5.14 Efficacy Results

5.14.1 Patient Disposition

653 patients were randomized to the 3 treatment groups out of 753 patients who were screened. All 653 randomized patients received at least one dose of study medication. The study was conducted in 8 countries.

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:

	Placebo N=215	GAL 12 mg b.i.d. N=220	GAL 16 mg b.i.d. N=218
Discontinued for any reason, n (%)	29 (13.5%)	44 (20%)	55 (25.2%)
Discontinued in first 4 weeks	6 (2.8%)	21 (9.5%)	29 (13.3%)
Discontinued after 4 weeks	23 (10.7%)	23 (10.5%)	26 (11.9%)
Reasons for discontinuation:			
- adverse events	19 (8.8%)	31 (14.1%)	48 (22%)
- other reasons	3 (1.4%)	8 (3.6%)	4 (1.8%)
- non-compliance	4 (1.9%)	4 (1.8%)	1 (0.5%)
- insufficient response	3 (1.4%)	1 (0.5%)	0
- ineligibility to continue	0	0	2 (0.9%)

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.

5.14.2 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 were small.

Protocol deviations	Placebo N=215	GAL 12 mg b.i.d. N=220	GAL 16 mg b.i.d. N=218	Total N=653
Total no. of patients	10 (4.7%)	5 (2.3%)	13 (6.0%)	28 (4.3%)
No efficacy data	3 (1.4%)	2 (0.9%)	1 (0.5%)	6 (0.9%)
Investigator's mistake (suspected code breaking)	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.2%)
Concomitant disease	0 (0.0%)	0 (0.0%)	4 (1.8%)	4 (0.6%)
Wrong diagnosis	1 (0.5%)	1 (0.5%)	0 (0.0%)	2 (0.3%)
Non-compliance	7 (3.3%)	2 (0.9%)	9 (4.1%)	18 (2.8%)

5.14.3 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 2 tables. The incidence of concomitant illnesses also appears to have been similar across treatment groups

Baseline characteristics	Placebo N=215	GAL 12 mg b.i.d. N=220	GAL 16 mg b.i.d. N=218	Total N=653
Sex: n (%)				
Male	83 (38.6%)	81 (36.8%)	80 (36.7%)	244 (37.4%)
Female	132 (61.4%)	139 (63.2%)	138 (63.3%)	409 (62.6%)

Baseline characteristics	Placebo N=215	GAL 12 mg b.i.d. N=220	GAL 16 mg b.i.d. N=218	Total N=653
Race: n (%)				
White	212 (99.5%)	217 (99.5%)	215 (99.1%)	644 (99.4%)
Black	0	0	2 (0.9%)	2 (0.3%)
Other	1 (0.5%)	1 (0.5%)	0	2 (0.3%)
Age, years (mean ± SE)	72.7 ±0.52	71.9 ±0.56	72.1 ±0.58	72.2 ±0.32
Body weight, kg (mean ± SE)	67.2 ±0.83	66.7 ±0.86	66.2 ±0.91	66.7 ±0.5
Smoker: n (%)	22 (10.2%)	20 (9.1%)	19 (8.7%)	61 (9.3%)
Age at onset of cognitive problems, years (mean ± SE)	69.7 ±0.55	68.8 ±0.6	68.9 ±0.61	69.1 ±0.34
Years since cognitive problem diagnosis (mean ± SE)	3.5 ±0.16	3.6±0.18	3.7±0.15	3.6±0.1
Age at diagnosis of probable AD, years (mean ± SE)	72.4 ±0.51	71.5 ±0.57	71.8 ±0.58	71.9 ±0.32
Years since diagnosis of AD (mean ± SE)	0.8 ±0.07	0.9 ±0.08	0.8 ±0.07	0.8 ±0.04
Relative(s) had AD, n (%)	75 (34.9%)	80 (36.4%)	63 (28.9%)	218 (33.4%)
Participated in cholinomimetics trial, n (%)	3 (1.4%)	5 (2.3%)	2 (0.9%)	10 (1.5%)
Total MMSE score (mean ± SE)	19.3 ±0.24	19.5 ±0.23	19 ±0.26	19.3 ±0.14
ADAS-cog/11 score (mean ± SE)	24.7 ±0.64	25.4 ±0.64	26.2 ±0.72	25.4 ±0.39
Apo- E type, n (%):				
4-4	34 (18.4%)	32 (17.4%)	27 (15.1%)	93 (17.0%)
2-4/3-4	83 (44.9%)	97 (52.7%)	95 (53.1%)	275 (50.2%)
2-2/2-3/3-3	68 (36.8%)	55 (29.9%)	57 (31.8%)	180 (32.8%)

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. 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	7.9 %	24.1 %	28.9 %

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

5.14.4 Primary Efficacy Analysis

5.14.4.1 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 Month 3. The treatment by country interaction was not significant

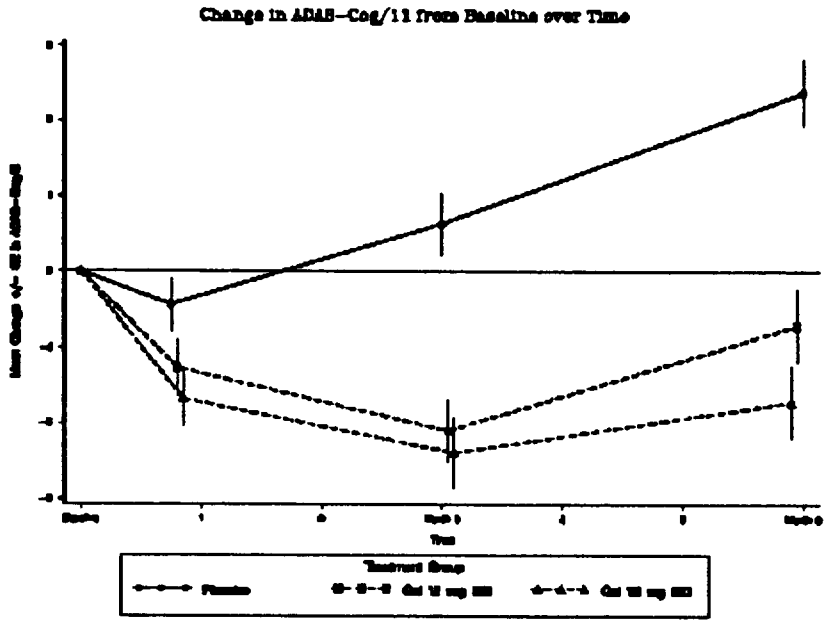
The table below shows mean scores and changes from baseline for the Observed Cases dataset (all patients)

	Placebo			Gal 12 mg b.i.d.			Gal 16 mg b.i.d.		
Time Point	n	Mean ±SE	Mean Change ±SE	n	Mean ±SE	Mean Change ±SE	n	Mean ±SE	Mean Change ±SE
Baseline	211	24.7 ±0.64		212	25.4 ±0.64		212	26.2 ±0.72	
Week 3	201	24.1 ±0.70	-0.4 ±0.36	197	24.0 ±0.66	-1.3 ±0.36	200	24.7 ±0.71	-1.7* ±0.37
Month 3	192	25.2 ±0.75	0.6 ±0.42	171	23.0 ±0.74	-2.1*** ±0.42	159	24.0 ±0.81	-2.4*** ±0.46
Month 6	171	26.7 ±0.83	2.4 ±0.44	156	24.0 ±0.74	-0.7*** ±0.48	152	24.6 ±0.86	-1.7*** ±0.47

Source: Display 13

*: p<0.05, ***: p<0.001, p-value for pairwise comparison 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; the 32 mg/day dose group showed a consistent improvement from baseline as compared with the placebo group which showed an overall deterioration.

	Placebo			Gal 12 mg b.i.d.			Gal 16 mg b.i.d.		
Time Point	n	Mean ±SE	Mean Change ±SE	n	Mean ±SE	Mean Change ±SE	n	Mean ±SE	Mean Change ±SE
Month 6	171	26.7 ±0.83	2.4 ±0.44	156	24.0 ±0.74	-0.7*** ±0.48	152	24.6 ±0.86	-1.7*** ±0.47
Trad. LOCF	207	27.0 ±0.78	2.2 ±0.40	201	24.8 ±0.69	-0.6*** ±0.40	205	24.9 ±0.73	-1.3*** ±0.38

	Placebo			Gal 12 mg b.i.d.			Gal 16 mg b.i.d.		
Time Point	n	Mean ±SE	Mean Change ±SE	n	Mean ±SE	Mean Change ±SE	n	Mean ±SE	Mean Change ±SE
Observed case+ ret. D.O.	178	26.7 ±0.81	2.4 ±0.42	168	24.0 ±0.70	-0.4*** ±0.46	171	25.5 ±0.89	-1.0*** ±0.51
Class. ITT	215	27.3 ±0.78	2.4 ±0.41	220	25.1 ±0.67	-0.5*** ±0.38	217	25.6 ±0.78	-0.8*** ±0.43

Source: Display 13 and Display 14

***: p<0.001, p-value for pairwise comparison with placebo

5.14.4.2 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 scores	Placebo n=174		Gal 12 mg b.i.d. n=161		Gal 16 mg b.i.d. n=155	
	n (%)	Cum. %	n (%)	Cum. %	n (%)	Cum. %
Markedly improved	0	0%	0	0%	0	0%
Moderately improved	1 (0.6%)	0.6%	6 (3.7%)	3.7%	8 (5.2%)	5.2%
Minimally improved	29 (16.7%)	17.2%	27 (16.8%)	20.5%	35 (22.6%)	27.7%
No change	56 (32.2%)	49.4%	75 (46.6%)	67.1%	63 (40.6%)	68.4%
Minimally worsened	58 (33.3%)	82.8%	43 (26.7%)	93.8%	41 (26.5%)	94.8%
Moderately worsened	28 (16.1%)	98.9%	7 (4.3%)	98.1%	8 (5.2%)	100%
Markedly worsened	2 (1.1%)	100%	3 (1.9%)	100%	0	100%

Source: Display 16

p=0.023 for GAL 12 mg b.i.d. and 16 mg b.i.d. compared to 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

Classical Intent-to-treat

CIBIC-Plus Rating	Placebo N=203	Galantamine 24 mg/day N=206	Galantamine 32 mg/day N=198	p-values
Moderately improved (%)	0.5	3.4	4.5	Gal 24 vs placebo: 0.038
Minimally improved (%)	15.8	14.1	19.7	Gal 32 vs placebo: <0.001
Unchanged (%)	33.5	44.2	40.9	
Minimally worse (%)	33.5	27.7	27.3	
Moderately worse (%)	15.8	8.3	7.1	
Markedly worse (%)	1.0	2.4	0.5	

LOCF

CIBIC-Plus Rating	Placebo N=199	Galantamine 24 mg/day N=191	Galantamine 32 mg/day N=183	p-values
Moderately improved (%)	0.5	3.7	5.5	Gal 24 vs placebo: 0.015 Gal 32 vs placebo: <0.001
Minimally improved (%)	15.6	15.2	23.0	
Unchanged (%)	35.7	46.1	38.3	
Minimally worse (%)	33.2	27.2	27.9	
Moderately worse (%)	14.1	6.3	5.5	
Markedly worse (%)	1.0	1.6	0.0	

