8.2 Appendix 2: CPK outlier and mean change from baseline analyses

CPK outliers by study

Study		Gal 4	Gal 8	Gal 12	Gal 16	Gal tot		PBO
USA-1	2xULN			3/181	3/175	6/356		4/194
	3xULN			1/181	1/175	2/356		1/194
	4xULN			1/181	1/175	2/356		0/194
INT-2								
	2xULN					4/201		0/115
	3xULN					1/201		0/115
USA-10								
	2xULN	0/120	1/236	0/238		1/594		1/251
	3xULN					0/594		0/251
USA-16								
	2xULN				0/68	0/68		0/61

CPK Mean change from baseline by study

USA-1			12mg	16mg	Comb	PBO
	End-BL		38.1	1.6		3
	End-BL*		7.4	1.6	4.5	3
	M6-BL		48.9	-1.7		1.9
	M6-BL*		5	-1.7		1.9
	M5-BL		12.3	-7.5		-0.3
	M4-BL		16.5	3.3		-1.3
	M3-BL		5.4	8		2.1
	M2-BL		13.9	5.1		4.4
	W3-BL		16.3	13.4		4.4
	Max-BL		75.2	45.5		36.2
	Max-BL*		47.7	45.5		36.2
INT-2					Gal	PBO
	End-BL				-1.9	1.2
	M3-BL				-5.6	0.5
	M2-BL				-3.5	0.5
	Max-BL				27.6	21.1
USA-10		4mg	8mg	12mg	Comb	PBO
	End-BL	0.1	3.1	4.5	3.1	0.5
	M5-BL	0	4.4	6.3	4.2	3.2
	M3-BL	2.6	2.7	5.3	3.7	-0.8
	W4-BL	-0.7	3.1	6.5	3.7	5.8
	Max-BL	18.1	26.1	28.1	25.2	24.1
USA-16					Gal 16	PBO
	End-BL				-5.9	-0.2

Review and Evaluation of Clinical Data
Addendum to NDA Safety Review

NDA: 21-169

Sponsor: Janssen Research Foundation

Drug- Generic Name: galantamine
Drug- Proposed Trade Name: Reminyl®

Proposed Indication: for the treatment of mild to moderate dementia of the Alzheimer's type

Proposed Dosage: 8-12 mg po BID

Date of the NDA Submission: September 29, 1999

Safety Reviewer: Judith A. Racoosin, MD, MPH

Date of Addendum: July 18, 2000

This document is an addendum to my safety review of the galantamine NDA, dated July 13, 2000.

I neglected to put the following statement in my review, so at the outset I want to state that the galantamine development program was large enough to adequately evaluate the safety of the drug by the standards set in the ICH guidelines.

In a meeting to review the safety of galantamine with DNDP Division Director Dr. Katz, ODEI Director Dr. Temple, representatives from Division of Drug Risk Evaluation I, and the Division of Drug Marketing, Advertising, and Communication, additional questions were raised that bear on the questions to ask the sponsor to clarify the safety of galantamine. These requests follow below, along with the clarification of one question that was asked at the meeting.

Creatinine Outliers

In his examination of laboratory data in INT-1, USA-1, and USA-10 in patients who had normal laboratory values at baseline to look for outliers, Dr. Boehm found that no patients in any of the treatment groups developed at creatinine elevation to 2.3 mg/dl. The question raised at the meeting was whether there was any excess of outliers at a cut-off below 2.3 mg/dl. Dr. Boehm examined this question and the results follow in the table below.

Comparison of serum creatinine outlier risk from studies USA-1 and INT-1 (pooled), and USA-10

Lab test Pathologic limit	INT-1, USA-1			USA-10	
	Placebo	Gal 12mg BID	Gal 16mg BID	Placebo	Gal
Creatinine ≥1.5 mg/dL	2.1% (8/384)	3.1% (12/387)	3.5% (13/369)	0.8% (2/248)	0.8% (5/605)
Creatinine ≥2.0 mg/dL	(0/384)	(0/387)	(0/369)	(0/248)	(0/605)

Patient Follow-up

There were several individual patients mentioned in the review who suffered adverse events, but for whom pertinent information about the AE was not available in the NDA submission or the amendment to the NDA. We will request that the sponsor review their records for the pertinent information on those patients.

In GAL-FRA-1, the study report described that one subject had a clinically significant decrease in platelet count at the post-study visit. What were the baseline and end-of-study platelet counts?

Patient INT-3/A03057 developed jaundice and discontinued from the trial for this reason. What were the patient's total bilirubin, AST, ALT, and alkaline phosphatase at baseline and at the time of discontinuation (and any that were measured in between)? What kind of work-up did the patient have for the jaundice and what was the outcome?

Patient 95-05X/B0406 was reported to have the AE "hepatic failure", yet it was evaluated as mild and non-serious. What were the patient's LFT values that led to the reporting of this AE?

Patient USA-6/A50135 was an 84 year old female who received galantamine during an RCT and continued on galantamine during this extension trial. She developed pancreatitis and was hospitalized. No other details from the hospitalization were available. Please examine your records for information about the patient's pancreatitis including amylase and lipase values, abdominal CT scan findings, and any other pertinent tests. What was the outcome?

Patient USA-10/A73226 developed early renal failure during the trial and was discontinued for this reason. What were the patient's BUN and creatinine at baseline and at the time of discontinuation (and any that were measured in between)? What was the outcome.

Patients USA-10/A73639 and USA-3/A50173 both developed substantial drops in hemoglobin during their respective trials. In each of these patients narratives, no information was provided concerning the patient's work-up for the cause of the anemia. Please provide any available information to explain the source of these two patient's anemia.

Medications that may have an additive effect on AV block

In my safety review, I requested that in the RCTS, the sponsor examine the frequency of heart rate and rhythm AEs among patients taking both digoxin and galantamine, digoxin alone, galantamine alone, and neither drug. I also requested that they calculate mean change from baseline and outlier analyses for heart rate as measured on vital signs and ECG and for PR interval as measured on ECG for the groups designated above. During the safety meeting, it was suggested that in addition to digoxin, other drugs known to prolong AV conduction be examined. Therefore I will add to the request that beta blockers and the calcium channel blockers diltiazem and verapamil be examined as well.

Adverse event coding issues

Dr. Boehm identified that verbatim terms coded to the AE preferred term "injury" included not just injuries, but also planned and unplanned surgical procedures. Given the common occurrence of injury in the study population, we will ask the sponsor to recalculate the risk of discontinuation due to the AE "injury", the frequency of the SAE "injury", and the overall frequency of the AE "injury" across treatment groups and studies.

/S/

Judith A. Racoosin, MD, MPH
Safety Team Leader

Cc: NDA 21-169
HFD-120: Katz/Mani/Racoosin/Boehm/Prohaska/Sevka

Review and Evaluation of Clinical Data
Requests for the Sponsor

NDA: 21-169

Sponsor: Janssen Research Foundation

Drug- Generic Name: galantamine
Drug- Proposed Trade Name: Reminyl®

Proposed Indication: for the treatment of mild to moderate dementia of the Alzheimer's type

Proposed Dosage: 8-12 mg po BID

Date of the NDA Submission: September 29, 1999

Safety reviewer: Judith A. Racoosin, MD, MPH

Date Review Completed: July 18, 2000

Exposure

- Please explain the discrepancy in the person-time exposure by treatment group in 93-01X and 93-01XX between the study report and the ISS-A admsum.xpt dataset.

Mortality

- One possible explanation for the twofold mortality excess in patients originally randomized to galantamine as compared to those originally randomized to placebo would be confounding by indication. Please compare the severity of illness of the GAL-GAL patients as compared to the PBO-GAL patients at the time of entry into the first long-term extension by examining concomitant medications, co-morbid conditions, and adverse events experienced during the RCT to investigate this possibility. If confounding by indication is not supported by the data, please put forth an explanation for the difference in mortality described above.

Common AEs

- Our safety review identified that verbatim terms coded to the AE preferred term "injury" included not just injuries, but also planned and unplanned surgical procedures. Given the common occurrence of injury in the study population, please recalculate the risk of discontinuation due to the AE "injury", the frequency of the SAE "injury", and the overall frequency of the AE "injury" across treatment groups and studies after excluding any verbatim terms that do not describe accidental injuries.

- On review we observed several instances wherein the same or similar verbatim terms were coded to several different AE preferred terms describing cardiac abnormalities.

These terms included Arrhythmia, Arrhythmia atrial, Arrhythmia ventricular, AV block, Bradycardia, Bundle branch block, ECG abnormal, ECG abnormal specific, Extrasystoles, Fibrillation atrial, Heart block, QT prolonged, Sick sinus syndrome, Sinoatrial block, Tachycardia, Tachycardia supraventricular, and Tachycardia ventricular. Please reexamine all AE verbatim terms coded to these preferred terms and reclassify them in a consistent manner to the most appropriate preferred term., Following reclassification, please recalculate new incidences for these events across treatment groups and studies.

- Please explain how the incidence of falls was calculated given that verbatim terms describing falls were coded to a variety of AE preferred terms including the following: Back pain, Dizziness, Fracture pathologic, Joint dislocation, Orthostatic hypotension, Purpura, and Syncope.

- Finally, all verbatim terms containing spasm or cramp should be examined for appropriate assignment to such preferred terms as Back pain, Cramps legs, Leg pain, Myalgia, Muscle contraction involuntary, and Muscle weakness. Following reclassification, please recalculate new incidences for these events across treatment groups and studies

Laboratory Data

- Please review the clinical histories of patients who had glucose measurements less than 60 mg/dl or who had AEs or SAEs of hypoglycemia to try to identify risk factors. Additionally, please look for hypoglycemia outliers among all patients on therapy for diabetes using cutoffs of 75 mg/dl, 60 mg/dl, and 45 mg/dl.

Drug Interactions

- In the RCTS, please examine the frequency of heart rate and rhythm AEs among patients taking both digoxin and galantamine, digoxin alone, galantamine alone, and neither drug. Please also perform mean change from baseline and outlier analyses for heart rate as measured on vital signs and ECG and for PR interval as measured on ECG for the groups designated above.
- In a separate analysis, please repeat the above analysis, but examine patients taking beta blockers, verapamil, or diltiazem.
- Finally, please repeat the original analysis combining the digoxin users with the users of beta blockers, verapamil, or diltiazem.

Patient Follow-up

There were several individual patients mentioned in the NDA who suffered adverse events, but for whom pertinent information about the AE was not available in the NDA submission or the amendment to the NDA. Please review your records for the pertinent information on these patients.

- In GAL-FRA-1, the study report described that one subject had a clinically significant decrease in platelet count at the post-study visit. What were the baseline and end-of-study platelet counts?

- Patient INT-3/A03057 developed jaundice and discontinued from the trial for this reason. What were the patient's total bilirubin, AST, ALT, and alkaline phosphatase at baseline and at the time of discontinuation (and any that were measured in between)? What kind of work-up did the patient have for the jaundice and what was the outcome?

- Patient 95-05X/B0406 was reported to have the AE "hepatic failure", yet it was evaluated as mild and non-serious. What were the patient's LFT values that led to the reporting of this AE?

- Patient USA-6/A50135 was an 84 year old female who received galantamine during an RCT and continued on galantamine during this extension trial. She developed pancreatitis and was hospitalized. No other details from the hospitalization were available. Please examine your records for information about the patient's pancreatitis including amylase and lipase values, abdominal CT scan findings, and any other pertinent tests. What was the outcome?

- Patient USA-10/A73226 developed early renal failure during the trial and was discontinued for this reason. What were the patient's BUN and creatinine at baseline and at the time of discontinuation (and any that were measured in between)? What was the outcome.

