

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-823

STATISTICAL REVIEW(S)

CLINICAL/STATISTICAL

NDA 20-823

Exelon™

(Rivastigmine Tartrate) Capsules

-1.5 mg, 3.0 mg, 4.5 mg, & 6.0 mg

Classification: 1S

<u>Date</u>	<u>Document</u>	<u>Tab</u>
8/5/97	Clinical Memorandum, A. Oliva, M.D.	F
8/6/97	Telecon with Firm: R. Nighswander	G
11/30/97	Efficacy Review # 1: R. Levin, M.D.	H
1/22/98	Safety Memorandum, J. Racoosin, M.D.	I
1/23/98	Team Leader Review # 1, R. Levin, M.D.	J
1/23/98	FAX transmission to firm	K
2/6/98	Telecon with Firm: G. Burkhardt, M.D.	L
2/18/98	Statistical Review # 1: D. Hoberman, Ph.D.	M
2/19/98	Telecon with Firm: G. Burkhardt, M.D.	Mc
3/9/98	Clinical Mortality Review # 1: G. Burkhardt, M.D.	N
3/10/98	Safety Review # 1: A. Oliva, M.D.	O
3/26/98	Clinical Mortality Review # 2: G. Burkhardt, M.D.	P
4/13/98	HFD-110 Consult Review: Sughok Chun, M.D.	Q
5/28/98	Clinical Mortality Review # 3: G. Burkhardt, M.D.	R
5/28/98	Safety Review # 2: A. Oliva, M.D.	S
6/12/98	REFERENCE REVIEW: NDA 20-914 Metrifonate, G. Burkhardt, M.D.	T
6/16/98	Team Leader Memo, R. Levin, M.D.	U
7/2/98	Division Director Memo, P. Leber, M.D.	V
7/7/98	Clinical Mortality Review # 4: G. Burkhardt, M.D.	W
7/7/98	NOT APPROVABLE Letter to Firm	
9/3/98	Memorandum: Burkhardt comment on firm's RS proposal	XYZ
10/31/98	Telecon with Firm: G. Burkhardt, M.D. & others	A

3/8/99	Safety Review # 3: R. Mani, M.D.	B
3/23/99	Joint Mortality Review-Exelon: Boehn, Feeney, Freiman	C
4/21/99	Joint Mortality Review-Aricept: Boehn, Feeney, Freiman	D
4/27/99	Clinical Mortality Review # 5: G. Burkhardt, M.D.	E
4/29/99	Safety Review # 4: R. Mani, M.D.	F
5/3/99	Team Leader Memo, R. Levin, M.D.	G
5/3/99	Acting Division Director Memo, R. Katz, M.D.	H
5/13/99	Office Director Memo, R. Temple, M.D.	I

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

DATE: August 5, 1997
 TO: Randy Levin, MD
 THRU:
 FROM: Armando Oliva, MD *AO*
 RE: Exelon, Request for Information
 from Sponsor

Based on discussions with you and Judy Racoosin, there is information we would like to request from the sponsor. The Exelon 120 day safety update is due next month. We have not received information regarding the format and content of that update. It is possible they may be able to provide some or all of the information in that update. If not, they should submit the information as a separate submission.

- 1, **Summary Tables.** The data presented in summary tables of key safety data in the 120 Day Safety Update, (e.g., deaths, SAE's, discontinuations, AE's, etc.) should be divided into three sets, or columns:
- the data presented in the original NDA submission,
 - the new data collected in the interim, and finally
 - a summary column which combines the two numbers.

Table 1: Sample Summary Table for 120 Day Safety Update

	NDA (%) N=3000	Interim N=3300	Total (%) N=3300
Exelon	30 (1)	10	40 (1.2)
Placebo	10 (0.3)	2	12 (0.4)

2. **Mortality Analysis.** In order to facilitate our analysis of the mortality rates within the Exelon NDA, we would like a file consisting of the variables described below. This file should contain the data for all patients exposed to Exelon (including patients treated with placebo during a randomized controlled trial who then received active drug during an extension):

ID# - the unique identifier for the patient (called PATFDA in the jmp files)
Age - age of the patient at randomization
Gender - (M) for male, (F) for female
Country - name of the country of residence of the patient (use US for United States)
Domestic - (Y) if patient resides in the US, (N) if the patient resides elsewhere
Year - calendar year when patient took first drug dose
RCT# - identification number of the randomized controlled trial the patient took part in
RCTdays - total number of days in randomized controlled trial

EXT# - identification number of the extension trial the patient took part in
EXTdays - total number of days in extension trial
Death - (Y) if patient died, (N) if the patient did not die
Deathdays - number of days between last drug dose and patient's death
Status - (Y) if patient continues in the trial at the data lock date, (N) if patient is finished trial

Please submit the data as a JMP file, one line per patient. If the patient was assigned to placebo during the randomized control trial, enter 999999 for the "RCTdays" data field. If the patient did not participate in an extension trial, enter 999999 for the "EXT#" and "EXTdays" data fields. If the patient was not known to have died, enter 999999 for the "deathdays" data field. See the attached Table 2 for a sample data file.

Sample Entries

Patient #301001 was a 75 year old French man who began taking study drug in study #301 on July 1, 1995 and completed the 6 month study on December 31, 1995. He began extension trial #302 on January 1, 1996 and withdrew from the trial on May 15, 1996 due to disease progression. The value for "RCTdays" is 184; the value for "EXTdays" is 125. He was not known to be dead at the data lock date, December 31, 1996, but his "status" was "N" because he was no longer in the study.

Patient #311001 was a 64 year old woman from the United States who began taking study drug in study #311 on January 1, 1995. She suffered a myocardial infarction on March 20, 1995 at which time her study drug was discontinued. She subsequently died on March 25, 1996. Her "RCTdays" value was 79. Her "deathdays" value was 5 because that number of days elapsed between the last drug dose and her death. Her "status" was "N" because she was no longer in the study at the data lock date, December 31, 1996.

Patient #311002 was an 81 year old woman from the United States who took placebo in study #311. She started study drug in extension trial #312 on September 1, 1996. Her "EXTdays" value was 122; her "status" was "Y" because she was still taking the study drug at the data lock date, December 31, 1996.

3. **Study B304.** According to the NDA, For multiple logistical reasons, B304 was not initiated as early as the other phase II/III studies. In order to include the maximum amount of data from the study B304, the decision was taken to conduct an unblinded interim safety analysis. Safety data from this is included in the Integrated Summary of Safety. No analysis will be conducted on efficacy data.

Upon review of the JMP safety datasets provided for B304, it appears that the safety dataset is complete, i.e., all patients have completed the study and all safety data from the study are included in the datasets.

Please confirm if this is true.

As mentioned in the NDA, no analysis of the efficacy data has been conducted. Please submit the efficacy datasets for B304, in the same format as the datasets submitted for B303, B351, and B352.

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Table 2: Sample Deaths Dataset

ID#	Age	Gender	Country	Domestic	Year	RCT#	RCTdays	EXT#	EXTdays	Death	Deathdays	Status
301001	75	M	France	N	1995	301	184	302	111	N	999999	N
311001	64	F	US	Y	1995	311	79	999999	999999	Y	5	N
311002	81	F	US	Y	1996	311	999999	312	122	N	999999	Y

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Notes from EXELON.PDF

Page 3

Note 1; Label: Randy Levin; Date: 8/5/97 1:22:36 PM

As described by Dr. Oliva in his memo, please ask the sponsor for the following:

1. Summary safety tables as described in this memo to be provided in safety updates. This is requested to improve the efficiency of our review.
2. Mortality data set as described in this memo. This is requested as a standard procedure for drugs for AD
3. confirmation that the B304 safety data is complete
4. provide the efficacy data sets for study B304, if available

IS/1-17

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**MEMORANDUM OF TELEPHONE CONVERSATION
NDA 20-823**

Drug: Exelon™ (_____) Capsules
Sponsor: Novartis Pharmaceuticals Corp.
Date: August 6, 1997
Conversation With: Robert Kowalski, Pharm.D.
Regulatory Affairs
Telephone #: (973) 503-6869

1. At Dr. Sager's request, I advised the firm that, upon cursory review, our EA staff felt that the Exelon application might qualify for a categorical exclusion under the recently published FR notice revising the Agency's EA regulations (62 FR 40569).

Dr. Kowalski replied that he would advise his EA/CMC staff of this and respond accordingly.

2. At Dr. Levin's request, I FAXed the attached list of questions to the firm regarding the 120-day safety update, a mortality analysis/data set, and for an update regarding Safety and Efficacy data for study B304.

Dr. Kowalski replied that the 120-day safety update was about ready for submission and should be to us in 2 weeks. He did explain that the safety update contained data in a format similar to what we were requesting. Also, the update would include safety data from study B304, however, efficacy data would be available at a later date.

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Robbin Nighswander
Regulatory Management Officer

cc:
Orig NDA
HFD-120
HFD-120/Levin/Oliva
/Burkhart/Racoosin
/Nighswander

FOOD AND DRUG ADMINISTRATION
DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS (HFD-120)
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857
FAX #'s (301) 594-2858/594-2859
TELECOPIER COVER SHEET

NOTE: THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone at (301) 594-2775 and return it to us at the above address by mail, Attn: (HFD-120). Thank you.

DATE: 8-6-97

TIME: 3:00 p.m.

PLEASE DELIVER THE FOLLOWING PAGE(S) TO:

Rob Kowalski
Novartis Pharmaceuticals

FAX # (973) 503-6325

FROM:

Robbiw Nighswander
Regulatory Project Manager

Total number of pages, including cover page: 5

If you do not receive all pages or have any problems with receiving, call (301) 594-2850.

MESSAGE: Rob: As discussed in my voice mail to you, we do not want you to create patient narratives that resemble the "Sample Entries". Rather, we have included the sample entry narratives to further explain the data that we want included in the data set. You should be able to look at the "Table 2: Sample Deaths Data set" and see how we arrived at the sample narrative. It was our thought that the text would help your understanding of the data set/table entries.

Thanks. Robbin

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311002	81	F	US	Y	1996	311	999999	312	122	N	999999	Y

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ON ORIGINAL

Background:

This report summarizes the sponsor's presentation of the evidence for the efficacy of the drug in the treatment of Alzheimer's disease. I have provided the results of my own analyses and my conclusions on the efficacy of the drug in a separate memo in which I also discuss the results of chemistry, nonclinical toxicology, biopharmaceutical, clinical safety and statistical reviews of the application. Dr. Armando Oliva is reviewing the safety data. Dr. David Hoberman is the consulting statistician.

ENA 713 is a carbamate cholinesterase inhibitor. ENA 713 mimics ACh as a substrate for AChE by forming a carbamylated instead of an acetylated complex with the enzyme. The hydrolysis and reactivation of the carbamylated enzyme proceeds at a considerably slower rate than that of the acetylated enzyme. Sequestration of AChE in its carbamylated form by ENA 713 precludes further enzyme-catalyzed hydrolysis of ACh for an extended period of time.

Hydrolysis of the ENA 713 AChE complex leads to the formation of a phenolic cleavage product, ZNS 114-666. This metabolite has very minimal pharmacological activity (<10% AChE inhibition compared to ENA) and is cleared relatively rapidly, primarily through the kidneys.

The sponsor evaluated Exelon (ENA 713). They conducted a total of 39 clinical studies worldwide. 25 of these studies were phase 1 clinical pharmacology studies, 8 were phase 2 and 3 controlled clinical trials and 6 were phase 2 and 3 uncontrolled clinical trials.

For the safety data base, a total of 3591 individuals have been exposed to the drug worldwide (US, Canada, Western Europe, Australia, South Africa and Japan). The sponsor has provided all safety data collected through April 30, 1996. The sponsor will provide information on approximately 2000 patients who have received the drug through 12/21/96 in the 120 day safety update.

For efficacy, the sponsor conducted 8 efficacy studies. Four of the studies were phase 2 dose ranging studies (B103, B104, B105 and OR1/ALZ/PH2L/01) and four were phase 2/3 studies (B303, B304, B351 and B352). The sponsor has identified studies B352 and B303 as pivotal trials and study B351 as supportive in providing evidence for the efficacy of the drug in the symptomatic treatment of Alzheimer's disease. The sponsor did not comment on study 304.

