1. Background

This submission contains the sponsor's response to the Agency's approvable letter for galantamine (Reminyl®) dated 7/29/00.

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

NDA # 21169 for the use of galantamine tablets 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 the original NDA and the amendment, were completed by me on 6/13/00. The safety review of the submission was completed by Drs Judith Racoosin, Jerry Boehm and Kevin Prohaska. Please see these reviews for full details.

Based on these and the other reviews of the above application, an "Approvable" letter was issued on 7/29/00. Please refer to that letter for full details. The letter included the following:

- Draft labeling, revised by the Agency, and containing several "Notes to Sponsor" requesting further revisions or clarifications
- Requests for information and additional analyses pertaining to the safety review
- Requests for information in regard to several toxicology studies, and for specific histopathological examinations in Phase 4
- Requests for information pertaining to Chemistry, Manufacturing and Controls
- A request to adopt a specific dissolution methodology for all galantamine tablets

This review is confined to

- Study GAL-USA-11, a withdrawal study, a complete report of which is included in this submission
- The following items in the label each of which are related to the efficacy of the drug.
  Description
  Clinical Pharmacology: Mechanism of Action and Clinical Trials
  Indications and Usage
  Dosage and Administration

The actual draft label, with revisions made by me, is in a separate document

2. Contents of Submission

The submission includes:

- Specific responses to questions, requests for information and further analyses in the "Approvable" letter pertaining to clinical safety, pharmacology, chemistry and biopharmaceutics
- A Safety Update
- Proposed labeling with attachments.

The only new efficacy data in this submission consists of the report for GAL-USA-11, a galantamine-withdrawal study and a sequel to GAL-USA-10.

3. Tabular Summary Of Efficacy Studies In Original NDA And Amendment

This summary is taken from my original efficacy review of this NDA

3.1 Main Efficacy Studies In Original NDA Submission

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

3.1.1 Outline Of Main Study Results

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

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

3.1.2 CIBIC-Plus Results: Responder Analysis

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

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

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

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

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

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

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

3.1.2.4 CIBIC-Plus results for GAL 95-05 study

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

3.1.3 Dose-Titration Schedules

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

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

3.1.3.2 Dose-Titration Schedule for GAL-INT-2

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

3.1.3.3 Dose-Titration Schedule for GAL 95-05

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

3.1.4 Results For Secondary Efficacy Measures

Study #	GAL-USA-1	GAL-INT-1	GAL-INT-2	GAL 95-05
Dosage	Galantamine 24 mg/day Galantamine 32 mg/day B.I.D. Dosing	Galantamine 24 mg/day Galantamine 32 mg/day B.I.D. Dosing	Galantamine flexible dose 24 mg/day to 32 mg/day B.I.D. Dosing	Galantamine 32 mg/day T.I.D. Dosing
Secondary Efficacy Measures	ADAS-Cog/13 ADAS-Cog/10 ADAS-Cog/mem ADAS-Cog/responder analysis DAD Total/Cluster Score PGWB Resource Utilization/Costs	ADAS-Cog/13 ADAS-Cog/10 ADAS-Cog/mem ADAS-Cog/responder analysis DAD Total/Cluster Score PGWB Resource Utilization/Costs	ADAS-Cog/13 ADAS-Cog/10 ADAS-Cog/mem ADAS-Cog/responder analysis DAD Total/Cluster Score Neuropsychiatry Inventory	EURO-ADAS-NonCog Mini Mental Status Examination NAB DSST
Results of secondary efficacy analysis ($p < 0.05$ comparisons only) Mean Drug-Placebo Difference At Study End. Observed Cases	Both galantamine groups superior to placebo on ADAS-Cog/13, ADAS-Cog/10 and ADAS-Cog/mem (see table below) ADAS-Cog/responder analysis (see table below)	Both galantamine groups superior to placebo on ADAS-Cog/13, ADAS-Cog/10 and ADAS-Cog/mem (see table below) ADAS-Cog/responder analysis (see table below)	ADAS-Cog/13: -2.1 (p=0.004) ADAS-Cog/10: -1.8 (p<0.001) ADAS-Cog/responder analysis (see table below) DAD (Total) =-4.3 (p=0.004)	DSST: 2.51 (p<0.001) NAB: 0.8 (0.032)