- Patients USA-10/A73639 and USA-3/A50173 both developed substantial drops in hemoglobin during their respective trials. In each of these patients narratives, no information was provided concerning the patient's work-up for the cause of the anemia. Please provide any available information to explain the source of these two patient's anemia.

/S/

Judith A. Racoosin, MD, MPH
Safety Team Leader

Cc: NDA 21-169
HFD-120: Katz/Mani/Racoosin/Boehm/Prohaska/Sevka

Review and Evaluation of Clinical Data
Review of Sponsor's Proposed Labeling

NDA: 21-169

Sponsor: Janssen Research Foundation

Drug- Generic Name: galantamine
Drug- Proposed Trade Name: Reminyl®

Proposed Indication: for the treatment of mild to moderate dementia of the Alzheimer's type

Proposed Dosage: 8-12 mg po BID

Date of the NDA Submission: September 29, 1999

Safety Reviewers: Judith A. Racoosin, MD, MPH

Date Review Completed: July 18, 2000

Background

NDA # 21169 for the use of galantamine in the treatment of mild to moderate dementia of the Alzheimer's type was submitted on 9/29/99 followed by an Amendment on 2/25/00. The draft labeling reviewed in this submission is the updated version submitted with the NDA Amendment of 2/25/00

This review contains comments and changes to the "Contraindications", "Warnings", "Adverse Reactions" and the "general" section of the "Precautions". The sections of the sponsor's draft label that have been deleted have been marked with the "strike-through" feature. New text has been highlighted in red. Reviewer's comments are highlighted in red italics.

Proposed Labeling

7 pages redacted from this section of the approval package consisted of draft labeling

Reviewer Conclusions

I have edited and added to the sponsor's proposed labeling for clarity and to reflect the data presented in the NDA. Two issues need to be addressed by the sponsor. First, what was the source of the pooled data in Table 3 of the adverse reactions section. Second, the list of "other adverse events observed during clinical trials" needs to be amended to include all AEs occurring during the clinical trials, even those events judged by the investigator to be unrelated to study drug. Generally, we have not paid heed to investigator attribution in performing NDA safety reviews because the investigators' judgment has not been shown to be predictive of drug-relatedness (e.g., a substantial number of syncope events in the ropinorole NDA occurring in placebo-treated patients were attributed to the drug by the investigator). Therefore, all AEs should be included in the calculation of frequent and infrequent AEs for the list, regardless of investigator causal assessment.

Judith A. Racoosin, MD, MPH
Safety Team Leader

Cc: NDA 21-167
Katz/Mani/Racoosin

CLINICAL EFFICACY REVIEW OF NDA

NDA	**21169**
Sponsor:	**Janssen**
Drug:	**Galantamine**
Proposed Indication:	**Alzheimer's Disease**
Material Submitted:	**New Drug Application**
Correspondence Date:	**9/29/99**
Date Received / Agency:	**9/29/99**
Date Review Completed:	**6/13/00**
Reviewer:	**Ranjit B. Mani, M.D.**

1. Background

The (main) submission reviewed here consists of an original New Drug Application (NDA) for galantamine (Reminyl®) tablets in the treatment of mild to moderate dementia of the Alzheimer's type.

An Amendment dated 2/25/00 is being reviewed along with the original NDA.

Reminyl® (galantamine) is a cholinesterase inhibitor which has been developed in this country under Investigational New Drug application (IND) #

The pharmacokinetics of this drug in humans may be summarized as follows (please review to the pharmacokinetic review of this submission for full details):

Following oral administration the drug has an absolute bioavailability of 88.5 % . It is absorbed fairly rapidly by that route with a t_{max} of 0.5 to 2.5 hours, but absorption is delayed by the presence of food. Protein-binding is low at 18 %. Metabolism in humans appears to occur through at least 5 pathways. The main products of Phase I metabolism have been identified as O-desmethyl-galantamine and galantamine-N-oxide, formed through CYP2D6 and CYP3A4, respectively. An active metabolite present in relatively low concentration is N-desmethyl-galantamine (norgalantamine). The terminal half-life ranges from about 7-8 hours. The pharmacokinetics of galantamine appear to be linear up to a dose of 36 mg/day. In moderate hepatic impairment exposure to galantamine (based on AUC) increased by about 33 %. In moderate and severe renal impairment, exposure to galantamine increased by 67 % and 37 %, respectively. Galantamine appeared to have a low potential for inhibiting the major CYP450 pathways. Concurrent use of ketoconazole and paroxetine increased the AUC of galantamine by 30 % and 40 %, respectively. No significant interactions have been seen with warfarin, digoxin, cimetidine, ranitidine and erythromycin.

This review will be confined to the efficacy of this drug. The statistical reviewer of this submission is Dr Kun He. A separate safety review of this application is being performed by Drs Judith Racoosin, Jerry Boehm and Kevin Prohaska.

Note that:

- Galantamine has also been spelled "galanthamine"
- The doses of galantamine referred to in this submission and review are those for galantamine base

2. Tabular Summary Of Efficacy Studies

2.1 Main Efficacy Studies In Original NDA Submission

A total of 4 main efficacy studies are included in the original NDA. These are summarized below. The sponsor considers GAL-USA-1 and GAL-INT-1 to be the key efficacy studies with GAL-INT-2 and GAL 95-05 being supportive. GAL 95-05 was conducted by Shire rather than Janssen

2.1.1 Outline Of Main Study Results

dy #	GAL-USA-1	GAL-INT-1	GAL-INT-2	GAL 95-05
ıign	Randomized, double-blind, placebo-controlled, parallel-group, 3-arm study, comparing 2 doses of galantamine with placebo	Randomized, double-blind, placebo-controlled, parallel-group, 3-arm study, comparing 2 doses of galantamine with placebo	Randomized, double-blind, placebo-controlled, parallel-group, comparison of flexible dose of galantamine with placebo	Randomized, double-blind, placebo-controlled, parallel-group, 2-arm trial comparing one fixed dose of galantamine with placebo
ıage	Galantamine 24 mg/day Galantamine 32 mg/day B.I.D. Dosing	Galantamine 24 mg/day Galantamine 32 mg/day B.I.D. Dosing	Galantamine flexible dose 24 mg/day to 32 mg/day B.I.D. Dosing	Galantamine 32 mg/day T.I.D. Dosing
ation of double-d treatment	26 weeks	26 weeks	12 weeks	29 weeks
ıdomized ulation	Placebo: 213 patients GAL 24: 212 patients GAL 32: 211 patients	Placebo: 215 patients GAL 24: 220 patients GAL 32: 218 patients	Placebo: 125 patients GAL: 261 patients	Placebo: 279 patients GAL: 275 patients
npleters	Placebo: 172 patients GAL 24: 144 patients GAL 32: 122 patients	Placebo: 186 patients GAL 24: 176 patients GAL 32: 163 patients	Placebo: 113 patients GAL: 175 patients	Placebo: 229 patients GAL: 180 patients
sion criteria	Probable Alzheimer's disease; Mini-Mental Status Examination score: 11-24; ADAS-Cog ≥ 12	Probable Alzheimer's disease; Mini-Mental Status Examination score: 11-24; ADAS-Cog ≥ 12	Probable Alzheimer's disease; Mini-Mental Status Examination score: 11-24; ADAS-Cog ≥ 12	Dementia of the Alzheimer's Type (DSM-IV); Probable Alzheimer's Disease; Mini-Mental Status Examination score: 12-24
nary outcome ıasures	ADAS-Cog CIBIC-Plus	ADAS-Cog CIBIC-Plus	ADAS-Cog CIBIC-Plus	ADAS-Cog (EURO-ADAS-Cog) CIBIC-Plus NOSGER*
ults of primary acy analysis tistically significant efit only) erences between tment groups are ressed as least are means e tables below for centages improved, hanged and worse CIBIC-Plus)	Treatment effects (individual dose vs placebo; traditional observed cases population at 26 weeks) ADAS-Cog: GAL 24: -3.9 (p<0.001) GAL 32: -3.8 (p<0.001) CIBIC-Plus: Analysis based on original 7-point scale favored galantamine GAL 24: p=0.023 GAL 32: p=0.017	Treatment effects (individual dose vs placebo; traditional observed cases population at 26 weeks) ADAS-Cog: GAL 24: -3.1 (p<0.001) GAL 32: -4.1 (p<0.001) CIBIC-Plus: Analysis based on original 7-point scale favored galantamine: GAL 24: p=0.002 GAL 32: p<0.001	Treatment effects (individual dose vs placebo; traditional observed cases population at 12 weeks) ADAS-Cog: -1.9 (p=0.002) CIBIC-Plus: Analysis based on original 7-point scale favored galantamine P=0.003	Treatment effects (individual dose vs placebo; original intent-to-treat** population at 29 weeks) ADAS-Cog: -3.0 (p=0.0001) CIBIC-Plus: Analysis based on original 7-point scale favored galantamine (p=0.024) NOSGER: Only memory showed a difference favoring galantamine (p=0.043)

* Nurses Observation Scale for Geriatric Patients
** Original intent-to-treat includes all randomized who received at least a single dose of study medication
GAL: Galantamine; GAL 24: Galantamine 24 mg daily; GAL 32: Galantamine 32 mg daily; GAL 36: Galantamine 36 mg daily

2.1.2 CIBIC-Plus Results: Responder Analysis

(p-values below are derived from analysis of the original 7-point scale)

2.1.2.1 CIBIC-Plus results for GAL-USA-1 study

	% Improved	% Unchanged	% Worsened	P-value Vs placebo
GAL 24	24.4	50.4	29.6	0.023
GAL 32	26.3	48.3	32.1	0.017
Placebo	13.2	42.1	44.7	

2.1.2.2 CIBIC-Plus results for GAL-INT-1 study

	% Improved	% Unchanged	% Worsened	P-value Vs placebo
GAL 24	20.5	46.6	32.9	0.002
GAL 32	27.8	40.6	31.7	<0.001
Placebo	17.3	32.2	50.5	

2.1.2.3 CIBIC-Plus results for GAL-INT-2 study

	% Improved	% Unchanged	% Worsened	P-value Vs placebo
Galantamine	28.8	50.6	20.5	0.003
Placebo	19.8	43.2	36.9	

2.1.2.4 CIBIC-Plus results for GAL 95-05 study

	% Improved	% Unchanged	% Worsened	P-value Vs placebo
Galantamine	25.3	40.3	30.6	0.034
Placebo	16.2	42.1	37	

2.1.3 Dose-Titration Schedules

2.1.3.1 Dose-Titration Schedule for GAL-USA-1 and GAL-INT-1

Week	Dose
Week 1	4 mg b.i.d
Week 2	8 mg b.i.d
Week 3	12 mg b.i.d
Week 4 Through 26	12 mg b.i.d or 16 mg b.i.d

2.1.3.2 Dose-Titration Schedule for GAL-INT-2

Week	Dose
Week 1	4 mg b.i.d
Week 2	8 mg b.i.d
Week 3	12 mg b.i.d
Week 4 through 12	Increase to 16 mg b.i.d at discretion of investigator; maintain at 16 mg b.i.d or reduce to 12 mg b.i.d

2.1.3.3 Dose-Titration Schedule for GAL 95-05

Week	Dose
Week 1	8 mg per day
Week 2	16 mg per day
Week 3	24 mg per day
Week 4	28 mg per day
Week 5 through 29	32 mg per day as a t.i.d regime