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ON ORIGINAL**

Overview of the efficacy data:

Of the 8 efficacy studies performed, a total of 5 studies, B103, B303, B304, B351 and B352, were adequate by design for providing evidence for efficacy. B104 had insufficient power to detect a difference between groups, study B105 was of insufficient duration to determine efficacy and study OR1 was

Studies B303, B304, 351 and 352 were all 26 week studies and study B103 was a 13 week study. All studies used the ADAS-cog and a clinical global as the primary outcome measures. Study B103 used a CGIC while the other studies used a structured CIBIC plus. Doses in all studies were given as two divided doses except for one group in study 304 who took three dose a day. In studies B103 and B351, patients were titrated to fixed doses, in studies 303 and 352, patients were titrated to one of two dose ranges, a low dose range of 1 to 4 mg/day or a high dose range of 6 to 12 mg/day, while in study 304, patients were titrated to 2 to 12 mg/day taken in either two or three divided doses.

Study B103 was an early study that evaluated doses of 0, 4 and 6 mg/day. No difference was detected between groups on the ADAS-cog and CGIC following the 13 weeks of treatment.

Study B351 was a 26 week study that evaluated 0, 3, 6 and 9 mg/day. A statistically significant difference was noted on the ADAS-cog when the 6 and 9 mg/day dose groups were compared to placebo. For the patients on treatment at the end of the 26 week study (observed cases), the difference from placebo was 1.61 and 1.77 points for the 6 and 9 mg/day groups, respectively. There was no statistically significant difference for the 3 mg/day group. For the CIBIC plus, the ratings were generally lower for the 9 and 6 mg/day groups but no statistically significant differences were noted at any time point during the study. The results are summarized below.

Study 351: ADAS-cog: Mean change from baseline (*p value < 0.05, ** p value < 0.01)				
	9 mg/day	6 mg/day	3 mg/day	placebo
ITT				
N	177	176	175	171
Baseline	22.11	21.88	21.97	21.82
Week 12	0.25	0.44	0.29	0.84
Week 18	0.73*	0.71*	0.72	1.74
Week 26	1.15*	0.86**	1.68	2.42
LOCF				
N	134	140	152	159
Baseline	22.15	21.81	21.53	21.93
Week 12	-0.30*	0.5	0.23	0.94
Week 18	0**	0.67*	0.76	1.93
Week 26	0.36**	0.98**	1.76	2.54
Observed cases				
Week 12 (N) (baseline)	-0.33* (87) (22.22)	0.50 (140) (21.81)	0.22 (150) (21.19)	0.94 (158) (21.75)
Week 18 (N) (baseline)	-0.07** (95) (22.28)	0.83 (126) (21.93)	0.87 (138) (21.30)	1.90 (141) (21.66)
Week 26 (N) (baseline)	0.84* (87) (21.70)	1.00* (108) (22.13)	2.09 (123) (21.00)	2.61 (129) (21.66)

Study 351: CIBIC plus: Mean rating of change from baseline (*P value < 0.05)				
	9 mg	6 mg	3 mg	placebo
ITT				
Week 12 (N)	4.00 (158)	4.06 (157)	4.02 (157)	3.95 (169)
Week 18 (N)	4.02 (161)	4.13 (157)	4.03 (160)	4.07 (169)
Week 26 (N)	4.06 (161)	4.19 (157)	4.19 (160)	4.21 (169)
LOCF				
Week 12 (N)	3.95 (132)	4.04 (141)	4.04 (148)	3.90 (161)
Week 18 (N)	3.94 (133)	4.10 (141)	4.08 (151)	4.03 (161)
Week 26 (N)	3.97 (133)	4.15 (141)	4.20 (151)	4.20(161)
Observed cases				
Week 12 (N)	3.95 (132)	4.04 (141)	4.04 (148)	3.90 (161)
Week 18 (N)	3.82 (93)	4.06 (124)	4.12 (139)	4.04 (141)
Week 26 (N)	3.97 (89)	4.11 (104)	4.23 (120)	4.20 (129)

Studies 303 and 352 were 26 week studies that compared a low dose (1 to 4 mg/day) and a high dose (6 to 12 mg/day) with placebo. Statistically significant differences were found with the high dose comparison with placebo for both the ADAS-cog and CIBIC in both studies. No differences were found in the low dose, placebo comparisons. The results are summarized below.

Study 303: ADAS-cog: Mean change from baseline				
	High dose (6 to 12 mg/day)	Low dose (1 to 4 mg/day)	Placebo	P value high vs placebo
ITT				
N	242	242	238	
Baseline	23.93	23.82	23.23	
Week 12	-1.48	0.10	0.13	0.009
Week 18	-0.32	0.43	0.94	0.023
Week 26	-0.26	1.37	1.34	0.011
LOCF				
N	199	226	225	
Baseline	24.35	23.94	23.10	
Week 12	-1.79	0.10	-0.08	0.003
Week 18	-0.69	0.51	1.08	0.003
Week 26	-0.83	1.24	1.45	0.001
Observed cases				
Week 12 (N) (baseline)	-1.84 (198) (24.46)	0.15 (223) (24.25)	-0.08 (224) (23.08)	0.002
Week 18 (N) (baseline)	-0.89 (172) (24.61)	0.34 (213) (23.84)	1.22 (210) (23.02)	0.001
Week 26 (N) (baseline)	-1.17 (157) (23.96)	1.24 (202) (24.03)	1.41 (205) (22.66)	0.001

Study 303: CIBIC-plus: Mean rating of change from baseline				
	High dose	Low dose	Placebo	P value high dose v placebo
ITT				
Week 12 (N)	3.89 (211)	4.04 (228)	3.99 (224)	0.408
Week 18 (N)	3.93 (219)	4.10 (233)	4.15 (228)	0.088
Week 26 (N)	3.91 (219)	4.24 (233)	4.38 (230)	0.000
LOCF				
Week 12 (N)	3.88 (190)	4.01 (220)	3.97 (222)	0.437
Week 18 (N)	3.91 (193)	4.07 (224)	4.11 (225)	0.134
Week 26 (N)	3.88 (193)	4.17 (224)	4.32 (226)	0.003
Observed cases				
Week 12 (N)	3.88 (190)	4.01 (220)	3.96 (222)	0.498
Week 18 (N)	3.85 (166)	4.06 (205)	4.09 (204)	0.100
Week 26 (N)	3.93 (155)	4.20 (198)	4.34 (197)	0.012

Study 352: ADAS-cog: Mean change from baseline				
	High dose (6 to 12 mg/day)	Low dose (1 to 4 mg/day)	Placebo	P value high vs placebo /low vs plb
ITT				
N	231	233	234	
Baseline	22.61	22.23	22.12	
Week 12	-0.56	1.45	2.06	0.000 /0.2
Week 18	0.18	1.80	3.35	0.000/0.002
Week 26	0.31	2.36	4.09	0.000/0.002
LOCF				
N	179	217	217	
Baseline	22.91	22.72	21.15	
Week 12	-1.02	1.40	2.22	0.000/0.113
Week 18	-0.49	1.66	3.34	0.000/0.002
Week 26	-0.45	2.22	3.88	0.000/0.004
Observed cases				
Week 12 (N) (baseline)	-1.05 (176) (22.86)	1.40 (216) (22.75)	2.27 (216) (21.19)	0.000/0.096
Week 18 (N) (baseline)	-0.53 (172) (23.28)	1.77 (207) (22.85)	3.45 (201) (20.79)	0.000/0.003
Week 26 (N) (baseline)	-0.79 (157) (23.65)	2.27 (194) (22.17)	4.15 (192) (21.12)	0.000/0.002

Study 352: CIBIC plus: Mean rating of change from baseline				
	High dose	Low dose	Placebo	P value high dose v placebo/ low dose v plb
ITT				
Week 12 (N)	4.00 (209)	4.20 (223)	4.18 (219)	0.047/0.885
Week 18 (N)	4.00 (214)	4.17 (225)	4.2 (223)	0.060/0.795
Week 26 (N)	4.20 (214)	4.23 (225)	4.49 (224)	0.010/0.019
LOCF				
Week 12 (N)	3.92 (174)	4.20 (215)	4.16 (213)	0.013/0.699
Week 18 (N)	3.88 (178)	4.17 (217)	4.18 (217)	0.05/0.919
Week 26 (N)	4.09 (178)	4.22 (217)	4.44 (218)	0.002/0.048
Observed cases				
Week 12 (N)	3.92 (174)	4.20 (215)	3.96 (213)	0.013/0.699
Week 18 (N)	3.87 (155)	4.14 (206)	4.09 (203)	0.012/0.885
Week 26 (N)	4.13 (145)	4.16 (195)	4.34 (197)	0.010/0.009

Study 304 was a 26 week study that compared a twice a day (bid) dosing regimen with a three times a day (tid) dosing regimen. Patients were titrated to 2 to 12 mg/day based on tolerance. Because of the late completion time for this study, no study report was submitted by the sponsor. The following information is from the sponsor's data sets. At 12 and 18 weeks, statistically significant differences were found with both groups in comparison with placebo for both the ADAS-cog and CIBIC plus. By the end of the study at 26 weeks, a statistically significant differences was only found with the bid dose comparison with placebo. The results are summarized below (p values were based on student t tests).

Study B304: ADAS-cog change from baseline for observed cases			
	Placebo	tid dose	bid dose
Week 12 (N)	0.81 (206)	-0.91* (197)	-1.70* (206)
Week 18 (N)	1.35 (191)	-0.58* (182)	-1.77* (196)
Week 26 (N)	2.00 (184)	0.60 (174)	-0.73* (180)

*P value < 0.05 in comparison with placebo

Study B304: CIBIC plus for observed cases			
	Placebo	tid dose	bid dose
Week 12 (N)	4.27 (199)	3.88* (189)	3.91* (200)
Week 18 (N)	4.33 (187)	4.04* (182)	3.91* (194)
Week 26 (N)	4.38 (179)	4.12 (167)	3.95* (177)

*P value < 0.05 in comparison with placebo

Conclusions:

The sponsor has demonstrated in two adequate and well controlled studies, statistically significant differences between patients treated for 26 weeks on 6 to 12 mg/day compared to those treated with placebo for both the ADAS-cog and CIBIC plus.

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Overview of phase 2 studies:

Study B103 was a 15 week, double blind, placebo controlled, parallel group, multicenter study that evaluated the efficacy and tolerability of 4 mg/day (2 mg bid) and 6 mg/day (3 mg bid) in patients with probable Alzheimer's disease. It was conducted in Europe from 3/16/91 to 3/29/92. A total of 402 patients were randomized to one of the three study treatments: placebo (133 patients), 4 mg/day of ENA 713 (136 patients, low-dose group), or 6 mg/day of ENA 713 (133 patients, high-dose group). Patients were titrated over 1 week for the 4 mg/day group or 2 weeks for the 6 mg/day group. The dose was maintained until the end of study Week 13. On completion of the treatment period, all patients underwent a 2-week, single-blind, placebo washout period. Patients who tolerated the drug and showed clinically relevant improvement had the option of entering a double-blind, 3-month extension phase followed by an open-label, long-term extension study.

54 centers enrolled patients. The disposition of patients is summarized in the following table. For the patients in the high dose group, 80% discontinued for adverse events.

Study 103: patient disposition			
	Placebo	4 mg/day	6 mg/day
Randomized	133	136	133
Intent to treat	128	132	126
Completed 13 weeks	125	119	113
Completed 15 weeks	123	113	110

The mean age was 69 to 71 with 51 to 65% female.

The primary outcome measure was the CGIC (Clinical global Impression of change) which was based on information obtained from an interview of the patient and caregiver. The results are summarized in the following table. There were no statistically significant differences seen.

Study B103: CGIC results			
	Placebo	4 mg/day	6 mg/day
Week 13 Intent to treat	3.31	3.46	3.33
Week 13 observed cases	3.30	3.42	3.22

Other outcome measures included the MMSE and various neuropsychiatric tests. The change from baseline for the MMSE for the ITT population was 0, -0.3 and 0.1 for the placebo, 4 mg/day and 6 mg/day groups, respectively. The sponsor also assessed plasma levels and butyrylcholinesterase activity. There was a statistically significant difference between groups at the end of week 13. There were no statistically significant differences between groups for either the CGIC or MMSE.