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

ADAS-Cog Cluster Analysis for GAL-USA-1

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

ADAS-Cog Cluster Analysis for GAL-INT-1

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

ADAS-Cog Cluster Analysis for GAL-INT-2

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

ADAS-Cog Responder Analysis for GAL-USA-1

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

ADAS-Cog Responder Analysis for GAL-INT-1

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

ADAS-Cog Responder Analysis for GAL-INT-2

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

3.2 Additional Efficacy Study In Original NDA Submission

3.2.1 Outline Of Study Results

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

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

3.2.2 Titration Schedule

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

3.2.3 Results For Secondary Efficacy Measures

3.2.3.1 Overall Results

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

3.2.3.2 Mean Change From Baseline For Secondary Efficacy Measures

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

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

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

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

3.3 Randomized Withdrawal Study In Original NDA

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

Study #	GAL-USA-5		
Design	Randomized, double-blind, placebo-controlled, parallel-arm		
Dosage	Galantamine 24 mg daily or 32 mg daily (BID dosing)		
Duration of randomized withdrawal	6 weeks		
Treatment Groups	PLA/PLA	GAL/GAL*	GAL/PLA*
Study entry	47	32	39
Completers	41	31	39
Main inclusion criteria	Completion of GAL-INT-2 (US centers only)		
Primary efficacy outcome measures	ADAS-Cog (change from initial visit of withdrawal study)		
Primary efficacy analysis	Change in ADAS-Cog during withdrawal study GAL/PLA group vs PLA/PLA group ANOVA		
Results of primary efficacy analysis	No statistically significant differences between treatment groups Mean ADAS-Cog changes from initial visit of GAL-USA-5 (Observed Cases) PLA/PLA: 0.8 GAL/GAL: -0.9 GAL/PLA: 1.4 Mean ADAS-Cog changes from initial visit of GAL-INT-2 (Observed Cases) PLA/PLA: 0.9 GAL/GAL: -1.5 GAL/PLA: 0.1		
Safety outcome measures	Adverse events, vital signs, physical examinations, laboratory tests and electrocardiograms		
Safety results	Incidence of adverse events comparable between GAL/PLA and PLA/PLA No deaths Incidence of serious and severe adverse events and adverse event dropouts low No important changes in laboratory tests, vital signs or electrocardiograms		

PLA/PLA: Placebo followed by galantamine
GAL/GAL: Galantamine followed by galantamine
GAL/PLA: Galantamine followed by placebo

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

3.4 Efficacy Study In NDA Amendment

3.4.1 Outline Of Study Results

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

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

3.4.2 Titration Schedule

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

APPEARS THIS WAY
ON ORIGINAL

3.4.3 Results For Secondary Efficacy Measures

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

ADAS-Cog Cluster Analysis for GAL-USA-10

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

ADAS-Cog Responder Analysis for GAL-USA-10

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

4. Study GAL-USA-11

This study was to enroll patients who completed GAL-USA-10.

4.1 Title

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

4.2 Objective

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

4.3 Design

- Randomized, double-blind, placebo-controlled, 6-week, parallel-arm, withdrawal study
- Subjects receiving placebo in GAL-USA-10 would continue to receive placebo in GAL-USA-11
- Subjects receiving galantamine 4 mg b.i.d and 8 mg b.i.d in GAL-USA-10 would continue to receive the same dose in GAL-USA-11
- Subjects receiving galantamine 24 mg/day in GAL-USA-10 would receive placebo in GAL-USA-11

The following schematic summarizes this design

GAL-USA-10		GAL-USA-11
Placebo	→→	Placebo
Galantamine 4 mg b.i.d.	→→	Galantamine 4 mg b.i.d
Galantamine 8 mg b.i.d	→→	Galantamine 8 mg b.i.d
Galantamine 12 mg b.i.d.	→→	Placebo

