9. Study GAL 93-01

This study was conducted by Shire Pharmaceuticals Limited.

9.1 Title

A group comparative, placebo-controlled, double-blind trial of the efficacy and safety of galantamine 6 mg t.i.d, 8 mg t.i.d, and 12 mg t.i.d taken orally for 12 weeks in patients with a diagnosis of Senile Dementia of the Alzheimer's type

9.2 Objective

- To establish the effect of 3 doses of galantamine (6 mg t.i.d, 8 mg t.i.d, and 12 mg t.i.d) taken orally for 12 weeks on measures of cognition in patients with a diagnosis of Senile Dementia of the Alzheimer's Type
- To establish the effect of 3 doses of galantamine (6 mg t.i.d, 8 mg t.i.d, and 12 mg t.i.d) taken orally for 12 weeks on measures of overall clinical response in patients with a diagnosis of Senile Dementia of the Alzheimer's Type
- To establish the safety and tolerance of 3 doses of galantamine (6 mg t.i.d, 8 mg t.i.d, and 12 mg t.i.d) taken orally for 12 weeks in patients with a diagnosis of Senile Dementia of the Alzheimer's Type
- To document the galantamine plasma concentrations in Alzheimer's patients treated with 6 mg t.i.d, 8 mg t.i.d, and 12 mg t.i.d

9.3 Design

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

9.4 Dosage

Galantamine 6 mg t.i.d
Galantamine 8 mg t.i.d
Galantamine 12 mg t.i.d
Placebo

The dose titration schedule for this study was as follows:

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

9.5 Duration

12 weeks of double-blind therapy comprising a 2-week titration phase and a 10-week double-blind treatment phase

9.6 Sample Size

Estimated enrollment: 240-360 patients

9.7 Main Inclusion Criteria

- Male or female
- Probable Alzheimer's disease by NINCDS-ADRDA criteria

- Dementia of the Alzheimer's type by DSM-III-R criteria
- Mini-Mental Status Examination score 12-24
- Age 45 years or older
- Reliable caregiver (criteria specified)
- Informed consent

9.8 Main Exclusion Criteria

- Untreated hypothyroidism and hypoparathyroidism
- Multi-infarct dementia include those with a Hachinski Ischemic Score ≥ 4 (except those with isolated lacunar infarcts where the infarct was not felt to be the cause of symptoms
- Persistent hypertension > 170/110
- Extracranial arterial disease
- Family history of epilepsy
- History of Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis, progressive supranuclear palsy and multiple sclerosis
- Carcinoma within the preceding 2 years considered clinically significant
- Syphilis
- Drug abuse
- Significant psychiatric disease
- Korsakoff syndrome
- Women of child-bearing potential
- Galantamine allergy
- Medications likely to interfere with "or confuse" the potential actions of galantamine
- Patients judged by the clinician to be incapable of participation in the study
- Use of any investigational drug within 30 days of study entry

9.9 Concomitant Medications

Prohibited medications include:

- Antidepressants
- Antipsychotic drugs
- Anti-Parkinsonian drugs
- Insulin in those patients with uncontrolled diabetes mellitus
- Sedatives unless the dose is stable and used only at night, with the following exceptions: promazine in a dose of < 50 mg daily for > 3 months; and temazepam in a dose < 20 mg daily
- Other centrally-acting cholinergic or anticholinergic drugs, except for inhaled drugs used for the treatment of asthma
- Anti-hypertensive medications with the exception of ACE inhibitors and diuretics

9.10 Efficacy Outcome Measures

9.10.1 Primary Efficacy Measures

ADAS-Cog

9.10.2 Secondary Efficacy Measures

CIBIC-Plus*
Progressive Deterioration Scale-1
IADL
ADAS-NonCog
ADAS-Total

*This rating scale was not recorded by an independent rater and was therefore not strictly a CIBIC-Plus. It is referred to as a CGIC when the results of the study are described

9.11 Analysis Plan

- The plan of analysis specified in the protocol is limited

- The primary measure of efficacy was the change in ADAS-Cog score between baseline and after completion of 12 weeks of treatment
- A sequential analysis would be performed on the ADAS-Cog data alone as follows:
  - The first interim analysis would be performed after the first 80 patients had completed the 12-week treatment period
  - Subsequent interim analyses were to be performed after the completion of every additional group of 20 patients in each treatment arm
  - 3 identical triangular tests, each comparing one dose of galantamine with placebo, would be performed at each interim analysis.
  - For a single triangular test to have 90 % power to detect a drug-placebo difference of 2 in ADAS-Cog (standard deviation of 4) 85 patients would be needed in each treatment arm
  - For each triangular test the stopping rule would operate as follows: if there was sufficient evidence that galantamine was better, the same or worse than placebo, the study would be stopped; if there was insufficient evidence to arrive at a conclusion the study would continue to recruit patients
  - The sequential interim analyses would be performed on all patients who had a baseline ADAS-Cog score, who commenced treatment and were not considered serious protocol violators. For patients who could not complete the study, the last available ADAS-Cog score would be used
- After the study ended a final analysis was to be performed on all patients enrolled. The main comparison would be between placebo and each dose of galantamine
- All secondary efficacy measures would be analyzed once the study was completed
- Summary statistics would be provided for demographic and baseline data
- Between group comparisons would be made "as appropriate"
- The number of further patients recruited after each interim analysis was to "depend on the accumulating data."

9.12 Protocol Amendments

These are incorporated into the above analysis plan.

9.13 Actual Analyses Performed

The sponsor states that the initial analyses were performed according to protocol.

Details are provided, however, for the 3 imputation schemes that were used for analysis of the ADAS-Cog

- **Intent-to-treat**: this included all patients who were successfully randomized into the trial and then received at least one dose of trial medication. For those who did not have a Week 12 ADAS-Cog score, the last available score was used (i.e., LOCF)
- **Per-protocol**: those who were in the intent-to-treat analysis and were not protocol violators were to be included in this analysis which was to be carried out only if it included 60-95 % of the intent-to-treat population
- **Completers**: all patients who successfully completed the 12-week treatment period (analyses were to be performed on both the ADAS-Cog and CGIC.

Full details are provided for the interim analysis scheme.

Additional analyses were then performed so as to enable comparison with the results of GAL-USA-1 and GAL-INT-1. These analyses consisted of the following standard imputation schemes performed on both the ADAS-Cog and CGIC.

- Classical intent-to-treat
- DNDP-LOCF
- Traditional Observed Cases

The definitions for these datasets are as recommended in the Division's draft guidelines.

A further additional analysis consisted of

- Adjusted intent-to-treat: here the ADAS-Cog rating for the original intent-to-treat population was adjusted for those who withdrew from treatment early. This was carried out because it

was noted after the first interim analysis that placebo patients deteriorated during the 12-week treatment period and it was felt that a LOCF approach to analyzing the original intent-to-treat dataset would overestimate the size of the treatment benefit. The adjustment was based on the deterioration rate for the relevant cohort of placebo patients

The statistical models used for these additional analyses are described below.

- For the ADAS-Cog, an ANOVA model would be used. In this model the response variable would be the change from baseline in ADAS-Cog; explanatory variables would include center, treatment and center-by-treatment interaction terms (only interaction terms with a p-value ≤ 0.10 would be included in the final model). Pairwise comparisons would be based upon Dunnett's test. Within group comparisons would be based on paired t-tests
- For the CGIC a Cochran-Mantel-Haenszel test with modified ridit scores would be used

9.14 Efficacy Results

9.14.1 Patient Disposition

A total of 285 patients were randomized. Their disposition is summarized in the following table which includes protocol violations

		GAL. base tid[1]			
Population, n	Placebo	6 mg	8 mg	12 mg	Total
Efficacy					
• Observed ITT	85	85	56	53	279[2]
• Adjusted ITT	87	88	56	54	285
• Per protocol	74	62	44	29	209
• Classical ITT	87	88	56	54	285
• Traditional DNDP-LOCF	82	81	55	51	269
• Observed Completers					
- week 6	81	81	55	51	268
- weeks 12	74	62	45	29	210[3]
Safety	87	88	56	54	285
Protocol violators	13	26	12	25	76
No. completed	73	63	42	28	206[3]
No. discontinued	14	25	14	26	79

[1] An imbalance in patient recruitment was observed between the treatment groups due to early termination of the 8 and 12 mg GAL base tid treatment groups.
[2] Six patients had no post-baseline data.
[3] More patients had observed completed data at week 12 than those who were counted as completing the trial at week 12 (210 vs 206). This was because a number of patients had measurements at weeks 12 but had in fact discontinued treatment prior to this timepoint.

Reasons for treatment discontinuation are indicated in the next table

		GAL base tid		
Reason, n (%)	Placebo	6 mg	8 mg	12 mg
Adverse event	8 (9.2)	19 (21.6)	10 (17.9)	24 (44.4)
Withdrew consent	2 (2.3)	4 (4.5)	2 (3.6)	1 (1.9)
Ineligible to continue	2 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)
Non-compliance	2 (2.3)	1 (1.1)	0 (0.0)	1 (1.9)
Other	0 (0.0)	1 (1.1)	2 (3.6)	0 (0.0)
Total	14 (16.1)	25 (28.4)	14 (25.0)	26 (48.1)

As the table indicates treatment discontinuations were most often due to adverse events, and were more common overall in the galantamine 36 mg/day group; this was at least partly because the study was terminated for that group at the second

interim analysis. The incidence of treatment discontinuations due to adverse events in that group were much higher than in each of the other groups; this was at least .