Observed Cases plus Retrieved Dropouts

CIBIC-Plus Rating	Placebo N=182	Galantamine 24 mg/day N=173	Galantamine 32 mg/day N=174	p-values
Moderately improved (%)	0.5	3.5	4.6	Gal 24 vs placebo: 0.002 Gal 32 vs placebo: <0.001
Minimally improved (%)	15.9	16.2	20.1	
Unchanged (%)	31.3	45.1	40.2	
Minimally worse (%)	34.1	27.2	27.6	
Moderately worse (%)	17.0	5.2	6.9	
Markedly worse (%)	1.1	2.9	0.6	

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

Observed Cases

	Placebo		Gal 12 mg bid		Gal 16 mg bid	
	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD
Month 6 scores	174	4.51 ± 1.01	161	4.17 ± 0.95	155	4.04 ± 0.95
p-values vs placebo			0.038		<0.001	

LOCF

	Placebo		Gal 12 mg bid		Gal 16 mg bid	
	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD
Month 6 scores	199	4.48 ± 0.97	191	4.22 ± 0.96	183	4.05 ± 0.97
p-values vs placebo			0.015		<0.001	

5.14.5 Analysis Of Secondary Efficacy Measures

5.14.5.1 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 b.i.d.			Gal 16 mg b.i.d.		
Time Point	n	Mean ±SE	Mean Change ±SE	n	Mean ±SE	Mean Change ±SE	n	Mean ±SE	Mean Change ±SE
Baseline	210	66.6 ±1.55		212	69.9 ±1.47		214	69.6 ±1.41	
Month 3	190	64.6 ±1.63	-2.7 ±0.93	172	70.4 ±1.77	0.6* ±0.96	157	68.3 ±1.75	-0.7 ±1.09
Month 6	177	62.2 ±1.82	-5.2 ±1.21	159	67.1 ±1.95	-2.7 ±1.17	157	68.2 ±1.88	-1.4C ±1.32

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	0.270
Galantamine 32 mg/day vs placebo	0.055

On the DAD clusters, the galantamine 32 mg/day group was superior to placebo at a statistically significant level (p=0.006) on the planning/organization cluster for the Observed Cases dataset at Month 6 as indicated by the following table

DAD cluster	Placebo			Gal 12 mg b.i.d.			Gal 16 mg b.i.d.		
	n	Mean ±SE	Mean Change ±SE	n	Mean ±SE	Mean Change ±SE	n	Mean ±SE	Mean Change ±SE
Initiation	177	67.3 ±1.80	-4.4 ±1.28	159	72.0 ±1.89	-4.0 ±1.23	157	73.2 ±1.84	-2.5 ±1.42
Planning/ organization	177	55.3 ±2.10	-6.8 ±1.53	159	59.9 ±2.34	-2.2C ±1.55	157	62.5 ±2.27	-0.1** ±1.74
Performance	177	62.3 ±1.91	-5.0 ±1.39	159	67.4 ±2.02	-2.0 ±1.36	157	67.6 ±1.99	-1.3 ±1.52
Basic	177	82.5 ±1.75	-4.3 ±1.18	159	86.2 ±1.62	-4.0 ±1.32	157	87.0 ±1.62	-2.3 ±1.12
Instrumental	177	44.5 ±2.29	-7.0 ±1.96	159	49.8 ±2.64	-1.6C ±1.63	157	51.2 ±2.48	-1.2C ±2.04
Leisure	174	53.4 ±2.86	-3.3 ±2.43	158	59.7 ±3.07	-4.8 ±2.68	149	65.6 ±2.88	-0.1 ±2.94

5.14.5.2 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 for the Observed Cases dataset at Month 6

Cluster	Drug-Placebo Difference For Mean Change From Baseline		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

5.14.5.3 ADAS-Cog Responder Analysis

The galantamine 24 mg/day and galantamine 32 mg/day dose groups were almost consistently superior to placebo as indicated by the following table for the Observed Cases dataset at Month 6

Category (based on improvement in ADAS-Cog score)	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

5.14.5.4 Psychological General Well-Being Index

No statistically significant differences between treatment groups were seen for either total or cluster scores as indicated by the following table. Neither is there any indication from the table of a trend to a drug effect at either dose.

	Placebo			GAL 12 mg b.i.d.			GAL 16 mg b.i.d.		
PGWB	n	Mean ± SE	Mean Change ± SE	n	Mean ± SE	Mean Change ± SE	n	Mean ± SE	Mean Change ± SE
Total PGWB	149	75.2 ±1.48	-1.1 ± 0.97	138	78.0 ± 1.42	-1.3 ± 1.12	132	79.5 ±1.37	-0.7 ± 0.94
Anxiety	152	17.3 ± 0.4	0.2 ±0.3	142	17.8 ± 0.38	0.0 ± 0.34	133	18 ± 0.4	-0.2 ± 0.28
Depression	153	11.7 ± 0.24	-0.1 ±0.2	143	12.2 ± 0.22	-0.1 ± 0.19	136	12.3 ± 0.21	-0.1 ± 0.16
Positive well-being	150	11.1 ± 0.3	-0.2 ± 0.21	142	11.9 ± 0.27	0.1 ± 0.26	133	12 ± 0.29	-0.4 ± 0.21
Self-control	152	11.4 ±0.24	-0.4 ± 0.19	141	12.3 ± 0.22	-0.0 ± 0.22	135	12.3 ± 0.21	0.0 ± 0.19
General health	151	10.5 ±0.24	0.0 ± 0.19	142	10.8 ± 0.26	-0.5 ± 0.21	135	11.2 ± 0.24	0.0 ± 0.21
Vitality	151	13.1 ± 0.28	-0.6 ± 0.22	142	13.2 ± 0.28	-0.6 ± 0.25	133	13.8 ± 0.29	-0.1 ± 0.25

5.14.5.5 Health/Social Care Resource Utilization

The results of the analysis that was performed on the allocation of caregiver time survey were as follows

- The time that the patient could be left alone on a typical day
  - Declined in the placebo group so that the difference between baseline and 6 months was statistically significant ($p < 0.001$)

- Declined to a lesser degree in the 2 active treatment groups and was not statistically significant in each of these groups in comparison with baseline

P-values for comparisons between treatment groups are not provided but the differences are reported to be not statistically significant

- The total daily time spent by the caregiver in assisting the patient in activities of daily living
  - Increased steadily between baseline and Month 6 in the placebo group, with the difference over that period for that group (p=0.027)
  - Decreased between baseline and Month 6 in each of the 2 treatment groups; however the p-values for the change in each group were not statistically significant (p-values of 0.830 and 0.866 for the galantamine 24 mg/day and 32 mg/day groups, respectively)

P-values for comparisons between treatment groups are not provided but the differences are reported to be not statistically significant

These data are summarized in the following table

	Placebo			GAL 12 mg b.i.d.			GAL 16 mg b.i.d.		
	n	Mean ± SE	Mean Change ± SE	n	Mean ± SE	Mean Change ± SE	n	Mean ± SE	Mean Change ± SE
Time patient can be left alone (minutes per day)									
- baseline	212	670.4 ±39.4	---	217	611.5 ±37.9	---	216	600.6 ±37.5	---
- month 6	183	567.5 ±41.3	-117 ±32.1	166	552.7 ±41.7	-35.2 ±32.7	160	608.2 ±46.4	-18.7 ±34.1
Caregiver time spent on all activities (minutes per day)									
- baseline	211	155.7 ±22.5	---	215	178.5 ±25.9	---	217	136.2 ±13.8	---
- month 6	182	160.9 ±14.9	22.6 ±16.4	165	152.6 ±13.2	-38 ±30.7	160	126.1 ±11	-14.9 ±16.2

5.15 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 over the period of the study
- Responder rates on the ADAS-Cog were better at a statistically significant level for each of the galantamine groups in comparison with placebo
- Although all treatment groups worsened on this measure over the course of the study, the galantamine 32 mg/day group showed a statistically significant superiority to placebo at Month 6 for the Disability Assessment for Dementia

5.16 Reviewer's Comments

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

- Neither galantamine groups was superior to placebo on the Total Disability Assessment for Dementia score

6. Pooled Analysis For GAL-USA-1 And GAL-INT-1

Since GAL-USA-1 and GAL-INT-1 were identical in design the sponsor has performed a pooled analysis of the efficacy data for both studies. The results for both primary outcome measures (ADAS-Cog and CIBIC-Plus) and for a single secondary outcome measure (Disability Assessment For Dementia) are summarized below

6.1 Pooled ADAS-Cog Analysis

The results of the Observed Cases analysis are shown below. In the pooled analysis, as in the individual studies, both galantamine dose groups showed a statistically significant superiority to placebo

The table below shows mean scores and changes from baseline for the Observed Cases dataset for the individual studies as well as for the pooled analysis.

Treatment	N	Within-Group Observed Mean		Change from Baseline at Month 6						
				Within-Group Change				Difference from Placebo		
		Baseline	Month 6	Mean[a]	SE	LSMean	SE	LSMean	SE	p value[b]
USA-1										
Placebo	357	24.5	26.7	2.2***	0.52	2.0	0.51	--	--	--
GAL 24 mg/day	331	24.1	22.4	-1.7***	0.45	-1.6	0.55	-3.6	0.73	<0.001
GAL 32 mg/day	317	25.4	23.9	-1.6*	0.66	-1.7	0.58	-3.7	0.75	<0.001
INT-1										
Placebo	171	24.3	26.7	2.4***	0.44	2.2	0.46	--	--	--
GAL 24 mg/day	156	24.7	24.0	-0.7	0.48	-0.8	0.48	-3.1	0.65	<0.001
GAL 32 mg/day	152	26.3	24.6	-1.7***	0.47	-1.9	0.49	-4.1	0.65	<0.001
USA-1 + INT-1										
Placebo	328	24.4	26.7	2.3***	0.34	2.3	0.33	--	--	--
GAL 24 mg/day	287	24.4	23.3	-1.2***	0.33	-1.2	0.36	-3.4	0.49	<0.001
GAL 32 mg/day	269	25.9	24.3	-1.6***	0.39	-1.7	0.37	-3.9	0.50	<0.001

a: Within group paired t-test for change from baseline = 0: *: p = 0.05, **: p = 0.01, ***: p = 0.001
b: Comparison with placebo from the two-way ANOVA model.

The results of the analyses of the Classical Intent-To-Treat and other datasets were similar

Based on the above pooled analysis, the galantamine 32 mg/day group has been compared with the galantamine 24 mg in the following table; the difference in efficacy between the groups was clinically negligible and not statistically significant

Comparison	ADAS-Cog Mean Change from Baseline at Month 6: Difference Between Treatment Groups. Observed Cases	p-value
GAL 32 vs GAL 24	-0.5	0.330

6.2 Pooled CIBIC-Plus Analysis

The results of the Observed Cases analysis are shown below. In the pooled analysis, as in the individual studies, both galantamine dose groups showed a statistically significant superiority to placebo

The table below shows mean scores and changes from baseline for the Observed Cases dataset, for the individual studies as well as for the pooled analysis. The analysis is based on the original 7-point scale.