2.1.4 Results For Secondary Efficacy Measures

	GAL-USA-1	GAL-INT-1	GAL-INT-2	GAL 95-05
sage	Galantamine 24 mg/day Galantamine 32 mg/day B.I.D. Dosing	Galantamine 24 mg/day Galantamine 32 mg/day B.I.D. Dosing	Galantamine flexible dose 24 mg/day to 32 mg/day B.I.D. Dosing	Galantamine 32 mg/day T.I.D. Dosing
condary icacy Measures	ADAS-Cog/13 ADAS-Cog/10 ADAS-Cog/mem ADAS-Cog/responder analysis DAD Total/Cluster Score PGWB Resource Utilization/Costs	ADAS-Cog/13 ADAS-Cog/10 ADAS-Cog/mem ADAS-Cog/responder analysis DAD Total/Cluster Score PGWB Resource Utilization/Costs	ADAS-Cog/13 ADAS-Cog/10 ADAS-Cog/mem ADAS-Cog/responder analysis DAD Total/Cluster Score Neuropsychiatry Inventory	EURO-ADAS-NonCog Mini Mental Status Examination NAB DSST
sults of condary efficacy alysis (p < 0.05 mparisons only) an Drug- icebo Difference Study End. served Cases	Both galantamine groups superior to placebo on ADAS-Cog/13, ADAS-Cog/10 and ADAS-Cog/mem (see table below) ADAS-Cog/responder analysis (see table below)	Both galantamine groups superior to placebo on ADAS-Cog/13, ADAS-Cog/10 and ADAS-Cog/mem (see table below) ADAS-Cog/responder analysis (see table below)	ADAS-Cog/13: -2.1 (p=0.004) ADAS-Cog/10: -1.8 (p<0.001) ADAS-Cog/responder analysis (see table below) DAD (Total) =-4.3 (p=0.004)	DSST: 2.51 (p<0.001) NAB: 0.8 (0.032)

PGWB: Psychological General Well Being Index
NAB: Nuremberg Alters-Beobachtungs-Skala (Nuremberg Geriatric Observation Scale)
DSST: Digit Symbol Substitution Test

ADAS-Cog Cluster Analysis for GAL-USA-1

Cluster	Drug-Placebo Difference For Mean Change From Baseline At Month 6		p-value GAL 24 Vs Placebo	p-value GAL 32 Vs Placebo
	GAL 24	GAL 32		
ADAS-Cog/13	-4.4	-4.1	< 0.001	< 0.001
ADAS-Cog/10	-2.9	-2.8	< 0.001	< 0.001
ADAS-Cog/mem	-1.4	-1.5	< 0.001	0.008

ADAS-Cog Cluster Analysis for GAL-INT-1

Cluster	Drug-Placebo Difference For Mean Change From Baseline At Month 6		p-value GAL 24 Vs Placebo	p-value GAL 32 Vs Placebo
	GAL 24	GAL 32		
ADAS-Cog/13	-3.1	-4.0	< 0.001	< 0.001
ADAS-Cog/10	-2.7	-2.9	< 0.001	< 0.001
ADAS-Cog/mem	-0.5	-1.4	0.008	< 0.001

ADAS-Cog Cluster Analysis for GAL-INT-2

Cluster	Drug-Placebo Difference For Mean Change From Baseline At Month 3	p-value Galantamine Vs Placebo
ADAS-Cog/13	-2.1	0.004
ADAS-Cog/10	-1.8	< 0.001
ADAS-Cog/mem		

ADAS-Cog Responder Analysis for GAL-USA-1

Category (based on improvement in ADAS-Cog score at Month 6)	Placebo (%) N=157	GAL 24 (%) N=131	GAL 32 (%) N=117	p-value GAL 24 Vs Placebo	p-value GAL 32 Vs Placebo
≥ 0 points	43.9	64.1	58.1	0.001	0.012
≥ 4 points	16.6	33.6	33.3	0.003	0.001
≥ 7 points	5.7	18.3	19.7	0.004	< 0.001
≥ 10 points	2.5	7.6	11.1	0.122	0.002

ADAS-Cog Responder Analysis for GAL-INT-1

Category (based on improvement in ADAS-Cog score at Month 6)	Placebo (%) N=211	GAL 24 (%) N=212	GAL 32 (%) N=212	p-value GAL 24 Vs Placebo	p-value GAL 32 Vs Placebo
≥ 0 points	39.8	65.4	63.8	< 0.001	< 0.001
≥ 4 points	15.2	30.8	34.9	< 0.001	< 0.001
≥ 7 points	5.8	15.4	19.7	< 0.001	< 0.001
≥ 10 points	1.2	4.5	7.9	0.072	0.002

ADAS-Cog Responder Analysis for GAL-INT-2

Category (based on improvement in ADAS-Cog score at Month 3)	Placebo (%) N=100	Galantamine (%) N=170	p-value
≥ 0 points	50	65.3	0.01
≥ 4 points	19.4	32.9	0.019
≥ 7 points	5.6	18.8	0.002
≥ 10 points	1.9	7.1	0.059

2.2 Additional Efficacy Study In Original NDA Submission

2.2.1 Outline Of Study Results

Study #	GAL 93-01			
Design	Randomized, double-blind, placebo-controlled, parallel-arm study			
Dosage	Galantamine 18 mg daily Galantamine 24 mg daily Galantamine 36 mg daily TID Dosing			
Duration of double-blind treatment	3 months			
Treatment Groups	Placebo	GAL 18	GAL 24	GAL 36
Randomized population	87	88	56	54
Completers	73	63	42	28
Main inclusion criteria	Probable Alzheimer's disease; Mini-Mental Status Examination score: 13-24			
Primary outcome measures	ADAS-Cog			
Results of primary efficacy analysis (statistically significant benefit only) Differences between treatment groups are expressed as least square means	Treatment effects (individual dose vs placebo; adjusted intent-to-treat -last-observation-carried-forward population at 12 weeks) GAL 18: -1.69 (p=0.11) GAL 24: -3.34 (p=0.01) GAL 36: -1.93 (p=0.13)			

GAL: Galantamine; **GAL 18**: Galantamine 18 mg daily; **GAL 24**: Galantamine 24 mg daily; **GAL 36**: Galantamine 36 mg daily

2.2.2 Titration Schedule

Trial Days	Daily Dose
1-2	4 mg b.i.d
3-4	4 mg t.i.d
5-7	6 mg t.i.d
8-10	8 mg t.i.d
11-13	10 mg t.i.d
14-84	12 mg t.i.d

2.2.3 Results For Secondary Efficacy Measures

2.2.3.1 Overall Results

Study #	GAL 93-01
Dosage	Galantamine 18 mg daily Galantamine 24 mg daily Galantamine 36 mg daily TID Dosing
Secondary Efficacy Measures	CGIC (rater not independent) Progressive Deterioration Scale-1 IADL ADAS-NonCog ADAS Total (analysis not performed)
Results of secondary efficacy analysis ($p < 0.05$ comparisons only) Mean Drug-Placebo Difference At Study End. Observed Cases	No drug-placebo differences were significant at a $p < 0.05$ level except for the responder percentage on the CGIC for the GAL 18 ($p=0.01$) and GAL 36 group ($p=0.02$) See detailed results in tables below

2.2.3.2 Mean Change From Baseline For Secondary Efficacy Measures

(p-values for these data have not been provided) ✓

	Mean Drug-Placebo Difference At Month 3 (Observed Cases)		
	GAL 18	GAL 24	GAL 36
CGIC	0.2	0.2	0.2
Progressive Deterioration Scale-1	85	174	89
IADL	0.3	0.2	0.1
ADAS-NonCog	-0.3	-0.3	-0.5

2.2.3.3 Responder Percentages For CGIC (Observed Cases At 3 Months)

	% Improved	% Unchanged	% Worsened	P-value vs placebo
GAL 18	45	39	16	0.01
GAL 24	34	48	18	0.14
GAL 36	50	43	7	0.02
Placebo	33	39	28	

2.3 Randomized Withdrawal Study In Original NDA

This study was an extension to GAL-INT-2, performed on US patients only. Note that this study was primarily intended to assess the safety of abrupt withdrawal of galantamine.

Study #	GAL-USA-5		
Design	Randomized, double-blind, placebo-controlled, parallel-arm		
Dosage	Galantamine 24 mg daily or 32 mg daily (BID dosing)		
Duration of randomized withdrawal	6 weeks		
Treatment Groups	PLA/PLA	GAL/GAL*	GAL/PLA*
Study entry	47	32	39
Completers	41	31	39
Main inclusion criteria	Completion of GAL-INT-2 (US centers only)		
Primary efficacy outcome measures	ADAS-Cog (change from initial visit of withdrawal study)		
Primary efficacy analysis	Change in ADAS-Cog during withdrawal study GAL/PLA group vs PLA/PLA group ANOVA		

Results of primary efficacy analysis	No statistically significant differences between treatment groups Mean ADAS-Cog changes from initial visit of GAL-USA-5 (Observed Cases) PLA/PLA: 0.8 GAL/GAL: -0.9 GAL/PLA: 1.4 Mean ADAS-Cog changes from initial visit of GAL-INT-2 (Observed Cases) PLA/PLA: 0.9 GAL/GAL: -1.5 GAL/PLA: 0.1
Safety outcome measures	Adverse events, vital signs, physical examinations, laboratory tests and electrocardiograms
Safety results	Incidence of adverse events comparable between GAL/PLA and PLA/PLA No deaths Incidence of serious and severe adverse events and adverse event dropouts low No important changes in laboratory tests, vital signs or electrocardiograms

PLA/PLA: Placebo followed by galantamine
GAL/GAL: Galantamine followed by galantamine
GAL/PLA: Galantamine followed by placebo
*Patients taking galantamine at the end of GAL-INT-2 who entered GAL-USA-5 were randomized to receive either galantamine in their previous dosage or placebo. Patients who took placebo in GAL-INT-2 continued on placebo

2.4 Efficacy Study In NDA Amendment

2.4.1 Outline Of Study Results

Study #	GAL-USA-10			
Design	Randomized, double-blind, placebo-controlled, parallel-group, 4-arm study, comparing 3 doses of galantamine with placebo			
Dosage	Galantamine 8 mg/day Galantamine 16 mg/day Galantamine 24 mg/day B.I.D. Dosing			
Duration of double-blind treatment	5 months			
Treatment Groups	Placebo	GAL 8	GAL 16	GAL 24
Randomized population (2:1:2:2)	286	140	279	273
Completers	240	108	219	212
Main inclusion criteria	Probable Alzheimer's disease; Mini-Mental Status Examination score: 10-22; ADAS-Cog ≥ 18			
Primary outcome measures	ADAS-Cog CIBIC-Plus			
ADAS-Cog Results of primary efficacy analysis (statistically significant benefit only) LOCF Differences between treatment groups are expressed as least square means	GAL 16 vs placebo: -3.1 ($p < 0.001$) GAL 24 vs placebo: -3.1 ($p < 0.001$)			
CIBIC-Plus Results of primary efficacy analysis (statistically significant benefit only) LOCF Percentage with improvement or no change	GAL 16 vs placebo: 66 % versus 49 % ($p < 0.001$) GAL 24 vs placebo: 64 % versus 49 % ($p < 0.001$)			

GAL: Galantamine; GAL 8: Galantamine 8 mg daily; GAL 16: Galantamine 16 mg daily; GAL 24: Galantamine 24 mg daily

2.4.2 Titration Schedule

Group	Run-in Phase	Double-Blind Phase		
		Weeks 1 through 4	Weeks 5 through 8	Weeks 9 through 21
Placebo	Placebo	Placebo	Placebo	Placebo
Gal 24	Placebo	8 mg	16 mg	24 mg
Gal 16	Placebo	8 mg	16 mg	16 mg
Gal 8	Placebo	8 mg	8 mg	8 mg