9.14.2 Baseline And Other Demographic Characteristics

These are summarized in the following table and were similar across treatment groups

Variable	Placebo	Galantamine 18 mg/day	Galantamine 24 mg/day	Galantamine 36 mg/day
% Female	59	56	59	57
% Caucasian	99	100	100	100
Age (mean)	74.2	72.7	72.9	75.4
Years since onset of Alzheimer's Disease (mean)	3.3	3.1	3.1	3.9
Mean Mini Mental Status Examination score	18.7	18.8	18.2	18.7

9.14.3 Primary Efficacy Analysis

The mean change from baseline in each treatment group at Week 12 for all the datasets analyzed are summarized in the following table

			GAL base tul					
	Placebo		6 mg		8 mg		12 mg	
Imputation[1]	n	mean (SE)	n	mean (SE)	n	mean (SE)	n	mean (SE)
• Observed ITT	85	1.6 (0.7)	85	-0.1 (0.7)	56	-1.3 (0.8)	53	-0.1 (0.9)
• Adjusted ITT[2]	87	1.8 (0.7)	88	0.5 (0.7)	56	-0.7 (0.9)	54	1.1 (0.9)
- up to 3rd interim[3]	62	2.7 (0.9)	-	-	-	-	-	-
• Observed completers								
- week 6	81	1.6 (0.6)	81	-0.4 (0.6)	55	-0.8 (0.6)	51	0.2 (0.7)
- week 12	74	1.1 (0.7)	62	-0.7 (0.8)	45	-1.7 (1.0)	29	-1.8 (0.9)
• Classical ITT	87	1.7 (0.7)	88	-0.1 (0.7)	56	-1.2 (0.8)	54	-0.1 (0.9)
• Traditional DNDP-LOCF	82	1.6 (0.7)	81	-0.1 (0.7)	55	-1.4 (0.9)	51	-0.7 (0.7)
• Traditional observed completers	74	1.1 (0.7)	62	-0.7 (0.8)	45	-1.7 (1.0)	29	-1.8 (0.9)

Positive changes = deterioration; negative changes = improvement

Source: Display 4 and Display 6.

1) 12 weeks, unless otherwise indicated.

2) A total of 6 patients (3 on the lowest dose, 1 on the highest dose, and 2 on placebo) did not have a post-baseline ADAS-cog score. They have been included in the analysis after extrapolation of the ADAS-cog score to week 12, after comparison to placebo deterioration. The appropriate placebo deterioration rates were: cohort 1=0.36 (±0.10 SE); cohort 2=0.18 (±0.07 SE); cohort 3=0.15 (±0.10 SE); cohort 4=0.06 (±0.09 SE).

3) The mean (SE) adjusted score for the placebo patients included up to the third cohort was applied in the comparison with the 8 mg and 12 mg groups.

Regardless of the dataset used a deterioration from baseline was seen in the placebo group. For the galantamine groups a consistent improvement from baseline was for the 24 mg/day group; improvements from baseline were less consistent across datasets for the other galantamine dose groups.

For the per-protocol analysis, the adjusted change from baseline for each treatment group in displayed in the following table:

		Placebo		GAL base tid		
		All	up to 3rd interim[1]	6 mg	8 mg	12 mg
Adjusted[1)]	Mean (SE)	1.1 (0.7)	2.3 (0.9)	-0.8 (0.8)	-1.9 (1.0)	-1.8 (0.9)
	Min ; Max					
	N	74	53	62	44	29

Positive changes = deterioration, negative changes = improvement.
1) The mean (SE) adjusted score for the placebo patients included up to the third cohort was applied in the comparison with the 8 mg and 12 mg groups.

P-values for the pairwise comparisons for several datasets are in the following table. A statistically significant superiority ($p < 0.05$) for the galantamine 24 mg/day group could be demonstrated consistently across all datasets. A p-value for the observed intent-to-treat analysis is not provided

Dataset	Galantamine 18 mg/day vs placebo	Galantamine 24 mg/day vs placebo	Galantamine 36 mg/day vs placebo
Adjusted intent-to-treat	0.11	0.01	0.13
Classical intent-to-treat	>0.05 Exact value not stated	<0.05 Exact value not stated	>0.05 Exact value not stated
DNDP-LOCF	>0.05 Exact value not stated	<0.05 Exact value not stated	>0.05 Exact value not stated
Traditional Observed Cases	>0.05 Exact value not stated	<0.05 Exact value not stated	>0.05 Exact value not stated
Per-protocol	0.03	0.001	0.004

9.14.4 Analysis Of Secondary Efficacy Measures

9.14.4.1 CGIC

The results of the observed (original intent-to-treat) analysis are in the table below. The data are presented as observed data

			GAL base tid					
	placebo		6 mg		8 mg		12 mg	
Week	6	12	6	12	6	12	6	12
Mean	4.0	4.0	3.8	3.8	3.8	3.8	4.0	3.8
Median	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0
Min								
Max								
n	78	83	64	83	46	54	32	48

Categorized data for the above analysis collapsed to a 5-point scale, for Week 12 only, are in the next table

			GAL base tid					
	placebo		6 mg		8 mg		12 mg	
Category	n	(%)	n	(%)	n	(%)	n	(%)
Much improved	0	0	0	0	2	3.7	0	0
Improved	26	31	28	34	13	24	15	31
No change	34	41	40	48	30	56	27	56
Worse	22	27	15	18	9	17	5	10
Much worse	1	1.2	0	0	0	0	1	2.1
All	83	100	83	100	54	100	48	100

Categorized results for several other datasets are below

Classical Intent-to-treat

Variable	Galantamine 18 mg/day	Galantamine 24 mg/day	Galantamine 36 mg/day	Placebo
% Markedly improved	0	3.7	0	0
% Moderately improved	6.0	1.9	2.0	1.2
% Minimally improved	28.6	22.2	28.6	29.4
% No Change	47.6	55.6	55.1	42.4
% Minimally worse	17.9	13.0	12.2	23.5
% Moderately worse	0	3.7	0	2.4
% Markedly worse	0	0	2.0	1.2

Traditional DNDP-LOCF at Week 12

Variable	Galantamine 18 mg/day	Galantamine 24 mg/day	Galantamine 36 mg/day	Placebo
% Markedly improved	0	3.8	0	0
% Moderately improved	6.3	1.9	2.1	1.2
% Minimally improved	30.4	22.6	29.8	30.1
% No Change	48.1	54.7	55.3	41.0
% Minimally worse	15.2	13.2	12.8	25.3
% Moderately worse	0	3.8	0	2.4
% Markedly worse	0	0	0	0

Traditional Observed Cases at Week 12

Variable	Galantamine 18 mg/day	Galantamine 24 mg/day	Galantamine 36 mg/day	Placebo
% Markedly improved	0	4.5	0	0
% Moderately improved	6.6	2.3	3.6	1.3
% Minimally improved	37.7	27.3	46.4	32.0
% No Change	39.3	47.7	42.9	38.7
% Minimally worse	16.4	13.6	7.1	26.7
% Moderately worse	0	4.5	0	1.3
% Markedly worse	0	0	0	0

The results of the per-protocol analysis are summarized in the following table which refers to observed change on the original 7-point scale

			GAL bide tid					
	placebo		6 mg		8 mg		12 mg	
Week[1]	6	12	6	12	6	12	6	12
Mean	3.9	3.9	3.8	3.7	3.8	3.8	3.9	3.6
Median	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0
Min								
Max								
n	72	74	60	61	44	44	29	29

For the CGIC, higher scores represent deterioration relative to baseline.
[1] The data for the last available visit are identical to those for week 12.

P-values for the pairwise comparisons for several datasets are in the following table.

Dataset	Galantamine 18 mg/day vs placebo	Galantamine 24 mg/day vs placebo	Galantamine 36 mg/day vs placebo
Adjusted intent-to-treat	Overall p-value = 0.25		
Classical intent-to-treat	0.08	0.14	0.14
DNDP-LOCF	0.01	0.14	0.02
Traditional Observed Cases	0.01	0.14	0.02
Per-protocol	< 0.05 Exact value not stated	> 0.05 Exact value not stated	< 0.05 Exact value not stated

9.14.4.2 ADAS-NonCog

Baseline and observed changes from baseline for the original intent-to-treat dataset are in the table below. All 4 groups were essentially unchanged. The overall p-value for the galantamine-placebo comparison was 0.92 and were considered to be not statistically significant

				GAL base tid								
	placebo			6 mg			8 mg			12 mg		
Week	0	6	12	0	6	12	0	6	12	0	6	12
n	87	80	84	88	66	83	56	47	55	54	33	51
Mean	3.1	0.3	0.5	3.0	0.1	0.2	2.7	0.1	0.2	2.9	0.7	0
Median	3	0	0	2	0	0	2	0	0	3	0	0
Min												
Max												

9.14.4.3 IADL

Baseline and observed changes from baseline for the original intent-to-treat dataset are in the table below. All 4 groups were essentially unchanged/slightly worse. The overall p-value for the galantamine-placebo comparison was 0.88 and were considered to be not statistically significant

			GAL base tid					
	placebo		6 mg		8 mg		12 mg	
Week	0	12	0	12	0	12	0	12
n	87	83	88	84	56	56	54	53
Mean	3.5	-0.5	3.8	-0.2	3.6	-0.3	3.4	-0.4
Median	4.0	0.0	4.0	0.0	3.0	0.0	4.0	0.0
Min								
Max								

9.14.4.4 Progressive Deterioration Scale-1

Baseline and observed changes from baseline for the original intent-to-treat dataset are in the table below. Deterioration was greatest in the placebo group; improvement was seen only in 24 mg/day group. The overall p-value for the galantamine-placebo comparison was 0.07 and were considered to be not statistically significant

			GAL base tid					
	placebo		6 mg		8 mg		12 mg	
Week	0	12	0	12	0	12	0	12
n	87	87	88	88	56	56	54	54
mean	1149	-148	1195	-63	1134	26	1124	-59
median	1150	-90	1182	1	1003	17	1074	-38
min								
max								

9.15 Sponsor's Conclusions

- The galantamine 24 mg/day dose group was superior to placebo at a statistically significant level on the ADAS-Cog in a consistent manner across datasets, including the protocol-specified primary efficacy analysis
- On the original protocol-specified analysis of the CGIC, a secondary outcome measure, there was no statistically significant superiority of galantamine over placebo. However one or more of the galantamine groups was superior to placebo at a statistically significant level using other imputation schemes.
- There was no evidence that galantamine was superior to placebo on the ADAS-NonCog, IADL or Progressive Deterioration Scale-1.