The results of the analyses of the Classical Intent-To-Treat and other datasets were similar

Treatment	N	Improved			No Change N (%)	Worse			p-value[a]
		Markedly N (%)	Moderately N (%)	Minimally N (%)		Minimally N (%)	Moderately N (%)	Markedly N (%)	
USA-1									
Placebo	159	0 (0)	7 (4.4)	14 (8.8)	67 (42.1)	47 (29.6)	23 (14.5)	1 (0.6)	—
GAL 24 mg/day	135	1 (0.7)	4 (3.0)	22 (16.3)	68 (50.4)	29 (21.5)	8 (5.9)	3 (2.2)	0.023
GAL 32 mg/day	118	2 (1.7)	4 (3.4)	17 (14.4)	57 (48.3)	30 (25.4)	7 (5.9)	1 (0.8)	0.017
INT-1									
Placebo	174	0 (0)	1 (0.6)	29 (16.7)	56 (32.2)	58 (33.3)	28 (16.1)	2 (1.1)	—
GAL 24 mg/day	161	0 (0)	6 (3.7)	27 (16.8)	75 (46.6)	43 (26.7)	7 (4.3)	3 (1.9)	0.002
GAL 32 mg/day	155	0 (0)	8 (5.2)	35 (22.6)	63 (40.6)	41 (26.5)	8 (5.2)	0 (0)	<0.001
USA-1 + INT-1									
Placebo	333	0 (0)	8 (2.4)	43 (12.9)	123 (36.9)	105 (31.5)	51 (15.3)	3 (0.9)	—
GAL 24 mg/day	296	1 (0.3)	10 (3.4)	49 (16.6)	143 (48.3)	72 (24.3)	15 (5.1)	6 (2.0)	<0.001
GAL 32 mg/day	273	2 (0.7)	12 (4.4)	52 (19.9)	120 (44.0)	71 (26.0)	15 (5.5)	1 (0.4)	<0.001

a: Van Elteren test for comparison with placebo

For the pooled analysis the pairwise comparison between the galantamine 24 mg/day and galantamine 32 mg/day groups was not statistically significant (p=0.527)

6.3 Pooled Disability Assessment For Dementia Analysis

The results of the Observed Cases analysis (for Total Disability Assessment for Dementia scores) are shown below. In the pooled analysis, the galantamine 32 mg/day group showed a statistically significant superiority to placebo that reached statistical significance

The table below shows mean scores and changes from baseline for the Observed Cases dataset, for the individual studies, as well as for the pooled analysis.

		Within-Group Observed Mean		Change from Baseline at Month 6						
				Within-Group Change				Difference from Placebo		
Treatment	N	Baseline	Month 6	Mean[a]	SE	LSMean	SE	LSMean	SE	p-value[b]
USA-1										
Placebo	164	72.7	70.0	-2.8**	1.23	-2.5	1.22	-	-	-
GAL 24 mg/day	139	71.7	68.8	-2.9**	1.27	-3.0	1.31	-0.5	1.75	0.943
GAL 32 mg/day	117	70.1	68.4	-1.7	1.46	-1.8	1.43	0.7	1.83	0.904
INT-1										
Placebo	177	67.5	62.2	-5.2***	1.21	-5.7	1.23	-	-	-
GAL 24 mg/day	159	69.8	67.1	-2.7*	1.17	-3.3	1.31	2.5	1.73	0.270
GAL 32 mg/day	157	69.6	68.2	-1.4	1.32	-1.9	1.30	3.8	1.74	0.055
USA-1 + INT-1										
Placebo	341	70.0	65.9	-4.0***	0.86	-4.0	0.84	-	-	-
GAL 24 mg/day	298	70.7	67.9	-2.8***	0.86	-2.8	0.90	1.2	1.24	0.317
GAL 32 mg/day	274	69.8	68.3	-1.5	0.96	-1.5	0.94	2.6	1.27	0.043

a: Within group paired t-test for change from baseline = 0: * p=0.05; ** p=0.01; *** p=0.001.
b: Comparison with placebo from the two-way ANOVA model.

For the pooled analysis the pairwise comparison between the galantamine 24 mg/day and galantamine 32 mg/day groups was not statistically significant (p=0.309)

6.4 Pooled Analyses Of Subgroups

The sponsor has performed analyses of the influence of demographic and baseline variables, genotype, baseline disease severity, years since onset of cognitive problems and years since diagnosis of probable Alzheimer's Disease, using the pooled efficacy data (primary outcome measures only) from GAL-USA-1 and GAL-INT-1. These analyses are summarized below:

6.4.1 Demographic And Baseline Variables, And Genotype

The tables below indicate that the efficacy of galantamine in doses of 24 mg/day and 32 mg/day, as based on the ADAS-Cog and CIBIC-Plus, was not influenced by these variables. The tables below refer to Observed Cases. Note that the CIBIC-Plus scores are collapsed into 2 categories ("improved or unchanged" and "worse") and that the percentages in the table refer to those in the "improved or unchanged" category.

ADAS-Cog

Subgroup Variable	Change from Baseline at Month 6 in ADAS-cog/11					
		Placebo		GAL 24 mg/day		GAL 32 mg/day
	N	Mean(95%CI)	N	Mean(95%CI)	N	Mean (95%CI)
Age						
<65 years	45	2.0(0.1, 3.8)	43	-1.8(-3.5, 0.0)*	47	0.2(-1.3, 1.8)
65-85 years	271	2.3(1.6, 3.0)	233	-0.9(-1.7,-0.2)*	208	-2.2(-3.1,-1.3)*
>85 years	12	3.2(-2.1, 8.5)	11	-3.4(-7.9, 1.2)*	14	0.0(-3.9, 3.9)
Race						
White	315	2.4 (1.7, 3.1)	275	-1.2 (-1.8,-0.5)*	259	-1.7 (-2.5, -0.9)*
Non-White	12	-1.6 (-5.6, 2.4)	11	-0.5 (-2.2, 1.3)	9	-0.9 (-4.5, 2.7)
First Degree Relative with Alzheimer Disease						
Yes	117	1.3 (0.3, 2.3)	102	-2.1 (-3.0,-1.2)*	78	-0.8 (-2.1, 0.5)*
No	211	2.8 (2.0, 3.7)	185	-0.6 (-1.5, 0.2)*	191	-2.0 (-3.0, -1.1)*
Gender						
Female	200	2.2 (1.3, 3.0)	165	-0.9 (-1.8,-0.1)*	149	-1.7 (-2.7,-0.6)*
Male	128	2.4 (1.3, 3.5)	122	-1.4 (-2.5,-0.4)*	120	-1.6 (-2.8, -0.5)*
Smoker						
No	301	2.3 (1.6, 3.0)	261	-1.1 (-1.8,-0.4)*	241	-1.8 (-2.6, -0.9)*
Yes	26	2.1 (-0.2, 4.3)	26	-1.8 (-4.3, 0.7)*	28	-0.7 (-2.8, 1.3)
Weight (Median by Gender)						
< Median	151	1.9 (0.9, 3.0)	127	-1.1 (-2.1,-0.2)*	120	-1.8 (-2.9, -0.6)*
≥ Median	173	2.6 (1.7, 3.5)	159	-1.2 (-2.1,-0.3)*	147	-1.7 (-2.7,-0.7)*
APO-E Genotype						
22/23/33	112	2.1 (0.8, 3.3)	86	-1.7 (-3.0,-0.5)*	79	-1.5 (-2.8,-0.1)*
24/34/44	180	2.5 (1.6, 3.4)	169	-0.9 (-1.7,-0.0)*	158	-1.5(-2.6,-0.5)*

* significantly different (p≤0.05) from placebo based on the 2-way ANOVA model

CIBIC-Plus

Subgroup Variable	Number (%) of Patients with Improved or Unchanged CIBIC-Plus Scores (1-4)					
		Placebo		GAL 24 mg		GAL 24 mg
	N	n (%)	N	n (%)	N	n (%)
Age						
<65 years	48	27 (56.3)	44	24 (54.5)	49	34 (69.4)
65-85 years	273	140 (51.3)	242	172 (71.1)*	213	144 (67.6)*
>85 years	12	7 (58.3)	10	7 (70.0)	11	8 (72.7)
Race						
White	321	169 (52.6)	285	198 (69.5)*	263	178 (67.7)*
Non-White	12	5 (41.7)	10	4 (40.0)	9	7 (77.8)
First Degree Relative with Alzheimer Disease						
Yes	118	69 (58.5)	103	71 (68.9)	80	45 (56.3)
No	215	105 (48.8)	193	132 (68.4)*	193	141 (73.1)*
Gender						
Female	207	103 (49.8)	175	116 (66.3)*	149	104 (69.8)*
Male	126	71 (56.3)	121	87 (71.9)*	124	82 (66.1)
Smoker						
No	306	157 (51.3)	270	185 (68.5)*	244	169 (69.3)*
Yes	26	16 (61.5)	26	18 (69.2)	29	17 (58.6)
Weight (Median by Gender)						
< Median	156	82 (52.6)	129	84 (65.1)*	121	80 (66.1)*
≥ Median	173	89 (51.4)	166	118 (71.1)*	150	105 (70.0)*
APO-E Genotype						
22/23/33	110	66 (60.0)	91	62 (68.1)	79	49 (62.0)
24/34/44	185	92 (49.7)	170	114 (67.1)*	160	114 (71.3)*

* significantly different (p≤0.05) from placebo based on CMH test controlling for trial effect

6.4.2 Baseline Disease Severity

The tables below indicate that the efficacy of galantamine in doses of 24 mg/day and 32 mg/day, as based on the ADAS-Cog and CIBIC-Plus, was influenced by baseline disease severity, as assessed by baseline ADAS-Cog and Mini Mental Status Examination as follows.

- The efficacy of both galantamine doses in all subgroups was maintained at a statistically significant level, on both outcome measures, except in those with an ADAS-Cog score < 20
- The effect sizes as measured by the ADAS-Cog mean change from baseline score and CIBIC-Plus score (drug-placebo difference) at Month 6 appeared to increase with increasing severity of dementia at baseline for both dose groups

The tables below refer to Observed Cases. Note that the CIBIC-Plus scores are collapsed into 2 categories ("improved or unchanged" and "worse") and that the percentages in the table refer to those in the "improved or unchanged" category.