4.4 Duration

6 weeks

4.5 Dosage

The 4 treatment groups are as follows
Galantamine 4 mg b.i.d (same dose as in GAL-USA-10)
Galantamine 8 mg b.i.d (same dose as in GAL-USA-11)
Placebo (galantamine 12 mg b.i.d in GAL-USA-10)
Placebo (placebo in GAL-USA-10)

4.6 Sample Size

About 910 patients

4.7 Main Inclusion Criteria

- Completion of GAL-USA-10
- Remaining in good general health as determined by medical history, complete physical examination, laboratory tests and electrocardiogram
- Reliable caregiver
- Informed consent

4.8 Main Exclusion Criteria

- Premature discontinuation from GAL-USA-10
- If any of the any neurological or psychiatric illness that could contribute to dementia, develops during GAL-USA-10, the investigator must contact the sponsor before enrolling the patient in GAL-USA-11
- Significant loss of consciousness, transient ischemic attacks, "drop attacks", other neurological signs or symptoms, stepwise deterioration or head injury during GAL-USA-10
- Stroke, hypoxic cerebral damage, infection, cerebral neoplasm (primary or metastatic)
- Clinically significant cardiovascular disease (criteria specified) during GAL-USA-10
- Approved, over-the-counter, or experimental agents, 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.

- 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
- Subjects who the investigator feels would be otherwise unsuitable for the study

4.9 Concomitant Medications

4.9.1 Prohibited Medications

These are listed above

4.9.2 Permitted Medications

These include

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

4.10 Efficacy Outcome Measures

4.10.1 Description of ADAS-Cog

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

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

4.10.2 Primary Efficacy Measures

ADAS-Cog

4.10.3 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

4.11 Analysis Plan

All tests of significance were to be 2-sided and at the < 0.05 level of significance

4.11.1 Baseline and Demographic Characteristics

- Descriptive statistics for all subjects were to be provided based on parameters at entry into GAL-USA-10
- Continuous variables were to be compared among the original treatment groups using ANOVA; the model was to include treatment and investigator as factors
- Categorical variables were to be compared among treatment groups using the Cochran-Mantel-Haenszel test

4.11.2 Primary Efficacy Parameter

- The purpose of the primary efficacy analysis was to explore whether there was a maintained benefit, as measured by the cognitive score of the ADAS-Cog, in subjects treated with galantamine 24 mg per day and then switched to placebo versus those treated with placebo throughout both GAL-USA-10 and GAL-USA -11
- To achieve the above objective, the analysis would compare **the Gal 24-placebo group** with the **placebo-placebo group** in the **change from baseline** (of the GAL-USA-10 trial) **to the end of the withdrawal phase** (of the GAL-USA-11 trial) in the **standard ADAS-Cog score**.
- The population for the primary efficacy analysis would consist of those who had taken at least one dose of trial medication during the withdrawal phase and who had post-treatment efficacy data. The dataset would consist of observed cases without imputation; a per-protocol analysis would be performed if a substantial number of protocol violators were found in this trial
- A secondary analysis of the primary efficacy variable would be performed on the same population using the traditional DNDP last-observation-carried-forward dataset
- An ANOVA model was to be used for the above analyses; this model was to include treatment and investigator as factors. 95 % confidence intervals would be provided for the mean and least square mean between-group differences. The parametric model assumptions for ANOVA would be assessed as follows: the Wilk-Shapiro statistic on the residuals would be used for verification of normality and Levene's test on the variances of the residuals would used for verification of the homogeneity of variances. A non-parametric analysis using the ANOVA model on the Tukey normalized rank was to be performed to corroborate the parametric results if the assumptions were found not to be appropriate
- Additional analyses on the primary efficacy variable were planned and are summarized below:

