPLC with MS/MS Detection	Method validation	NA	NA	NA	NA	Completed; Final Report

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colspan="10"	**5.2 Tabular Listing of Clinical Studies**
Study Type	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product (s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Completed; Final CSR
PK	E2020-A001-021	5.3.3.1.1	Primary objective: to evaluate the PK of a single dose of 14 mg and 23 mg sustained-release formulations following oral administration Secondary objective: to evaluate safety and tolerability and to evaluate the relationship between plasma concentrations of donepezil and RBC-AChE inhibition.	Double-blind, single dose PK/PD Study	Single dose of donepezil HC1 14 mg and 23 mg sustained-release oral tablets or donepezil HC1 immediate release 10 mg oral tablets	84 subjects	Healthy subjects	Single dose study	Completed; Final Report
PK	E2020-A001-022	5.3.3.1.2	Primary objective: to evaluate the PK of mutiple doses of the tablets following oral administration to healthy subjects. Secondary objective: evaluate the safety and tolerability and to evaluate the relationship between plasma concentrations and inhibition of peripheral acetylcholinesterase in red blood cells	Double-blind, placebo-controlled, repeated-dose PK/PD Study	Donepezil HCl; 5mg immediate release oral tablets or matching placebo once daily for 7 days; then 14 mg oral tablets or matching placebo once daily for 14 days; then 23 mg oral tablets or matching placebo once daily for 14 days	77 subjects	Healthy subjects	5 weeks	Completed; Final Report

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5.2 Tabular Listing of Clinical Studies

Study Type	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product (s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Completed; Final CSR
Phase III	E2020-G000-326	5.3.5.1.1	Primary objective: to compare 23 mg donepezil SR with 10 mg donepezil IR. Secondary objective: to assess secondary effficacy parameters, to perform exploratory quality-of-life assessments in patients administered 23 mg donepezil SR and in the caregivers for comparsion with 10 mg donepezil IR, to assess the safety and tolerability of 23 mg donepezil SR during administration, to determine whether treatment response is related to rate of drug metabolism and whether treatment response is related to the presence of AD risk factor APOE4.	Double-blind, double-dummy, parallel-group comparison	Donepezil HCl sustained-release 23 mg oral tablets once daily + placebo; or donepezil HCl immediate release 10 mg oral tablets once daily + placebo	1200 patients planned; 1467 patients randomized	Patients with moderate to severe Alzheimer's Disease	24 wks	Completed; Final Report

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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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/

Ju Ping LAI
11/24/2009

YUXIN MEN
11/24/2009