2.4.3 Results For Secondary Efficacy Measures

Study #	GAL-USA-10
Dosage	Galantamine 24 mg/day Galantamine 16 mg/day Galantamine 8 mg/day Placebo B.I.D. Dosing
Secondary Efficacy Measures	ADAS-Cog/13 ADAS-Cog/10 ADAS-Cog/mem ADAS-Cog/responder analysis NPI ADCS-ADL
Results of secondary efficacy analysis ($p < 0.05$ comparisons only) Mean Drug-Placebo Difference At Study End. Observed Cases	ADAS-Cog/13: see below ADAS-Cog/10: see below ADAS-Cog/mem: see below ADAS-Cog/responder analysis: see below Neuropsychiatry Inventory: GAL 16 vs placebo: -2.4 (p=0.026) GAL 24 vs placebo: -2.4 (p=0.022) ADCS-ADL: GAL 16 vs placebo: 3.5 (p<0.001) GAL 24 vs placebo: 2.4 (p=0.003)

ADAS-Cog Cluster Analysis for GAL-USA-10

Cluster	Drug-Placebo Difference For Mean Change From Baseline			p-value GAL 24 Vs Placebo	p-value GAL 16 Vs Placebo	p-value GAL 8 Vs Placebo
	GAL 24	GAL 16	GAL 8			
ADAS-Cog/13	-3.9	-3.5	-1.7	< 0.001	< 0.001	0.06
ADAS-Cog/10	-3.1	-3.1	-1.8	< 0.001	< 0.001	0.004
ADAS-Cog/mem	-1.0	-0.7	-0.1	0.005	0.051	0.751

ADAS-Cog Responder Analysis for GAL-USA-10

Category (based on improvement in ADAS-Cog score)	Placebo (%) N=225	GAL 24 (%) N=211	GAL 16 (%) N=208	GAL 8 (%) N=101	p-value GAL 24 Vs Placebo	p-value GAL 16 Vs Placebo	p-value GAL 8 Vs Placebo
≥ 0 points	41.8	64.9	65.4	46.5	< 0.001	< 0.001	0.556
≥ 4 points	19.6	37.0	35.6	25.7	< 0.001	< 0.001	0.266
≥ 7 points	7.6	22.3	15.9	13.9	< 0.001	< 0.001	0.106
≥ 10 points	3.6	10.4	7.2	5.9	0.004	0.102	0.378

3. Rating Scales Used

3.1 Primary Efficacy Variables

The primary efficacy variables for all studies (except GAL 93-01) consisted of a
A cognitive measure which was the ADAS-Cog (11-item) in all studies

A global measure which was the CIBIC-Plus

GAL 93-01 had only one primary efficacy variable, the ADAS-Cog

3.1.1 Alzheimer's Disease Assessment Scale-Cog (ADAS-Cog)

This is a validated instrument consisting of the following 11 items: Word Recall Task, Naming Fingers and Objects, Orientation Questions, Constructional Praxis Task, Following Commands, Ideational Praxis Task, Word Recognition Task, Rating of Spoken Language, Rating of Language Comprehension, Rating of Word Finding Difficulty and Rating of Ability to Recall Test Instructions. The total scores range from 0-70 with higher scores indicating greater cognitive impairment.

Note that extended forms and subsets of the ADAS-Cog have been used as secondary efficacy measures in clinical studies of galantamine. These include:
ADAS-Cog/13 consisting of the standard ADAS-Cog and 2 additional items: Concentration and Distractibility and Delayed Word Recall
ADAS-Cog/10 consisting of the non-memory section of the ADAS-Cog
ADAS-Cog/mem comprising the memory items of the ADAS-Cog: Word Recall, Delayed Word Recall and Word Recognition

A different version of the ADAS-Cog was used in a single supportive efficacy study (GAL 95-05): this version is referred to as the EURO-ADAS-Cog, a further variant of which is the GRECO-ADAS-Cog used in France only. The differences between these scales and the standard ADAS-Cog are minor and relate mainly to the order in which individual items are tested and the specific items in the word lists in the Word Recall Task.

3.1.2 Clinician Interview Based Impression of Change-Plus (CIBIC-Plus)

The format for this instrument, as used in the galantamine efficacy studies, consisted of the assessment of an independent clinician, with experience in Alzheimer's Disease. At the randomization visit this investigator assessed the patient's clinical status using all available information including tests of cognition and history. Subsequently this rater was denied access to any information about the patient's condition other than that derived from observation of the patient at an interview, and information provided by the caregiver, and was not allowed to have any additional involvement in the trial. The caregiver could be asked to provide factual information only about the patient only, such as information about recent events, and was asked not to make an overall judgment about the patient's condition or provide information about adverse events.

4 major areas of patient functioning were assessed: general, cognitive, behavioral and activities of daily living.

A 7-point categorical rating scale was used as follows

1 = markedly improved relative to baseline
2 = moderately improved relative to baseline
3 = minimally improved relative to baseline
4 = no change relative to baseline
5 = minimally worse relative to baseline
6 = moderately worse relative to baseline
7 = markedly worse relative to baseline

The CIBIC-Plus is not a standardized measure and its validity has never been established

3.1.3 Nurse's Observation Scale for Geriatric Patients (NOSGER)

This caregiver-rated scale assesses 6 different dimensions: memory, instrumental activities of daily living, self-care, mood, social behavior and disturbing behavior. A total of 30 items are rated, with five items to each dimension. Each item is rated on a scale from 1 through 5; for 19/30 items a higher score indicates greater impairment; for 11/30 items a higher score indicates less impairment. Total scores are computed for each dimension and can range from 5 to 25. Each dimension is analyzed separately.

3.2 Secondary Efficacy Variables

3.2.1 Disability Assessment in Dementia

This is a validated instrument intended to evaluate activities of daily living. The following activities are evaluated under 3 categories
Basic activities of daily living: hygiene, dressing, continence, and eating
Instrumental activities of daily living: meal preparation, going on an outing, telephoning, finance/correspondence, housework, taking medication and staying safely at home
Leisure activities

3 levels of performance are assessed for the above activities
Initiation
Planning and organization
Effective performance

The number of items scored at each level is as follows:
Initiation: 15 items
Planning and organization: 11 items
Effective performance: 20 items
Total: 46 items

Each item is scored as follows
0: not performed in the last 2 weeks
1: performed in the last 2 weeks
Not applicable: no opportunity to perform task in the last 2 weeks

The maximum possible score is 46. Higher scores indicate less disability, while lower scores indicate more disability.

3.2.2 Neuropsychiatry Inventory

This is an instrument that assesses the following 10 domains (subscales): delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability and aberrant motor behavior. Each item is rated according to its frequency and severity; rating is based on interviewing a caregiver. The maximum total score (the sum of the subscale scores) is 120 with a higher score indicating greater behavioral abnormality.

3.2.3 Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL)

This is a rating scale used to assess basic and instrumental activities of daily living. 23 items are rated by the investigator using information supplied by the caregiver. Each item has a score range varying from 0-1 to 0-4. The maximum possible total score is 78 with a higher score indicating better function

3.2.4 Progressive Deterioration Scale-1

This is a 27-item caregiver-rated instrument assessing selected "activities of daily living". Each item is scored by placing an "X" on a 10 cm line that extends between 2 extreme descriptions of that function (e.g., "drives car safely" and "driving is too dangerous-must be restricted"). The rater is asked to place the "X" at a point nearest to the characteristic that best describes the patient. Higher scores indicate better function and scores for individual items range from 0 to 100. The total score is the aggregate of individual item scores.

3.2.5 Nuremberg Alters-Beobachtungs-Skala (Nuremberg Geriatric Observation Scale) (NAB)

This is a 15-item scale that assesses: instrumental and basic activities of daily living; ability to communicate verbally, in writing or by gesture; hearing; and vision. It may be rated by relatives, nurses, or clinical staff. Each of the 15 items consists of a statement that is rated on a scale from 1 to 3. The scoring system is structured and each score represents a defined level of functioning Higher total scores indicate greater impairment

3.2.6 Alzheimer's Disease Assessment Scale-NonCog (ADAS-NonCog)

This is a rating scale assessing the following 10 items: depression, tearfulness, delusions, hallucinations, pacing, increased motor activity, tremors, concentration/distractabililty, uncooperativeness during testing, and decreased/increased appetite. The sum score on this scale ranges from 0-50, with a higher score indicating greater abnormality.

3.2.7 Clinical Global Impression of Change (CGIC)

This was largely similar to the CIBIC-Plus; the only significant difference was that the clinical rater was not independent for the CGIC. The clinician was asked to assess appearance, behavior, speech, mood, thought content, insight, any abnormal experiences and cognitive span

3.2.8 Digit Symbol Substitution Test (DSST)

This test involves the substitution of specific digits by symbols according to a key. 90 seconds are allotted for completing the entire task that consists of substituting symbols for 67 digits. Each correctly substituted symbol is allotted a score of 1 with the maximum possible total score being 67.

3.2.9 Psychological General Well Being Index

This is a measure intended to assess caregiver quality-of-life. It assesses feelings of psychological well-being and distress. The scale has 22 items and assesses positive and negative feelings in six dimensions: anxiety, depression, positive well-being, self-control, vitality, and general health. Higher scores indicate better quality of life.

3.2.10 Health/Care Resource Use

This measure consisted of a resource use questionnaire containing 11 modules which included
Patient-related items such as demographics, physician visits and days of hospitalization
Caregiver-related items such as demographics, and time spent assisting the patient with activities of daily living

Time spent assisting the patient with activities of daily living was assessed by the allocations of caregiver time survey which evaluated how long the patient could be left alone during a typical 24-hour period, and time spent in the care of the patient on each of a number of specific activities of daily living.

4. Study GAL-USA-1

4.1 Title

Efficacy and safety of galantamine 12 mg b.i.d and 16 mg b.i.d compared with placebo in the treatment of Alzheimer's Disease

4.2 Objective

4.2.1 Primary

To evaluate the efficacy, safety and tolerability of galantamine 24 mg/day or 32 mg/day compared with placebo

4.2.2 Secondary

- To document the plasma concentrations and pharmacokinetics of galantamine in patients with Alzheimer's Disease, and to investigate the relationship between plasma concentrations and the effect on psychometric testing
- To determine the effect of treatment on informal family caregiver quality-of-life and on health/social care resource use

4.3 Design

Randomized, double-blind, placebo-controlled, parallel-arm, fixed-dose study

4.4 Duration

26 weeks (of double-blind treatment)

This period was to be preceded by a 4-week placebo run-in phase. Randomization was to occur at the time of commencement of double-blind treatment.