9.16 Reviewer's Comments

- Many of the analyses carried out were not specified in the original protocol or formal protocol amendments. It is unclear if these analyses were formulated after the original analysis was completed and the results reviewed (as in GAL 95-05).
- Based on the ADAS-Cog analysis this study does provide supportive evidence for the efficacy of galantamine in a dose of 24 mg/day. The lack of evidence for efficacy at a dose of 36 mg/day may be attributable in part to the high dropout rate in that arm. The lack of efficacy on this measure at a dose of 18 mg/day does not appear to be explained by a small sample size alone as the effect size was smaller than for the 24 mg/day dose
- The galantamine dose most consistently superior to placebo on the CGIC was 18 mg/day (6 mg t.i.d). Curiously none of the imputation schemes used could demonstrate a superiority at a statistically significant level for the 24 mg/day dose over placebo

10. Study GAL-USA-5

This study was to enroll US patients who completed GAL-INT-2. The primary objective of the study was to assess the safety of galantamine withdrawal

10.1 Title

Safety and Efficacy of Galantamine During Withdrawal in the Treatment of Alzheimer's Disease

10.2 Objective

To evaluate the safety and efficacy of randomized withdrawal of galantamine in subjects with Alzheimer's disease

10.3 Design

- Randomized, double-blind, placebo-controlled, 6-week, parallel-arm, withdrawal study
- Subjects receiving placebo in GAL-INT-2 will continue to receive placebo in GAL-USA-5
- Subjects receiving galantamine in GAL-INT-2 will be randomized to receive either galantamine (in the same dose) or placebo in GAL-USA-5

The following schematic summarizes this design

GAL-INT-2		GAL-USA-5
Placebo	→→	Placebo
Galantamine 16 mg b.i.d.	→→	Galantamine 16 mg b.i.d or placebo
Galantamine 12 mg b.i.d.	→→	Galantamine 12 mg b.i.d or placebo

10.4 Duration

6 weeks

10.5 Dosage

Galantamine 16 mg b.i.d
Galantamine 12 mg b.i.d
Placebo

10.6 Sample Size

150 to 200 subjects

10.7 Main Inclusion Criteria

- Completion of GAL-INT-2 (completion of 6 months of double-blind medication and final visit of that study)
- Remaining in good general health as determined by medical history, complete physical examination, laboratory tests and electrocardiogram

10.8 Main Exclusion Criteria

- Premature discontinuation from GAL-INT-2
- If any of the following develop during GAL-INT-2, the investigator must contact the sponsor before enrolling the patient in GAL-USA-5: any neurological or psychiatric illness that could contribute to dementia, loss of consciousness, transient ischemic attacks, "drop attacks", other neurological signs or symptoms, stepwise deterioration or head injury
- History of epilepsy or convulsions, other than febrile convulsions during childhood
- Active peptic ulcer (criteria specified)
- Clinically significant cardiovascular disease
- Clinically significant hepatic, renal, pulmonary, metabolic or endocrine disorder
- Use of any agent being currently tested as an antidementia agent, including, but not limited to nootropics, cholinomimetics, choline, estrogens taken without medical need, non-steroidal anti-inflammatory drugs (taken for more than 30 days), vitamin E (> 30 IU daily) and deprenyl.
- History of drug or alcohol abuse: within the past year or prolonged in the past
- Female subjects of child bearing potential without adequate contraception: all female subjects of child bearing 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 hypersensitivity to cholinesterase inhibitors, choline agonists or similar agents, or bromide
- Use of an investigational agent other than galantamine within 30 days prior to beginning the protocol under review
- Conditions that could interfere with the absorption of the compound or evaluation of the disease
- Subjects who the investigator feels would be otherwise unsuitable for the study

10.9 Concomitant Medications

10.9.1 Prohibited Medications

These are listed above

10.9.2 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

10.10 Efficacy Outcome Measures

10.10.1 Primary Efficacy Measures

ADAS-Cog

10.10.2 Secondary Efficacy Measures

ADAS-Cog/13
ADAS-Cog/10
ADAS-Cog/mem
ADAS-Cog responders: 4 definitions were to be used
≥ 0 points
≥ 4 points
≥ 7 points
≥ 10 points

10.11 Analysis Plan

- Imputation schemes to be used for the efficacy analysis consisted of : Classical Intention-to-Treat, Last-Observation-Carried-Forward, and Observed Cases.
- The efficacy data at the endpoints of this study were to be compared with those at the initial visit; they were also to be compared with those at the beginning of GAL-INT-2.
- The groups to be compared were galantamine→galantamine, galantamine→placebo and placebo→placebo.
- Within group comparisons of efficacy data were to be made using the paired t-test or Wilcoxon signed ranks test, depending on the way the data are distributed.
- Between group comparisons for continuous efficacy data were to use ANCOVA with treatment, investigator and their interaction as factors and subsequent comparisons of pairwise data by Fisher's LSD procedure (non-parametric methods were to be used if parametric methods are found to be inappropriate)
- Descriptive statistics would be provided for all demographic and baseline variables, for all subjects and for all treatment groups. These variables will be compared between treatment groups as follows: for continuous variables a two-way ANOVA model was to be used with factors for treatment group, investigator and their interaction term; ordinal variables were to be compared using the Van Elteren test, controlling for investigator; nominal variables were to be compared using the Cochran-Mantel-Haenszel test for general association, controlling for investigator.
- All statistical tests were to be two-tailed and at the 5 % level of significance; no power calculation has been performed for this study.
- Although not specified in the protocol, the primary efficacy comparison was between the galantamine→placebo and placebo→placebo groups

10.12 Protocol Amendments

No amendments appear to have been made to the protocol

10.13 Actual Analyses Performed

The analyses were performed as specified in the protocol with the following exception.

For continuous data a one-way ANOVA was used rather than the ANCOVA model described in the protocol. The center effect was not included in the ANOVA model owing to small center sizes. A longitudinal analysis using a mixed model approach was not performed.

10.14 Efficacy Results

10.14.1 Patient Disposition

118 patients out of 134 who completed GAL-INT-2 in the United States continued into the randomized treatment withdrawal phase. Their reasons for treatment discontinuation are summarized in the following table

Treatment group	PLA/PLA	GAL/PLA	GAL/GAL	Total
Total randomized	47	39	32	118
Reason for discontinuation				
Adverse event	1 (2.1%)	0 (0%)	0 (0.0%)	1 (0.8%)
Other[a]	3 (6.4%)	0 (0%)	1 (3.1%)	4 (3.4%)
Lost to follow-up	1 (2.1%)	0 (0%)	0 (0%)	1 (0.8%)
Withdrew consent	1 (2.1%)	0 (0%)	0 (0%)	1 (0.8%)
Total discontinued	6 (12.8%)	0 (0%)	1 (3.1%)	7 (5.9%)
Total completed	41 (87.2%)	39 (100%)	31 (96.9%)	111 (94.1%)

a: Wrong medication dispensed, or wrong dosage taken, or medication stopped early.

10.14.2 Protocol Deviations

19 patients had protocol deviations, the reasons for which are outlined in the following table:

Treatment group	PLA/PLA	GAL/PLA	GAL/GAL	Total
Total randomized	47	39	32	118
Reason for protocol deviation				
Insufficient data	2 (4.3%)	0 (0%)	0 (0%)	2 (1.7%)
Intercurrent event	2 (4.3%)	1 (2.6%)	1 (3.1%)	4 (3.4%)
Intercurrent forbidden therapy	3 (6.4%)	3 (7.7%)	3 (9.4%)	9 (7.6%)
Treatment deviation	2 (4.3%)	2 (5.1%)	0 (0%)	4 (3.4%)
Total with protocol deviations	9 (19.1%)	6 (15.4%)	4 (12.5%)	19 (16.1%)

In addition to the above, 28 patients were randomized out of sequence

10.14.3 Baseline And Other Demographic Characteristics

Demographic and baseline characteristics at the time of entry into GAL-INT-2 are summarized in the following table; these characteristics appear to have been balanced across treatment groups for those patients who entered GAL-USA-5 (there were no statistically significant differences between the 3 groups). These characteristics are summarized in the following table

Characteristic or variable	PLA/PLA n=47	GAL/PLA n=39	GAL/GAL n=32	Total N=118
Sex: N (%)				
Male	19 (40.4%)	19 (48.7%)	11 (34.4%)	49 (41.5%)
Female	28 (59.6%)	20 (51.3%)	21 (65.6%)	69 (58.5%)
Race: N (%)				
White	42 (89.4%)	34 (87.2%)	31 (96.9%)	107 (90.7%)
Black	0 (0%)	1 (2.6%)	1 (3.1%)	2 (1.7%)
Hispanic	3 (6.4%)	2 (5.1%)	0 (0%)	5 (4.2%)
Oriental	1 (2.1%)	1 (2.6%)	0 (0%)	2 (1.7%)
Other	1 (2.1%)	1 (2.6%)	0 (0%)	2 (1.7%)
Age (mean ± SE) years	74 ± 1.17	76.5 ± 1.26	75.3 ± 1.12	75.2 ± 0.7
Weight (mean ± SE) kg	67.99 ± 2.47	69.41 ± 2.63	70.13 ± 2.72	69.04 ± 1.50
Smoker: yes n (%)	1 (2.1%)	4 (10.3%)	0 (0.0%)	5 (4.2%)
Age at onset of cognitive problem (mean ± SE)	71.4 ± 1.23	73.4 ± 1.37	72.3 ± 1.32	72.3 ± 0.76
Years since cognitive problem diagnosis (mean ± SE)	3.62 ± 0.35	4.18 ± 0.44	4.11 ± 0.41	3.94 ± 0.23
Age at diagnosis of probable AD (mean ± SE)	73.8 ± 1.2	76.4 ± 1.33	75.5 ± 1.15	75.1 ± 0.72
Years since probable AD diagnosis (mean ± SE)	1.1 ± 0.21	1.11 ± 0.21	0.83 ± 0.12	1.03 ± 0.11
Relative(s) with AD: N (%)	11 (23%)	12 (31%)	8 (25%)	31 (26%)
Cholinomimetics trial participant: N (%)	0 (0%)	2 (5.1%)	1 (3.1%)	3 (2.5%)
MMSE score (mean ± SE)	20.3 ± 0.47	20 ± 0.51	19.9 ± 0.78	20.1 ± 0.33
ADAS-cog/11 score (mean ± SE)	22.3 ± 1.39	24.9 ± 1.45	23.6 ± 2.18	23.5 ± 0.94

10.14.4 Primary Efficacy Analysis

10.14.4.1 ADAS-Cog/11

The primary analysis compared the change in ADAS-Cog/11 from the initial visit of GAL-USA-5 on the Observed Cases dataset. The primary comparison was between the PLA/PLA and GAL/PLA groups. Mean ADAS-Cog scores at the initial and Week 6 visits as well as the change from baseline, for the Observed Cases dataset are summarized in the following table. Initial differences between those receiving galantamine and those receiving placebo were not statistically significant (p=0.881)

Timepoint	PLA/PLA		GAL/PLA		GAL/GAL	
	n	Mean ± SE	n	Mean ± SE	n	Mean ± SE
Initial	46	22.6 ± 1.43	36	23.8 ± 1.46	31	23.1 ± 2.65
Week 6[a]	41	23.0 ± 1.41	36	25.2 ± 1.77	29	22.3 ± 2.76
Change from initial visit		0.8 ± 0.83		1.4 ± 0.89		-0.9 ± 1.02

a: Patients with ADAS-cog/11 score at initial visit (start of this trial)