Study B104 was an 18-week, double blind, placebo controlled, parallel group, multicenter study that investigated the efficacy at the MTD and also compared the tolerability of bid and tid dosing regimens of ENA 713, and the efficacy of concomitant antiemetics as a means of controlling the nausea and vomiting induced by acetylcholinesterase inhibition and subsequently increasing the MTD of ENA 713. This trial was conducted in European and Canadian centers. A total of 114 patients entered the study. Of these, 45 were randomized to receive ENA 713 bid, 45 to receive ENA 713 tid, and 24 to receive placebo.

The primary outcome measure were the CIBIC plus and the ADAS-cog at week 18. Other tests included the NOSGER and other neuropsychiatric tests. The differences between the active and placebo groups for the ADAS-cog were not statistically significant. For the CIBIC plus, only a subset analysis of evaluable patients taking the dose bid reached a statistically significant difference from placebo. No significant differences were reported for the ADAS-cog.

Study B105 was a 9-week, double blind, placebo controlled, parallel group study conducted at a single center in the US. The study design was similar to Study B104, but was only 9 weeks, followed by a one week treatment free follow up. The MMSE and an unstructured CIBIC-Plus rating were used for the efficacy assessments. These instruments did not provide evidence of a cognitive effect of ENA among the 37 of 40 ENA-treated patients completing the 9 week titration, compared to the 8 of 10 placebo-treated completers. The sponsor concluded that the duration of the study was too short and that the number of patients too few to provide acceptable evidence of efficacy.

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Overview of phase 3 studies:

There were four phase 2/3 studies, B351, B352, B303 and B304. These studies were all 26 week, multicenter, double blind, randomized, placebo controlled, parallel group comparisons trials in patients with mild to moderate dementia. The primary outcome measures were the change in the ADAS-cog, and the CIBIC plus score at week 26. Secondary measures included the Progressive Deterioration Scale (PDS), Mini Mental Status Exam (MMSE), Global Deterioration Scale (GDS), Caregiver Activity Survey (CAS).

Ratings scales:

Efficacy measures were assessed at weeks 0, 12, 18 and 26. Some centers had multiple raters.

Clinician Interview Based Impression of Change plus (CIBIC plus): The CIBIC plus was a "semi structured" assessment of the overall change in the patient's condition relative to baseline. A rater completed the baseline interview and was allowed to refer to the baseline information only. An alternate rater was also assigned. They were allowed to have access the baseline information as well. Some interviews were videotaped.

The rater conducted two interviews per visit one with the patient, one with the caregiver. In the interview with the patient, the assessor was instructed to rate the patient using the cognitive component of the Brief Cognitive Rating Scale (BCRS axes I-IV) and the Empirical Behavioral Pathology in Alzheimer's Disease Rating Scale (E-BEHAVE-AD).

On the BCRS, the patients were rated in 4 categories on a scale from 1= no impairment to 7 = most impairment. The raters were provided with specific instructions for rating the patient. Some of the ratings instructions are provided in the following table.

BCRS rating scale parameter	Examples of ratings
Concentration	Problems with Serial 7's (rated 4), serial 2's (rated 5), count backwards from 10 (rated 6)
Recent Memory	Cannot recall of current events (rated 4), cannot recall current presidents (rated 5), little idea of current address (rated 6)
Past memory	Cannot recall past teachers or friends (rated 4), Cannot recall name of all schools (rated 6), cannot recall place of origin, name of parents (rated 7)
Orientation	Mistakes date (rated 4), unsure of month, year or season (rated 5), identifies spouse (rate 6)
Total score	Sum 1 through 4 range between 4 and 28

On the BEHAVE-AD, the patients were rated in 12 different categories of a 4 point scale from 0 = not present to 3 = severely present. Some examples of the ratings are included in the following table:

E-BEHAVE-AD	
Component	Examples of ratings
Paranoid and delusional ideation	Expresses suspicious or false beliefs with an emotional component (rating of 2) or both an emotional and physical component (rating of 3)
Hallucinations	Vague hallucinations (rated 1), clearly defined (rated 2), verbal, physical and emotional responses to hallucinations (rated 3).
Pacing and wandering	Patient needs mild restraints (rated 2). Patient needs restraints and a conversation is impossible because of restlessness (rated 3)
Repetitive activities	Not interfering with conversation (rated 2), interfering with conversation (rated 3)
Inappropriate activities	Talks excessively, takes off clothes, sexual remarks or actions moderately (rated 2), requires intervention by examiner (rated 3)
Agitation	Present and accompanied by anger (rated 2), present and accompanied by anger clearly directed toward other person.
Physical threats and violence	Physical violence (rated 2), needs intervention (rated 3)
Other behaviors indicating agitation	Non verbal anger, refuses to stay with examiner, panting or banging that interferes with interview (rated 2), that makes interview difficult or impossible (rated 3)
Tearfulness or crying	With clear emotional component (rated 2) with emotional and physical component (rated 3)
Depression	With clear concomitants (rated 2), with emotional and physical concomitants (rated 3)
General anxiety	Interferes with interview (rated 2), affects entire interview (rated 3)
Fear of being left alone	Patient is too anxious to be left alone for extended periods (rated 2). Patient cannot be left alone for a moment (rated 3).
Total	Sum 1 through 12 range from 0 to 36

In the caregiver interview, the patients were rated in two components, functional and behavioral. In the functional component, patients were rated on scored from 1 = no difficulty to 7= incontinence, overabundance, loss of ambulation and immobility. For the behavioral component, the patients were rated on a scale from 0 = no problem to 3 worst problem, for 25 categories. A global score and a listing of symptoms most troubling to the caregiver were also recorded. The categories and behavior leading to a 3 rating is summarized in the following table.

Caregiver's interview - Behavioral rating	
Component	Behaviors given a rating of 3
Paranoid and delusional ideation	<ul style="list-style-type: none"> ...talking and listening to people coming into the home (rated 3). Violence in response to attempts to forcibly restrict exit (rated 3) Violence toward caregiver for being an impostor Accusation of impending desertion or Institutionalization Violence toward spouse or other caregiver for their infidelity Violence as a result of suspicions Physical actions or violence as a result of delusions
Hallucinations	<ul style="list-style-type: none"> Verbal or physical actions or emotional responses to visual hallucinations Verbal or physical actions or emotional responses to auditory hallucinations Verbal or physical actions or emotional responses to olfactory hallucinations Verbal or physical actions or emotional responses to haptic (sense of touch) hallucinations Verbal or physical actions or emotional responses to other hallucinations (e.g., passes an imaginary object saying "take this").
Activity disturbance	<ul style="list-style-type: none"> Verbal or physical actions or emotional responses to attempts to prevent wandering Abrasion or physical harm resulting from purposeless activity Present and sufficient inappropriate activity to require restraint and accompanied by anger or violence when restraint is used
Aggressiveness	<ul style="list-style-type: none"> Verbal outbursts accompanied by anger and clearly directed at other persons Physical violence accompanied by vehemence (e.g. Points fist and says, "I'll smash your face," pulls hair of caregiver angrily) Agitation other than above (non verbal, negativity, hyperventilation with emotion and physical component.
Diurnal rhythm disturbance	Complete disturbance of diurnal rhythm if it has occurred on two or more occasions in the preceding two weeks.
Affective disturbance	<ul style="list-style-type: none"> Tearfulness accompanied by affective and physical component (e.g. Wring of hands or other gestures) Depressed mood with emotional and physical concomitants
Anxieties and phobias	<ul style="list-style-type: none"> Anxiety regarding upcoming events intolerable to caregivers Other anxieties (e.g. Regarding money, the future, being away from home, healthy, memory, etc. intolerable to caregivers Fear of being alone vocalized and sufficient to require patient to be accompanied at all times Other phobias sufficient to prevent patient activities
Total score	Sum items 1 to 25 range 0 to 75
Global score	
Symptoms most troubling to caregiver	

After completing the interviews and the rating scales, a CIBIC plus symptoms domain summary worksheet was completed indicating the degree of change (minimal, moderate or marked improvement/worsening or no change) from the baseline interview for three categories: (1) cognition from the patient interview, (2) functioning from the caregiver interview and (3) behavior from the patient and caregiver interview.

Finally, a total CIBIC score from 1 to 7 (from 1= marked improvement, to 4 = no change to 7= marked worsening) was provided by the rater. The guidelines for the CIBIC plus rating was summarized by the sponsor in the following table:

GUIDELINES FOR CIBIC-PLUS RATINGS	
MINIMAL DOMAIN CRITERIA	CIBIC -PLUS RATING
A <i>dramatic</i> improvement in clinical status, seen as 2 in two domains, or 1 in one domain usually with 2 in another	1 = Markedly improved
A <i>clearly apparent</i> improvement in clinical status, seen as 3 in two domains, or 2 in one domain usually with 3 in another	2 = Moderately improved
A <i>modest but detectable</i> improvement in clinical status, seen as 3 in one domain	3 = Minimally improved
No change in all three domains	4 = Unchanged
A <i>modest but detectable</i> worsening in clinical status, seen as 5 in one domain	5 = Minimally worse
A <i>clearly apparent</i> worsening in clinical status, seen as 5 in two domains, or 6 in one domain usually with 5 in another	6 = Moderately worse
A <i>dramatic</i> worsening in clinical status, seen as 6 in two domains, or 7 in one domain usually with 6 in another	7 = Markedly worse

Alzheimer's disease Assessment Scale -cognitive (ADAS-cog): The ADAS-cog included the following tests: Word recall, Naming objects and fingers, following commands, constructional praxis, ideational praxis, orientation, word recognition, remembering test instructions, spoken language ability, word finding and comprehension. The sponsor also added concentration/distractibility to the ADAS-cog based on recommendations from Richard Mohs, Ph.D.. The score ranges from 0 = best to 70 = worst without the concentration item and 75 with the concentration item. The sponsor noted that a patient with mild to moderate disease has an ADAS-cog score of 15 to 25 with an increase of 6 to 10 points per year.

Other scales:

ADAS-noncog: The ADAS-noncog includes 8 items: concentration/distractibility, depressed mood, tearful, delusions, hallucinations, pacing, increased motor activity and uncooperative

testing. The rating in this scale ranged from 0 = best to 40 = worst with the concentration item or 35 without the concentration item.

Progressive Deterioration Scale (PDS): For the PDS, the rater, usually the caregiver, placed an x on a line that best described the patient on 29 items. The items assess the patient's activity of daily living. The total score was based on the mean of all available item scores. The higher the score the better with a range from -100 to +100 with a positive score meaning improvement.

Mini Mental Status Exam (MMSE): The MMSE is a 10 item test evaluating orientation, recent memory, attention, language and praxis. The scores range from 30 = best to 0 = worst. The range of change scores is -26 to +20.

Global Deterioration Scale (GDS): The GDS is a global scale used to identify the level of disease from information obtained from the patient and caregiver. Areas of memory, self care and activities of daily living were used to rate the patient on a score of 1= no cognitive decline to 7= very severe cognitive decline. The possible change score was -6 to +6 with a positive score associated with improvement

Caregiver Activity Survey (CAS): The CAS was developed by the sponsor to measure the amount of time the caregiver spent with the patient assisting in various activities of daily living. It was introduced in 7/95, after the studies were underway.

Clinical Global Impression of Change (CGIC): The CGIC used the same 7 point scale as the CIBIC plus. The CGIC differed from the CIBIC in allowing a joint, unstructured interview of the patient and caregiver and allowing access to post baseline data including safety and efficacy information.

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Study 351:

Protocol:

Design:

This was a 26 weeks, multicenter (in the US), randomized, placebo controlled, double blind, parallel study. Patients were randomized equally to one of four groups. In one group, patients were titrated to 3 mg/day (1.5 mg bid with food in the morning and evening). In the second group, patients were titrated to a dose of 6 mg/day (3 mg bid). The third group received 9 mg/day (4.5 mg/day). In the fourth group, patients received placebo.

During weeks 1 to 12, dose titration phase, all patients were titrated to their assigned dose. On days 1 to 3, doses were 1 mg, 1 mg and 1.5 mg/day total dose given bid for the 3, 6 and 9 mg/day group, respectively. On days 4 to 7, patients received doses of 1, 1.5 and 2 mg/day total dose given bid for the 3, 6 and 9 mg/day group, respectively. From week 1 to week 12, the dose could be increased weekly by 0.5 mg/day, depending on tolerability, until the fixed dose is reached. The fastest a patient could reach their assigned dose was week 9.