4.5 Dosage

The 3 dose-groups are:
Galantamine 12 mg b.i.d
Galantamine 24 mg b.i.d
Placebo

The dose titration schedule for the 2 galantamine dose groups was as follows:

Week	Galantamine 24 mg/day dose group	Galantamine 32 mg/day dose group
Week 1	4 mg b.i.d	4 mg b.i.d
Week 2	8 mg b.i.d	8 mg b.i.d
Week 3	12 mg b.i.d	12 mg b.i.d
Week 4 through 26	12 mg b.i.d	16 mg b.i.d

4.6 Sample Size

540 patients randomized equally to the 3 treatment groups

4.7 Main Inclusion Criteria

- Male or female
- If living in a residential home for the elderly, must be independent and approved by sponsor
- Probable Alzheimer's disease by NINCDS-ADRDA criteria
- Mini-Mental Status Examination score 11-24 and ADAS-Cog score of at least 12
- Cognitive decline that is gradual in onset, progressive over a period of at least 6 months, and with evidence of sustained memory deterioration in an otherwise alert subject plus additional involvement in at least one of the following 5 areas: orientation, judgement and problem solving, functioning in community affairs, functioning in home and hobbies, and functioning in personal care
- Reliable caregiver (criteria specified)
- Informed consent

4.8 Main Exclusion Criteria

- Neurodegenerative disorders such as Parkinson's disease, Pick's disease, and other entities; mild extrapyramidal signs for which no treatment is needed were not criteria for exclusion
- Cognitive impairment due to head trauma, hypoxia, vitamin deficiency, infection, neoplasm, endocrine or metabolic disease and mental retardation
- Multi-infarct dementia or clinically active cerebrovascular disease, for which the sponsor had specified certain ad hoc criteria listed below. There should have been evidence of :

a. A history of a significant cerebro-vascular event yielding a physical or neurological deficit likely to confound the assessment of the subject's intellectual function.

b. Multiple focal signs on neurological examination indicative of multiple ischemic attacks.

c. One or more of the following findings on a CT or MRI scan (taken within the last 12 months):
   - Multiple (2 or more) infarcts or white matter lacunes
   - A single strategically placed infarct in the angular gyrus, the thalamus, the basal forebrain, the Posterior Cerebral Artery (PCA) or Anterior Cerebral Artery (ACA) territory.
   - Extensive periventricular white matter lesions. Leukoaraiosis (periventricular white matter, low attenuation) is to be distinguished from multiple infarction. Leukoaraiosis is common in normal elderly individuals and persons with Alzheimer's disease. White matter deterioration should not result in exclusion unless it is abnormal and widespread (e.g., Binswanger's disease).

Note: subjects with an isolated cerebral infarct confirmed by appropriate imaging techniques, e.g., CT or MRI (both within the last year), can be included if the infarct is not strategically placed, as defined above. A CT or MRI must be repeated before inclusion if the subject has experienced significant loss of consciousness or other neurological signs or symptoms, stepwise deterioration, or has sustained head injury since the last scan. Subjects with an isolated loss of consciousness, transient ischemic attack or 'drop attacks', may be considered for inclusion providing that these did not occur in the previous 12 months.

At inclusion a CT or MRI scan not older than 12 month has to be available.

- Any of the following coexisting medical conditions: history of epilepsy or convulsions (other than febrile convulsions), clinically significant psychiatric disease, active peptic ulcer (criteria specified), clinically significant urinary outflow obstruction, and clinically significant cardiovascular (criteria specified), hepatic, renal, pulmonary, metabolic or endocrine disease
- Any agent being used for the treatment of dementia such as nootropics, cholinomimetic drugs, non-steroidal anti-inflammatory drugs for more than 30 consecutive days, estrogens without medical need, Vitamin E > recommended adult daily requirement, and deprenyl. Subjects who had previously received cholinesterase inhibitors, whether approved or experimental, could be included in the trial provided they had been through a washout period of 3 months
- Drug or alcohol abuse within the previous year or prior prolonged history
- Women of childbearing potential without adequate contraception; those of childbearing potential must not be pregnant at screening and must agree not to become pregnant during the trial
- History of severe drug allergy or hypersensitivity including to cholinomimetic agents or bromide
- Enrollment in other galantamine trials
- Enrollment in other clinical trials except with approval of sponsor
- Conditions that could interfere with absorption of compound or evaluation of disease

- Use of any other investigational medication within 30 days prior to enrollment
- Conditions that could interfere with absorption of the compound or with the evolution of the disease
- Unsuitability for a trial of this type as per the investigator

4.9 Concomitant Medications

4.9.1 Prohibited Medications

These are listed above

4.9.2 Permitted Medications

These include

- sedative/hypnotics, if used when essential, not more than twice a week, and not less than 48 hours prior to cognitive testing (if benzodiazepines are used, short acting ones are preferred)
- antidepressants if they do not have anticholinergic effects
- antipsychotics, provided those with a high tendency to anticholinergic effects and extrapyramidal adverse effects are avoided
- cough and cold remedies provided sedating drugs are discontinued where possible at least 48 hours before cognitive testing is carried out
- cholinergic agents, except for cholinomimetic drugs intended to treat dementia
- anti-emetics provided these are used for short periods of time
- antihypertensives except that methyldopa, clonidine and beta-blockers should be prescribed with caution

4.10 Efficacy Outcome Measures

4.10.1 Primary Efficacy Measures

ADAS-Cog (ADAS-Cog/11)
CIBIC-Plus

4.10.2 Secondary Efficacy Measures

Disability Assessment For Dementia (total and cluster scores; 6 separate clusters were to be used)
ADAS-Cog/13
ADAS-Cog/10
ADAS-Cog/mem
Psychological General Well Being Index
Health/Social Care Resource Use

4.11 Analysis Plan

4.11.1 General Considerations

- All randomized subjects would be included in the analysis of demographic and baseline characteristics, as well as in the classical intent-to-treat imputation scheme
- All other efficacy analyses would be performed on all randomized subjects who took at least one dose of double-blind study medication and who provided follow-up data for one or more key efficacy variables

4.11.2 Demographic And Baseline Characteristics

- The 3 treatment groups would be compared for these variables
- For continuous variables a 2-way ANOVA, with factors for treatment group and investigator would be used when appropriate, otherwise the Van Elteren test controlling for investigator would be applied
- The Van Elteren test controlling for investigator would be used for ordinal categorical variables
- For nominal categorical variables, the Cochran-Mantel-Haenszel test for general association controlling for investigator would be used

4.11.3 Primary Efficacy Parameters

- The primary efficacy parameters were the change from baseline in ADAS-Cog at 6 months and the CIBIC-Plus at 6 months
- 5 imputation schemes were to be used for the primary efficacy): classical intention-to-treat, traditional DNDP-last-observation-carried-forward, traditional observed cases, retrieved dropouts and observed cases plus retrieved dropouts. The original protocol did not designate any single one of these imputation schemes as constituting the primary analysis. However a protocol amendment did specify that the primary efficacy analysis would be on the Observed Cases dataset at Month 6
- The primary efficacy parameters would be compared between the treatment groups not only at the study endpoint but at each scheduled timepoint as well
- For continuous data (i.e., ADAS-Cog) a 2-way ANOVA model would be used, with treatment and investigator as factors, to compare treatment groups. The interaction of treatment with investigator would be examined, if the interaction was not significant when evaluated at the 10 % significance level it would not be included in the final ANOVA model. The impact of prognostic factors such as baseline score and age would also be examined. If some of these prognostic factors were determined to be important they would also be incorporated into the analysis. Following ANOVA, Dunett's test would be performed to account for multiple comparisons when comparing the two galantamine groups with placebo. If a parametric method was not appropriate (normality assumption violated), a non-parametric method (e.g., 2-way ANOVA on ranked data, van Elteren test controlling for investigator) would be utilized Subsequent comparisons between the 2 galantamine groups versus placebo would use Holm's procedure to control the Type 1 error rate..
- For ordinal categorical data (i.e., CIBIC-Plus), the Van Elteren test, controlling for investigator, would be used for the between group comparison. The CIBIC-Plus analysis was to be based on the original 7-point scale.
- If a significant proportion of subjects discontinued prematurely, other analyses, such as a per-protocol analysis might be performed to assess the impact on the results
- Subgroup analyses would be done based on age, gender and race and, if the size of the study permitted, other demographic variables, ApoE status, use of psychotropic medications and possible more entities
- Within group comparison (baseline versus each visit) would be done using the paired t-test when appropriate; otherwise the Wilcoxon signed rank test would be used

4.11.4 Secondary Efficacy Parameters

- The approach would be similar to that for the primary efficacy parameters

4.11.5 Sample Size Rationale

- The sample size calculation was based on the change from baseline in standard ADAS-Cog at month 6
  - The sample size calculation used data from previous studies in Alzheimer's Disease, not using galantamine, Indicating that placebo-treated patients experienced a mean deterioration of about 2.4 points (standard deviation of 7) on this measure over a 6-month period.
  - Based on the placebo data from the above studies, data from clinical trials of other cholinesterase inhibitors, and interim analysis of GAL 93-01, a Phase II study of galantamine, it was assumed that a difference of 2.75 points in ADAS-Cog change score between placebo- and drug-treated subjects would be clinically meaningful
  - With 80 % power and a 2-sided Type 1 error of 0.025 (taking into account that 2 separate treatment groups would be compared with placebo), 125 patients would be needed in each treatment group. Assuming a dropout rate of 30 % in each treatment group, approximately 179 subjects per group (537 subjects total) would need to be randomized
  - Given that the expected effect size on the ADAS-Cog had previously beerr associated with a significant effect on the CIBIC-Plus the proposed sample size was expected to have sufficient power to detect the difference between the galantamine and placebo groups for the CIBIC-Plus data

4.12 Protocol Amendments

The single protocol amendment (A) is included in the above summary

4.13 Actual Analyses Performed

All planned analyses were performed. In addition a further set of analyses excluded a single site ( ); number of patients: 10). See Section 4.14.4. below for further details.

4.14 Efficacy Results

4.14.1 Patient Disposition

636 patients were randomized to the 3 treatment groups out of 764 patients who were screened. All 636 randomized patients received at least one dose of study medication.

The number and percentage of patients in each treatment group who discontinued study medication, and the timing and reasons for their doing so are indicated in the following table:

Reason	Placebo (N = 213)	GAL 12 mg bid (N = 212)	GAL 16 mg bid (N =211)
Any reason	41 (19.2%)	68 (32.1%)	89 (42.2%)
During first 4 weeks	6 (2.8%)	22 (10.4%)	35 (16.6%)
After Week 4	35 (16.9%)	46 (24.2%)	54 (30.7%)
Adverse event	16 (7.5%)	49 (23.1%)	67 (31.8%)
Patient withdrew consent	19 (8.9%)	11 (5.2%)	13 (6.2%)
Patient lost to follow up	1 (0.5%)	2 (0.9%)	1 (0.5%)
Patient noncompliant	2 (0.9%)	3 (1.4%)	4 (1.9%)
Other	3(1.4%)	3(1.4%)	4(1.9%)

As the table indicates the overall discontinuation rate as well as the discontinuation rate for adverse events was highest in the galantamine 32 mg/day group. Adverse events were the commonest reason for treatment discontinuation.