The differences between treatment groups in change ADAS-Cog scores across GAL-USA-5 and related p-values are summarized in the following table

Comparison	Mean Difference In ADAS-Cog At Week 6 (Observed Cases)	p-values
GAL/PLA vs PLA/PLA	0.6	0.637
GAL/GAL vs GAL/PLA	2.3	0.095

The results of the LOCF analysis of ADAS-Cog are indicated in the following table and are not substantially different from the Observed Cases analysis

Treatment Group	PLA/PLA	GAL/PLA	GAL/GAL	P-values
N	43	36	30	
Mean Change From Initial Visit Of GAL-USA-5	0.8	1.4	-1.9	GAL/PLA vs PLA/PLA: 0.665 GAL/GAL vs GAL/PLA: 0.095

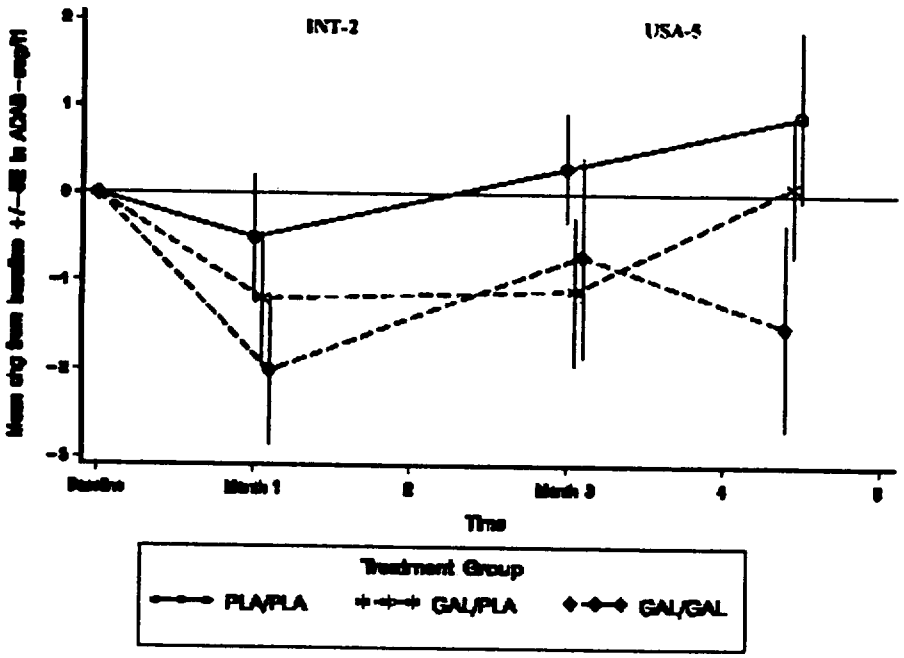
10.14.4.2 Additional Analysis On ADAS-Cog/11

An Observed Cases analysis was performed on the mean change from baseline visit of GAL-INT-2 to the end of GAL-USA-5. The data indicate that while the PLA/PLA group worsened, the GAL/GAL group improved overall and the GAL/PLA group returned to the original baseline.

The results of this analysis are displayed in the following 2 tables and graph

Timepoint	PLA/PLA		GAL/PLA		GAL/GAL	
	n	Mean ± SE	n	Mean ± SE	n	Mean ± SE
Baseline	47	22.3 ± 1.39	39	24.9 ± 1.45	32	23.6 ± 2.18
Week 6[a]	42	22.8 ± 1.39	38	24.8 ± 1.70	30	21.9 ± 2.70
Change from baseline		0.9 ± 0.97		0.1 ± 0.79		-1.5 ± 1.16

Comparison	Mean Difference In ADAS-Cog Change From Baseline Of GAL-INT-2 To Week 6 Of GAL-USA-5 (Observed Cases)	p-values
GAL/PLA vs PLA/PLA	0.8	0.568
GAL/GAL vs GAL/PLA	2.4	0.265



The results of the LOCF analysis of ADAS-Cog are indicated in the following table and are not substantially different from the Observed Cases analysis

Treatment Group	PLA/PLA	GAL/PLA	GAL/GAL	P-values
N	43	36	30	
Mean Change From Initial Visit Of GAL-INT-2	1.1	0.1	-1.6	GAL/PLA vs PLA/PLA: 0.448 GAL/GAL vs GAL/PLA: 0.211

10.14.5 Analysis Of Secondary Efficacy Measures

10.14.5.1 ADAS-Cog Clusters

The mean score at Week 6 and change from initial visit of GAL-USA-5 are summarized in the following table (Observed Cases)

	PLA/PLA			GAL/PLA			GAL/GAL		
ADAS cluster score	n	Mean ± SE	Mean change ± SE	n	Mean ± SE	Mean change ± SE	n	Mean ± SE	Mean change ± SE
ADAS-cog/13	40	31.9 ± 1.67	0.2 ± 0.94	36	34.6 ± 2.06	1.1 ± 1.01	29	30.7 ± 3.18	-1.7 ± 1.15
ADAS-cog/mem	40	21.3 ± 0.87	0.1 ± 0.58	36	23.7 ± 0.82	0.4 ± 0.63	30	20.6 ± 1.21	-0.8 ± 0.78
ADAS-cog/10	41	10.7 ± 1.02	0.1 ± 0.50	37	11.5 ± 1.61	0.9 ± 0.78	29	10.3 ± 2.18	-0.8 ± 0.75

P-values based on comparisons of the groups in the above table are listed below

Cluster	GAL/PLA vs PLA/PLA	GAL/GAL vs GAL/PLA
ADAS-Cog/13	0.527	0.561
ADAS-Cog/10	0.399	0.083
ADAS-Cog/mem	0.780	0.155

The mean score and change from initial visit of GAL-INT-2 are summarized in the next table (Observed Cases)

	PLA/PLA			GAL/PLA			GAL/GAL		
ADAS cluster score	n	Mean ± SE	Mean change ± SE	n	Mean ± SE	Mean change ± SE	n	Mean ± SE	Mean change ± SE
ADAS-cog/13	42	31.9 ± 1.61	0.4 ± 1.09	38	34.2 ± 1.98	-0.2 ± 0.93	30	30.3 ± 3.09	-2.3 ± 1.39
ADAS-cog/mem	42	21.4 ± 0.84	-0.6 ± 0.63	38	23.4 ± 0.81	0.2 ± 0.59	31	20.4 ± 1.18	-0.8 ± 0.73
ADAS-cog/10	42	10.5 ± 1.00	1.1 ± 0.80	39	11.4 ± 1.53	-0.1 ± 0.75	30	10.1 ± 2.12	-1.4 ± 0.87

P-values based on comparisons of the groups in the above table are listed below

Cluster	GAL/PLA vs PLA/PLA	GAL/GAL vs GAL/PLA
ADAS-Cog/13	0.676	0.211
ADAS-Cog/10	0.276	0.290
ADAS-Cog/mem	0.336	0.289

No statistically significant differences between treatment groups were seen for any of the above analyses.

10.14.5.2 ADAS-Cog Responder Analysis

Data for the responders from the initial visit of GAL-USA-5 to Week 6 of that study are displayed in the next table

Response Definition	PLA/PLA	GAL/PLA	GAL/GAL	p-values
≥ 0 points	61 %	47 %	55 %	GAL/PLA vs PLA/PLA: 0.230 GAL/GAL vs GAL/PLA: 0.527
≥ 4 points	15 %	19 %	28 %	GAL/PLA vs PLA/PLA: 0.576 GAL/GAL vs GAL/PLA: 0.442
≥ 7 points	5 %	6 %	14 %	GAL/PLA vs PLA/PLA: 0.894 GAL/GAL vs GAL/PLA: 0.258
≥ 10 points	0 %	0 %	7 %	GAL/PLA vs PLA/PLA: Not done GAL/GAL vs GAL/PLA: 0.112

As the above table indicates none of the comparisons were statistically significant. In general the response rates for the GAL/GAL group were best and those for the GAL/PLA group intermediate

10.15 Sponsor's Conclusions Regarding Efficacy

- Patients who had received placebo during both GAL-INT-2 and GAL-USA-5 continued to deteriorate cognitively during GAL-USA-5
- Patients who had received galantamine during GAL-INT-2 and placebo during GAL-USA-5 had returned to almost the level of the original (i.e., GAL-INT-2) cognitive baseline at the end of the withdrawal period

- Patients who received galantamine during both GAL-INT-2 and GAL-USA-5 continued to improve cognitively during GAL-USA-5
- The lack of statistically significant differences between treatment groups was most likely due to the small sample size and short duration of GAL-USA-5

10.16 Reviewer's Comments

- The randomized withdrawal paradigm has been proposed as a means of distinguishing between a symptomatic effect and a disease-modifying effect of a drug developed for the treatment of dementia
- For that purpose the most appropriate comparison would have been between the GAL/PLA and GAL/GAL groups
- The differences between the 2 groups did not reach statistical significance probably because of the small sample size and short duration of the study
- However the diverging slopes for the GAL/GAL and the GAL/PLA groups and the return of the GAL/PLA group to its original GAL-INT-2 baseline suggests that the effect of galantamine is purely symptomatic
- GAL-USA-5 enrolled only US patients participating in GAL-INT-2

11. Study GAL-USA-10

11.1 Title

Placebo-controlled evaluation of galantamine in Alzheimer's Disease: evaluation of safety and efficacy under a slow-titration regime

11.2 Objectives

- To evaluate the safety and/or efficacy of galantamine 8, 16, and 24 mg/day (4, 8, and 12 mg b.i.d) when a slow titration regime is employed
- To further explore the dose-response relationships for galantamine doses from 8-24 mg/day

11.3 Design

- An initial single-blind placebo run-in period of 1 month would involve all patients
- There would next be a randomized, double-blind, placebo-controlled, parallel group phase during which subjects would be randomized to one of 4 treatment groups
  - Placebo
  - Titration to galantamine 24 mg daily over 8 weeks (Gal 24)
  - Titration to galantamine 16 mg daily over 4 weeks (Gal 16)
  - Galantamine 8 mg daily without titration (Gal 8)
- The double-blind phase would last a total period of 5 months (21 weeks), without altering the above duration of the titration phase. Thus
  The Placebo group would receive only placebo for the entire 21 weeks of the double-blind phase
  The Gal 24 group would receive galantamine 24 mg daily for 13 weeks
  The Gal 16 group would receive galantamine 16 mg daily for 17 weeks
  The Gal 8 group would receive galantamine 8 mg daily for the entire 21 weeks of the double-blind phase