To improve tolerability, patients were instructed to take their dose with food. Investigators could stop dosing for up to 3 consecutive doses/week or delay advancement of the dose.

During weeks 13 to 26, fixed dose phase, patients were maintained on their assigned dose.

An open label study was offered after the 26 week double blind phase.

Drug:

Capsules of 0.5, 1, 1.5, 3, 4.5 and 6 mg were used

Sample:

600 patients were to be enrolled at 10 to 12 centers with at least 15 patients per treatment group. Power based on responder rates on the CIBIC plus (scores of 1, 2 or 3) of 35% compared to 15% for placebo or ADAS-cog difference of 3.5 points.

Selection:

Patients, age 50 to 85, with probable AD by the NINCDS criteria with scores of 10 to 26 on the MMSE were enrolled. The patients were otherwise generally healthy. Patients requiring skilled nursing care were not excluded. Patients with a total score of ≥ 5 on the modified Hachinski ischemia scale were excluded.

Terminate:

Drop outs were to be retrieved.

Medication:

Psychoactive medication was prohibited except for occasional use of chloral hydrate (doses up to 0.5 grams), low dose of haldol (0.5 to 3 mg/day). A month withdrawal period was used for patients on cholinergic drugs.

Outcome:

Primary: ADAS-cog, CIBIC plus. Initially, the protocol called for adding the ADAS-noncog attention score to the ADAS-cog.

Analysis:

No interim analysis was to be performed. There was an independent safety monitoring board.

The primary outcome was the change from baseline for the week 26 ADAS-cog and the week 26 CIBIC plus. Data sets include the LOCF, ITT, retrieved drop outs and observed cases as defined in the DNDP imputation schemes. Assessments from day 1 to 105 were assigned to analysis week 12. Assessments from day 106 to 154 were assigned to analysis week 18 and assessments done after day 155 were to be assigned to week 26. The primary analysis will be the comparison of the high dose with placebo. If this is significant, then pairwise comparisons will be performed for the other comparisons. ANCOVA will be used to analyze the ADAS-cog with baseline as a covariate. The CIBIC plus will be analyzed using ANOVA.

Proportion of patients showing improvement (An improvement in the ADAS-cog is a change score of ≥ 4 points and in the CIBIC plus, it is a score of 1, 2 or 3.

Subgroup analyses will be patients who had elevated LFTs on tacrine or were intolerant to other anti dementia drugs, severity of AD at baseline, early onset of AD, therapeutic failures on tacrine, sex, race, exceptional responders (> 7 point change on the ADAS-cog or a rating of 1 or 2 on the CIBIC plus)

When scale items are missing, the total will be calculated number by taking the

**Text Table 9.1.1
Patient Disposition: By Treatment**

Variable		9mg	6mg	3mg	PLB
Randomized	N	178	176	175	173
Completed	n Pct	91 (51)	111 (63)	130 (74)	130 (75)
Discontinued	n Pct	87 (49)	65 (37)	45 (26)	43 (25)
Reason for Disc:	Adverse Experiences	60 (34)	37 (21)	17 (10)	21 (12)
	--Adverse Events	60 (34)	37 (21)	17 (10)	21 (12)
	Withdr. of Consent	16 (9)	15 (9)	12 (7)	4 (2)
	Protocol Violation	2 (1)	3 (2)	4 (2)	4 (2)
	Treatment Failure	1 (1)	0	1 (1)	0
	Failure Return Visits	5 (3)	5 (3)	3 (2)	4 (2)
	Other	3 (2)	5 (3)	8 (5)	10 (6)

mean of the items present and multiplying by the number of items for the complete scale. If more than half of the items are absent, no value will be assigned.

Amendments: Amendment 7 (5/2/95) separated the worksheets of the CIBIC plus so that the rater would not have continuous access to notes from previous assessments. Amendment 11 called for using the 11 point ADAS-cog scale.

Results:

The first patient was enrolled on 12/28/94 and the last patient completed the study on 3/22/96.

Disposition: 943 patients were screened and a total of 702 patients were enrolled into the study with 466 completing.

Data populations: The ITT population included all patients who were randomized, regardless if they took study treatment. In the LOCF data set, patients received at least one dose of study treatment and had at least one on drug post baseline assessment. 58 patients were discontinued early and retrieved for efficacy evaluations. The number of patients in the data sets were summarized by the sponsor in table 9.4.1.

Population summary by treatment				
	Placebo	3 mg/day	6 mg/day	9 mg/day
Randomized	173	175	176	178
received medication	172	170	175	177
LOCF	161	152	142	136
Retrieved drop outs	13	17	10	18

Patients who were randomized and did not receive treatment 13041, 13011, 02028, 03066, 07013, 10052, 13033, 12035

Demographics and baseline characteristics: The groups were similar for demographics and baseline characteristics. The mean age was 73.3 to 74.9 (range of 41 to 92). There were 54 to 59% females. 85 to 90% of the patients were white. The mean duration of the dementia was 36 to 38 months. The severity of the dementia was mild in 44% of patients. The mean MMSE score was 20. 5 to 8% of patients took cholinesterase inhibitors.

Concomitant medication: There were no differences in the use of other medication during the study.

Dosage: By week 9, around 80% of patients had reached their assigned dose, by week 12, the number was 98% and by week 16, all patients had reached their assigned dose. The mean dosage was summarized by the sponsor in table 6.4. At week 26, the mean dose was 8.5, 5.7, 2.8 for the 9, 6 and 3 mg groups, respectively.

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Table 6.4
Dosage Summary Statistics for All Patients: By Treatment

Weeks	3mg			6mg			1mg		
	N	Mean	SD	N	Mean	SD	N	Mean	SD
1	177	1.8	0.22	175	1.3	0.10	170	1.0	0.09
2	174	2.9	0.33	173	2.0	0.19	167	1.0	0.10
3	173	3.4	0.45	171	2.4	0.33	165	1.0	0.09
4	169	3.9	0.54	170	2.9	0.32	162	1.0	0.05
5	168	4.7	0.69	168	3.4	0.38	160	1.0	0.11
6	163	5.6	1.02	165	3.8	0.46	158	1.4	0.24
7	155	6.4	1.10	161	4.3	0.52	157	1.9	0.33
8	145	7.3	1.34	158	4.7	0.60	157	2.3	0.36
9	136	8.0	1.32	156	5.3	0.96	155	2.7	0.39
10	127	8.3	1.37	153	5.6	0.91	153	2.8	0.34
11	119	8.5	1.22	147	5.7	0.65	150	2.9	0.31
12	112	8.8	0.75	144	5.7	0.70	148	2.9	0.28
14	109	8.6	1.00	137	5.8	0.63	147	2.9	0.24
16	105	8.7	0.94	131	5.8	0.43	145	2.9	0.28
18	100	8.8	0.51	127	5.8	0.49	142	2.9	0.27

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ADAS-cog: The mean change in the ADAS-cog is summarized in the following table. The data in the tables comes from the sponsor's tables 9.7.2.1 to 9.7.2.3. The differences in the change scores for the 9 and 6 mg groups when compared to placebo were statistically significant.

ADAS-cog: Mean change from baseline (*p value < 0.05, ** p value < 0.01)				
	9 mg/day	6 mg/day	3 mg/day	placebo
ITT				
N	177	176	175	171
Baseline	22.11	21.88	21.97	21.82
Week 12	0.25	0.44	0.29	0.84
Week 18	0.73*	0.71*	0.72	1.74
Week 26	1.15*	0.86**	1.68	2.42
LOCF				
N	134	140	152	159
Baseline	22.15	21.81	21.53	21.93
Week 12	-0.30*	0.5	0.23	0.94
Week 18	0**	0.67*	0.76	1.93
Week 26	0.36**	0.98**	1.76	2.54
Observed cases				
Week 12 (N) (baseline)	-0.33* (87) (22.22)	0.50 (140) (21.81)	0.22 (150) (21.19)	0.94 (158) (21.75)
Week 18 (N) (baseline)	-0.07** (95) (22.28)	0.83 (126) (21.93)	0.87 (138) (21.30)	1.90 (141) (21.66)
Week 26 (N) (baseline)	0.84* (87) (21.70)	1.00* (108) (22.13)	2.09 (123) (21.00)	2.61 (129) (21.66)

CIBIC plus: The results of the CIBIC plus is in the following table. The data comes from the sponsor's tables of 9.7.2.10 to 12. A lower number indicates improvement. P values based on pairwise t test using pooled error terms from ANOVA.

CIBIC plus: Mean rating of change from baseline (*P value < 0.05)				
	9 mg	6 mg	3 mg	placebo
ITT				
Week 12 (N)	4.00 (158)	4.06 (157)	4.02 (157)	3.95 (169)
Week 18 (N)	4.02 (161)	4.13 (157)	4.03 (160)	4.07 (169)
Week 26 (N)	4.06 (161)	4.19 (157)	4.19 (160)	4.21 (169)
LOCF				
Week 12 (N)	3.95 (132)	4.04 (141)	4.04 (148)	3.90 (161)
Week 18 (N)	3.94 (133)	4.10 (141)	4.08 (151)	4.03 (161)
Week 26 (N)	3.97 (133)	4.15 (141)	4.20 (151)	4.20(161)
Observed cases				
Week 12 (N)	3.95 (132)	4.04 (141)	4.04 (148)	3.90 (161)
Week 18 (N)	3.82 (93)	4.06 (124)	4.12 (139)	4.04 (141)
Week 26 (N)	3.97 (89)	4.11 (104)	4.23 (120)	4.20 (129)

ADAS-cog with attention: The difference of the mean change from baseline for the 6 and 9 mg groups when compared to the placebo group at week 26 was associated with p values < 0.05 in all data subset populations.

PDS: No differences in the PDS mean change from baseline was found between any active treatment groups and the placebo group.

Study 351: PDS: Mean change from baseline (higher score means greater improvement)					
	-9 mg	6 mg	3 mg	Placebo	P value 9 vs placebo /6 vs plb
ITT					
N	176	173	173	173	
Baseline	54.39	56.54	56.15	53.96	
Week 12	-0.70	-1.52	-0.97	-1.70	
Week 18	-1.72	-2.15	-1.13	-2.40	0.5/0.8
Week 26	-2.15	-2.53	-2.93	-3.13	0.4/0.6
LOCF					
N	129	140	150	160	
Baseline	54.81	56.88	57.12	53.98	
Week 12	-0.72	-1.41	-0.63	-1.43	0.5/1
Week 18	-1.88	-2.03	-1.03	-2.26	0.8/0.8
Week 26	-2.06	-2.69	-2.59	-3.02	0.5/0.8

MMSE: The mean change in the MMSE was -0.11, 0.04, 0.23 and -0.73 in the 9, 6, 3 and placebo groups, respectively for the ITT population. The differences were associated with p values < 0.05 for the 3 and 6 mg groups. For the LOCF population, the mean change was 0.12, -0.26, 0.42 and -0.85 for the 9, 6, 3 and placebo group, respectively. The 9 and 3 mg groups were associated with a p value of < 0.05.

GDS: There were no differences in the mean GDS rating change between the active treatment groups and the placebo groups.

Sponsor's conclusions:

Despite difficulties associated with the fixed-dose design, patients treated with ENA 9 mg and 6 mg compared with placebo demonstrated the following significant findings at Week 26:

- a difference in the ADAS-Cog mean change from baseline in all populations,
- a greater percentage of patients with a clinically significant improvement in the ADAS-Cog total score in the LOCF population.

Supportive evidence was obtained from the Week 26 analyses of the ADAS-Cog and the MMSE, which indicated that the ENA 9 mg and 6 mg groups achieved a greater therapeutic benefit than the placebo group.

ENA 9 mg, 6 mg and 3 mg groups demonstrated a significant outcome on the MMSE.

Based upon the predetermined criteria, these findings are considered supportive, although not definitive. evidence of the efficacy of ENA in the treatment of patients with Alzheimer's disease. Furthermore, the large number of patient discontinuations in the ENA 9 mg and 6 mg groups may have adversely affected the overall efficacy results. The fixed-dose design prohibited any dose-reduction even in the presence of clinical significant symptoms requiring dose reductions.

This forces patients to continue to experience dose-limiting adverse events. This may mask the efficacy of treatment, and maybe the case here.