4.14.2 Protocol Deviations

The number and percentage of protocol deviations in each treatment group are summarized in the following table. The percentage of patients with specific categories of protocol deviation are also indicated in the same table. Overall these percentages are small

Protocol deviations	Placebo (N=213)	GAL 12 mg bid (N=212)	GAL 16 mg bid (N=211)
Total patients with protocol deviations	23 (10.8%)	24 (11.3%)	15 (7.1%)
Intercurrent forbidden therapy	17 (8.0%)	16 (7.5%)	8 (3.8%)
No efficacy data	5 (2.3%)	5 (2.4%)	6 (2.8%)
Baseline disease condition out of limits	1 (0.5%)	1 (0.5%)	1 (0.5%)
Investigator error	0 (0.0%)	1 (0.5%)	0 (0.0%)
Noncompliance over 50%	0 (0.0%)	1 (0.5%)	0 (0.0%)

4.14.3 Baseline And Other Demographic Characteristics

The key baseline and demographic variables appear to have been well-balanced across treatment groups as indicated by the following table. The incidence of concomitant illnesses also appears to have been similar across treatment groups

Characteristics	Placebo N=213	GAL 12 mg bid N=212	GAL 16 mg bid N=211	Total N=636
Sex: n (%)				
Male	82 (38.5%)	73 (34.4%)	87 (41.2%)	242 (38.1%)
Female	131 (61.5%)	139 (65.6%)	124 (58.8%)	394 (61.9%)
Race: n (%)				
White	196 (92.0%)	195 (92.0%)	190 (90.0%)	581 (91.4%)
Black	11 (5.2%)	11 (5.2%)	8 (3.8%)	30 (4.7%)
Hispanic	4 (1.9%)	5 (2.4%)	12 (5.7%)	21 (3.3%)
Oriental	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.2%)
Other	2 (0.9%)	0 (0.0%)	1 (0.5%)	3 (0.5%)
Age (mean ± SE)	75.3 ± 0.58	75.9 ± 0.51	75.0 ± 0.58	75.4 ± 0.32
Weights (kg) (mean ± SE)	67.08 ± 0.97	67.54 ± 1.01	67.34 ± 1.00	67.32 ± 0.57
Smoker - Yes: n (%)	11 (5.2%)	16 (7.5%)	17 (8.1%)	44 (6.9%)
Age at onset of cognitive problems (mean ± SE)	71.5 ± 0.65	72.5 ± 0.55	71.4 ± 0.60	71.8 ± 0.35
Years since cognitive problem diagnosis (mean ± SE)	4.34 ± 0.20	3.8 ± 0.18	4.13 ± 0.18	4.09 ± 0.11
Age at diagnosis of probable AD (mean ± SE)	74.7 ± 0.59	75.3 ± 0.53	74.1 ± 0.59	74.7 ± 0.33
Years of AD diagnosis (mean ±SE)	1.13 ± 0.105	1.02 ± 0.102	1.45 ± 0.125	1.2 ± 0.064
AD first degree relative(s) n (%)	72 (33.8%)	66 (31.1%)	59 (28.0%)	197 (31.0%)
Cholinomimetics trial participant: n (%)	12 (5.6%)	12 (5.7%)	14 (6.6%)	38 (6.0%)
Total MMSE score (mean ± SE)	19.2 ± 0.27	19.5 ± 0.27	19.1 ± 0.29	19.3 ± 0.16
ADAS-cog/11 score at baseline (mean ± SE)	25.7 ± 0.78	24.8 ± 0.67	25.8 ± 0.83	2.5 ± 0.4
Apo- E type: n (%)				
2-2/2-3/3-3	81 (41.8%)	80 (40.0%)	72 (38.3%)	233 (40.0%)
2-4/3-4	81 (41.8%)	91 (45.5%)	93 (49.5%)	265 (45.5%)
4-4	32 (16.5%)	29 (14.5%)	23 (12.2%)	84 (14.4%)

During the course of the study, drugs belonging to the antispasmodic, anticholinergic and propulsive category were used more commonly in those in the galantamine groups than in those in the placebo group. Haloperidol, temazepam and fluoxetine were used more commonly in the placebo group than in the galantamine groups; however the overall incidence of psychotropic drug use was similar across treatment groups

Treatment group	Placebo N=213	Galantamine 24 mg/day N=212	Galantamine 32 mg/day N=211
Antispasmodic, anticholinergic and propulsive	3.8 %	9.0 %	11.8 %
Haloperidol	5.2 %	4.2 %	0.9 %
Fluoxetine	5.6 %	2.8 %	1.9 %
Temazepam	3.8 %	1.4 %	1.4 %

The proportion of patients who took psychotropic medications within 48 hours of ADAS-Cog testing was similar across treatment groups

4.14.4 Primary Efficacy Analysis

Note that in addition to the planned analysis of the primary efficacy measures that included all the study centers, a second analysis excluded a single site (# number of patients: 10). This reanalysis was on account of deficiencies noted at a single site in GAL-USA-10; the 2 Principal Investigators at that site (for GAL-USA-10) had been associated with in GAL-USA-1.

4.14.4.1 ADAS-Cog/11

As specified in the protocol, an ADAS-Cog score was calculated only when all 11 items were available; missing items were imputed only for the classical intent-to-treat dataset.

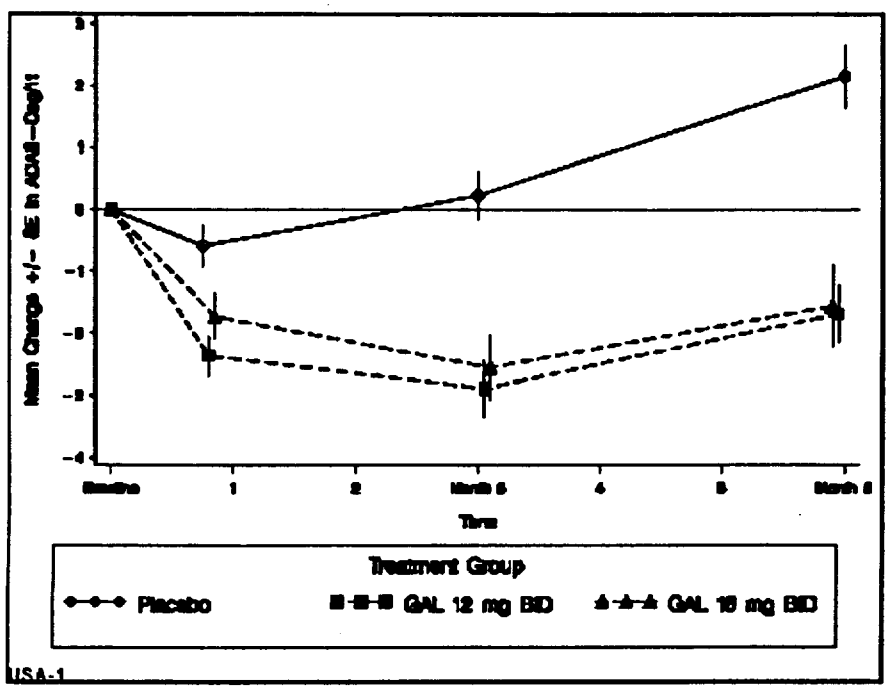
The results of the (primary) Observed Cases analysis are shown below. As the table indicates both galantamine groups showed a statistically significant superiority to placebo on the pairwise comparison at Month 6. As the table also indicates, the galantamine 24 mg/day and galantamine 32 mg/day groups had improved relative to baseline at the timepoint, while the placebo group had worsened. Statistically significant differences between the galantamine and placebo groups were evident as early as Week 3

The table below shows mean scores and changes from baseline for the Observed Cases dataset (all patients)

	Placebo			GAL 12 mg bid			GAL 16 mg bid		
Analysis timepoint	n	Mean ± SE	Mean change ± SE	n	Mean ± SE	Mean change ± SE	n	Mean ± SE	Mean change ± SE
Baseline	213	25.7 ± 0.78	—	207	24.8 ± 0.67	—	209	25.8 ± 0.83	—
Week 3	204	25.0 ± 0.85	-0.6 ± 0.35	202	22.5 ± 0.68	-2.4*** ± 0.32	195	24.0 ± 0.81	-1.7* ± 0.37
Month 3	184	25.5 ± 0.98	0.2 ± 0.40	153	22.2 ± 0.76	-2.9*** ± 0.45	133	23.1 ± 0.96	-2.6*** ± 0.54
Month 6	157	26.7 ± 1.13	2.2 ± 0.52	131	22.4 ± 0.85	-1.7*** ± 0.45	117	23.9 ± 1.08	-1.6*** ± 0.66

Source: Display 14
*: p≤0.05; **: p≤0.01; ***: p≤0.001 with the Dunnett's test procedure comparing each galantamine-treatment group with placebo

The mean change from baseline (± SE) in ADAS-Cog scores over time for the 4 treatment groups is displayed in the following figure for the Observed Cases dataset



The results of the Observed Cases analysis at Month 6 is compared with that of other imputation schemes in the following table, which shows standard ADAS-Cog scores as well as mean change from baseline. As the table indicates the galantamine 24 mg/day and galantamine 32 mg/day groups were consistently superior to placebo, at a statistically significant level, regardless of the imputation scheme used; both these dose groups showed a consistent improvement from

baseline as compared with the placebo groups which showed an overall deterioration.

	Placebo			GAL 12 mg bid			GAL 16 mg bid		
Analysis Timepoint	n	Mean ± SE	Mean change ± SE	n	Mean ± SE	Mean change ± SE	n	Mean ± SE	Mean change ± SE
Observed Case: Month 6	157	26.7 ± 1.13	2.2 ± 0.52	131	22.4 ± 0.85	-1.7*** ± 0.45	117	23.9 ± 1.08	-1.6*** ± 0.66
Classical ITT	213	27.8 ± 0.97	2.2 ± 0.44	212	24.0 ± 0.75	-1.1*** ± 0.39	211	25.2 ± 0.85	-0.8*** ± 0.45
Traditional LOCF	207	27.6 ± 0.98	2.0 ± 0.45	202	23.0 ± 0.71	-1.9*** ± 0.36	197	24.3 ± 0.84	-1.4*** ± 0.44
OC+RET D/O	164	26.6 ± 1.11	2.2 ± 0.51	155	22.5 ± 0.82	-1.4*** ± 0.42	140	23.8 ± 1.00	-1.3*** ± 0.59

Source: Display 14 and Display 15
*: p≤0.05; **: p≤0.01; ***: p≤0.001 with the Dunnett's test procedure comparing each galantamine-treatment group with placebo

Analyses of Observed Cases and 2 other imputation schemes excluding data from Site # 30 yielded effects and conclusions that were no different from the above

	Placebo			GAL 12 mg bid			GAL 16 mg bid		
Analysis Timepoint	n	Mean ± SE	Mean change ± SE	n	Mean ± SE	Mean change ± SE	n	Mean ± SE	Mean change ± SE
Observed Case: Month 6	155	26.8 ±1.14	2.2 ±0.52	130	22.5 ±0.86	-1.7*** ±0.46	116	23.9 ±1.09	-1.4*** ±0.65
Traditional LOCF	204	27.7 ±0.99	2.0 ±0.45	200	23.0 ±0.71	-1.9*** ±0.36	193	24.2 ±0.85	-1.3*** ±0.44
OC+RET D/O	162	26.7 ± 1.12	2.2 ±0.51	154	22.6 ±0.83	-1.4*** ±0.42	138	23.8 ±1.01	-1.1*** ±0.58

Source: Display EFF.ADAS.2AX
*: p≤ 0.05; **: p≤ 0.01; ***: p≤ 0.001 with the Dunnett's test procedure comparing each galantamine dose with placebo.