11.4 Dosage

Total daily doses (using a BID regime) are indicated in the following table

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

11.5 Sample Size

Approximately 910 patients would be randomized (in a 2:2:2:1 ratio), distributed as follows among the 4 groups:
Placebo: 260 patients
Gal 24: 260 patients
Gal 16: 260 patients
Gal 8: 130 patients

About 1100 patients would be enrolled so that 910 patients could be randomized

11.6 Main Inclusion Criteria

Approximately 910 patients would be randomized (in a 2:2:2:1 ratio), distributed as follows among the 4 groups:
Placebo: 260 patients
Gal 24: 260 patients
Gal 16: 260 patients
Gal 8: 130 patients

About 1100 patients would be enrolled so that 910 patients could be randomized

11.7 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, estrogens without medical need, non-steroidal anti-inflammatory drugs for > 30 days, Vitamin E > 30 IU daily, and deprenyl. Subjects who had previously received cholinesterase inhibitors or M_1 agonists, whether approved or experimental, could be included in the trial, provided there was a washout period of at least 60 days prior to screening
- 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
- Unsuitability for a trial of this type as per the investigator

11.8 Concomitant Medications

Prohibited Medications are listed above
Permitted Medications 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

11.9 Efficacy Outcome Measures

11.9.1 Primary Efficacy Measures

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

11.9.2 Secondary Efficacy Measures

- 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
- Percentage of responders at end of 3 months on standard ADAS-Cog using 0, 4 and 7 points of improvement as cut-off
- Neuropsychiatry Inventory
- Alzheimer's Disease Cooperative Study-ADL

11.10 Analysis Plan

11.10.1 Primary Efficacy Parameters

- The primary efficacy parameters were the change from baseline in ADAS-Cog at 5 months and the CIBIC-Plus at 5 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. Of these the primary timepoint would be the traditional observed cases at Month 5
- The primary efficacy parameters would be compared between the treatment groups not only at the study endpoint but at Day 28 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. The impact of baseline score on change from baseline would be examined and if baseline score was a relevant predictor, a further analysis using an ANCOVA model would be performed to assess treatment effects and interaction between treatment and baseline score. If a parametric method was not appropriate, a non-parametric method would be utilized. Following ANOVA, Fisher's LSD test would be used for pairwise comparisons between each galantamine group and placebo. If the primary analysis showed that both the 24 mg/day dose and the 16 mg/day dose showed a statistically significant difference from placebo the 8 mg dose would be compared with placebo at the 0.05 level. . A linear contrast on the main effect of treatment would used to test the dose-response relationship.
- For ordinal categorical data (i.e., CIBIC-Plus), the Van Elteren test would be used for the between group comparison. The primary analysis for the CIBIC-Plus was to be based on scores that used the original 7-point scale
- If a significant proportion of subjects discontinued prematurely, other analyses 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

11.10.2 Secondary Efficacy Parameters

- The approach would be similar to that for the primary efficacy analysis, except that subgroup analyses will not be performed
- For nominal data (percentage of responders at the end of 3 months) the Cochran-Mantel-Haenszel test for general association controlling for investigator would be used

11.10.3 Sample Size Rationale

- The sample size calculation was based on the change from baseline in standard ADAS-Cog at month 5 and CIBIC-Plus at month 5
  - The sample size calculation used data from GAL-USA-1. In that protocol the standard deviation for changes in ADAS-Cog at month 3 was 5.4 for placebo and 5.6 for galantamine 24 mg daily. For the CIBIC-Plus 55 % of the placebo patients rated as "no change or better" compared to 70 % of those getting galantamine 24 mg daily. The discontinuation rate at month 3 was 12 % for placebo and 25 % for galantamine 24 mg daily
  - The sample size calculation had used the dose of galantamine 16 mg daily and assumed that the differences between galantamine 16 mg daily and placebo in the 2 primary efficacy endpoints at month 5 would be similar to those between galantamine 24 mg/day and placebo at month 3 in GAL-USA-1. Assuming a dropout rate of only 20 % given the slower titration schedule and a type I error of 0.05 (2-sided), 208 patients in this treatment group completing the study would provide > 95 % power to detect a mean difference of 3.0 (standard deviation of 6.0) in change from baseline in ADAS-Cog score at month 5 between the placebo and Gal 16 groups; the same number completing the study would provide 88 % power to detect a 15 % between group difference in percentage of subjects with "no change" or "improved" CIBIC-Plus scores. An equal number of patients had been proposed to be randomized to the Gal 24 group (galantamine 24 mg daily is believed to be the most efficacious dose) whereas only 130 patients had been proposed to be randomized to the believed least efficacious galantamine 8 mg daily dose which had not been powered for analysis, but been included merely to help detect a trend
  - No adjustment for multiplicity had been made as efficacy will need to be demonstrated by a positive result on both parameters

11.11 Protocol Amendments

The above description incorporates the only amendments made to the protocol

11.12 Actual Analyses Performed

The analyses were performed as planned.

11.13 Efficacy Results

11.13.1 Patient Disposition

A total of 1178 patients entered the trial. 979 patients were randomized across the 4 treatment groups; of these 978 patients received at least 1 dose of study medication and their disposition across treatment groups is indicated in the following table which also indicates the number and percentage of discontinuations in each treatment group and the reasons for discontinuation

Trial Termination Reason	Placebo (N = 286)	GAL 4 mg bid (N = 140)	GAL 8 mg bid (N = 279)	GAL 12 mg bid (N =273)
Any reason	46 (16.1%)	32 (22.9%)	60 (21.5%)	61 (22.3%)
During first 8 weeks	22 (7.7%)	13 (9.3%)	27 (9.7%)	22 (8.1%)
After Week 8	24 (9.1%)	19 (15.0%)	33 (13.1%)	39 (15.5%)
Adverse event	20 (7.0%)	9 (6.4%)	19 (6.8%)	27 (9.9%)
Inefficacy	0 (0.0%)	1 (0.7%)	0 (0.0%)	2 (0.7%)
Other reasons[a]	23 (8.0%)	18 (12.9%)	30 (10.8%)	20 (7.3%)
Patient ineligible to continue trial	0 (0.0%)	0 (0.0%)	4 (1.4%)	2 (0.7%)
Non-compliant	3 (1.0%)	4 (2.9%)	7 (2.5%)	10 (3.7%)

a: The majority of those in the "other reasons" category were for withdrawal of consent

As the table above indicates, discontinuations due to adverse events were only slightly higher in the highest dose group as compared with the lower dose groups and placebo.

11.13.2 Protocol Deviations

These are illustrated in the next table which indicates that, overall, these were slightly more frequent in the higher dose groups

Protocol deviations	Placebo (N=286)	GAL 4 mg bid (N=140)	GAL 8 mg bid (N=279)	GAL 12 mg bid (N=273)
Total patients with protocol deviations	39 (13.6%)	17 (12.1%)	43 (15.4%)	45 (16.5%)
No efficacy data	3 (1.0%)	2 (1.4%)	1 (0.4%)	1 (0.4%)
Investigator error	20 (7.0%)	7 (5.0%)	19 (6.8%)	15 (5.5%)
Intercurrent forbidden therapy	9 (3.1%)	4 (2.9%)	17 (6.1%)	17 (6.2%)
Selection criteria NOS not met	6 (2.1%)	2 (1.4%)	6 (2.2%)	7 (2.6%)
Noncompliance	1 (0.3%)	2 (1.4%)	1 (0.4%)	2 (0.7%)
Treatment interruption too long	0 (0.0%)	2 (1.4%)	1 (0.4%)	4 (1.5%)
Treatment too short	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)

11.13.3 Baseline And Other Demographic Characteristics

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

Characteristics	Placebo N=286	GAL 4 mg bid N=140	GAL 8 mg bid N=279	GAL 12 mg bid N=273
Sex: n (%)				
Male	108 (37.8%)	50 (35.7%)	105 (37.6%)	90 (33.0%)
Female	178 (62.2%)	90 (64.3%)	174 (62.4%)	183 (67.0%)
Race: n (%)				
Caucasian	267 (93.4%)	132 (94.3%)	260 (93.2%)	249 (91.2%)
Black	13 (4.5%)	5 (3.6%)	12 (4.3%)	14 (5.1%)
Hispanic	3 (1.0%)	3 (2.1%)	5 (1.8%)	4 (1.5%)
Oriental	3 (1.0%)	0 (0.0%)	1 (0.4%)	3 (1.1%)
Other	0 (0.0%)	0 (0.0%)	1 (0.4%)	3 (1.1%)
Age (mean ± SE)	77.1 ± 0.46	76 ± 0.61	76.3 ± 0.49	77.7 ± 0.43
Weights (kg) (mean ± SE)	67.55 ± 0.835	69.88 ± 1.413	68.12 ± 0.867	66.55 ± 0.803
Smoker - Yes: n (%)	15 (5.2%)	6 (4.3%)	15 (5.4%)	11 (4.0%)
Age at onset of cognitive problems (mean ± SE)*	73.2 ± 0.49	72.3 ± 0.64	72.6 ± 0.5	74.2 ± 0.47
Years since cognitive problem diagnosis (mean ± SE)	4.33 ± 0.152	4.14 ± 0.212	4.22 ± 0.164	3.92 ± 0.164
Age at diagnosis of probable AD (mean ± SE)	76.1 ± 0.47	75.2 ± 0.63	75.4 ± 0.5	76.8 ± 0.44
Years of AD diagnosis (mean ±SE)	1.42 ± 0.104	1.26 ± 0.122	1.42 ± 0.11	1.32 ± 0.108
First degree relative(s) with AD: n (%)	74 (25.9%)	41 (29.5%)	83 (30.0%)	76 (27.8%)
Previously taken cholinomimetic agent: n (%)	127 (44.4%)	60 (42.9%)	141 (50.5%)	118 (43.2%)
Total MMSE score (mean ± SE)	17.7 ± 0.21	18 ± 0.3	17.8 ± 0.21	17.7 ± 0.23
ADAS-cog/11 score at baseline (mean ± SE)	29.4 ± 0.63	27.8 ± 0.94	29.4 ± 0.66	29.0 ± 0.67
APO-E type: n (%)				
2-2/2-3/3-3	90 (35.3%)	48 (37.5%)	112 (44.1%)	88 (35.5%)
2-4/3-4	133 (52.2%)	64 (50.0%)	105 (41.3%)	131 (52.8%)
4-4	32 (12.5%)	16 (12.5%)	37 (14.6%)	29 (11.7%)

11.13.4 Primary Efficacy Analysis

During a phone conversation on 4/12/00, the sponsor informed me that on account of deficiencies that had been noted in the CIBIC-Plus data at Site) for GAL-USA-10, the primary efficacy analysis had been performed excluding data from this center. Note that this information was not provided in the text of the "Results" section of the study report and was elicited from the sponsor in response to questions about a re-analysis of data from GAL-USA-1, excluding a study center, with which these 2 investigators were associated. The exclusion of this center is mentioned briefly in the "Statistical Methods" section of the study report.