Reviewer's analysis:

To conduct my analysis, I took all patient who were on drug for at least 60 days and had an assessment on study day ≤ 105 and included them in the 12 week analysis. For the week 18 analysis, I included patients who were on drug for at least 106 days and had an assessment between days 106 and 154. For the week 26 analysis, I included patients who had an assessment after day 154 and were on drug for > 154 days. The results are summarized in the following table. P values were based on student t tests.

Study B351: ADAS-cog change from baseline for observed cases				
	Placebo	3 mg	6 mg	9 mg
Week 12 (N)	1.05 (156)	0.31 (152)	0.40 (149)	0.13 (128)
Week 18 (N)	2.03 (145)	0.93 (140)	0.82 (130)	0.26*# (99)
Week 26 (N)	2.78 (133)	2.05 (137)	0.70*# (111)	0.95*# (90)

*P value < 0.05 in comparison with placebo

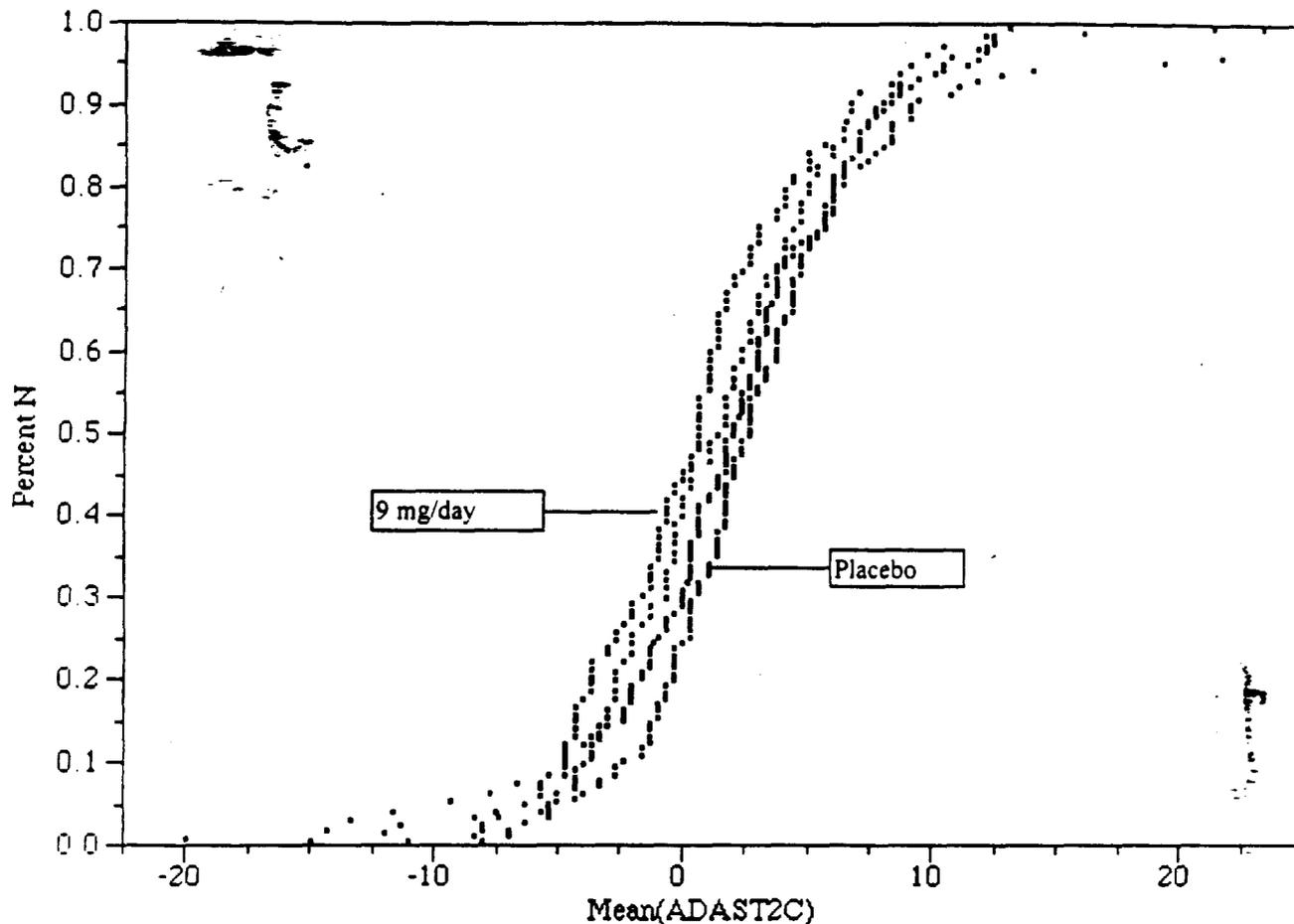
#p value < 0.05 in comparison with 3 mg dose

+p value < 0.05 in comparison with 6 mg dose

By center: I compared the mean ADAS-cog change score for treatment group for each of the 14 centers for the week 26 observed cases. There was 1 center where the mean change for the 3 mg or placebo patients score was ≤ 0 . For the 6 mg dose, the mean change score was ≤ 0 in 6 centers and for the 9 mg dose, there were 5 centers where the mean changes score was ≤ 0 .

By patient: I compared the cumulative percentage of patients with ADAS-cog change scores for each group. The results are summarized in the following figure.

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CIBIC plus: By the end of the study, the differences between any group and placebo were associated with a p values > 0.05. This was true for the intent to treat, LOCF and observed cases data sets at week 12, 18 and 26.

To conduct my analysis, I took all patient who were on drug for at least 60 days and had an assessment on study day \leq 105 and included them in the 12 week analysis. For the week 18 analysis, I included patients who were on drug for at least 106 days and had an assessment between days 106 and 154. For the week 26 analysis, I included patients who had an assessment after day 154 and were on drug for > 154 days. The results are summarized in the following table. P values were based on student t test for comparison of each pair.

Study B351: CIBIC plus for observed cases				
	Placebo	3 mg	6 mg	9 mg
Week 12 (N)	3.9 (158)	4.1 (151)	4.1 (150)	3.9 (128)
Week 18 (N)	4.0 (145)	4.1 (140)	4.1 (128)	3.8 (96)
Week 26 (N)	4.2 (133)	4.2 (134)	4.2 (108)	4.0 (91)

*P value < 0.05 in comparison with placebo
 #p value < 0.05 in comparison with low dose

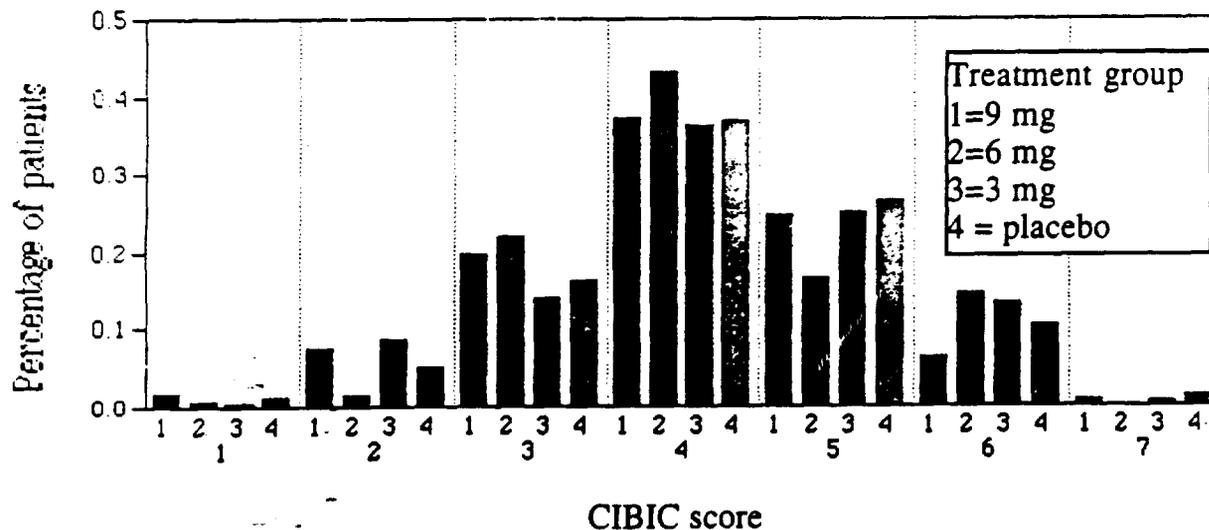
By center: I compared the CIBIC plus scores for 14 centers for the week 26 observed cases. In 10 of the centers, the 9 mg/day dose group had better scores than placebo group. In 6 of the centers, the 6 mg/day dose had better scores than the placebo group. In 5 of the center, the 3 mg/day group had better scores than the placebo group. In 4 of the centers, the placebo group had better scores than any of the active treatment groups.

By component: I took the week 26 observed cases data set and compared the results for the cognitive, functional and behavioral sections of the CIBIC plus. The results are summarized in the following table:

Study B351 comparison of the CIBIC plus components				
	Placebo (N=133)	3 mg (N=134)	6 mg (N=107)	9 mg (N=91)
Cognitive	4.2	4.2	4.0	4.1
Functional	4.1	4.2	4.1	4.1
Behavioral	3.9	4.0	4.0	3.8

*P value < 0.05 in comparison with placebo
 #p value < 0.05 in comparison with low dose

By patient: I took the percentage of patients in the week 26 observed cases data set with each CIBIC plus score for each group and summarized the information in the following figure:



Responders: I arbitrarily defined a responder as a patients who improved on both the ADAS-cog and CIBIC plus and as patients who did not worsen on either the ADAS-cog and CIBIC plus.

%responders = no change or better on ADAS-cog and CIBIC plus				
	Placebo	3 mg/day	6 mg/day	9 mg/day
Week 12 (N)	35% (162)	36% (154)	39% (154)	43% (129)
Week 18 (N)	28% (151)	38% (141)	37% (132)	35% (97)
Week 26 (N)	17% (132)	23% (142)	33% (107)	36%*# (91)

*P value < 0.05 in comparison with placebo

#p value < 0.05 in comparison with low dose

%responders = improvement on ADAS-cog and CIBIC plus				
	Placebo	3 mg/day	6 mg/day	9 mg/day
Week 12 (N)	13% (162)	16% (154)	13% (154)	17% (129)
Week 18 (N)	16% (151)	16% (141)	11% (132)	16% (97)
Week 26 (N)	6% (132)	11% (142)	14% (107)	15% (91)

*P value < 0.05 in comparison with placebo

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Study 352:

Protocol:

Design: This was a 26 weeks, multinational, randomized, placebo controlled, double blind, parallel study. Patients were randomized equally to one of three groups. In one group, patients were titrated the maximally tolerated dose between 1 and 4 mg/day (0.5 to 2 mg bid with food in the morning and evening). In the second group, patients were titrated to a dose ranging between 6 to 12 mg/day (3 to 6 mg bid). The third group received placebo.

During the dose titration phase, from weeks 1 to 7, patients were titrated to their maximally titrated dose. To increase dose tolerability, dose interruption for up to 3 consecutive doses per week and antiemetic treatment was allowed. See the following table for the most rapid titration schedule. During the fixed dose phase, single dose decreases were allowed.

Group	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9
Low dose	1 mg	1 mg	1 mg	1 mg	1.5 mg	2 mg	2.5 mg	2.5 mg	4 mg
High dose	2 mg	4 mg	5 mg	6 mg	7 mg	8 mg	9 mg	10.5 mg	12 mg

An open label study was offered after the 26 week double blind phase.

Drug: Capsules of 0.5, 1, 1.5, 3, 4.5 and 6 mg were used

Sample: 600 patients were to be enrolled.

Selection: Patients, age 50 to 85, with probable AD by the NINCDS criteria with scores of 10 to 26 on the MMSE were enrolled. The patients were otherwise generally healthy. Patients requiring skilled nursing care were excluded. Patients with a total score of ≥ 5 on the Hachinski were excluded.

Terminate: Drop outs were to be retrieved.

Medication: Psychoactive medication was prohibited except for occasional use of chloral hydrate (doses up to 500 mg).

Outcome: Primary ADAS-cog, CIBIC plus. Initially, the protocol called for adding the ADAS-noncog attention score to the ADAS-cog.

Analysis: No interim analysis was to be performed. There was an independent safety monitoring board.