4.14.4.2 CIBIC-Plus

The results of the CIBIC-Plus responder analysis for the Observed Cases dataset are shown in the following table. Both the galantamine 24 mg/day and galantamine 32 mg/day groups showed a statistically significant superiority to placebo

CIBIC-plus Rating	Placebo (N=159)		GAL 12 mg bid (N=135)		GAL 16 mg bid (N=118)	
	n (%)	Cum.%	n (%)	Cum.%	n (%)	Cum.%
Marked improvement	0	0%	1 (0.7%)	0.7%	2 (1.7%)	1.7%
Moderate improvement	7 (4.4%)	4.4%	4 (3.0%)	3.7%	4 (3.4%)	5.1%
Minimal improvement	14 (8.8%)	13.2%	22 (16.3%)	20.0%	17 (14.4%)	19.5%
No change	67 (42.1%)	55.3%	68 (50.4%)	70.4%	57 (48.3%)	67.8%
Minimal worsening	47 (29.6%)	84.9%	29 (21.5%)	91.9%	30 (25.4%)	93.2%
Moderate worsening	23 (14.5%)	99.4%	8 (5.9%)	97.8%	7 (5.9%)	99.2%
Marked worsening	1 (0.6%)	100%	3 (2.2%)	100%	1 (0.8%)	100%

Source: Display 19
p ≤0.05 from the Van Elteren test for GAL 12 mg bid and GAL 16 mg bid groups compared with placebo (scores lower than placebo)

Analyses performed on the CIBIC-Plus for 3 other imputation schemes showed that both the galantamine 24 mg/day and galantamine 32 mg/day groups were superior to placebo at a statistically significant level, except for the 32 mg/day group with the Observed Cases plus Retrieved Dropouts population

Classical Intent-to-treat

CIBIC-Plus Rating	Placebo N=199	Galantamine 24 mg/day N=199	Galantamine 32 mg/day N=191	p-values
Markedly improved (%)	0.5	1.0	1.0	Gal 24 vs placebo: 0.022
Moderately improved (%)	3.5	3.0	2.1	Gal 32 vs placebo: 0.033
Minimally improved (%)	10.1	15.1	12.0	
Unchanged (%)	42.2	51.3	52.9	
Minimally worse (%)	30.7	20.6	20.1	
Moderately worse (%)	12.6	7.0	6.8	
Markedly worse (%)	0.5	2.0	1.0	

LOCF

CIBIC-Plus Rating	Placebo N=196	Galantamine 24 mg/day N=186	Galantamine 32 mg/day N=171	p-values
Markedly improved (%)	0.5	1.6	1.2	Gal 24 vs placebo: 0.003
Moderately improved (%)	3.6	3.2	2.3	Gal 32 vs placebo: 0.021
Minimally improved (%)	9.7	19.9	15.8	
Unchanged (%)	42.9	53.2	53.2	
Minimally worse (%)	30.6	19.4	25.1	
Moderately worse (%)	12.2	5.4	5.3	
Markedly worse (%)	0.5	2.2	2.6	

Observed Cases plus Retrieved Dropouts

CIBIC-Plus Rating	Placebo N=166	Galantamine 24 mg/day N=158	Galantamine 32 mg/day N=140	p-values
Markedly improved (%)	0.0	0.6	1.4	Gal 24 vs placebo: 0.016
Moderately improved (%)	4.2	3.2	1.9	Gal 32 vs placebo: 0.075
Minimally improved (%)	9.0	16.5	12.1	
Unchanged (%)	42.8	50.6	49.3	
Minimally worse (%)	28.9	20.9	25.0	
Moderately worse (%)	14.5	6.3	8.6	
Markedly worse (%)	0.6	1.9	0.7	

Similar results were seen for the Observed Cases and LOCF analyses performed on the CIBIC-Plus excluding Site

Observed Cases

CIBIC-plus Rating	Placebo		GAL 12 mg bid		GAL 16 mg bid	
	n (%)	Cum.%	n (%)	Cum.%	n (%)	Cum.%
Marked improvement	0	0%	1 (0.8%)	0.8%	2 (1.7%)	1.7%
Moderate improvement	7 (4.5%)	4.5%	4 (3.0%)	3.8%	4 (3.4%)	5.1%
Minimal improvement	14 (8.9%)	13.4%	22 (16.7%)	20.5%	17 (14.5%)	19.7%
No change	66 (42.0%)	55.4%	66 (50.0%)	70.5%	56 (47.9%)	67.5%
Minimal worsening	47 (29.9%)	85.4%	29 (22.0%)	92.4%	30 (25.6%)	93.2%
Moderate worsening	22 (14.0%)	99.4%	8 (6.1%)	98.5%	7 (6.0%)	99.1%
Marked worsening	1 (0.6%)	100%	2 (1.5%)	100%	1 (0.9%)	100%

Source: Display EFF.CIB.1AX
Both GAL 12 mg bid and 16 mg bid doses were significantly more effective than placebo with p=0.024 and p=0.021, respectively

LOCF

CIBIC-plus Rating	Placebo		GAL 12 mg bid		GAL 16 mg bid	
	n (%)	Cum.%	n (%)	Cum.%	n (%)	Cum. %
Marked improvement	1 (0.5%)	0.5%	3 (1.6%)	1.6%	2 (1.2%)	1.2%
Moderate improvement	7 (3.6%)	4.1%	6 (3.3%)	4.9%	4 (2.4%)	3.6%
Minimal improvement	19 (9.8%)	14.0%	28 (15.3%)	20.2%	21 (12.5%)	16.1%
No change	82 (42.5%)	56.5%	97 (53.0%)	73.2%	88 (52.4%)	68.5%
Minimal worsening	60 (31.1%)	87.6%	36 (19.7%)	92.9%	43 (25.6%)	94.0%
Moderate worsening	23 (11.9%)	99.5%	10 (5.5%)	98.4%	9 (5.4%)	99.4%
Marked worsening	1 (0.5%)	100%	3 (1.6%)	100%	1 (0.6%)	100%

Source: Display EFF.CIB.1AX
Both GAL 12 mg bid and 16 mg bid doses were significantly more effective than placebo with p=0.003 and p=0.031, respectively

Dr Kun He has performed separate analyses on the CIBIC-Plus data: mean CIBIC-Plus scores for each treatment group at Month 6, and p-values for the pairwise comparisons are in the following tables; these analyses

Observed Cases

	Placebo		Gal 12 mg bid		Gal 16 mg bid	
	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD
Mean Scores at Month 6	159	4.43 ± 1.01	134	4.15 ± 0.99	118	4.14 ± 0.99
p-values vs placebo			0.019		0.017	

LOCF

	Placebo		Gal 12 mg bid		Gal 16 mg bid	
	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD
Mean Scores at Month 6	196	4.38 ± 0.99	185	4.10 ± 1.01	171	4.17 ± 0.90
p-values vs placebo			0.002		0.021	

His analyses with Site included have yielded similar results.

4.14.5 Analysis Of Secondary Efficacy Measures

4.14.5.1 Disability Assessment For Dementia

Neither galantamine dose group could be demonstrated to have statistically significant superiority to placebo on Total DAD scores at Month 6 for the Observed Cases dataset as indicated in the following table.

	Placebo			GAL 12 mg bid			GAL 16 mg bid		
Analysis Timepoint	n	Mean ± SE	Mean change ± SE	n	Mean ± SE	Mean change ± SE	n	Mean ± SE	Mean change ± SE
Baseline	213	70.4 ± 1.62	—	210	71.1 ± 1.52	—	211	70.3 ± 1.60	—
Month 3	188	69.1 ± 1.77	-2.2 ± 0.94	160	71.5 ± 1.74	0.1 ± 0.84	135	69.3 ± 2.10	-0.4 ± 1.19
Month 6	164	70.0 ± 2.03	-2.8 ± 1.23	139	68.8 ± 2.10	-2.9 ± 1.27	117	68.4 ± 2.31	-1.7 ± 1.40

The p-values for the comparison of each galantamine group with placebo at Month 6 are in the following table

Comparison	P-value
Galantamine 24 mg/day vs placebo	0.943
Galantamine 32 mg/day vs placebo	0.901

On the DAD clusters, there were no statistically significant differences between either of the galantamine groups and the placebo group for the Observed Cases dataset at Month 6 as indicated by the following table

	Placebo			GAL 12 mg bid			GAL 16 mg bid		
DAD cluster	n	Mean ± SE	Mean change ± SE	n	Mean ± SE	Mean change ± SE	n	Mean ± SE	Mean change ± SE
DAD-initiation	164	74.8 ± 1.90	-4.0 ± 1.37	139	74.9 ± 2.08	-2.0 ± 1.36	117	74.8 ± 2.16	-1.1 ± 1.78
DAD-planning/ organization	164	67.5 ± 2.19	-1.6 ± 1.47	139	63.8 ± 2.32	-5.1 ± 1.36	117	63.6 ± 2.69	-3.5 ± 1.73
DAD-performance	164	67.7 ± 2.16	-2.4 ± 1.34	139	66.9 ± 2.18	-2.5 ± 1.49	117	66.1 ± 2.43	-1.2 ± 1.48
DAD-basic	164	88.3 ± 1.69	-3.2 ± 1.22	139	88.7 ± 1.71	-2.4 ± 1.26	117	87.3 ± 1.95	-1.0 ± 1.45
DAD-instrumental	164	54.9 ± 2.69	-2.8 ± 1.73	139	52.7 ± 2.77	-3.8 ± 1.79	117	52.2 ± 3.03	-2.3 ± 1.88
DAD-leisure	164	63.1 ± 3.09	2.4 ± 3.02	139	60.9 ± 3.25	-1.3 ± 2.82	115	65.7 ± 3.20	-0.2 ± 2.92

4.14.5.2 ADAS-Cog Clusters

The galantamine 24 mg/day and galantamine 32 mg/day dose groups were consistently superior to placebo as indicated by the following table

Cluster	Drug-Placebo Difference For Mean Change From Baseline. Observed Cases. Month 6		p-value GAL 24 Vs Placebo	p-value GAL 32 Vs Placebo
	GAL 24	GAL 32		
ADAS-Cog/13	-4.4	-4.1	< 0.001	< 0.001
ADAS-Cog/10	-2.9	-2.8	< 0.001	< 0.001
ADAS-Cog/mem	-1.4	-1.5	< 0.001	0.008

4.14.5.3 ADAS-Cog Responder Analysis

The galantamine 24 mg/day and galantamine 32 mg/day dose groups were virtually consistently superior to placebo as indicated by the following table

Category (based on improvement in ADAS-Cog score) Observed Cases. Month 6	Placebo (%) N=157	GAL 24 (%) N=131	GAL 32 (%) N=117	p-value GAL 24 Vs Placebo	p-value GAL 32 Vs Placebo
≥ 0 points	43.9	64.1	58.1	0.001	0.012
≥ 4 points	16.6	33.6	33.3	0.003	0.001
≥ 7 points	5.7	18.3	19.7	0.004	< 0.001
≥ 10 points	2.5	7.6	11.1	0.122	0.002

4.14.5.4 Psychological General Well-Being Index

There was a statistically significant ($p < 0.05$) difference between the galantamine 32 mg/day group and placebo for the total score (p=0.049) and the anxiety cluster score (p=0.039); after applying Dunnett's test for multiple comparisons these differences were no longer significant

	Placebo			GAL 12 mg bid			GAL 16 mg bid		
PGWB	N	Mean ± SE	Mean Change ± SE	N	Mean ± SE	Mean Change ± SE	N	Mean ± SE	Mean Change ± SE
Overall PGWB	149	79.6 ±1.39	-1.8 ±1.06	126	80.1 ±1.39	-2.8 ±0.99	112	78.6 ±1.39	1.1 ±1.25*
Anxiety	149	17.2 ±0.40	-0.4 ±0.31	126	17.7 ±0.36	-0.7 ±0.31	112	17.2 ±0.39	0.3 ±0.40*
Depression	149	12.2 ±0.20	-0.5 ±0.18	126	12.4 ±0.20	-0.2 ±0.16	112	12.4 ±0.19	-0.0 ±0.20
Positive well-being	149	12.6 ±0.31	-0.3 ±0.24	126	12.6 ±0.32	-0.6 ±0.24	112	12.5 ±0.32	0.4 ±0.30
Self-control	149	12.5 ±0.20	-0.3 ±0.18	126	12.6 ±0.23	-0.4 ±0.21	112	12.5 ±0.20	0.1 ±0.22
General health	149	11.4 ±0.21	0.1 ±0.22	126	11.2 ±0.23	-0.2 ±0.21	112	10.8 ±0.26	0.2 ±0.25
Vitality	149	13.6 ±0.29	-0.4 ±0.26	126	13.6 ±0.33	-0.7 ±0.29	112	13.2 ±0.34	0.1 ±0.33

4.14.5.5 Health/Social Care Resource Utilization

There were no statistically significant differences between treatment groups in the allocation of caregiver time survey.