38 patients were randomized at Site of these 25 patients did not complete the study.

A primary efficacy analysis including data from this center does not appear to have been performed by the sponsor

11.13.4.1 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 all 3 galantamine groups showed a statistically significant superiority to placebo on the pairwise comparison at Month 5. As the table also indicates, the galantamine 16 mg/day and galantamine 24 mg/day groups had improved relative to baseline at the timepoint, while the placebo group had worsened and the galantamine 8 mg/day group was unchanged.

The table below shows mean scores and changes from baseline for the Observed Cases dataset.

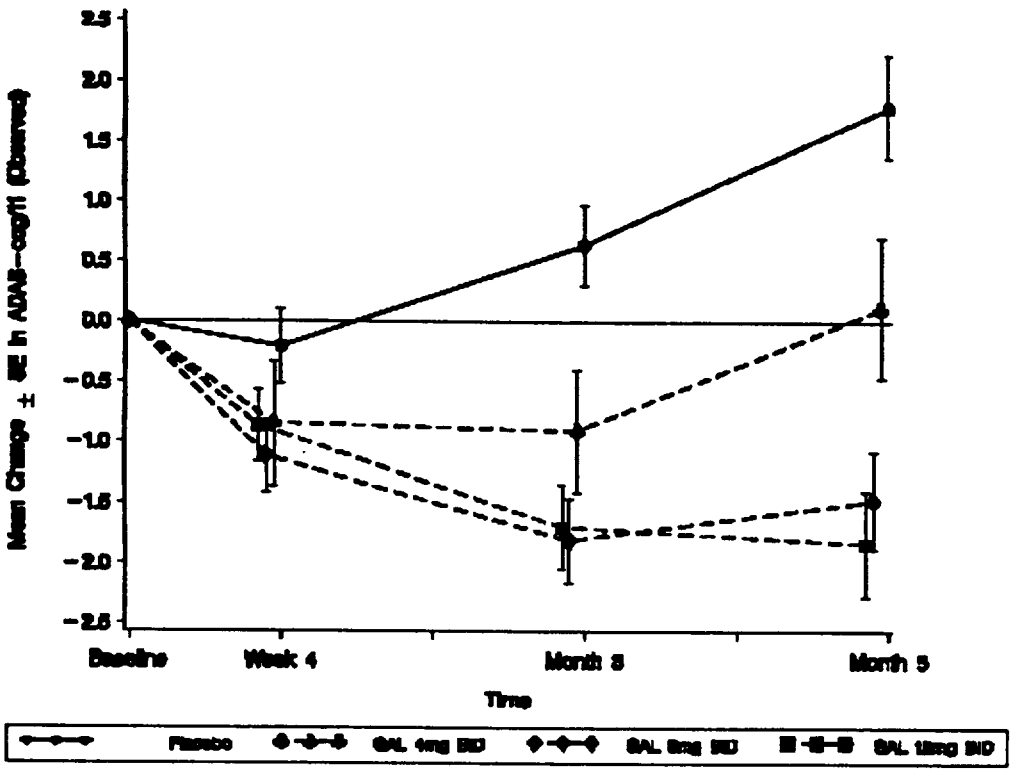
	Placebo			GAL 4 mg bid			GAL 8 mg bid			GAL 12 mg bid		
Analysis timepoint	N	Mean ±SE	Mean change ±SE	n	Mean ±SE	Mean change ±SE	n	Mean ±SE	Mean change ±SE	n	Mean ±SE	Mean change ±SE
Baseline	269	29.4 ±0.63	—	132	27.8 ±0.94	—	266	29.4 ±0.66	—	262	29.0 ±0.67	—
Week 4	254	29.0 ±0.71	−0.2 ± 0.31	126	27.0 ±1.04	−0.8 ± 0.51	253	27.8 ±0.70	−1.1* ± 0.30	252	27.8 ±0.68	−0.9 ± 0.30
Month 3	236	29.6 ±0.79	0.6 ± 0.33	114	26.5 ±1.11	−0.9* ± 0.50	231	26.6 ±0.75	−1.8*** ± 0.35	229	27.0 ±0.74	−1.7*** ± 0.35
Month 5	225	30.3 ±0.85	1.8 ± 0.43	101	27.3 ±1.12	0.1* ± 0.58	208	26.9 ±0.85	−1.5*** ± 0.40	211	26.7 ±0.79	−1.8*** ± 0.44

*: $p < 0.05$; ***: $p < 0.001$ based on a two-way ANOVA model comparing each galantamine-treatment group with placebo

Based on the above analysis p-values for the following comparisons are as displayed in the following table:

Comparison	ADAS-Cog Mean Change from Baseline at Month 5: Difference Between Treatment Groups	p-value
GAL 24 vs GAL 8	-1.9	0.007
GAL 16 vs GAL 8	-1.6	0.028

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 5 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 16 mg/day and galantamine 24 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 4 mg bid			GAL 8 mg bid			GAL 12 mg bid		
Analysis timepoint	n	Mean ±SE	Mean change ±SE	n	Mean ±SE	Mean change ±SE	n	Mean ±SE	Mean change ±SE	n	Mean ±SE	Mean change ±SE
Month 5 Observed Case	225	30.3 ±0.85	1.8 ±0.43	101	27.3 ±1.12	0.1* ±0.58	208	26.9 ±0.85	-1.5*** ±0.40	211	26.7 ±0.79	-1.8*** ±0.44
Classical ITT	269	31.0 ±0.78	1.5 ±0.38	132	28.6 ±1.06	0.8 ±0.54	266	28.0 ±0.73	-1.4*** ±0.34	262	27.6 ±0.73	-1.4*** ±0.38
Traditional LOCF	255	30.9 ±0.81	1.7 ±0.39	126	28.3 ±1.07	0.4 ±0.52	253	27.5 ±0.75	-1.4*** ±0.35	253	27.3 ±0.73	-1.4*** ±0.39
OC+RET D/O	228	30.2 ±0.85	1.7 ±0.43	104	27.5 ±1.13	0.4 ±0.63	216	26.9 ±0.82	-1.4*** ±0.39	221	27.1 ±0.79	-1.5*** ±0.43

Source: Display EFF.ADAS.1A
*: p≤0.05; ***: p≤0.001 based on a two-way ANOVA model comparing each galantamine treatment group with placebo

In none of the above datasets was a statistically significant (or clinically meaningful difference) seen between the galantamine 24 mg/day and galantamine 16 mg/day groups at Month 5.

Dr Kun He, statistical reviewer, has performed additional analyses on the ADAS-Cog using the Observed Cases and LOCF datasets, including Site . The results are similar to those analyses that excluded this site.

11.13.4.2 CIBIC-Plus

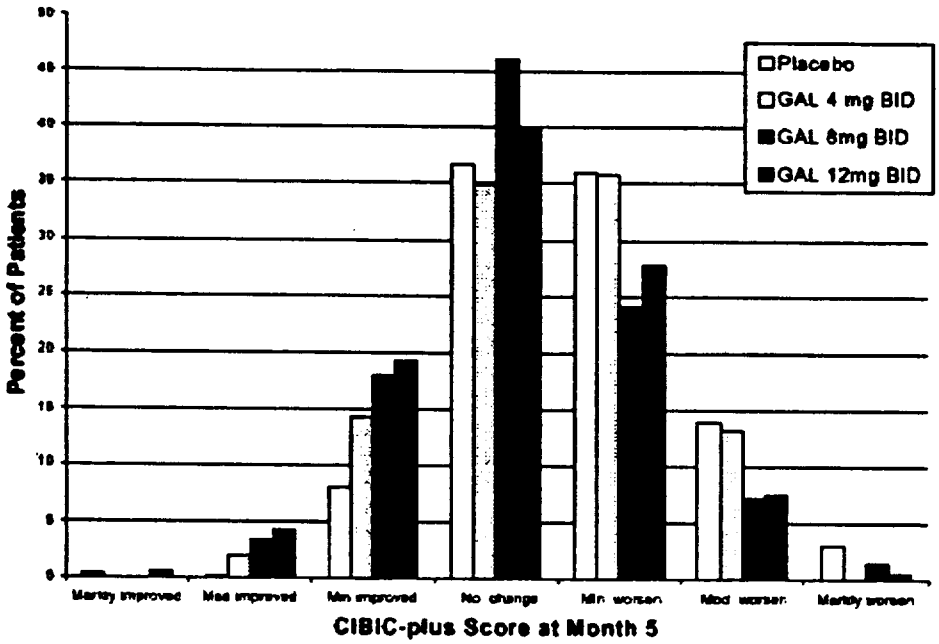
The results of the CIBIC-Plus responder analysis for the Observed Cases and LOCF datasets at Month 5 are shown in the following table. Both the galantamine 16 mg/day and galantamine 24 mg/day groups showed a statistically significant superiority to placebo; the analysis, however, did not show a statistically significant or clinically meaningful difference between these two galantamine dose groups

	Placebo (N = 237)		GAL 4 mg bid (N = 106)		GAL 8 mg bid*** (N = 212)		GAL 12 mg bid*** (N = 212)	
CIBIC-plus Rating	n (%)	Cum.%	n (%)	Cum.%	n (%)	Cum.%	n (%)	Cum.%
7-Point Rating								
Marked improvement (1)	1 (0.4)	0.4	0 (0.0)	0.0	0 (0.0)	0.0	1 (0.5)	0.5
Moderate improvement (2)	5 (2.1)	2.5	2 (1.9)	1.9	7 (3.3)	3.3	9 (4.2)	4.7
Minimal improvement (3)	19 (8.0)	10.5	15 (14.2)	16.0	38 (17.9)	21.2	41 (19.3)	24.1
No change (4)	87 (36.7)	47.3	37 (34.9)	50.9	98 (46.2)	67.5	85 (40.1)	64.2
Minimal worsening (5)	85 (35.9)	83.1	38 (35.8)	86.8	51 (24.1)	91.5	59 (27.8)	92.0
Moderate worsening (6)	33 (13.9)	97.0	14 (13.2)	100.0	15 (7.1)	98.6	16 (7.5)	99.5
Marked worsening (7)	7 (3.0)	100.0	0 (0.0)	100.0	3 (1.4)	100.0	1 (0.5)	100.0
Compressed Rating (collapsed into 2-point scale)								
Improved or no change (1-4)	112 (47.3)	47.3	54 (50.9)	50.9	143 (67.5)	67.5	136 (64.2)	64.2
Worsened (5-7)	125 (52.7)	100.0	52 (49.1)	100.0	69 (32.5)	100.0	76 (35.8)	100.0
Compressed Rating (collapsed into 2-point scale: last observed-case carried forward)								
Improved or no change (1-4)	128 (48.7)	48.7	68 (53.1)	53.1	169 (66.3)	66.3	162 (64.0)	64.0
Worsened (5-7)	135 (51.3)	100.0	60 (46.9)	100.0	86 (33.7)	100.0	91 (36.0)	100.0

Source: Displays EFF.CIB.1A and EFF.CIB.2.