ADAS-Cog

Subgroup	Change from Baseline at Month 6 in ADAS-cog/11					
		Placebo		GAL 24 mg/day		GAL 32 mg/day
Variable	N	Mean (95%CI)	N	Mean (95%CI)	N	Mean (95%CI)
Baseline ADAS-Cog/11						
<20	113	1.0 (0.1, 1.9)	95	0.4 (-0.5, 1.3)	89	0.8 (-0.3, 1.8)
20-30	136	2.3 (1.1, 3.5)	119	-0.9 (-2.0, 0.2)*	95	-1.8 (-2.9,-0.8)*
>30	79	3.9 (2.6, 5.2)	73	-3.6 (-5.0,-2.3)*	85	-4.0 (-5.7, -2.3)*
Baseline MMSE Score						
<18	87	5.3 (3.9, 6.7)	79	-1.3 (-2.9, 0.4)*	92	-2.4 (-4.0, -0.8)*
≥ 18	241	1.2 (0.5, 1.9)	208	-1.1 (-1.8,-0.4)*	177	-1.2 (-2.1,-0.4)*

* significantly different (p≤0.05) from placebo based on the 2-way ANOVA model

CIBIC-Plus

Subgroup	Number (%) of Patients with CIBIC-Plus Scores Improved or Unchanged (1-4)					
		Placebo		GAL 24 mg		GAL 24 mg
Variable	N	n (%)	N	n (%)	N	n (%)
Baseline ADAS-Cog/11						
<20	113	76 (67.3)	92	69 (75.0)	90	70 (77.8)
20-30	133	69 (51.9)	118	79 (66.9)*	92	65 (70.7)*
>30	84	28 (33.3)	76	48 (63.2)*	87	49 (56.3)*
Baseline MMSE Score						
<18	94	34 (36.2)	85	49 (57.6)*	96	57 (59.4)*
≥ 18	239	140 (58.6)	211	154 (73.0)*	177	129 (72.9)*

* significantly different (p≤0.05) from placebo based on CMH test controlling for trial effect

6.4.3 Years Since Onset Of Cognitive Difficulties And Since Diagnosis Of Alzheimer's Disease

The tables below indicate that the efficacy of galantamine in doses of 24 mg/day and 32 mg/day, as based on the ADAS-Cog and CIBIC-Plus, was influenced by the number of years since the onset of cognitive difficulty and the number of years since diagnosis of Alzheimer's Disease as follows.

- The efficacy of both galantamine doses in all subgroups was maintained at a statistically significant level, on both outcome measures.
- The effect sizes as measured by the ADAS-Cog mean change from baseline score (drug-placebo difference) at Month 6 appeared to, in general, increase with increasing duration since onset of cognitive difficulty and diagnosis of Alzheimer's Disease. In contrast, no clear trend to an increase or decrease in effect sizes was seen, using the CIBIC-Plus, with either increasing or decreasing duration since onset of cognitive difficulty and diagnosis of Alzheimer's Disease

The tables below refer to Observed Cases. Note that the CIBIC-Plus scores are collapsed into 2 categories ("improved or unchanged" and "worse") and that the percentages in the table refer to those in the "improved or unchanged" category.

ADAS-Cog

Subgroup Variable	Change from Baseline at Month 6 in ADAS-cog/11					
		Placebo		GAL 24 mg/day		GAL 32 mg/day
	N	Mean (95%CI)	N	Mean (95%CI)	N	Mean (95%CI)
Years since onset of cognitive problems (by Tertile)						
≤2.3 years	114	1.2 (-0.1, 2.5)	104	-1.0 (-2.1, 0.0*)	82	-1.0 (-2.4, 0.4)*
2.4-4.2 years	107	2.0 (0.9, 3.1)	98	-0.1 (-1.3, 1.2)*	94	-2.6 (-4.0, -1.3)*
≥4.3 years	107	3.6 (2.6, 4.7)	84	-2.6 (-3.7,-1.4)*	91	-1.4 (-2.7, -0.1)*
Years since diagnosis of probable Alzheimer's disease (by Tertile)						
≤0.2 year	126	1.3 (0.2, 2.4)	105	-1.4 (-2.5,-0.4)*	97	-1.6 (-2.9, -0.3)*
0.3-0.9 year	98	2.4 (1.2, 3.6)	92	-1.0 (-2.3, 0.4)*	75	-1.6 (-2.9, -0.2)*
≥1.0 year	104	3.3 (2.1, 4.5)	89	-1.2 (-2.2,-0.2)*	97	-1.8, (-3.1, -0.4)*

* significantly different (p≤0.05) from placebo based on the 2-way ANOVA model

CIBIC-Plus

Subgroup Variable	Number (%) of Patients with CIBIC-Plus Scores Improved or Unchanged (1-4)					
		Placebo		GAL 24 mg		GAL 24 mg
	N	n (%)	N	n (%)	N	n (%)
Years since onset of cognitive problems (by Tertile)						
≤2.3 years	116	63 (54.3)	112	77 (68.8)*	84	61 (72.6)*
2.4-4.2 years	111	61 (55.0)	100	70 (70.0)*	94	68 (72.3)*
≥4.3 years	106	50 (47.2)	83	55 (66.3)*	93	56 (60.2)*
Years since diagnosis of probable Alzheimer's disease (by Tertile)						
≤0.2 year	129	70 (54.3)	107	80 (74.8)*	101	71 (70.3)*
0.3-0.9 year	101	48 (47.5)	96	61 (63.5)*	76	49 (64.5)*
≥1.0 year	103	56 (54.4)	92	61 (66.3)	96	66 (68.8)*

Significantly different (p≤ 0.05) from placebo based on CMH test controlling for trial effect.

Note the error in the above table: the last column should be headed GAL 32 mg.

6.5 Reviewer's Comments

- There was no evidence, using the pooled analysis, that the galantamine 32 mg/day dose was superior to the galantamine 24 mg/day dose on the ADAS-Cog, CIBIC-Plus or Disability Assessment for Dementia
- In post-hoc analyses of subgroups delineated by demographic and baseline variables, genotype, baseline disease severity, years since onset of cognitive problems and years since diagnosis of probable Alzheimer's Disease, the efficacy of galantamine in doses of 24 mg/day and 32 mg/day was maintained across virtually all subgroups using the ADAS-Cog and CIBIC-Plus as outcome measures. The analyses suggested that greater treatment effects were seen with greater baseline disease severity and with increasing duration at baseline since the onset of cognitive difficulties and since the diagnosis of Alzheimer's Disease

7. Study GAL-INT-2

7.1 Title

Galantamine in the treatment of Alzheimer's Disease: flexible dose-range trial

7.2 Objective

7.2.1 Primary

To evaluate the efficacy and safety of galantamine using a flexible dose-range trial

7.2.2 Secondary

- To evaluate the effects of galantamine on activities of daily living and sleep
- To document the plasma concentrations and pharmacokinetics of galantamine in the Alzheimer's Disease population

7.3 Design

Randomized (2:1), double-blind, placebo-controlled, parallel-arm, flexible-dose study

7.4 Dosage

Galantamine 24 to 32 mg/day (12 mg b.i.d to 16 mg b.i.d)
Placebo

The titration regime used was as follows:

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

7.5 Duration

12 weeks of double-blind treatment

7.6 Sample Size

402 patients to be randomized to the galantamine and placebo groups in a 2:1 ratio

7.7 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

7.8 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. Patients who had participated in previous trials with M_1 muscarinic agonists could be included if a 30-day period was allowed to elapse between the last dose of the muscarinic agonist and the enrollment into GAL-INT-2
- 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

7.9 Concomitant Medications

7.9.1 Prohibited Medications

These are listed above

7.9.2 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

7.10 Efficacy Outcome Measures

7.10.1 Primary Efficacy Measures

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

7.10.2 Secondary Efficacy Measures

Disability Assessment For Dementia (total and cluster scores; 6 separate clusters were to be used)
Neuropsychiatry Inventory
ADAS-Cog/13
ADAS-Cog/10
ADAS-Cog/mem

7.11 Analysis Plan

7.11.1 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

7.11.2 Demographic And Baseline Characteristics

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

7.11.3 Primary Efficacy Parameters

- The primary efficacy parameters were the change from baseline in ADAS-Cog at 3 months and the CIBIC-Plus at 3 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 primary analysis was to be on Observed Cases at 3 months
- The primary efficacy parameters would be compared between the treatment groups not only at the end of the study but also during the study course using graphical displays
- For continuous data (i.e., ADAS-Cog) a 2-way ANOVA model would be used, with treatment and country/investigator as factors, to compare treatment groups. The interaction of treatment with country/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, gender 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. If a parametric method was not appropriate (normality assumption violated), a non-parametric method (e.g., the Wilcoxon ranked sum test or the van Elteren test controlling for country/investigator) would be utilized
- For ordinal categorical data (i.e., CIBIC-Plus), the Van Elteren test, controlling for country/investigator, would be used for the between group comparison. The CIBIC-Plus analysis was to be based on the original 7-point scale.
- For nominal data the Cochran-Mantel-Haenszel test controlling for country/investigator would be used
- 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 possibly 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

7.11.4 Secondary Efficacy Parameters

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

7.11.5 Sample Size Rationale

- The sample size calculation was based on the change from baseline in standard ADAS-Cog at month 3
  - 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.
  - The present study was powered to detect a drug-placebo difference at 3 months of 2.5 points (standard deviation of 7). In previous clinical trials of cholinesterase inhibitors, a clinically meaningful and significant effect on the CIBIC-Plus at 3 months had been associated with a difference of 2.5 points or more on the ADAS-Cog
  - With 80 % power and a 2-sided Type 1 error of 0.05, 188 patients would be needed in the galantamine group and 94 patients would be needed in the placebo group. Assuming a dropout rate of 30 % in each treatment group, approximately 268 patients would be needed in the galantamine group and 134 patients in the placebo group

7.12 Protocol Amendments

These have been incorporated into the above protocol

7.13 Actual Analyses Performed

The analyses were conducted as planned, controlling for country effects. However in the ANOVA model used for the ADAS-Cog analysis no testing of the interaction between treatment and country

7.14 Efficacy Results

7.14.1 Patient Disposition

A total of 386 patients were randomized to the two treatment groups: 125 patients were randomized to placebo and 261 patients were randomized to galantamine. All 386 patients received at least one dose of study medication.