OBJECTIVE	ANALYSIS
To determine if the relative advantage of galantamine treatment for 5 months would be maintained after withdrawal of active treatment for 6 weeks	Within group change, for the galantamine-placebo group, in ADAS-Cog scores from the baseline of the GAL-USA -10 study to the end of the GAL-USA -11 study, would be assessed using the paired t-test
To determine if the effect induced by treatment with galantamine was maintained or lost during the 6-week withdrawal period following treatment with galantamine for 5 months	Within group change, for the Gal24-placebo group, in ADAS-Cog scores from the baseline of GAL-USA -11 to the end of that trial, would be assessed using the paired t-test
To determine the between-group differences in changes from the beginning to the end of GAL-USA-11	Comparison of between-group differences in mean change in ADAS-Cog from the beginning to the end of GAL-USA-11 (using ANOVA?)
To assess the effects of continuous treatment with galantamine 8 mg or 16 mg doses for 6.5 months versus that of placebo	Between group differences, comparing each of the Gal8 and Gal16 groups with placebo, for the mean change in ADAS-Cog from the baseline of the GAL-USA-10 study to the end of the GAL-USA-11 study, using ANOVA

4.11.3 Secondary Efficacy Parameters

- As noted earlier the secondary efficacy parameters were the ADAS-Cog/13, the ADAS-Cog/10 and the ADAS-Cog/mem
- These were to be analyzed using methods similar to the primary efficacy analysis as described above

4.12 Safety Parameters

- The safety parameters include adverse events, vital signs, safety laboratory tests and electrocardiograms
- All subjects who had taken at least one dose of study medication in this study would be included in the safety analysis
- Vital signs, physical examinations and electrocardiograms would be assessed as follows:
  - Descriptive statistics would evaluate the change from baseline in vital signs and electrocardiograms
  - Paired t-test would be used for the within-group comparison
  - ANOVA would be used for the between-group comparison with a model similar to that for the ADAS-Cog
- The incidence of adverse events during the preceding trial and the withdrawal protocol would be summarized. Summaries would also be provided for discontinuations due to adverse events as well as severe and serious adverse events
- Laboratory data would be analyzed as follows:
  - Descriptive statistics would be calculated for each laboratory parameter at each time point
  - Changes from baseline would be presented in shift tables
  - Listings of those with adverse events outside the reference range would be provided

4.12.1 Sample Size Rationale

- A mean difference of 2 units in change in ADAS-Cog score, from the baseline of GAL-USA-10 to the end of GAL-USA-11, between the placebo-placebo and gal24-placebo groups was considered clinically meaningful
- The pooled standard deviation of the difference in mean ADAS-Cog between the placebo-placebo and the gal24-placebo groups in the previously completed trial GAL-USA-5 was 5.8.
- Assuming a 20 % drop-out rate for GAL-USA-10, about 208 patients in the gal24-placebo group and about 104 patients in the placebo-placebo group should enter GAL-USA-11
- With 208 patients in the gal24-placebo group and 104 patients in the placebo-placebo group entering GAL-USA-11, this withdrawal trial should have > 90 % power to detect the above difference in change in ADAS-Cog scores between the 2 groups (α= 0.05; 2-sided)

4.13 Protocol Amendments

The only amendment to the protocol pertained to the method of recording and interpretation of electrocardiograms

4.14 Actual Analyses Performed

The analyses were performed as specified in the protocol

4.15 Efficacy Results

4.15.1 Patient Disposition

724 patients entered the trial from 54 sites; of these 1 patient was not treated because he lost medication. 687 patients completed the trial. Their disposition across the 4 treatment groups and reasons for treatment discontinuation are summarized in the following table

	PLA/PLA (N = 219)	GAL4/4mg b.i.d. (N = 104)	GAL8/8mg b.i.d. (N = 202)	GAL12mg b.i.d /PLA (N =198)
Any reason	13 (5.9%)	5 (4.8%)	9 (4.5%)	9 (4.5%)
Adverse event	4 (1.8%)	1 (1.0%)	5 (2.5%)	4 (2.0%)
Other	3 (1.4%)	2 (1.9%)	1 (0.5%)	2 (1.0%)
Ineligible to continue	1 (0.5%)	0 (0.0%)	1 (0.5%)	1 (0.5%)
Lost to follow-up	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Withdrew consent	4 (1.8%)	2 (1.9%)	2 (1.0%)	2 (1.0%)
During first 3 weeks	5 (2.3%)	4 (3.8%)	3 (1.5%)	2 (1.0%)
Month 5.75/Week 4 to > Month 6.5/Week 6	7 (3.2%)	1 (1.0%)	5 (2.5%)	6 (3.0%)
> Month 6.5/Week 6	1 (0.5%)	0 (0.0%)	1 (0.5%)	1 (0.5%)