***p≤0.001 with the 7-point rating using the Van Elteren test controlling for center comparing the GAL 8 mg bid and 12 mg bid groups with placebo.

The distribution of CIBIC-Plus scores at Month 5 for the Observed Cases dataset is also displayed in the following histogram:



Analyses of the CIBIC-Plus using additional datasets (classical intent-to-treat, observed cases plus retrieved dropouts) do not appear to have been performed

Dr Kun He has performed a separate set of analyses on the CIBIC-Plus data: mean CIBIC-Plus scores for each treatment group at Month 5, and p-values for the pairwise comparisons are in the following tables. The analyses below excluded Site [redacted] but additional analyses including data from that site yielded similar results

Observed Cases

	Placebo		Gal 4 mg bid		Gal 8 mg bid		Gal 12 mg bid	
	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD
Month 5 scores	235	4.59 ± 1.02	105	4.44 ± 0.96	212	4.18 ± 0.97	212	4.15 ± 1.01
p-values vs placebo			0.231		0.001		0.001	

LOCF

	Placebo		Gal 4 mg bid		Gal 8 mg bid		Gal 12 mg bid	
	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD
Month 5 scores	260	4.55 ± 1.01	127	4.42 ± 0.99	255	4.21 ± 0.95	253	4.17 ± 0.99
p-values vs placebo			0.260		0.001		0.001	

11.13.5 Analysis Of Secondary Efficacy Measures

11.13.5.1 ADAS-Cog Clusters

3 protocol-designated clusters derived from the ADAS-Cog were analyzed in a manner similar to the ADAS-Cog. The results are in the following. The galantamine 24 mg/day dose group showed a consistent statistically significant superiority to placebo on each of these measures, and the galantamine 24 mg/day dose group was superior on 2 measures. On the ADAS-Cog/10 (which excluded the memory item of the ADAS-Cog) all 3 dose groups were superior to placebo.

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

11.13.5.2 ADAS-Cog Responder Analysis

The results of the Observed Cases analysis are in the following table. Except for the group showing an improvement ≥ 10 points, which was small, the galantamine 16 mg/day and galantamine 24 mg/day groups were consistently superior to placebo at a statistically significant level

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

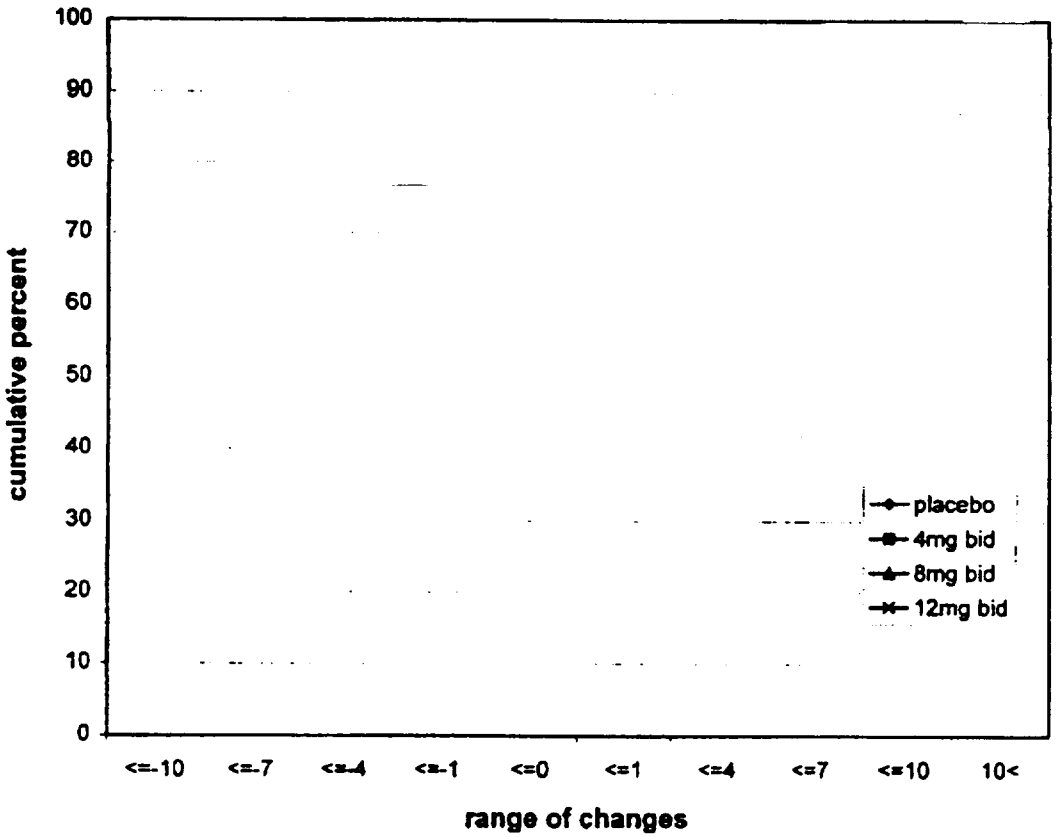
11.13.5.3 ADCS-ADL

The results of the sponsor's analysis are in the following table which provides total score data for the Observed Cases dataset. As the table indicates, both the galantamine 16 mg/day and galantamine 24 mg/day showed a statistically significant superiority to placebo. It is noteworthy that a mean improvement relative to baseline did not occur in any treatment group

Treatment Group	N	Mean Change From Baseline At Month 5	p-value vs placebo
Placebo	235	-4.0 (range -32 to 22)	
Galantamine 8 mg/day	106	-3.1 (range -36 to 14)	0.308
Galantamine 16 mg/day	212	-0.5 (range -22 to 27)	<0.001
Galantamine 24 mg/day	212	-1.6 (range -39 to 33)	0.003

Additional analyses of this outcome measure have been performed by Dr Kun He, an Agency statistician who has determined the percentage of responders in each treatment group at various levels (intervals) of response. The cumulative percentages responding at each level are displayed graphically in the diagram below. As the diagram indicates the slopes for the galantamine 16 mg/day and

galantamine 24 mg/day dose groups are consistently to the right of those for the placebo group indicating a consistently better response in the groups at all levels of response



The proportion of patients who had either no change or specified levels of improvement are illustrated in the table below:

Treatment Group		≥ 0 points %	≥ 4 points %	≥ 7 points %	≥ 10 points %
Placebo (n=235)		35	16.9	8.4	3.8
Galantamine 8 mg/day (n=106)		42	23.4	12.1	6.5
Galantamine 16 mg/day (n=212)		51.6	30.2	16.3	10.2
Galantamine 24 mg/day (n=212)		47.4	24.2	14.4	7.4
p-value*	GAL 8 vs placebo	0.281	0.103	0.233	0.182
	GAL 16 vs placebo	0.001	0.001	0.010	0.004
	GAL 24 vs placebo	0.009	0.061	0.073	0.165

*p-value based on Cochran-Mantel-Haenszel test (row mean scores difference)

Dr He's analyses have included Site # 34, as have the sponsor's analyses

11.13.5.4 Neuropsychiatry Inventory

The results of the analysis are in the following table which provides total score data for the Observed Cases dataset. As the table indicates, both the galantamine 16 mg/day and galantamine 24 mg/day showed a nominally statistically significant superiority to placebo; both groups appear to have remained stable during the course of the study

Treatment Group	N	Mean Change From Baseline At Month 5	p-value vs placebo
Placebo	234	2.3	
Galantamine 8 mg/day	106	2.3	0.871
Galantamine 16 mg/day	211	-0.1	0.026
Galantamine 24 mg/day	212	-0.1	0.022

- Galantamine in doses of 16 mg/day and 24 mg/day showed a statistically significant superiority to placebo on both primary efficacy endpoints at Month 5. These doses were also superior to galantamine 8 mg/day, but were not significantly different from each other.
- Galantamine in a dose of 8 mg/day showed a statistically significant superiority to placebo at Month 5 on the ADAS-Cog/11 alone
- Analysis of the ADAS-Cog/10, ADAS-Cog/13 and ADAS-Cog/mem were consistent with the results of the ADAS-Cog/11, as was the ADAS-Cog responder analysis
- Galantamine in doses of 16 mg/day and 24 mg/day showed a statistically significant superiority to placebo on total scores for the ADCS-ADL inventory and Neuropsychiatry Inventory, at Month 5
  (note that a responder analysis based on the ADCS-ADL conducted by the Agency's statistician had results that were generally consistent with the sponsor's analysis)

11.14 Reviewer's Comments

- The titration rate for this study is identical to that proposed in labeling.
- This is the only study that has demonstrated the efficacy of galantamine 16 mg/day (8 mg b.i.d)
- Patients treated with galantamine in doses of 16 mg/day and 24 mg/day had shown improvement relative to baseline, on the ADAS-Cog/11 over the duration of the study
- It is unclear whether the small overall treatment differences between the galantamine 16 mg/day and 24 mg/day groups and placebo, on the ADCS-ADL, although statistically significant, would be readily apparent to an observer. However the scoring system is highly structured and each score represents a clearly-defined best level of functioning. For example, eating is rated on a scale from 0 to 3 as follows:
  0: usually or always was fed by someone else
  1: used fingers to eat
  2: used a fork or spoon, but not a knife, to eat
  3: ate without physical help, and used a knife
- It is even less clear that the very small drug-placebo treatment differences on the Neuropsychiatry Inventory are clinically meaningful. Although the treatment differences are nominally statistically significant, they would not be if the Type 1 error is adjusted for multiple comparisons

12. Open-Label Extension Studies

The sponsor has used the results of multiple open-label, uncontrolled, extension studies to support the contention that galantamine has efficacy in the treatment of mild to moderate Alzheimer's Disease for at least 1 year. The sponsor has compared the rate of decline for patients enrolled in open-label trials of galantamine with historical untreated controls, and with placebo-treated patients in other clinical trials of drugs for Alzheimer's Disease; based on such comparisons the sponsor has concluded that those treated with galantamine declined more slowly than other groups.