Patient disposition by treatment and timepoint is summarized in the following table

	Placebo N=125			Galantamine N=261		
	DC: AE	DC: Other	Continued	DC: AE	DC: Other	Continued
Week 3	2 (1.6%)	3 (2.4%)	120 (96.0%)	30 (11.5%)	8 (3.1%)	223 (85.4%)
Week 4	2 (1.6%)	1 (0.8%)	117 (93.6%)	21 (8.0%)	8 (3.1%)	194 (74.3%)
Month 2	1 (0.8%)	2 (1.6%)	114 (91.2%)	13 (5.0%)	2 (0.8%)	179 (68.6%)
Month 3	0	1 (0.8%)	113 (90.4%)	2 (0.8%)	2 (0.8%)	175 (67.0%)

DC: AE: Discontinuations due to adverse events
DC: Other: Discontinuations due to reasons other than adverse events

More detailed reasons for patient discontinuation are in the next table

Reason	Placebo	Galantamine	Total
Any	12 (9.6%)	86 (33.0%)	98 (25.4%)
Adverse event	5 (4.0%)	66 (25.3%)	71 (18.4%)
Ineligible to continue trial	2 (1.6%)	2 (0.8%)	4 (1.0%)
Noncompliant	0 (0%)	3 (1.1%)	3 (0.8%)
Withdrew consent	1 (0.8%)	1 (0.4%)	2 (0.5%)
Other	4 (3.2%)	14 (5.4%)	18 (4.7%)

As the above tables indicate discontinuations were more common in the galantamine group than in the placebo group. In both groups discontinuations were most commonly due to adverse events

7.14.2 Protocol Deviations

Protocol deviations were infrequent and only slightly more common in those treated with galantamine than in those treated with placebo as indicated by the following table

Protocol deviations	Placebo (N=125)	Galantamine (N=261)	Total (N=386)
Total number of patients with protocol deviations	10 (8.0%)	28 (10.7%)	38 (9.8%)
Intercurrent forbidden therapy	10 (8.0%)	10 (3.8%)	20 (5.2%)
Insufficient data	1 (0.8%)	10 (3.8%)	11 (2.8%)
Selection criteria not met	0	4 (1.5%)	4 (1.0%)
Treatment deviation	0	4 (1.5%)	4 (1.0%)
Intercurrent event	0	1 (0.4%)	1 (0.3%)

7.14.3 Baseline And Other Demographic Characteristics

As the following table indicates most key baseline and demographic characteristics were comparable across treatment groups

Characteristics or variable	GAL-INT-2 flexible-dose trial	
	Placebo N=125	Galantamine N=261
Gender: N (%) Male Female	 58 (46.4%) 67 (53.6%)	 113 (43.3%) 148 (56.7%)
Race: N (%) white	117 (93.6%)	246 (94.3%)
Age (mean ± SE)	74.6 ± 0.68	75.2 ± 0.45
Smoker: N (%)	9 (7.2%)	21 (8.0%)
Weight, kg (mean ± SE)	68.5 ±1.37	66.1 ± 0.86
Age at onset of cognitive problems (mean ± SE)	71.9 ± 0.69	71.9 ± 0.49
Years since cognitive problem diagnosis (mean ± SE)	3.22 ± 0.19	3.8 ± 0.20
Months since onset of AD (mean ± SE)	-	-
Age at diagnosis of probable AD (mean ± SE)	74.4 ± 0.69	75.1 ± 0.46
Years of AD diagnosis (mean ± SE)	0.69 ± 0.10	0.71 ± 0.07
First-degree AD relatives: N (%)	32 (25.6%)	69 (26.5%)
Cholinomimetics trial participant: N (%)	2 (1.6%)	14 (5.4%)
Total MMSE score (mean ± SE)	19.6 ± 0.32	19.7 ± 0.24
ADAS-cog/11 score (mean ± SE)	24.7 ± 0.85	25.6 ± 0.65
APO-E type: n (%) 2-3/3-3 2-4/3-4 4-4	 38 (35.2%) 56 (51.8%) 14 (13.0%)	 78 (34.4%) 111 (48.9%) 38 (16.7%)

7.14.4 Primary Efficacy Analysis

7.14.4.1 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.

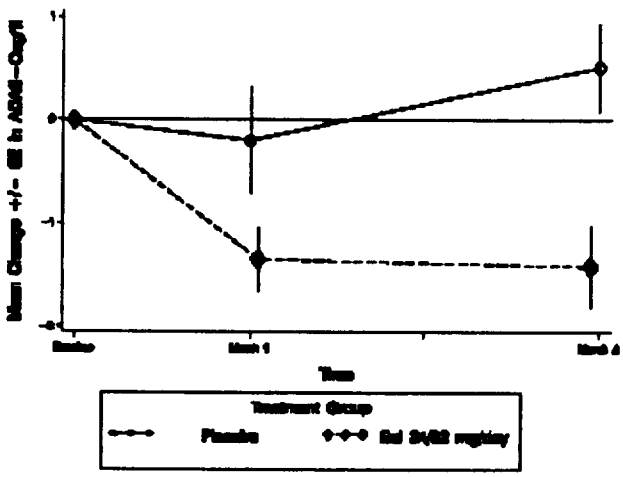
The results of the (primary) Observed Cases analysis are shown below. As the table indicates the galantamine group showed a statistically significant superiority to placebo on the pairwise comparison at Month 3. As the table also indicates, the galantamine group had improved relative to baseline at that timepoint, while the placebo group had worsened marginally/remained unchanged. Statistically significant differences between the galantamine and placebo groups were evident as early as Week 4. The treatment by country interaction was not significant

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

	Placebo		Galantamine		
	Mean ± SE	Mean Change ± SE	Mean ± SE	Mean Change[a] ± SE	p-value[b]
Baseline	24.7 ± 0.85 (n = 123)	---	25.6 ± 0.65 (n = 258)	---	---
Week 4	24.1± 0.85 (n = 117)	-0.2 ± 0.52	24.4 ± 0.72 (n = 223)	-1.3±0.31***	0.046
Month 3	25.0 ± 0.97 (n = 108)	0.5 ± 0.42	23.7 ± 0.81 (n = 170)	-1.4±0.40***	0.002

a: Paired t-test for no within-group difference from baseline: **: p≤0.01; *** p≤0.001
b: Comparison with placebo from the two-way ANOVA model.

The mean change from baseline (± SE) in ADAS-Cog scores over time for the 2 treatment groups is displayed in the following figure for the Observed Cases dataset



The results of the Observed Cases analysis at Month 3 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 group was consistently superior to placebo, at a statistically significant level, regardless of the imputation scheme used; the galantamine group showed a consistent, but slight, improvement from baseline as compared with the placebo group which showed an overall deterioration.

	Placebo			Galantamine		
Month 3 Analysis time point method	N	Mean ± SE	Mean Change ± SE	N	Mean ± SE	Mean Change ± SE
Observed Case	108	25.0 ± 0.97	0.5 ± 0.42	170	23.7 ± 0.81	-1.4 ± 0.40**
Classical ITT	125	25.6 ± 0.92	0.7 ± 0.47	260	24.8 ± 0.68	-0.9 ± 0.31**
Traditional LOCF	120	25.0 ± 0.90	0.6 ± 0.45	239	24.7 ± 0.72	-1.1 ± 0.33**
OC + Retrieved D/O	110	25.2 ± 0.96	0.8 ± 0.46	197	24.2 ± 0.77	-1.1 ± 0.37**

**: p≤0.01 test for no difference between treatments from ANOVA model on change from baseline

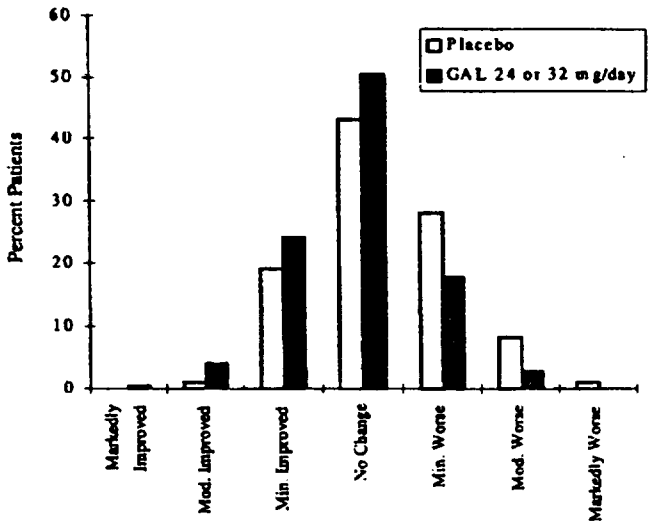
7.14.4.2 CIBIC-Plus

The distribution of the CIBIC-Plus scores at Month 3 in each treatment group is indicated by the following table (Observed Cases)

CIBIC-plus	Placebo (N=111)		Galantamine (N=170)	
	N (%)	Cumulative %	N (%)	Cumulative %
1= markedly improved	0	0	1 (0.6%)	0.6%
2= moderately improved	1 (0.9%)	0.9%	7 (4.1%)	4.7%
3= minimally improved	21 (18.9%)	19.8%	41 (24.1%)	28.8%
4= no change	48 (43.2%)	63.1%	86 (50.6%)	79.4%
5= minimally worse	31 (27.9%)	91.0%	30 (17.6%)	97.1%
6= moderately worse	9 (8.1%)	99.1%	5 (2.9%)	100%
7=markedly worse	1 (0.9%)	100%	0	0

The difference between the galantamine and placebo groups was statistically significant (p=0.003).

The following diagram provides a graphic comparison the percentage of patients in each of the original 7-point CIBIC-Plus ratings at Month 3 for both the galantamine and placebo groups (Observed Cases)



Mean CIBIC-Plus scores for each treatment group at Month 3 are in the following table (Observed Cases)

Treatment Group	N	Mean CIBIC-Plus score at Month 3 (± standard deviation)
Galantamine 24-32 mg/day	170	3.89 (± 0.86)
Placebo	111	4.26 (± 0.92)

7.14.5 Analysis Of Secondary Efficacy Measures

7.14.5.1 Disability Assessment For Dementia

There was essentially no deterioration in the galantamine group and a deterioration in the placebo group as indicated by the Observed Cases Analysis for the total scores displayed in the following table; the difference between the 2 groups was statistically significant at Month 3

Group	N	Mean Change From Baseline At Month 3	p-value for galantamine vs placebo
Galantamine	172	0.1	0.004
Placebo	110	-4.2	

The differences between treatment groups for the classical intent-to-treat, LOCF and Observed Cases + Retrieved Dropouts dataset.

Statistically significant differences were seen between the galantamine and placebo groups for most of the Disability Assessment for Dementia cluster scores as indicated by the following table (Month 3; Observed Cases)

	Placebo			Galantamine		
DAD cluster	N	Mean ± SE	Mean change ± SE	N	Mean ± SE	Mean change ± SE
DAD-initiation	110	73.5 ± 2.24	-4.6 ± 1.45	172	74.5 ± 1.72	-0.2 ± 0.98*
DAD-planning/organization	110	67.0 ± 2.36	-2.9 ± 1.46	172	67.8 ± 1.90	0.8 ± 1.17*
DAD-performance	110	65.0 ± 2.27	-4.5 ± 1.30	172	68.1 ± 1.74	0.0 ± 0.97**
DAD-basic	110	89.0 ± 1.79	-1.7 ± 1.41	172	91.3 ± 1.23	1.9 ± 0.66*
DAD-instrumental	110	50.9 ± 2.85	-6.4 ± 1.47	172	52.8 ± 2.50	-1.3 ± 1.31*
DAD-leisure	110	62.5 ± 3.86	-6.8 ± 3.06	171	60.9 ± 3.12	0.8 ± 2.37

**: p≤0.01; *: p≤0.05 test for no difference between treatments from ANOVA model on change from baseline

7.14.5.2 Neuropsychiatry Inventory

Mean total Neuropsychiatry Inventory and Neuropsychiatry Inventory-Distress scores at Month 3, as well as change from baseline at that timepoint are displayed in the following table. There were no significant differences between treatment groups (p = 0.546 for total Neuropsychiatry Inventory score).