4.15.2 Protocol Deviations

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

Protocol deviations	PLA/PLA (N = 219)	GAL4/4mg b.i.d. (N = 104)	GAL8/8mg b.i.d. (N = 202)	GAL 12mg b.i.d /PLA (N =198)
Any protocol deviations	2 (0.9%)	2 (1.9%)	4 (2.0%)	3 (1.5%)
Investigator mistake	0 (0.0%)	2 (1.9%)	1 (0.5%)	2 (1.0%)
Intercurrent forbidden therapy	1 (0.5%)	0 (0.0%)	1 (0.5%)	0 (0.0%)
Non-compliance	1 (0.5%)	0 (0.0%)	2 (1.0%)	0 (0.0%)
Treatment interruption too long	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)

4.15.3 Baseline And Other Demographic Characteristics

Demographic and baseline characteristics at the time of entry into GAL-USA-11 are summarized in the following table; these characteristics appear to have been balanced across treatment groups. These characteristics are summarized in the following table

Characteristics	PLA/PLA (N = 219)	GAL4/4mg b.i.d. (N = 104)	GAL8/8mg b.i.d. (N = 202)	GAL12mg b.i.d./PLA (N = 198)
Sex: n (%)				
Male	77 (35.2%)	41 (39.4%)	77 (38.1%)	66 (33.3%)
Female	142 (64.8%)	63 (60.6%)	125 (61.9%)	132 (66.7%)
Race: n (%)				
White	205 (93.6%)	100 (96.2%)	188 (93.1%)	182 (91.9%)
Black	9 (4.1%)	1 (1.0%)	8 (4.0%)	9 (4.5%)
Hispanic	3 (1.4%)	3 (2.9%)	5 (2.5%)	2 (1.0%)
Oriental	2 (0.9%)	0 (0.0%)	0 (0.0%)	3 (1.5%)
Other	0 (0.0%)	0 (0.0%)	1 (0.5%)	2 (1.0%)
Age (mean ± SE)	77.1 ± 0.53	76 ± 0.76	76.6 ± 0.58	77.9 ± 0.48
Weights (kg) (mean ± SE)	67.33 ± 0.96	70.53 ± 1.59	67.92 ± 0.99	65.41 ± 0.92
Smoker - Yes: n (%)	10 (4.6%)	6 (5.8%)	10 (5.0%)	9 (4.5%)
Age at onset of cognitive problems (mean ± SE)*	72.6 ± 0.57	72 ± 0.79	72.5 ± 0.58	73.8 ± 0.53
Years since cognitive problem diagnosis (mean ± SE)	4.97 ± 0.17	4.5 ± 0.23	4.62 ± 0.18	4.58 ± 0.20
Age at diagnosis of probable AD (mean ± SE)	75.6 ± 0.56	74.7 ± 0.77	75.4 ± 0.59	76.6 ± 0.49
Years of AD diagnosis (mean ± SE)	2 ± 0.12	1.84 ± 0.14	1.77 ± 0.11	1.78 ± 0.13
First degree relative(s) with AD n (%)	62 (28.3%)	31 (30.1%)	65 (32.5%)	63 (31.8%)
Cholinomimetic agent: n (%)	104 (47.5%)	49 (47.1%)	102 (50.5%)	91 (46.0%)
Total MMSE score (mean ± SE)	17.7 ± 0.25	18.2 ± 0.34	18 ± 0.25	17.9 ± 0.26
ADAS-cog/11 score at Baseline (mean ± SE)	28.9 ± 0.72	27.2 ± 1.05	28.4 ± 0.75	28.6 ± 0.75
APO-E group n (%)				
APO-E (22/23/33)	65 (33.9%)	34 (35.8%)	82 (43.6%)	56 (31.3%)
APO-E (24/34/44)	127 (66.1%)	61 (64.2%)	106 (56.4%)	123 (68.7%)

There were no differences in the medical history or concomitant disease profile among the treatment groups. Concomitant medication use by class was comparable across treatment groups.