The primary outcome was the change from baseline for the week 26 ADAS-cog and the week 26 CIBIC plus. Data sets include the LOCF, ITT, retrieved drop outs and observed cases as defined in the DNDP imputation schemes. Assessments from day 1 to 105 were assigned to analysis week 12. Assessments from day 106 to 154

were assigned to analysis week 18 and assessments done after day 155 were to be assigned to week 26. The primary analysis will be the comparison of the high dose with placebo. If this is significant, then pairwise comparisons will be performed for the other comparisons. ANCOVA will be used to analyze the ADAS-cog with baseline as a covariate. The CIBIC plus will be analyzed using ANOVA.

Proportion of patients showing improvement (An improvement in the ADAS-cog is a change score of ≥ 4 points and in the CIBIC plus, it is a score of 1, 2 or 3.

Subgroup analyses will be patients who had elevated LFTs on tacrine or were intolerant to other anti dementia drugs, severity of AD at baseline, early onset of AD, therapeutic failures on tacrine, sex, race, exceptional responders (> 7 point change on the ADAS-cog or a rating of 1 or 2 on the CIBIC plus)

When scale items are missing, the total will be calculated number by taking the mean of the items present and multiplying by the number of items for the complete scale. If more than half of the items are absent, no value will be assigned.

Amendments 1 to 12: Amendment 7 (5/2/95) separated the worksheets of the CIBIC plus so that the rater would not have continuous access to notes from previous assessments.

Results:

Disposition:

The first patient was recruited 1/16/95 and the last patient complete on 4/22/96.

The planned sample sized was 600. 925 patients were screened with 699 patients randomized. The patient disposition is summarized by the sponsor in text table 9.1.1. Two patients were randomized but withdrew prior to receiving any doses. The number of patients in each population was summarized by the sponsor in text table 9.4.1.

**Text Table 9.1.1
Patient Disposition: By Treatment**

Variable		6-12mg	1-4mg	PBO
Randomized	N	231	233	235
Completed	n Pct	149 (65)	199 (85)	197 (84)
Discontinued	n Pct	82 (35)	34 (15)	38 (16)
Reason for Disc:	Adverse Experiences	67 (29)	19 (8)	17 (7)
	--Adverse Events	66 (29)	19 (8)	17 (7)
	--ECG Abnormalities	1 (<1)	0	0
	Death	1 (<1)	0	0
	Withdr. of Consent	9 (4)	10 (4)	10 (4)
	Protocol Violation	0	0	1 (<1)
	Treatment Failure	0	0	4 (2)
	Failure Return Visits	2 (1)	1 (<1)	0
	Other	3 (1)	4 (2)	6 (3)

Text Table 9.4.1
Population Summary: By Treatment

Population Grouping	6-12mg	1-4mg	PBO	Total
	N	N	N	N
Randomized (Intent-to-Treat)	231	233	235	699
Patients receiving study medication	230	232	235	697
Safety - Patients with at least one on drug safety evaluation	230	232	235	697
Last Observation Carried Forward - Efficacy	181	217	218	616
Retrieved Dropouts at Week 26 - Efficacy	33	11	17	61

Patients randomized but not receiving study medication -
6-12mg: 14021
1-4mg: 16015

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Baseline characteristics: The demographics and baseline characteristics of the treatment groups were similar. The mean age was 74 to 75 years old with a range from 45 to 89. 57 to 68% of the patients were female and 94 to 97% were white. The mean duration of the dementia was 38 to 40 months with 42% rated as mild and 57% rated as moderate according to the NINCDS criteria. The mean MMSE was 19.7. 6 to 12% of patients took cholinesterase inhibitors. The previous medication use was similar between groups. Differences in use of medication during the study is summarized in the following table:

Change in concomitant medication from baseline:			
	High dose (n=231)	Low dose (N=233)	Placebo (N=235)
Antacids, other treatments for GI ulcers	13%	8	6
antidiarrheals	10	5	3
propulsive	6	2	2
benzodiazepine derivatives	3	4	3

Dosage: The cumulative duration of exposure is summarized by the sponsor in Text Table 9.6.1 and the mean dose by week is summarized by the sponsor in Table 6.4. After 18 weeks, there was little change in the mean dose. At week 26, the mean dose was 9.7 for the high dose group and 3.5 for the low dose group. At 26 weeks, 53% of the patients in the high dose group were titrated to the maximum dose of 12 mg/day and 77% of the patients in the low dose group were titrated to the maximum dose of 4 mg/day.

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Text table 9.6.1
Cumulative duration of exposure: by treatment group

Exposure	6- 12 mg	1- 4 mg	PBO	Total
Any Exposure	230	232	235	697
>= 1 week	229	231	235	695
>= 2 weeks	226	230	233	689
>= 3 weeks	223	226	231	680
>= 4 weeks	213	222	228	663
>= 5 weeks	205	222	227	654
>= 6 weeks	195	222	225	642
>= 7 weeks	189	221	224	634
>= 8 weeks	185	219	223	627
>= 9 weeks	182	217	221	620
>= 10 weeks	174	216	219	609
>= 11 weeks	168	215	217	600
>= 12 weeks	167	214	214	595
>= 18 weeks	157	206	205	568
>= 26 weeks	117	159	148	424

Table 6.4
Mean dose by treatment week (up to week 16)

Treatment week	High dose			Low dose		
	N	Dose	SD	N	Dose	SD
1	230	2.6	0.19	232	1.0	0.06
4	223	5.6	0.80	224	1.0	0.12
8	188	8.8	2.03	221	2.7	0.54
12	167	10.1	2.43	215	3.6	0.75
16	163	10.0	2.30	209	3.6	0.73

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ADAS-cog: The results of the ADAS-cog (without the attention item) for the ITT, LOCF and OC population are summarized in the following table. The data from the tables are from the sponsor's tables 9.7.2.1 - 9.7.2.3 (Lower score indicates greater improvement, baseline adjusted change from ANCOVA, p value from t test using pooled error term from ANCOVA/ANOVA). There was no statistically significant difference between the low dose group and placebo.

Study 352: ADAS-cog: Mean change from baseline				
	High dose (6 to 12 mg/day)	Low dose (1 to 4 mg/day)	Placebo	P value high vs placebo /low vs plb
ITT				
N	231	233	234	
Baseline	22.61	22.23	22.12	
Week 12	-0.56	1.45	2.06	0.000 /0.2
Week 18	0.18	1.80	3.35	0.000/0.002
Week 26	0.31	2.36	4.09	0.000/0.002
LOCF				
N	179	217	217	
Baseline	22.91	22.72	21.15	
Week 12	-1.02	1.40	2.22	0.000/0.113
Week 18	-0.49	1.66	3.34	0.000/0.002
Week 26	-0.45	2.22	3.88	0.000/0.004
Observed cases				
Week 12 (N) (baseline)	-1.05 (176) (22.86)	1.40 (216) (22.75)	2.27 (216) (21.19)	0.000/0.096
Week 18 (N) (baseline)	-0.53 (172) (23.28)	1.77 (207) (22.85)	3.45 (201) (20.79)	0.000/0.003
Week 26 (N) (baseline)	-0.79 (157) (23.65)	2.27 (194) (22.17)	4.15 (192) (21.12)	0.000/0.002

CIBIC plus: The results of the CIBIC plus is in the following table. The data comes from the sponsor's tables of 9.7.2.10 to 12. A lower number indicates improvement. P values based on pairwise t test using pooled error terms form ANOVA.

Study 352 CIBIC plus: Mean rating of change from baseline				
	High dose	Low dose	Placebo	P value high dose v placebo/ low dose v plb
ITT				
Week 12 (N)	4.60 (209)	4.20 (223)	4.18 (219)	0.047/0.885
Week 18 (N)	4.00 (214)	4.17 (225)	4.2 (223)	0.060/0.795
Week 26 (N)	4.20 (214)	4.23 (225)	4.49 (224)	0.010/0.019
LOCF				
Week 12 (N)	3.92 (174)	4.20 (215)	4.16 (213)	0.013/0.699
Week 18 (N)	3.88 (178)	4.17 (217)	4.18 (217)	0.05/0.919
Week 26 (N)	4.09 (178)	4.22 (217)	4.44 (218)	0.002/0.048
Observed cases				
Week 12 (N)	3.92 (174)	4.20 (215)	3.96 (213)	0.013/0.699
Week 18 (N)	3.87 (155)	4.14 (206)	4.09 (203)	0.012/0.885
Week 26 (N)	4.13 (145)	4.16 (195)	4.34 (197)	0.010/0.009

ADAS-cog plus the attention score: This was initially the primary outcome measure but the sponsor changed it to a secondary measure after discussion with the division. The results of the comparison of the placebo and high dose group were similar with a statistically significant difference between groups at 12, 18 and 26 weeks and significant difference between the low dose group and placebo at weeks 18 and 26.

PDS: The PDS was also a secondary outcome measure where the caregiver rated the activities of daily living. The higher change score indicates greater improvement. The sponsor adjusted scores when ANCOVA assumptions were not met. The following data summarizes the data contained in the sponsor tables 9.7.8.7 and 9.7.8.8.

Study 352: PDS: Mean change from baseline				
	High dose (6 to 12 mg/day)	Low dose (1 to 4 mg/day)	Placebo	P value high vs placebo /low vs plb
ITT				
N	231	231	233	
Baseline	51.54	54.73	52.91	
Week 12	-0.80	-3.24	-1.83	0.190/0.070
Week 18	-0.65	-3.40	-3.80	0.000/0.650
Week 26	-1.52	-5.19	-4.90	0.000/0.765
LOCF				
N	181	215	216	
Baseline	51.34	54.58	54.03	
Week 12	-0.64	-3.56	-1.92	0.150/0.055
Week 18	-0.55	-3.39	-4.00	0.000/0.516
Week 26	-1.01	-5.33	-5.17	0.000/0.874

MMSE: The week 26 results for the ITT data set was summarized by the sponsor in table 9.7.8.11.

Text Table 9.7.3.11

Mini-Mental State Examination Total Scores: Summary of Mean Change From Baseline in the ITT Population

Visit	Statistic	6-12	1-4	PBO	6-12 vs PBO	1-4 vs PBO
Week 26	N	231	233	235		
	Baseline Mean	19.62	19.61	19.90		
	Mean Change (adj)	0.20	-0.36	-0.88	0.000*	0.065

Higher change scores indicate greater improvement. Baseline adjusted change indicated by (adj). Where adjusted changes not given, ANCOVA assumptions not met. * 0.05 (Two-Tailed). Based on pairwise t tests using pooled error term from ANCOVA/ANOVA (SAS Type III). Results of the analysis are found in the appendices.

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GDS: The week 26 results for the ITT data set was summarized by the sponsor in table 9.7.8.13.

Text Table 9.7.3.13
Global Deterioration Scale: Mean Change From Baseline in the ITT Population

Visit	Statistic	6-12	1-4	Pl0	6-12 vs Pl0	1-4 vs Pl0
Week 26	N	231	233	235		
	Baseline Mean	4.01	3.98	3.95		
	Mean Change	-0.13	-0.16	-0.32	0.003*	0.014*

Higher change scores indicate greater improvement.
Baseline adjusted change indicated by (adj). Where adjusted changes not given, ANCOVA assumptions n
* P < 0.05 (Two-Tailed). Based on pairwise t tests using pooled error term from ANCOVA/ANOVA (SAS T-
analysis).
Details of the analysis are found in the appendices.

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Subgroup analyses: The sponsor reported that the subgroup analyses by sex, age at onset of disease (<65 years versus ≥ 65 years), baseline severity of disease (mild versus moderate), prior family history of disease, and intolerance or therapeutic failure with other anti-dementia drugs revealed no obvious trends in the characteristics of patients responding to treatment as defined by improvement in ADAS-Cog or CIBIC-Plus evaluations.