	Placebo			Galantamine		
Parameter	N	Mean ± SE	Mean change ± SE	N	Mean ± SE	Mean change ± SE
Total NPI score	110	8.8 ± 1.06	-0.0 ± 0.65	172	8.1 ± 0.76	-0.7 ± 0.77
Total NPI distress score	92	6.3 ± 0.67	-0.3 ± 0.45	138	5.2 ± 0.43	-0.5 ± 0.45

7.14.5.3 ADAS-Cog Clusters

The analysis of the ADAS-Cog clusters is summarized in the following table (Observed Cases) and is largely consistent with the analysis of the ADAS-Cog/11

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	-0.4	0.315

7.14.5.4 ADAS-Cog Responder Analysis

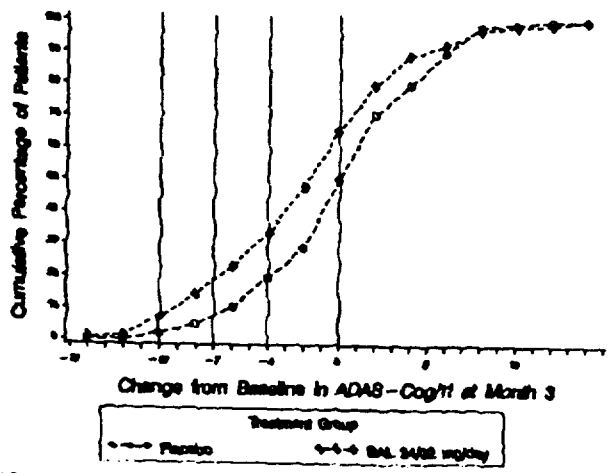
This analysis is summarized in the following table (Observed Cases) and is consistent with the analysis of the ADAS-Cog/11

Category (based on improvement in ADAS-Cog score)	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

The following graph indicates the cumulative percentage of patients with specified levels of response in ADAS-Cog

GAL-INT-2: cumulative percentage of patients with specified changes from baseline at Month 3 in ADAS-cog/11 scores



7.14.6 Analysis Based On Actual Dose Received

The sponsor has performed an exploratory analysis comparing those who received galantamine 32 mg/day with those who received 24 mg/day on 3 efficacy measures. The results for the Observed Cases dataset is provided in the following tables. Other datasets yielded similar results. Formal hypothesis testing does not appear to have been performed by the sponsor.

ADAS-Cog

	Galantamine 24 mg/day	Galantamine 32 mg/day
N	71	99
ADAS-Cog Mean Change From Baseline ± SE	-1.5 ± 0.54	-1.4 ± 0.57

CIBIC-Plus

	Galantamine 24 mg/day	Galantamine 32 mg/day
N	72	98
CIBIC-Plus % improved or no change	74 %	84 %

Disability Assessment For Dementia

	Galantamine 24 mg/day	Galantamine 32 mg/day
N	73	99
DAD Mean Change From Baseline ± SE	-0.5 ± 1.24	-0.5 ± 1.24

7.15 Sponsor's Conclusions

- Galantamine 24-32 mg/day was superior to placebo at a statistically significant level on the ADAS-Cog and CIBIC-Plus. This superiority was small but demonstrable on the Observed Cases dataset as well as with 3 imputation schemes
- Galantamine 24-32 mg/day was superior to placebo at a statistically significant level on the Disability Assessment for Dementia.
- Galantamine 24-32 mg/day was superior to placebo at a statistically significant level on two ADAS-Cog cluster scores and on the ADAS-Cog responder analysis
- No significant differences were seen between the treatment groups on the Neuropsychiatry Inventory

7.16 Reviewer's Comments

- This study provides additional evidence that galantamine doses of 24-32 mg/day have modest effectiveness on a cognitive as well as a global outcome measure.
- The efficacy of galantamine as measured by the Disability Assessment For Dementia, an activities of daily living scale, is statistically significant in comparison with placebo even when adjusted for multiple comparisons

8. Study GAL 95-05

This study was jointly conducted by Janssen and Shire Pharmaceuticals Limited.

Note that in the original protocol for this study

- Galantamine was spelt "galanthamine"
- Doses of galantamine were specified in mg of the hydrobromide salt, not the base

However in the description below, the doses stipulated in are in mg of base

8.1 Title

A European multicenter study to determine the safety and efficacy of galantamine 32 mg/day in patients diagnosed with Alzheimer-type dementia

8.2 Objective

- To determine the efficacy of galantamine 32 mg daily in patients diagnosed with Alzheimer-type dementia over 24 weeks compared with placebo
- To determine the safety of galantamine 32 mg daily in patients diagnosed with Alzheimer-type dementia over 24 weeks compared with placebo
- To further determine the efficacy and safety of galantamine 32 mg daily in the study population in an additional 24-week extension study.

8.3 Design

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

8.4 Dosage

Galantamine 32 mg daily (given as t.i.d dosing)
Placebo

The titration schedule for this study was as follows:

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

8.5 Duration

29 weeks of double-blind therapy divided into

- An initial dose-titration phase lasting 5 weeks
- A later maintenance dose phase of 24 weeks

8.6 Sample Size

560 patients (total) to be randomized to the 2 treatment groups

8.7 Main Inclusion Criteria

- Male or female
- Probable Alzheimer's disease by NINCDS-ADRDA criteria
- Dementia of the Alzheimer's type by DSM-IV criteria
- Mini-Mental Status Examination score 12-24
- Age 45 years or older
- Reliable caregiver (criteria specified)
- Informed consent

8.8 Main Exclusion Criteria

- Neurodegenerative disorders such as Parkinson's disease, Pick's disease, and other entities
- Cognitive impairment due to head trauma, hypoxia, vitamin deficiency, infection, neoplasm, endocrine or metabolic disease and mental retardation
- Multi-infarct dementia (Hachinski Ischemic Score ≥ 4) of history of a significant cerebrovascular event that was likely to confound the assessment of the patient's intellectual function. Patients with an isolated cerebral infarct confirmed by appropriate imaging techniques performed within the previous 2 years could be included. Imaging would need to be repeated before inclusion if the patients has experienced significant loss of consciousness or other neurological signs or symptoms, stepwise deterioration or a head injury since the last scan. Patients with an isolated loss of consciousness, transient ischemic attack or "drop attack" could be considered for inclusion provided these did not occur within the previous 12 months
- Cerebral arteritides
- Any of the following coexisting medical conditions: history of epilepsy or convulsions (other than febrile convulsions), clinically significant psychiatric disease, neoplasia (criteria specified), active peptic ulcer (criteria specified), clinically significant urinary outflow obstruction, and clinically significant cardiovascular (criteria specified), hepatic, renal, pulmonary, metabolic or endocrine disease

- Any of the following classes of drugs: psychotropic agents (see exceptions under permitted medications), anticonvulsants, cholinomimetics, nootropics, anti-parkinsonian agents, anti-emetics (except for use of domperidone or metoclopramide for a maximum of 5 continuous days during the period of dose escalation) and anti-hypertensive agents such as methyldopa and clonidine
- 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 this trial
- Use of any other investigational medication within 90 days prior to enrollment. 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
- 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

8.9 Concomitant Medications

8.9.1 Prohibited Medications

These are listed above

8.9.2 Permitted Medications

These include

- sedative/hypnotics/tranquilizers, 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)
- cough and cold remedies provided sedating drugs are discontinued where possible at least 48 hours before cognitive testing is carried out
- metoclopramide and domperidone for continuous periods of upto 5 days during dose titration
- diuretics, ACE inhibitors, calcium antagonists and beta-blockers

8.10 Efficacy Outcome Measures

8.10.1 Primary Efficacy Measures

ADAS-Cog (EURO ADAS-Cog*)
CIBIC-Plus
NOSGER

*In France a version referred to as the GRECO-ADAS-Cog was to be used

8.10.2 Secondary Efficacy Measures

EURO ADAS-NonCog
Mini Mental Status Examination
NAB [Nuremberg Alters-Beobachtungs-Skala (Nuremberg Geriatric Observation Scale)]
DSST (Digit Symbol Substitution Test)

8.11 Analysis Plan

- The key analysis population for all efficacy measures was to be the intent-to-treat population defined, as all those randomized who received at least one dose of study medication. An additional per-protocol analysis was to be performed if it included 60 % to 95 % of the intent-to-treat patients. Criteria for major protocol violations were stipulated
- The timepoint for the efficacy analyses would be Week 29
- Continuous data would be analyzed by general linear model methods such as ANOVA or ANCOVA
- Ordinal categorical data would be analyzed using the Cochran-Mantel-Haenszel test with modified ridit scores or the Kruskall-Wallis test
- Nominal or binary data would be analyzed by the chi-square or Fisher's exact test
- To minimize bias in due to withdrawals, data missing at Week 29 due to early withdrawal would have the worst possible score or change substituted in non-parametric analyses

- The sample size calculation was based on the following:
  - Based on the published literature it was felt reasonable to assume that the treatment difference at the end of the study would be 2.5 on the ADAS-Cog with a standard deviation of 9
  - Assuming a significance level of 0.05 and 80 % power 200 patients were felt to be needed for both the drug and placebo groups; with an expected 30 % dropout rate, a total recruitment level of 560 patients was felt to be needed

8.12 Protocol Amendments

All protocol amendments have been incorporated into the above protocol summary.

8.13 Actual Analyses Performed

The initial set of analyses were performed using the general plan stated in the original protocol but with the following additional details provided (which were not specified in the original protocol)

- Continuous data were to be analyzed using 2-way ANOVA: the model included treatment and country as factors. The interaction between treatment and country was to be first examined. If the treatment by country interaction was not significant at the 10% level, it was not to be included in the final model
- It is also stated that continuous data were to be analyzed using ANCOVA with baseline value and country as covariates. The treatment by country interaction was to be examined first and this not included in the model unless the interaction had a p-value < 0.05.
- Continuous data were also to be analyzed using the Kruskall-Wallis test
- The CIBIC-Plus was analyzed using the Cochran-Mantel-Haenszel test with modified ridit scores (considered equivalent to the van Elteren test), controlling for country.

Additional sets of primary efficacy analyses were carried out **after review of the draft statistical report**. They included the following

- At the request of Shire Pharmaceuticals Limited, co-sponsor of the study, an analysis was performed on the Euro-ADAS-Cog and CIBIC-Plus changing the method of imputation used for the efficacy scores of patients discontinuing prior to Week 29. 3 new methods were used, all on the original intent-to-treat population
  - Expected rate of change
  - LOCF
  - Endpoint (presumably this refers to the Observed Cases population)
- At the request of Janssen and for comparison with data from the GAL-USA-1 and GAL-INT-1 trials of galantamine the following additional analyses were to be performed on the ADAS-Cog and CIBIC-Plus data
  - Intent-to-treat population as defined by Janssen: all randomized patients who took at least one dose of double-blind study medication and who had post-baseline data in the double-blind phase for any of the key efficacy variables
  - Classical intent-to-treat population: all patients randomized
  - Completers: all patients who completed the Week 29 assessment and did not discontinue treatment prematurely: also referred to as Traditional Observed Cases at Week 29

At least some of the analyses appear to have been performed as specified above

8.14 Efficacy Results

8.14.1 Patient Disposition

A total of 554 patients were randomized to the 2 treatment groups: 275 to galantamine and 279 to placebo.