4.15.4 Excluded Study Site

Data from Site # (Principal Investigators: was excluded from the efficacy analysis on account of a reported failure to adhere to Good Clinical Practice guidelines.

13 patients were at this site. Their disposition across study groups was as follows

Placebo/Placebo	5
Gal 8/Gal 8	2
Gal 16/Gal 16	3
Gal 24/Gal 24	3

Gal 8: galantamine 8 mg/day
Gal 16: galantamine 16 mg/day
Gal 24: galantamine 24 mg/day

4.15.5 Primary Efficacy Analysis

4.15.5.1 ADAS-Cog/11

The primary analysis compared the mean change in ADAS-Cog/11 from the initial visit of GAL-USA-10 to the Week 6 (Month 6.5 of the combined study) visit of GAL-USA-11 on the Observed Cases dataset. The primary comparison was between the Placebo/Placebo and Gal 24/Placebo groups. The difference between these groups was not statistically significant at Week 6, although it was significant at Week 3 as indicated in the following table. Similar results were seen at Week 6 for the traditional DNDP-LOCF population.

	PLA/PLA (N = 219)			GAL4/4mg b.i.d. (N = 104)			GAL8/8mg b.i.d. (N = 202)			GAL12mg b.i.d./PLA (N = 198)		
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 (USA10)	209	28.9 ±0.72	—	101	27.2 ±1.05	—	198	28.4 ±0.75	—	195	28.6 ±0.75	—
Week 4 (USA10)	208	28.7 ±0.79	−0.2 ±0.34	100	25.9 ±1.04	−1.3 ±0.54	198	27.3 ±0.79	−1.1 ±0.33	194	27.6 ±0.77	−1.1 ±0.35
Month 3 (USA10)	205	29.3 ±0.84	0.5 ±0.36	100	26.2 ±1.10	−1.1* ±0.53	195	26.1 ±0.82	−2.1*** ±0.37	195	26.5 ±0.78	−2.2*** ±0.38
Month 5 (USA10)	204	30.1 ±0.89	1.6 ±0.44	100	27.4 ±1.12	0.2 ±0.58	194	26.7 ±0.86	−1.6*** ±0.39	195	26.6 ±0.82	−2.0*** ±0.47
Month 5.75 (Week 3/USA11)	184	30.3 ±0.92	2.0 ±0.51	93	26.8 ±1.17	0.3* ±0.78	186	26.5 ±0.87	-1.8*** ±0.43	186	28.1 ±0.89	-0.3*** ±0.43
Month 6.5 (Week 6/USA11)	186	29.3 ±0.92	1.4 ±0.49	93	26.0 ±1.15	-0.5 ±0.70	179	26.4 ±0.91	-1.6*** ±0.46	182	29.4 ±0.97	0.8 ±0.49
Traditional LOCF	200	30.3 ±0.99	1.8 ±0.48	94	26.2 ±1.15	-0.4* ±0.70	194	26.8 ±0.89	−1.3*** ±0.45	199	29.3 ±0.97	0.7 ±0.48