The results of open-label extension studies that lack concurrent controls cannot be used as evidence for the efficacy of galantamine, especially in view of the minor treatment effect seen with this drug, and with other cholinesterase inhibitors. These studies have therefore not been reviewed here.

13. Labeling Review

The sponsor's draft label has been reviewed as a separate document.

14. Financial Disclosure Certification

Financial disclosure certification has been submitted with both the original NDA (of 9/29/99) and with the NDA Amendment (of 2/25/00).

14.1 Original NDA

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

- The sponsor has further certified that no investigator was granted a proprietary interest in the product as defined by 21 CFR 54.2 (c)

- Since none of the clinical trials contained in the application was ongoing on 2/2/99, in accordance with 63FR72181 (12/31/98), no information was collected retroactively from clinical investigators regarding significant equity interest or significant payments of other sorts as defined in 21 CFR 54.2(b) & (f)

14.2 NDA Amendment

-

- In all the above instances the sponsor has stated under "Steps Taken To Minimize Bias" that for the analyses data from multiple sites was pooled.

14.3 Reviewer's Comment

It appears unlikely that
significant bias into the results of studies carried out with galantamine, and submitted with this NDA.

15. Reviewer's Overall Comments And Conclusions

- The efficacy of galantamine has been demonstrated in relation to placebo across 6 randomized, double-blind, placebo-controlled, parallel arm studies on a protocol-designated primary cognitive outcome measure (ADAS-Cog)
- The efficacy of galantamine has been demonstrated in relation to placebo across 5 randomized, double-blind, placebo-controlled, parallel arm studies on a protocol-designated primary global outcome measure (CIBIC-Plus)
- The effective dose of galantamine, based on the above primary outcome measures has varied across studies
  - 24 mg/day (12 mg b.i.d) and 32 mg (16 mg b.i.d) in GAL-USA-1 and GAL-INT-1
  - 16 mg/day (8 mg b.i.d) and 24 mg/day (12 mg b.i.d) in GAL-USA-10
  - 24-32 mg/day (12 mg b.i.d to 16 mg b.i.d; variable dose) in GAL-INT-2
  - 32 mg/day (t.i.d dosing) in GAL 95-05
  - 24 mg/day (t.i.d dosing) in GAL 93-01
- From a pooled analysis of the similar studies GAL-USA-1 and GAL-INT-1 there was no evidence that a dose of 32 mg/day was superior to 24 mg/day on the ADAS-Cog and CIBIC-Plus
- In GAL-USA-10 there was no evidence that a dose of 24 mg/day was superior to 16 mg/day based on the ADAS-Cog and CIBIC-Plus
- The efficacy of galantamine in relation to placebo on measures of activities of daily living (secondary outcome measures in all studies) has been inconsistent across studies in terms of statistical significance. In the GAL 95-05 study, the nominally significant p-value of 0.032 may not be as significant once adjusted for multiple comparisons (4 secondary outcome measures were used). The most robust results were seen in the GAL-USA-10 study in which the ADCS-ADL measure was used. It is also unclear whether the small effect sizes seen in GAL-INT-2, GAL-USA-10 and GAL 95-05 are clinically meaningful. P-values for drug placebo comparisons are shown in the next table

Note that the method of rating the CIBIC-Plus, in all efficacy studies in which that measure was used, included an assessment of activities of daily living, based on caregiver input.

Study	Activities of daily living measure	p-value for galantamine-placebo comparison
GAL-USA-1	Disability Assessment in Dementia	GAL 24: 0.943 GAL 32: 0.901
GAL-INT-1	Disability Assessment in Dementia	GAL 24: 0.270 GAL 32: 0.055
GAL-INT-2	Disability Assessment in Dementia	0.004
GAL 95-05	Nuremberg Geriatric Observation Scale	0.032
GAL 93-01	Progressive Deterioration Scale 1	0.88
	IADL	0.07
GAL-USA-10	ADCS-ADL	GAL 8: 0.308 GAL 16: < 0.001 GAL 24: 0.003

- The evidence that galantamine has efficacy, in relation to placebo, as measured by the Neuropsychiatry Inventory or ADAS-NonCog , in treating behavioral manifestations of Alzheimer's Disease, is questionable. Both the Neuropsychiatry Inventory and ADAS-NonCog were secondary outcome measures. In the studies in which these outcome measures were used, the p-values for the galantamine-placebo comparisons were either not even nominally statistically significant ($p < 0.05$) or would not be nominally statistically significant if adjustment was made for multiple comparisons. It is also unclear if the very small drug-placebo treatment differences on the Neuropsychiatry Inventory are clinically meaningful. The results are in the table below

Note that the method of rating the CIBIC-Plus, in all efficacy studies in which that measure was used, included an assessment of behavioral symptoms, based on caregiver input.

A recent FDA Psychopharmacological Drugs Advisory Committee meeting (March 9, 2000) was held to discuss the development of drugs for behavioral manifestations of Alzheimer's Disease. Among the conclusions at the meeting were:

- Outcome measures should reflect not only behavioral symptoms but also functional outcomes
- There is a better consensus at to how to study psychosis, in contrast to agitation.

Study	Behavioral Measure	p-value for galantamine-placebo comparison
GAL-INT-2	Neuropsychiatry Inventory	0.546
GAL 95-05	ADAS-NonCog	"Not significant"*
GAL 93-01	ADAS-NonCog	0.92
GAL-USA-10	Neuropsychiatry Inventory	GAL 8: 0.871 GAL 16: 0.026 GAL 24: 0.021

*p-value > 0.05; exact p-value not provided

- **Overall, it may be concluded that galantamine (Reminyl®) has sufficient evidence of efficacy in comparison with placebo in treating the symptoms of mild to moderate Alzheimer's Disease to satisfy current regulatory requirements.**

- However, it should be noted that the beneficial effects of Reminyl® are small, and similar to those of other cholinesterase inhibitors, when compared with placebo; as with other cholinesterase inhibitors, only a small minority of patients actually improve in relation to baseline; the efficacy of galantamine (Reminyl®) beyond 6 months of treatment is uncertain, as randomized controlled studies longer than 6 months in duration have not been carried out. There is also no evidence that galantamine has a disease-modifying effect, and at least some evidence that it may not.
- Whether the small beneficial effects of galantamine outweigh the risks of its use is at present unclear, pending the completion of the NDA Safety Review by Dr Judith Racoosin and other members of her team.

16. Recommendation

I would recommend that galantamine be approved for marketing for the treatment of mild to moderate Alzheimer's Disease, if it is clear, after review of the safety component of this NDA, that the benefits of that drug outweigh the risks

/S/

Ranjit B. Mani, M.D.
Medical Reviewer

R. Katz, M.D. /S/

rbm 6/13/00
cc:
HFD-120
NDA 21169
Fanari

CLINICAL EFFICACY REVIEW OF NDA/Review of Draft Labeling

NDA	**21169**
Sponsor:	**Janssen**
Drug:	**Galantamine**
Proposed Indication:	**Alzheimer's Disease**
Material Submitted:	**New Drug Application/Draft Label**
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

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

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 efficacy review of both the original NDA and the amendment, which has been completed by me is in a separate document.

The draft labeling reviewed in this submission is the updated version submitted with the NDA Amendment of 2/25/00

The "Clinical Trials", "Indications and Usage" and "Dosing and Administration" sections have been reviewed. The sections of the sponsor's draft label that have been deleted have been highlighted using the "strike-through" feature. Added text has been highlighted in red.

2. Clinical Trials

DRAFT

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

5. Comments

5.1 Overall

- The labeling for Reminyl® has been re-drafted in a manner consistent with that for the following already-approved cholinesterase inhibitors: Cognex®, Aricept® and Exelon®.

5.2 Clinical Trials

- Detailed descriptions have been provided for the following key efficacy studies:GAL-USA-1, GAL-INT-1, GAL-INT-2 and GAL-USA-10
- Shorter descriptions have been provided for the additional efficacy studies: GAL 95-05 and GAL 93-01
- The sponsor's description of open-label extension studies has been deleted: these studies have no role in establishing the efficacy of a drug that is used to treat Alzheimer's Disease
- The sponsor's description of the Disability Assessment in Dementia (DAD) has been deleted. The evidence for efficacy on this activities of daily living scale was inconsistent across studies
- Although the evidence for efficacy using the ADCS-ADL, another measure of activities of daily living, was quite robust in GAL-USA-10, this was not a protocol-designated primary outcome measure, activities of daily living were already evaluated under the rubric of the CIBIC-Plus, and the evidence for efficacy on this measure was not evaluated in a second study.
- The evidence for efficacy based on the Neuropsychiatry Inventory was inconsistent across studies. Although the analysis of this measure in GAL-USA-10 was nominally statistically significant in favor of 2 doses of galantamine, it might no longer be significant when adjusted for multiple comparisons; furthermore the effect size seen is very small and may not be clinically meaningful.

5.3 Indications And Usage

- I have specified that the indication for REMINYL® is the treatment of mild to moderate dementia of the Alzheimer's type

5.4 Dosing And Administration

- This section has been expanded
- The effects of galantamine withdrawal have been described
- The "Doses In Special Populations" subsection has been rewritten after a discussion with the OCPB reviewers

6. Recommendation

Please see the main efficacy review for my recommendation in regard to Agency action on this New Drug Application.

/S/

Ranjit B. Mani, M.D.
Medical Reviewer

R. Katz, M.D. /S/

rbm 6/13/00
cc:
HFD-120
NDA 21169
Fanari