The number of patients remaining in the study at specified timepoints in each treatment group is indicated by the next table

Timepoint	Galantamine	Placebo
Baseline	275	279
Week 2	270	279
Week 5	260	272
Week 11	231	261
Week 17	200	252
Week 23	192	238
Week 29 (Study Endpoint)	186	235
Percentage Remaining In Study At Week 29	67.6 %	84.2 %

Reasons for patient discontinuation are in the next table

Reason	Placebo	Galantamine	Total
Any	12 (9.6%)	86 (33.0%)	98 (25.4%)
Adverse event	5 (4.0%)	66 (25.3%)	71 (18.4%)
Ineligible to continue trial	2 (1.6%)	2 (0.8%)	4 (1.0%)
Noncompliant	0 (0%)	3 (1.1%)	3 (0.8%)
Withdrew consent	1 (0.8%)	1 (0.4%)	2 (0.5%)
Other	4 (3.2%)	14 (5.4%)	18 (4.7%)

As the above tables indicate discontinuations were more common in the galantamine group than in the placebo group; in both groups the most common reason for discontinuation was an adverse event

8.14.2 Protocol Deviations

A total of 160 patients had major protocol violations. Their distribution among the treatment groups are indicated in the following table.

Treatment Group	Placebo (n=279)	Galantamine (n=275)
Number With Major Protocol Violations	57	103
% With Major Protocol Violations	20.7 %	37.5 %

Further details regarding the nature of the protocol violations is not provided. Given the relatively high incidence of these violations a per-protocol analysis has been performed by the sponsor.

8.14.3 Baseline And Other Demographic Characteristics

Key baseline and demographic characteristics are summarized in the following table which indicates that these were comparable across treatment groups

Variable	Placebo (n=279)	Galantamine (n=275)
% Female	62.4	61.1
% Caucasian	97.5	98.5
Age (mean ± SE)	71.9 ± 8.8	73.9 ± 8.1
Months since onset of Alzheimer's Disease (mean ± SE)	37.7 ± 24.5	36.6 ± 24.2
Mean Mini Mental Status Examination score	19.3	19.3

The incidence of concomitant illnesses appears to have been similar across treatment groups. Concomitant medications were not compared across treatment groups

8.14.4 Primary Efficacy Analysis

8.14.4.1 ADAS-Cog/11

All ADAS-Cog data below refer to the Euro-ADAS-Cog

8.14.4.1.1 Protocol-Specified ADAS-Cog Analysis

The ADAS-Cog analysis on the original protocol-defined intent-to-treat population is shown in the table below. As the table indicates the placebo group had deteriorated compared with baseline at Week 29, but the galantamine group was essentially unchanged in regard to mean scores. The difference between the treatment groups was statistically significant. Note that the patient numbers at Week 29 correspond to the Observed Cases dataset and not to the actual intent-to-treat dataset

	Placebo		32 mg/day GAL hbr		
Analysis timepoint	mean ± SD	mean change ± SD	mean ± SD	mean change ± SD	p-value[1]
Baseline	27.6±9.4 (n = 278)	--	28.7±9.3 (n = 270)	--	
Week 2	27.2±9.6 (n = 266)	-0.3±4.8 (n = 266)	27.1±9.8 (n = 258)	-1.4±5.1 (n = 258)	ND
Week 5	27.3±9.6 (n = 270)	-0.3±5.3 (n = 270)	27.3±9.3 (n = 254)	-1.4±5.2 (n = 254)	ND
Week 17	27.9±10.4 (n = 247)	0.6±6.5 (n = 247)	27.0±8.9 (n = 195)	-2.1±6.2 (n = 195)	ND
Week 29	30.0±11.3 (n = 232)	2.6±7.1 (n = 232)	28.6±10.2 (n = 181)	-0.4±7.0 (n = 181)	0.0001

[1] ANOVA model correcting for treatment and country effects
ND: Not Done

8.14.4.1.2 Additional ADAS-Cog Analyses

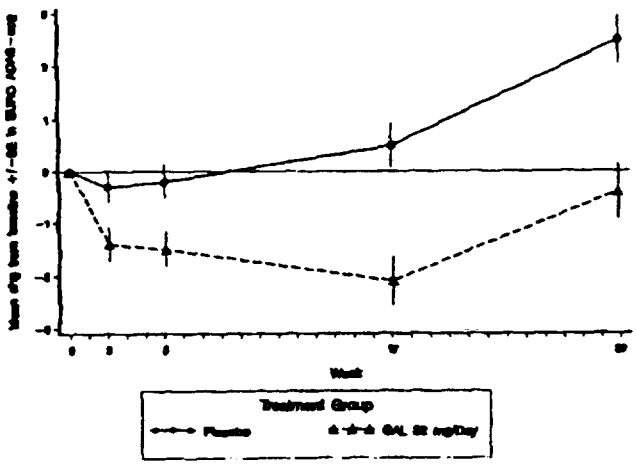
The results of the Observed Cases analysis are shown below. As the table indicates the galantamine group showed a statistically significant superiority to placebo on the pairwise comparison at Week 29. As the table also indicates, the galantamine group had improved relative to baseline at that timepoint, while the placebo group had worsened. Statistically significant differences between the galantamine and placebo groups were evident as early as Week 2. The treatment by country interaction was not significant

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

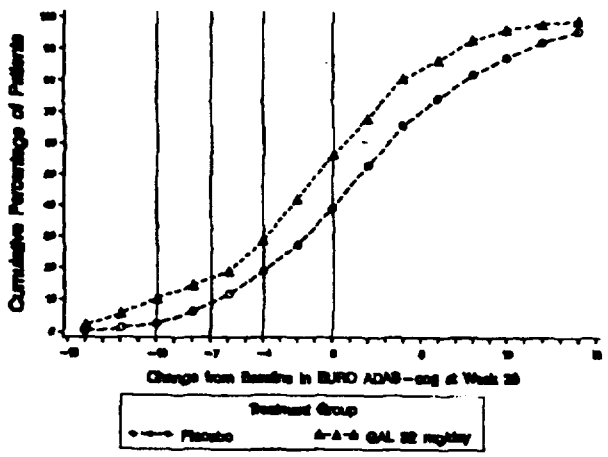
	Placebo		32 mg/day GAL basc		
	Mean ± SE	Mean change ± SE	Mean ± SE	Mean change[a] ± SE	p-value[b]
Baselinc	27.1 ± 0.6 (n = 271)	---	28.7 ± 0.6 (n = 263)	---	---
Week 2	27.0 ± 0.6 (n = 261)	-0.3 ± 0.3 (n = 257)	27.1 ± 0.6 (n = 257)	-1.4*** ± 0.3 (n = 252)	0.0152
Week 5	27.1 ± 0.6 (n = 265)	-0.2 ± 0.3 (n = 259)	27.2 ± 0.6 (n = 251)	-1.5*** ± 0.3 (n = 246)	0.0046
Week 17	27.7 ± 0.7 (n = 241)	0.5 ± 0.4 (n = 235)	27.0 ± 0.6 (n = 194)	-2.1*** ± 0.5 (n = 190)	0.0001
Week 29	29.6 ± 0.7 (n = 229)	2.5 ± 0.5 (n = 223)	28.3 ± 0.7 (n = 178)	-0.4 ± 0.5 (n = 174)	0.0001

a: Paired t-test for no within-group difference from baseline: *** p≤0.001.
b: Comparison with placebo from the two-way ANOVA model correcting for country effect.

The mean change from baseline in ADAS-Cog score over time is also indicated in the following graph (Observed Cases)



The cumulative percentages of patients with specified levels of response in ADAS-Cog are summarized in the following graph (Observed Cases)



Results for the Janssen-defined intent-to-treat, LOCF and classical intent-to-treat populations are in the following table. In all instances the placebo group worsened in comparison with baseline and the galantamine group was for all practical purposes unchanged. The difference between the treatment groups was statistically significant for all 3 datasets

	Placebo		32 mg/day GAL base		
	mean ± SE	mean change ± SE	mean ± SE	mean change ± SE	p-value[1]
Baseline	27.1 ± 0.6 (n = 271)	-	28.7 ± 0.6 (n = 263)	-	-
Week 2	27.0 ± 0.6 (n = 261)	-0.3 ± 0.3 (n = 257)	27.1 ± 0.6 (n = 257)	-1.4 ± 0.3 (n = 252)	0.0152
Week 5	27.1 ± 0.6 (n = 265)	-0.2 ± 0.3 (n = 259)	27.2 ± 0.6 (n = 251)	-1.5 ± 0.3 (n = 246)	0.0046
Week 17	27.7 ± 0.7 (n = 241)	0.5 ± 0.4 (n = 235)	27.0 ± 0.6 (n = 194)	-2.1 ± 0.5 (n = 190)	0.0001
Week 29	29.6 ± 0.7 (n = 229)	2.5 ± 0.5 (n = 223)	28.3 ± 0.7 (n = 178)	-0.4 ± 0.5 (n = 174)	0.0001
Traditional DNDP-LOCF-ITT	30.0 ± 0.7 (n = 275)	2.6 ± 0.4 (n = 269)	28.4 ± 0.6 (n = 267)	-0.3 ± 0.4 (n = 261)	0.0001
Classical ITT	30.1 ± 0.7 (n = 278)	2.6 ± 0.4 (n = 278)	28.4 ± 0.6 (n = 275)	-0.3 ± 0.4 (n = 275)	0.0001

[1] ANOVA model correcting for treatment and country effects

Note that the patient numbers at Week 29 correspond to the Observed Cases dataset and not to the actual intent-to-treat dataset

The results of a per-protocol analysis are shown in the following table (changes in score are least square estimates)

	Placebo	Galantamine	Treatment Difference
PP population	n=203	n=146	
Change at week 29	2.856	-0.592	-3.449*
95% confidence intervals (CI)	+1.765, +3.948	-1.847, +0.662	-4.941, -1.956

* p<0.000008

8.14.4.2 CIBIC-Plus

8.14.4.2.1 Protocol-Specified CIBIC-Plus Analysis

The results of the protocol-specified CIBIC-Plus analysis on the original intent-to-treat dataset are in the following table. Based on the van Elteren test there was a statistically significant difference between the galantamine and placebo groups (p=0.024). Note that the patient numbers in the dataset correspond closely to Observed Cases and not to what the term "intent-to-treat" conventionally implies.