4.15 Sponsor's Conclusions

- Both galantamine groups were superior at a statistically significant level to placebo on the ADAS-Cog and CIBIC-Plus at Month 6 and at most earlier timepoints on the Observed Cases group; these findings tended to be replicated using other imputation schemes. A mean improvement from baseline was seen with the ADAS-Cog in both galantamine groups over the period of the study. Treatment effects as measured by the ADAS-Cog increased over time
- The analysis of responder rates for the standard ADAS-Cog as well as the ADAS-Cog clusters tended to confirm the results of primary ADAS-Cog analysis
- There were no statistically significant differences between each of the galantamine groups and placebo on the Disability Assessment For Dementia

4.16 Reviewer's Comments

I concur with the sponsor's conclusions regarding the efficacy of galantamine as measured by the ADAS-Cog and CIBIC-Plus

5. Study GAL-INT-1

5.1 Title

Efficacy and safety of galantamine 12 mg b.i.d and 16 mg b.i.d compared with placebo in the treatment of Alzheimer's Disease

5.2 Objective

5.2.1 Primary

To evaluate the efficacy, safety and tolerability of galantamine 24 mg/day or 32 mg/day compared with placebo

5.2.2 Secondary

- To document the plasma concentrations and pharmacokinetics of galantamine in patients with Alzheimer's Disease, and to investigate the relationship between plasma concentrations and the effect on psychometric testing
- To determine the effect of treatment on informal family caregiver quality-of-life and on health/social care resource use

5.3 Design

Randomized, double-blind, placebo-controlled, parallel-arm, fixed-dose study

5.4 Duration

26 weeks (of double-blind treatment)

This period was to be preceded by a 4-week placebo run-in phase. Randomization was to occur at the time of commencement of double-blind treatment.

5.5 Dosage

The 3 dose-groups are:
Galantamine 12 mg b.i.d
Galantamine 24 mg b.i.d
Placebo

The dose titration schedule for the 2 galantamine dose groups was as follows:

Week	Galantamine 24 mg/day dose group	Galantamine 32 mg/day dose group
Week 1	4 mg b.i.d	4 mg b.i.d
Week 2	8 mg b.i.d	8 mg b.i.d
Week 3	12 mg b.i.d	12 mg b.i.d
Week 4 through 26	12 mg b.i.d	16 mg b.i.d

5.6 Sample Size

540 patients randomized equally to the 3 treatment groups

5.7 Main Inclusion Criteria

- Male or female
- If living in a residential home for the elderly, must be independent and approved by sponsor
- Probable Alzheimer's disease by NINCDS-ADRDA criteria
- Mini-Mental Status Examination score 11-24 **and** ADAS-Cog score of at least 12
- Cognitive decline that is gradual in onset, progressive over a period of at least 6 months, and with evidence of sustained memory deterioration in an otherwise alert subject plus additional involvement in at least one of the following 5 areas: orientation, judgement and problem solving, functioning in community affairs, functioning in home and hobbies, and functioning in personal care
- Reliable caregiver (criteria specified)
- Informed consent

5.8 Main Exclusion Criteria

- Neurodegenerative disorders such as Parkinson's disease, Pick's disease, and other entities; mild extrapyramidal signs for which no treatment is needed were not criteria for exclusion
- Cognitive impairment due to head trauma, hypoxia, vitamin deficiency, infection, neoplasm, endocrine or metabolic disease and mental retardation
- Multi-infarct dementia or clinically active cerebrovascular disease, for which the sponsor had specified certain ad hoc criteria listed below. There should have been evidence of :

a. A history of a significant cerebro-vascular event yielding a physical or neurological deficit likely to confound the assessment of the subject's intellectual function.
b. Multiple focal signs on neurological examination indicative of multiple ischemic attacks.
c. One or more of the following findings on a CT or MRI scan (taken within the last 12 months):
   - Multiple (2 or more) infarcts or white matter lacunes
   - A single strategically placed infarct in the angular gyrus, the thalamus, the basal forebrain, the Posterior Cerebral Artery (PCA) or Anterior Cerebral Artery (ACA) territory.
   - Extensive periventricular white matter lesions. Leukoaraiosis (periventricular white matter, low attenuation) is to be distinguished from multiple infarction. Leukoaraiosis is common in normal elderly individuals and persons with Alzheimer's disease. White matter deterioration should not result in exclusion unless it is abnormal and widespread (e.g., Binswanger's disease).

Note: subjects with an isolated cerebral infarct confirmed by appropriate imaging techniques, e.g., CT or MRI (both within the last year), can be included if the infarct is not strategically placed, as defined above. A CT or MRI must be repeated before inclusion if the subject has experienced significant loss of consciousness or other neurological signs or symptoms, stepwise deterioration, or has sustained head injury since the last scan. Subjects with an isolated loss of consciousness, transient ischemic attack or 'drop attacks', may be considered for inclusion providing that these did not occur in the previous 12 months.

At inclusion a CT or MRI scan not older than 12 month has to be available.

- Any of the following coexisting medical conditions: history of epilepsy or convulsions (other than febrile convulsions), clinically significant psychiatric disease, active peptic ulcer (criteria specified), clinically significant urinary outflow obstruction, and clinically significant cardiovascular (criteria specified), hepatic, renal, pulmonary, metabolic or endocrine disease
- Any agent being used for the treatment of dementia such as nootropics, cholinomimetic drugs, non-steroidal anti-inflammatory drugs for more than 30 consecutive days, estrogens without medical need, Vitamin E > recommended adult daily requirement, and deprenyl. Subjects who had previously received cholinesterase inhibitors, whether approved or experimental, could not be included in the trial, unless they had received tacrine and that drug was stopped on account of hepatotoxicity prior to an effective dose being reached or unless it could be confirmed that they had received placebo Drug or alcohol abuse within the previous year or prior prolonged history
- Women of childbearing potential without adequate contraception; those of childbearing potential must not be pregnant at screening and must agree not to become pregnant during the trial
- History of severe drug allergy or hypersensitivity including to cholinomimetic agents or bromide
- Enrollment in other galantamine trials
- Enrollment in other clinical trials except with approval of sponsor
- Conditions that could interfere with absorption of compound or evaluation of disease
- Use of any other investigational medication within 30 days prior to enrollment
- Conditions that could interfere with absorption of the compound or with the evolution of the disease

5.9 Concomitant Medications

5.9.1 Prohibited Medications

These are listed above

5.9.2 Permitted Medications

These include

- sedative/hypnotics, if used when essential, not more than twice a week, and not less than 48 hours prior to cognitive testing (if benzodiazepines are used, short acting ones are preferred)
- antidepressants if they do not have anticholinergic effects
- antipsychotics, provided those with a high tendency to anticholinergic effects and extrapyramidal adverse effects are avoided
- cough and cold remedies provided sedating drugs are discontinued where possible at least 48 hours before cognitive testing is carried out
- cholinergic agents, except for cholinomimetic drugs intended to treat dementia
- anti-emetics provided these are used for short periods of time
- antihypertensives except that methyldopa, clonidine and beta-blockers should be prescribed with caution

5.10 Efficacy Outcome Measures

5.10.1 Primary Efficacy Measures

ADAS-Cog (ADAS-Cog/11)
CIBIC-Plus

5.10.2 Secondary Efficacy Measures

Disability Assessment For Dementia (total and cluster scores; 6 separate clusters were to be used)
ADAS-Cog/13
ADAS-Cog/10
ADAS-Cog/mem
Psychological General Well Being Index
Health/Social Care Resource Use

5.11 Analysis Plan

5.11.1 General Considerations

- All randomized subjects would be included in the analysis of demographic and baseline characteristics, as well as in the classical intent-to-treat imputation scheme
- All other efficacy analyses would be performed on all randomized subjects who took at least one dose of double-blind study medication and who provided follow-up data for one or more key efficacy variables

5.11.2 Demographic And Baseline Characteristics

- The 3 treatment groups would be compared for these variables
- For continuous variables a 2-way ANOVA, with factors for treatment group and investigator would be used when appropriate, otherwise the Van Elteren test controlling for investigator would be applied
- The Van Elteren test controlling for investigator would be used for ordinal categorical variables
- For nominal categorical variables, the Cochran-Mantel-Haenszel test for general association controlling for investigator would be used

5.11.3 Primary Efficacy Parameters

- The primary efficacy parameters were the change from baseline in ADAS-Cog at 6 months and the CIBIC-Plus at 6 months
- 5 imputation schemes were to be used for the primary efficacy): classical intention-to-treat, traditional DNDP-last-observation-carried-forward, traditional observed cases, retrieved dropouts and observed cases plus retrieved dropouts. The original protocol did not designate any single one of these imputation schemes as constituting the primary analysis. However the single protocol amendment (A) did specify that the primary efficacy analysis would be on the Observed Cases dataset at Month 6
- The primary efficacy parameters would be compared between the treatment groups not only at the study endpoint but at each scheduled timepoint as well

- For continuous data (i.e., ADAS-Cog) a 2-way ANOVA model would be used, with treatment and investigator as factors, to compare treatment groups. The interaction of treatment with investigator would be examined, if the interaction was not significant when evaluated at the 10 % significance level it would not be included in the final ANOVA model. The impact of prognostic factors such as baseline score and age would also be examined. If some of these prognostic factors were determined to be important they would also be incorporated into the analysis. Following ANOVA, Dunett's test would be performed to account for multiple comparisons when comparing the two galantamine groups with placebo. If a parametric method was not appropriate (normality assumption violated), a non-parametric method (e.g., 2-way ANOVA on ranked data, van Elteren test controlling for investigator) would be utilized Subsequent comparisons between the 2 galantamine groups versus placebo would use Holm's procedure to control the Type 1 error rate..
- For ordinal categorical data (i.e., CIBIC-Plus), the Van Elteren test, controlling for investigator, would be used for the between group comparison. The CIBIC-Plus analysis was to be based on the original 7-point scale.
- If a significant proportion of subjects discontinued prematurely, other analyses, such as a per-protocol analysis might be performed to assess the impact on the results
- Subgroup analyses would be done based on age, gender and race and, if the size of the study permitted, other demographic variables, ApoE status, use of psychotropic medications and possible more entities
- Within group comparison (baseline versus each visit) would be done using the paired t-test when appropriate; otherwise the Wilcoxon signed rank test would be used

5.11.4 Secondary Efficacy Parameters

- The approach would be similar to that for the primary efficacy measures

5.11.5 Sample Size Rationale

- The sample size calculation was based on the change from baseline in standard ADAS-Cog at month 6
  - The sample size calculation used data from previous studies in Alzheimer's Disease, not using galantamine, Indicating that placebo-treated patients experienced a mean deterioration of about 2.4 points (standard deviation of 7) on this measure over a 6-month period.
  - Based on the placebo data from the above studies, data from clinical trials of other cholinesterase inhibitors, and interim analysis of GAL 93-01, a Phase II study of galantamine, it was assumed that a difference of 2.75 points in ADAS-Cog change score between placebo- and drug-treated subjects would be clinically meaningful
  - With 80 % power and a 2-sided Type 1 error of 0.025 (taking into account that 2 separate treatment groups would be compared with placebo), 125 patients would be needed in each treatment group. Assuming a dropout rate of 30 % in each treatment group, approximately 179 subjects per group (537 subjects total) would need to be randomized
  - Given that the expected effect size on the ADAS-Cog had previously been associated with a significant effect on the CIBIC-Plus the proposed sample size was expected to have sufficient power to detect the difference between the galantamine and placebo groups for the CIBIC-Plus data

5.12 Protocol Amendments

Protocol amendments are either included in the above summary or were minor

5.13 Actual Analyses Performed

The planned analyses were performed.