*p < 0.05; **p < 0.001 on a 2-way ANOVA compared to the Placebo/Placebo group

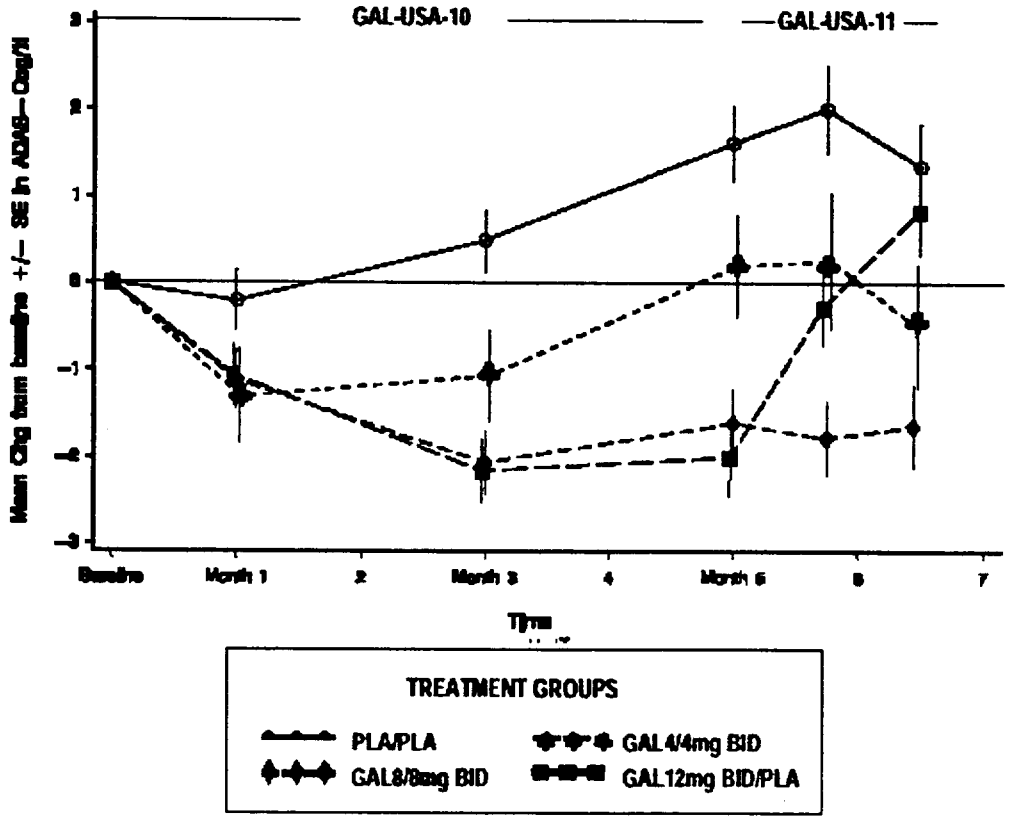
Differences between the placebo-placebo group and the other 3 groups in the mean change in ADAS-Cog/11 from the baseline of GAL-USA-10 to the end of GAL-USA-11 are in the table below.

Comparison	Difference in ADAS-Cog/11 mean change from baseline of GAL-USA-10 to Week 6 of GAL-USA-11
Gal 24/placebo vs placebo/placebo	-0.6
Gal 16/placebo vs placebo/placebo	-3.1
Gal 8/placebo vs placebo/placebo	-2.2

Based on the first of the above 2 tables and the figure below

- The Placebo/Placebo group continued to deteriorate throughout both studies although a marginal improvement may have occurred between Weeks 3 and 6 of GAL-USA-11
- The Gal 24/Placebo improved relative to baseline throughout GAL-USA-10 but deteriorated during GAL-USA-11 during which ADAS-Cog/11 scores appear to have deteriorated slightly below baseline scores for GAL-USA-10
- The Gal 8 and Gal 16 groups continued to maintain an improvement relative to the baseline of GAL-USA-10 at the end of GAL-USA-11.

The figure below shows the mean change (± standard error) from the baseline visit of GAL-USA-10 to the final visit of GAL-USA-11 for each of the 4 treatment groups on Observed Cases data



4.15.6 Analysis Of Secondary Efficacy Measures

4.15.6.1 ADAS-Cog Clusters

The mean scores and mean change from baseline (of GAL-USA-10) to Month 6.5 (Week 6 of GAL-USA-11) in ADAS-Cog cluster scores is summarized in the following table. As the table indicates there were no significant differences between the Gal 24/placebo and placebo/placebo groups