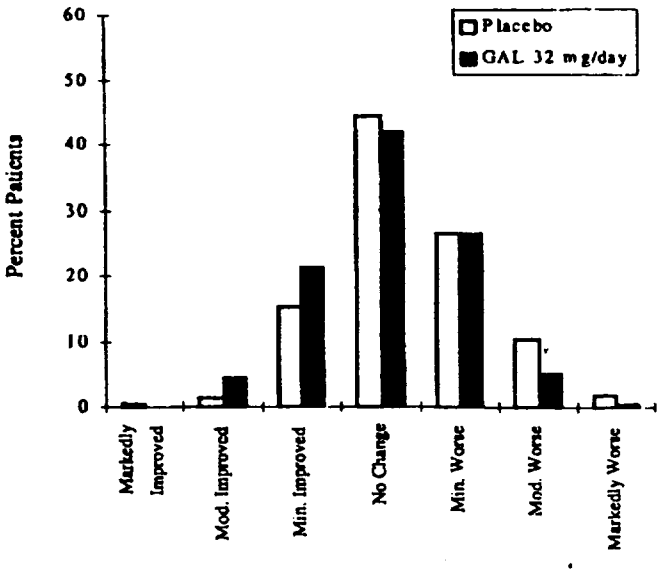
	Original ITT			
	Placebo		32 mg/day GAL base	
Score	n	%	n	%
1 Marked improvement	1	0.4	0	0.0
2 Moderate improvement	3	1.3	8	4.3
3 Minimal improvement	34	14.5	39	21.0
4 No change	99	42.1	75	40.3
5 Minimal worsening	59	25.1	47	25.3
6 Moderate worsening	23	9.8	9	4.8
7 Marked worsening	5	2.1	1	0.5
Missing	11	4.7	7	3.8
Total	235	100.0	186	100.0

8.14.4.2.2 Additional CIBIC-Plus Analyses

The results of the Observed Cases analysis are presented in the following tables and diagram which indicates the percentage of patients in each of the original 7-point CIBIC-Plus ratings at Week 29 for both the galantamine and placebo groups. The tables were generated by Dr Kun He, statistical reviewer.

Variable	Galantamine (n=178)	Placebo (n=223)
% Markedly improved	0	0.4
% Moderately improved	4.5	1.3
% Minimally improved	21.3	15.2
% No Change	42.1	44.4
% Minimally worse	26.4	26.5
% Moderately worse	5.1	10.3
% Markedly worse	0.6	1.8

Treatment Group	Mean CIBIC-Plus Score at Week 29 Observed Cases	Difference Between Groups	p-value for galantamine vs placebo (Cochran-Mantel-Haenszel)
Galantamine (n=178)	4.09	0.24	0.034
Placebo (n=223)	4.33		



The results for the Observed Cases dataset analysis collapsed into 2 categories are presented below: a statistically significant superiority for galantamine over placebo is demonstrable.

Treatment	N	Improved or No Change (%)	Worse (%)	p-value
Placebo	235	137 (58.3)	41 (36.9)	0.034
Galantamine	186	121 (65.1)	57 (30.6)	

The p-value is for the galantamine-placebo comparison using the Van Elteren test

Results for additional datasets are presented below. P-values have not been provided by the sponsor except for the LOCF dataset but the responder percentages are similar at each level to those seen with the Observed Cases population

Janssen Intent-To-Treat

	JRF ITT			
	Placebo		32 mg/day GAL base	
Score	n	%	n	%
1 Marked improvement	1	0.4	0	0.0
2 Moderate improvement	3	1.3	8	4.3
3 Minimal improvement	34	14.5	38	20.4
4 No change	99	42.1	75	40.3
5 Minimal worsening	59	25.1	47	25.3
6 Moderate worsening	23	9.8	9	4.8
7 Marked worsening	4	1.7	1	0.5
Missing	12	5.1	8	4.3
Total	235	100.0	186	100.0

LOCF (p = 0.03)

	JRF1TT			
	Placebo		32 mg/day GAL base	
Score	n	%	n	%
1 Marked improvement	1	0.4	0	0.0
2 Moderate improvement	3	1.1	9	3.6
3 Minimal improvement	42	15.7	53	21.5
4 No change	123	45.9	107	43.3
5 Minimal worsening	71	26.5	64	25.9
6 Moderate worsening	24	9.0	12	4.9
7 Marked worsening	4	1.5	2	0.8
Missing	0	0.0	0	0.0
Total	268	100.0	247	100.0

Classical Intent-To-Treat

	JRF1TT			
	Placebo		32 mg/day GAL base	
Score	n	%	n	%
1 Marked improvement	1	0.4	0	0.0
2 Moderate improvement	3	1.1	9	3.6
3 Minimal improvement	42	15.4	50	19.8
4 No change	126	46.3	115	45.5
5 Minimal worsening	72	26.5	64	25.3
6 Moderate worsening	24	8.8	13	5.1
7 Marked worsening	4	1.5	2	0.8
Missing	0	0.0	0	0.0
Total	272	100.0	253	100.0

Completers

	JRF1TT			
	Placebo		32 mg/day GAL base	
Score	n	%	n	%
1 Marked improvement	1	0.4	0	0.0
2 Moderate improvement	3	1.3	8	4.4
3 Minimal improvement	34	14.7	37	20.2
4 No change	99	42.9	75	41.0
5 Minimal worsening	58	25.1	47	25.7
6 Moderate worsening	23	10.0	8	4.4
7 Marked worsening	4	1.7	1	0.5
Missing	9	3.9	7	3.8
Total	231	100.0	183	100.0

Note that the patient numbers in the Janssen-defined intent-to-treat dataset correspond closely to Observed Cases and not to "intent-to-treat" as it is conventionally understood

The results of a per-protocol analysis are in the next table

	% Improved	% Unchanged	% Worsened	P-value Vs placebo
Galantamine	24.8	40.1	24.0	0.005
Placebo	14.6	40.3	34.3	

8.14.4.3 NOSGER

When the analysis was conducted "according to the original protocol", the results are as follows.

The following table represents mean scores for all dimensions at baseline and Week 29 for the original protocol-specified intent-to-treat dataset which in fact corresponds most closely to an Observed Cases dataset

Original ITT	Placebo		32 mg/day GAL base	
	Baseline mean (n)	Week 29 mean (n)	Baseline mean (n)	Week 29 mean (n)
Memory	14.0 (273)	14.7 (228)	14.9 (270)	15.0 (179)
IADL	13.8 (269)	14.6 (224)	14.8 (266)	15.5 (180)
Self-care	7.4 (274)	7.9 (227)	7.7 (265)	8.3 (179)
Mood	10.2 (271)	10.8 (227)	10.2 (267)	10.6 (180)
Social behaviour	12.1 (270)	13.2 (227)	13.0 (268)	13.8 (179)
Disturbing behaviour	8.3 (273)	8.8 (226)	8.4 (266)	9.0 (179)

The next table represents least square means of change at Week 29, and treatment differences. Statistically significant differences between treatment groups were nominally statistically significant for the memory dimension alone; in that regard galantamine appeared superior to placebo

Original ITT	Placebo	Galantamine	Treatment difference		
	Change at week 29 (n)	Change at week 29 (n)	Change at week 29	95% CI	p-value
Memory	0.70 (224)	0.09 (179)	-0.61	-1.19, -0.02	0.043
IADL	1.21 (218)	0.75 (178)	-0.46	-1.18, +0.26	NS
Self-care	0.37 (225)	0.41 (176)	0.04	-0.55, +0.63	NS
Mood	0.50 (222)	0.22 (178)	-0.28	-0.89, +0.34	NS
Social behaviour	0.88 (221)	0.42 (177)	-0.46	-1.16, +0.23	NS
Disturbing behaviour	0.36 (222)	0.48 (177)	0.11	-0.41, +0.63	NS

NS = not significant

8.14.5 Analysis Of Secondary Efficacy Measures

The data are summarized in the following table which has mean data for the original protocol-specified intent-to-treat dataset which in fact corresponds most closely to an Observed Cases dataset

Original ITT	Placebo			32 mg/day GAL base		
Timepoint	Baseline (n)	Week 17 (n)	Week 29 (n)	Baseline (n)	Week 17 (n)	Week 29 (n)
EURO-ADAS-cognitive	4.7 (278)	4.2 (248)	4.8 (234)	4.7 (270)	4.5 (197)	4.9 (184)
MMSE	19.3 (278)	-	19.0 (233)	19.3 (270)	-	19.5 (185)
DSST	11.7 (275)	12.1 (245)	11.5 (226)	11.4 (267)	13.0 (193)	12.8 (182)
NAB	23.0 (270)	23.6 (241)	24.2 (220)	24.1 (264)	24.3 (195)	24.8 (181)

Least square mean estimates of change at Week 29 for this dataset, together with treatment differences and their statistical significance are in the next table. As the table indicates treatment differences of nominal ($p < 0.05$) statistical significance in favor of galantamine was seen with the Digit Symbol Substitution

Test and NAB [Nuremberg Alters-Beobachtungs-Skala (Nuremberg Geriatric Observation Scale)]. The sponsor has observed that galantamine-treated patients improved on the Digit Symbol Substitution Test and remained stable on the NAB; on the other hand, placebo-treated patients remained stable on the Digit Symbol Substitution Test and worsened on the NAB.

Original ITT	Placebo	Galantamine	Treatment Difference		
	Change at week 29 (n)	Change at week 29 (n)	Change at week 29	95% CI	p-value
EURO-ADAS noncog	0.066 (234)	0.073 (184)	0.007	-0.773, +0.787	NS
MMSE	-0.185 (223)	0.210 (185)	0.394	-0.265, +1.054	NS
DSST	-0.013 (224)	2.507 (181)	2.520	+1.376, +3.665	< 0.001
NAB	1.256 (215)	0.499 (177)	-0.757	-1.447, -0.067	0.032

NS = not significant

Values in this table do not correspond to absolute change from baseline.

8.15 Sponsor's Conclusions

- Galantamine in a dose of 32 mg daily showed a statistically significant superiority to placebo on the Euro-ADAS-Cog and CIBIC-Plus after 29 weeks of treatment. Similar results were seen regardless of the dataset analyzed suggesting that premature discontinuations did not selectively influence the results
- A statistically significant difference between galantamine 32 mg/day and placebo was seen on only the memory dimension of the NOSGER
- Galantamine-treated patients improved on the Digit Symbol Substitution Test and remained stable on the NAB; on the other hand, placebo-treated patients remained stable on the Digit Symbol Substitution Test and worsened on the NAB. These differences were statistically significant.

8.16 Reviewer's Comments

- The majority of analyses on the primary efficacy measures were performed after the blind was broken and a draft statistical report was reviewed. The "protocol-specified" intent-to-treat dataset is similar to an Observed Cases dataset when the results are presented and not to an intent-to-treat dataset as it is conventionally understood, and as it appears to have been described in the original protocol.
- Although consistent across imputation schemes, the efficacy of galantamine 32 mg/day, as measured by the Euro-ADAS-Cog and CIBIC-Plus, is modest
- The clinical relevance of the minor galantamine-placebo treatment differences seen on the Digit Symbol Substitution Test, NAB and NOSGER is unclear; in addition the differences seen on the latter 2 measures may not be statistically significant when the Type 1 error is adjusted for multiple comparisons. The relevance of any changes in total score for the individual dimensions of the NOSGER is made even more difficult to interpret by the method of scoring; for some items in each dimension higher scores indicate greater impairment, and for other items lesser impairment