Sponsor's conclusions:

The following significant differences were found at Week 26 (or early termination) between patients treated with ENA 713 compared with patients given placebo:

- showed improvement in the ADAS-Cog mean change from baseline in the 6-12 mg group (LOCF and OC populations) and showed less worsening in the ITT population. The placebo group demonstrated worsening in all populations. In the 1-4 mg group, there was less worsening in the ADAS-Cog mean change from baseline (ITT, LOCF and OC populations). There was evidence of a dose-response relationship in favor of the ENA 6-12 mg group compared with the 1-4 mg group (endpoint effect size of 3.78 versus 1.73 [ITT], 4.33 versus 1.66 [LOCF], and 4.94 versus 2.2 [OC]);
- a greater percentage of 6-12 mg and 1-4 mg patients with a clinically significant improvement (at least 4 points) in the ADAS-Cog total score in the LOCF population (23% and 12% versus 6%), and a greater percentage of 6-12 mg patients with such improvement in the ITT (17% versus 7%) and OC (25% versus 7%) populations;
- a greater percentage of 6-12 mg and 1-4 mg patients rated improved (score of 1, 2 or 3) on the CIBIC-Plus in the OC population (24% and 25% versus 16%), and a greater percentage of 6-12 mg patients rated improved in the LOCF population (24% versus 16%);
- less worsening in the CIBIC-Plus mean rating of change from baseline in the 6-12 mg and 1-4 mg groups (ITT, LOCF, and OC);

- less worsening in the ADAS-COG mean change from baseline in the 6-12 mg (improvement in the LOCF and OC populations) and 1-4 mg groups in the ITT, LOCF, and OC populations;
- a greater percentage of 6-12 mg (ITT, LOCF, OC) and 1-4 mg (LOCF) patients with clinically significant improvement in the ADAS-COG. A total score;
- less worsening in activities of daily living in the PDS mean change from baseline in the 6-12 mg patients and placebo group with an endpoint effect size of 3.38 (ITT) and 4.16 LOCF;
- a greater percentage of 6-12 mg patients with clinically significant improvement in the PDS score (10% or greater improvement from baseline) in the ITT (23% versus 14%) and LOCF (25% versus 15%) populations.

Supportive evidence was obtained from the endpoint analyses of the MMSE and GDS. The MMSE mean change score was significantly different (indicates improvement) in the ENA 6-12 mg group compared with the placebo group (ITT and LOCF). The GDS mean score change from baseline showed significantly less worsening in the ENA 6-12 mg and 1-4 mg groups compared with the placebo group (ITT and LOCF). Based on the predetermined criteria, these findings provide definitive evidence of the efficacy of ENA 6-12 mg and ENA 1-4 mg in the treatment of patients with Alzheimer's disease.

Reviewer's analysis:

ADAS-cog: By the endpoint of the study, there was a statistically significant difference in favor of the drug in comparison with placebo for both the high and low dose. Statistical significance was seen with the ITT, LOCF and observed cases data sets. With the high dose group, the differences were associated with p values < 0.05 after 12 weeks. The treatment difference between the high dose group and placebo was about 3.5 points after 26 weeks. For the observed cases data set, the mean ADAS-cog change from baseline was minimally improved for the high dose group. The differences between the high and low dose groups were numerically in favor of the high dose group but the differences did not were not associated with p values < 0.05.

To conduct my analysis, I took all patient who were on drug for at least 60 days and had an assessment on study day \leq 105 and included them in the 12 week analysis. For the week 18 analysis, I included patients who were on drug for at least 106 days and had an assessment between days 106 and 154. For the week 26 analysis, I included patients who had an assessment after day 154 and were on drug for > 154 days. The results are summarized in the following table. P values were based on Tukey-Kramer HSD.

Study B352: ADAS-cog change from baseline for observed cases			
	Placebo	Low dose	High dose
Week 12 (N)	2.16 (222)	1.26 (217)	-1.07*# (179)
Week 18 (N)	3.27 (203)	1.64* (208)	-0.71*# (161)
Week 26 (N)	3.99 (200)	2.02* (200)	-0.63*# (153)

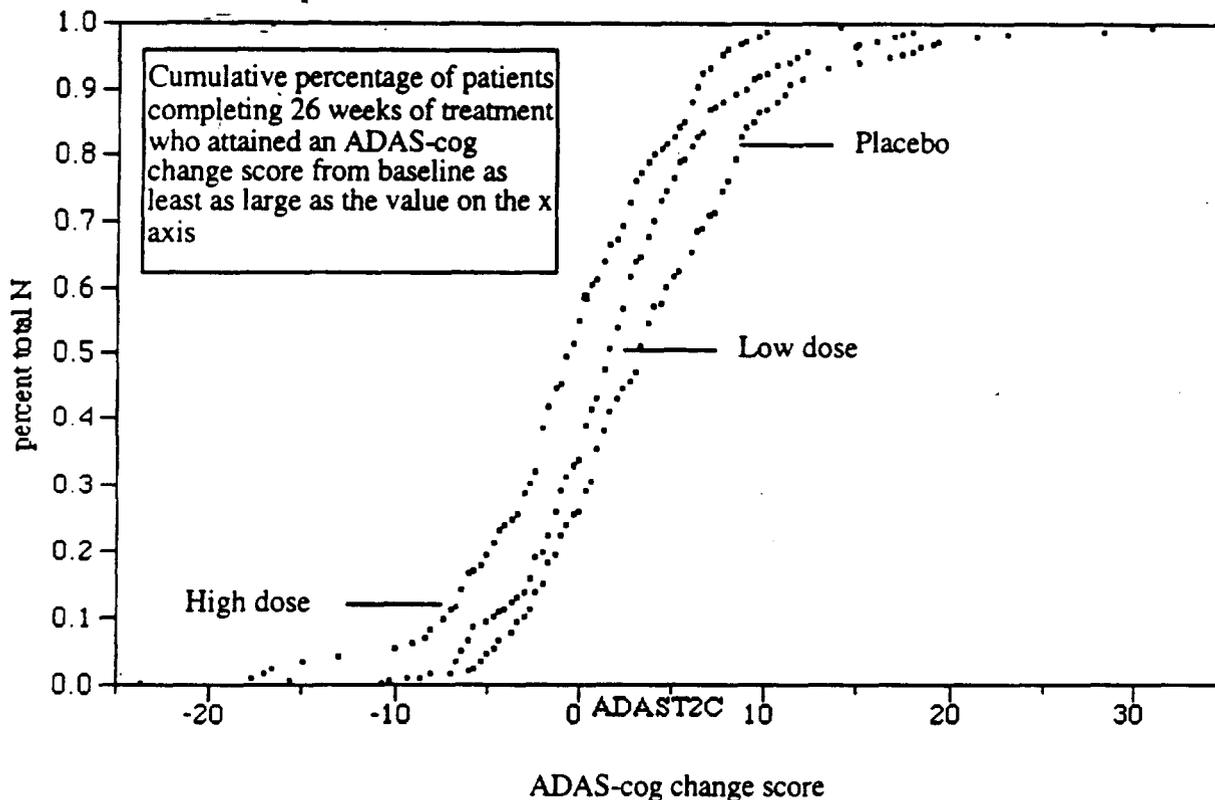
*P value < 0.05 in comparison with placebo

#p value < 0.05 in comparison with low dose

By center: I compared the mean ADAS-cog change score for treatment group for each of the 22 centers for the week 26 observed cases. In 21 of the 22 centers, the mean ADAS-cog change score was lower (better) in the high dose group compared to placebo. In 17 of the 22 centers, the mean ADAS-cog change score was lower in the low dose group compared to placebo. There was one

center where the mean change for placebo patients score was ≤ 0 . For the low dose, the mean change score was ≤ 0 in 3 centers and for the high dose, there were 14 centers where the mean changes score was ≤ 0 .

By patient: I compared the cumulative percentage of patients with ADAS-cog change scores for each group. The results are summarized in the following figure.



by dose: For the week 26 observed cases, there were only 17 patients on a dose of 9 mg/day and 19 patients on 6 mg/day, so I did not analyze the data by specific dose. I took all patients in the high dose group and divided by the actual dose they were taking at the time of the assessment into two groups; those who were taking 12 mg/day and those who were taking < 12 mg/day.

Study B352: ADAS-cog change score for observed cases			
	Placebo	high dose <12 mg/day	High dose 12 mg/day
Week 26 (N)	3.90 (192)	0.15* (67)	-1.48* (77)

*P value < 0.05 in comparison with placebo

CIBIC plus: By the end of the study, the differences between either drug group and placebo were associated with a p value of < 0.05. This was true for the intent to treat, LOCF and observed cases data sets. At week 12 and 18, only the difference between the high dose group and placebo were associated with p values ≤ 0.05 . This was true for all data subsets except for the ITT for week 18 where the p value was 0.06.

To conduct my analysis, I took all patient who were on drug for at least 60 days and had an

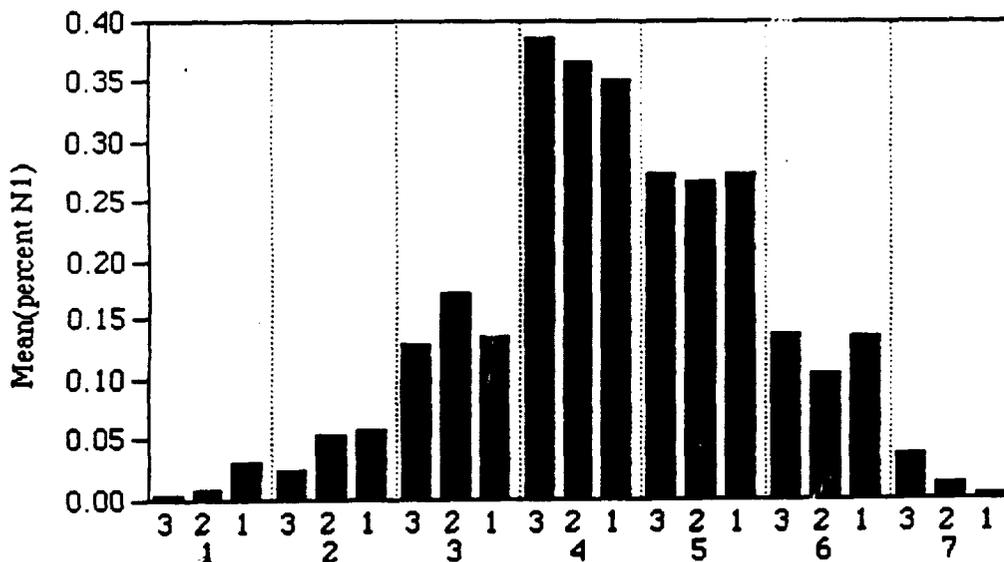
assessment on study day ≤ 105 and included them in the 12 week analysis. For the week 18 analysis, I included patients who were on drug for at least 106 days and had an assessment between days 106 and 154. For the week 26 analysis, I included patients who had an assessment after day 154 and were on drug for > 154 days. The results are summarized in the following table. P values were based on student t test for comparison of each pair.

Study B352: CIBIC plus for observed cases			
	Placebo	Low dose	High dose
Week 12 (N)	4.2 (218)	4.2 (216)	4.0# (177)
Week 18 (N)	4.2 (158)	4.1* (207)	3.9* (158)
Week 26 (N)	4.5 (201)	4.2* (200)	4.2* (153)

*P value < 0.05 in comparison with placebo
 #p value < 0.05 in comparison with low dose

By center: I compared the CIBIC plus scores for the 22 centers for the week 26 observed cases. In 2 of 22 centers, the placebo group had better scores than either dose group. In 10 centers, the low dose group scored better than any other group. In 8 of 22 centers, the high dose group scores better than any of the other groups. In two centers, the high dose and low dose scored the same but better than placebo.

By patient: I took the percentage of patients with each CIBIC plus score for each group and summarized the information in the following figure:



A comparison of the CIBIC scores (1 to 7) for the treatment groups with 1= high dose, 2= low dose and 3= placebo

By adverse event: Because of the high adverse event rate, I compared the CIBIC plus and component scores for patients with and without the common AEs (diarrhea, dizziness, nausea, vomiting) and found that the treatment effects were smaller in the patients with adverse events.

By component: I took the week 26 observed cases data set and compared the results for the cognitive, functional and behavioral sections of the CIBIC plus. The results are summarized in the following table:

Study B352 comparison of the CIBIC plus components			
	Placebo (N=200)	Low dose (N=200)	High dose (N=153)
Cognitive	4.35	4.26	4.04*#
Functional	4.34	4.19*	4.12*
Behavioral	4.21	3.92*	4.06

*P value < 0.05 in comparison with placebo

#p value < 0.05 in comparison with low dose

by dose: For the week 26 observed cases, only 17 patients were on a dose of 9 mg and 19 patients were on 6 mg, so I did not analyze the data by the specific dose. I took all patients in the high dose group and divided by the actual dose they were taking at the time of the assessment into two groups; those who were taking 12 mg/day and those who were taking < 12 mg/day.

Study B352: CIBIC plus for observed cases at 26 weeks			
	Placebo	high dose <12 mg/day	High dose 12 mg/day
Week 26 (N)	4.48 (197)	4.21* ()	4.08* (78)

*P value < 0.05 in comparison with placebo

Responders: I arbitrarily defined a responder as a patients who improved on both the ADAS-cog and CIBIC plus and as patients who did not worsen on either the ADAS-cog and CIBIC plus.

%responders = no change or better on ADAS-cog and CIBIC plus			
	Placebo	Low dose	High dose
Week 12 (N)	28 (225)	31 (216)	43*# (178)
Week 18 (N)	21 (206)	29 (208)	35* (161)
Week 26 (N)	19 (200)	27 (201)	32* (159)

*P value < 0.05 in comparison with placebo

#p value < 0.05 in comparison with low dose

%responders = improvement on ADAS-cog and CIBIC plus			
	Placebo	Low dose	High dose
Week 12 (N)	9 (225)	7 (216)	13# (178)
Week 18 (N)	8 (206)	10 (208)	16* (161)
Week 26 (N)	6 (200)	15* (201)	14* (159)

*P value < 0.05 in comparison with placebo

#p value < 0.05 in comparison with low dose

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Study 303:

Protocol:

Design: This was a 26 weeks, multinational, randomized, placebo controlled, double blind, parallel study. Patients were randomized equally to one of three groups. In one group, patients were titrated the maximally tolerated dose between 1 and 4 mg/day (0.5 to 2 mg bid with food in the morning and evening). In the second group, patients were titrated to a dose ranging between 6 to 12 mg/day (3 to 6 mg bid with food). The third group received placebo.

For the high dose group, patients were started on 1 mg bid. The dose was increased on day 4 to 1.5 mg bid. On day 7, the dose was increased to 2 mg bid. Thereafter, the dose was increased by 0.5 mg bid every week, if tolerated or until the maximum dose was reached. For the low dose group, patients were started on 0.5 mg bid. This dose was maintained until week 5 when the dose was increased to 0.5 mg in the morning and 1 mg at night. On week 6, the dose was increased to 1 mg bid, on week 7, the dose was increased to 1 mg in the morning and 1.5 mg at night. On week 8, the dose was increased to 1.5 mg bid and on week 9 the dose was increased to 2 mg bid. Investigators could allow patients to stay on a dose for an additional week, hold the dose for up to three doses or use antiemetics during the titration phase to improve tolerability. By the end of week 12, all patients were on their highest tolerated dose in their dose range. If the patients could not tolerate the lowest dose in the range, they were discontinued from the study.

During the maintenance phase, dose increase or decrease within the assigned range was allowed based on tolerance with the aim to achieve the maximum dose. The investigator was allowed to stop the dose for up to 3 doses in a week except 24 hours prior to a safety visit and 72 hours before an efficacy assessment.

An open label study was offered after the 26 week double blind phase.

Drug: Capsules of 0.5, 1, 1.5, 3, 4.5 and 6 mg were used

Sample: 600 patients were to be enrolled at 30 to 40 centers in Europe and Canada and 5 centers in the US with at least 6 per treatment group per center.

Selection: Patients, age 50 to 85, with probable AD by the NINCDS criteria with scores of 10 to 26 on the MMSE were enrolled. The patients were otherwise generally healthy. Patients requiring skilled nursing care were excluded. Patients with a total score of ≥ 5 on the modified Hachinski ischemia scale were excluded.

Terminate: Drop outs were to be retrieved.

Medication: Psychoactive medication was prohibited except for occasional use of chloral hydrate (doses up to 2 grams), low dose of haldol (0.5 to 3 mg/day) and short acting benzodiazepines (temazepam up to 20 mg/day). There was a one month washout for patients on cholinergic agents.

Outcome: Primary ADAS-cog, CIBIC plus. Initially, the protocol called for adding the ADAS-noncog attention score to the ADAS-cog.

Analysis: No interim analysis was to be performed. There was an independent safety monitoring board.

The primary outcome was the change from baseline for the week 26 ADAS-cog and the week 26 CIBIC plus score. Data sets include the LOCF, ITT, retrieved drop outs and observed cases as defined in the DNDP imputation schemes. Assessments from day 1 to 105 were assigned to analysis week 12. Assessments from day 106 to 154 were assigned to analysis week 18 and assessments done after day 155 were to be assigned to week 26. The primary analysis will be the comparison of the high dose with placebo. If this is significant, then pairwise comparisons will be performed for the other comparisons. ANCOVA will be used to analyze the ADAS-cog with baseline as a covariate. The CIBIC plus will be analyzed using ANOVA.

Proportion of patients showing improvement (An improvement in the ADAS-cog is a change score of ≥ 4 points and in the CIBIC plus, it is a score of 1, 2 or 3.

Subgroup analyses will be patients who had elevated LFTs on tacrine or were intolerant to other anti dementia drugs, severity of AD at baseline, early onset of AD, therapeutic failures on tacrine, sex, race, exceptional responders (> 7 point change on the ADAS-cog or a rating of 1 or 2 on the CIBIC plus)

When scale items are missing, the total will be calculated number by taking the mean of the items present and multiplying by the number of items for the complete scale. If more than half of the items are absent, no value will be assigned.

Amendments: Amendment 7 (5/3/95) separated the worksheets of the CIBIC plus so that the rater would not have continuous access to notes from previous assessments. Amendment 11 called for using the 11 point ADAS-cog scale.

Results:

Disposition: The planned sample size was 600, 831 patients were screened with 725 randomized. The sponsor notes that the number of patients randomized was higher than planned because patients were in screening at the time 600 patients were reached and the sponsor considered it unethical to deny these patients entry into the study. Most of the 109 screened patients who were not enrolled failed to meet selection criteria or withdrew consent. A total of 20% discontinued with 13, 14 and 33% of patients discontinued in the placebo, low dose and high dose groups, respectively. The disposition of patients is summarized by the sponsor in table 9.1.1. No patients were excluded for protocol violations including those patients under the age of 50 (4 patients) and patients with an MMSE > 26 (2 patients).

All 725 patients randomized were included in the ITT populations. This included three patients, one in each group, that did not received study treatment. The LOCF data set included 660 patients who received at least one dose of study treatment and had at least one post baseline outcome assessment. Patients who remained on treatment at the time of the observation were included in the observed cases data set. 72 patients who discontinued early, were retrieved. The results are summarized in Table 9.3.1.

**Text Table 9.1.1
Patient Disposition by Treatment**

Variable		6-12mg	1-4mg	PBO
Randomized	N	243	243	239
Completed	n Pct	164 (67)	209 (86)	208 (87)
Discontinued	n Pct	79 (33)	34 (14)	31 (13)
Reason for Disc:	Adverse Experiences	55 (23)	18 (7)	16 (7)
	--Adverse Events	55 (23)	18 (7)	16 (7)
	Death	1 (<1)	0	0
	Withdr. of Consent	11 (5)	5 (2)	6 (3)
	Protocol Violation	3 (1)	2 (1)	1 (<1)
	Treatment Failure	2 (1)	1 (<1)	2 (1)
	Failure Return Visits	2 (1)	3 (1)	2 (1)
	Other	5 (2)	5 (2)	4 (2)

Populations by treatments			
	Placebo	1 to 4 mg/day	6 to 12 mg/day
Randomized	239	243	243
receiving treatment	239	242	242
LOCF	228	229	203
Retrieved dropouts	17	19	36

patients randomized but not receiving treatment 6 to 12 mg 35015 and 1 to 4 mg 10011

Baseline characteristics: The demographics and baseline characteristics of the treatment groups were similar. The mean age was 71 to 72 years old with a range from 45 to 95. 56 to 61% of the patients were female and 95 to 98% were white. The mean duration of the dementia was 39 months with 41% rated as mild and 57% rated as moderate according to the NINCDS criteria. The mean MMSE was 19.9. 4 to 6% of patients took cholinesterase inhibitors. The previous medication use was similar between groups. Differences in use of medication during the study is summarized in the following table:

Concomitant medication:			
	High dose (n=243)	Low dose (N=243)	Placebo (N=239)
antacids	14	9	8
H2 antagonists	7	4	2
propulsive	26	5	3
Benzodiazepine derivatives	14	13	9

Dosage: The mean dose by week is summarized by the sponsor in Table 6.4. After 18 weeks, there was little change in the mean dose. At week 26, the mean dose was 10.4 for the high dose group and 3.7 for the low dose group.

Table 6.4
Dosage Summary Statistics for All Patients: By Treatment

Weeks	6-12mg			1-4mg		
	N	Mean	SD	N	Mean	SD
1	242	2.6	0.17	242	1.0	0.06
2	242	3.9	0.88	240	1.0	0.04
3	240	4.8	0.48	238	1.0	0.06
4	239	5.7	0.62	234	1.0	0.06
5	238	6.4	0.97	234	1.4	0.23
6	234	7.2	1.17	232	1.8	0.31
7	228	8.0	1.35	232	2.3	0.40
8	217	9.0	1.81	231	2.7	0.49
9	214	9.7	2.44	230	3.4	0.73
10	208	10.1	2.49	229	3.7	0.67
11	197	10.4	2.39	227	3.8	0.63
12	191	10.4	2.39	226	3.8	0.62
14	187	10.4	2.28	225	3.8	0.60
16	184	10.4	2.49	222	3.8	0.67
18	179	10.4	2.27	219	3.7	0.69

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ADAS-cog: The results of the ADAS-cog (without the attention item) for the ITT, LOCF and OC population are summarized in the following table. The data from the tables are from the sponsor's tables 9.7.2.1 - 9.7.2.3 (Lower score indicates greater improvement, baseline adjusted change from ANCOVA, p value from t test using pooled error term from ANCOVA/ANOVA). There was no statistically significant difference between the low dose group and placebo.

ADAS-cog: Mean change from baseline				
	High dose (6 to 12 mg/day)	Low dose (1 to 4 mg/day)	Placebo	P value high vs placebo
ITT				
N	242	242	238	
Baseline	23.93	23.82	23.23	
Week 12	-1.48	0.10	0.13	0.009
Week 18	-0.32	0.43	0.94	0.023
Week 26	-0.26	1.37	1.34	0.011
LOCF				
N	199	226	225	
Baseline	24.35	23.94	23.10	
Week 12	-1.79	0.10	-0.08	0.003
Week 18	-0.69	0.51	1.08	0.003
Week 26	-0.83	1.24	1.45	0.001
Observed cases				
Week 12 (N) (baseline)	-1.84 (198) (24.46)	0.15 (223) (24.25)	-0.08 (224) (23.08)	0.002
Week 18 (N) (baseline)	-0.89 (172) (24.61)	0.34 (213) (23.84)	1.22 (210) (23.02)	0.001
Week 26 (N) (baseline)	-1.17 (157) (23.96)	1.24 (202) (24.03)	1.41 (205) (22.66)	0.001

CIBIC plus: The results of the CIBIC plus is in the following table. The data comes from the sponsor's tables of 9.7.2.10 to 12. A lower number indicates improvement. P values based on pairwise t test using pooled error terms from ANOVA.

CIBIC plus: Mean rating of change from baseline				
	High dose	Low dose	Placebo	P value high dose v placebo
ITT				
Week 12 (N)	3.89 (211)	4.04 (228)	3.99 (224)	0.408
Week 18 (N)	3.93 (219)	4.10 (233)	4.15 (228)	0.088
Week 26 (N)	3.91 (219)	4.24 (233)	4.38 (230)	0.000
LOCF				
Week 12 (N)	3.88 (190)	4.01 (220)	3.97 (222)	0.437
Week 18 (N)	3.91 (193)	4.07 (224)	4.11 (225)	0.134
Week 26 (N)	3.88 (193)	4.17 (224)	4.32 (226)	0.003
Observed cases				
Week 12 (N)	3.88 (190)	4.01 (220)	3.96 (222)	0.498
Week 18 (N)	3.85 (166)	4.06 (205)	4.09 (204)	0.100
Week 26 (N)	3.93 (155)	4.20 (198)	4.34 (197)	0.012