	PLA/PLA (N=219)			GAL4/4mg b.i.d. (N=104)			GAL8/8mg b.i.d. (N=202)			GAL12mg b.i.d./PLA (N=198)		
ADAS cluster score	n	Mean ± SE	Mean change ± SE	n	Mean ± SE	Mean change ± SE	n	Mean ± SE	Mean change ± SE	n	Mean ± SE	Mean change ± SE
ADAS-cog/13	185	38.7 ±1.02	1.0 ±0.53	93	35.4 ±1.28	-1.0 ±0.75	177	36.1 ±1.04	-2.1*** ±0.53	181	39.3 ±1.11	0.9 ±0.56
ADAS-cog/10	191	15.4 ±0.79	1.6 ±0.44	95	12.4 ±0.89	-0.2** ±0.52	180	13.2 ±0.70	-1.0*** ±0.36	184	15.1 ±0.80	1.1 ±0.42
ADAS-cog/mem	187	23.9 ±0.35	-0.4 ±0.23	93	22.9 ±0.52	-0.7 ±0.38	177	22.8 ±0.42	-1.1 ±0.29	181	24.2 ±0.39	-0.3 ±0.26

* p < 0.05; ***p < 0.001 on a 2-way ANOVA compared to the placebo/placebo group

4.15.6.2 ADAS-Cog Responder Analysis

The number and percentage of responders based on improvement in ADAS-Cog/11 scores from baseline (of GAL-USA-10) at Month 6.5 (Week 6 of GAL-USA-11) is summarized in the next table. Again there were no significant differences between the Gal 24/placebo and placebo/placebo groups

Category	PLA/PLA N = 186	GAL4/4mg b.i.d. N = 93	GAL8/8mg b.i.d. N = 179	GAL12mg b.i.d./PLA N = 182
Responder (0)	86 (46.2%)	50 (53.8%)	110 (61.5%)**	84 (46.2%)
Responder (4)	39 (21%)	24 (25.8%)	65 (36.3%)**	44 (24.2%)
Responder (7)	20 (10.8%)	15 (16.1%)	40 (22.3%)**	22 (12.1%)
Responder (10)	6 (3.2%)	8 (8.6%)	15 (8.4%)	12 (6.6%)

**p < 0.01 based on the CMH test, controlling for center, comparing each treatment group with the placebo/placebo group

4.15.6.3 Subgroup Analyses

4.15.6.3.1 Demographic Variables

The effects of treatment were consistent across subgroups. However

- The female subgroup in the Gal 24/placebo group worsened from baseline of GAL-USA-10 to Week 6 of GAL-USA-11 on ADAS-Cog/11 scores
- Regardless of demographic characteristics a small but consistent improvement was seen in the change in ADAS-Cog/11 scores (from the baseline of GAL-USA-10 to Week 6 of GAL-USA-11) in the Gal 24/placebo group, as compared with the placebo/placebo group

The subgroups used for the above analyses were very small and the conclusions that could be drawn from such analyses are very limited.

4.15.6.3.2 Baseline Disease Severity

When analyzing baseline disease severity patients were assessed based on baseline ADAS-Cog scores and also using baseline Mini-Mental Status Examination scores. The following were observed in regard to changes in ADAS-Cog/11 scores from baseline of GAL-USA-10 to Week 6 of GAL-USA-11

- Those with greater baseline severity of dementia had greater deterioration if they received placebo in GAL-USA-11 than if they received galantamine
- Regardless of baseline severity a small but consistent improvement was seen in the change in ADAS-Cog/11 scores (from the baseline of GAL-USA-10 to Week 6 of GAL-USA-11) in the Gal 24/placebo group, as compared with the placebo/placebo group

The subgroups used for the above analyses were very small and the conclusions that could be drawn from such analyses are very limited.

4.16 Safety Analyses

These are being performed by the safety reviewers, Drs Judith Racoosin and Jerry Boehm.

4.17 Sponsor's Overall Conclusions

- In patients with Alzheimer's Disease, no adverse safety consequences were observed over 6 weeks following the withdrawal of galantamine treatment
- Galantamine continued to be safe and well-tolerated in patients with Alzheimer's Disease when used continuously for 6.5 months in doses of 8 mg/day and 16 mg/day
- The efficacy of galantamine was diminished following withdrawal, as expected, but was maintained during continued treatment with 8 mg/day and 16 mg/day.

4.18 Reviewer's Comments

- The withdrawal paradigm used for this study does not correspond to the randomized withdrawal paradigm as it is usually understood. "Randomized withdrawal" generally refers to a study design where a proportion of a group receiving active drug during the treatment phase is then randomized to receive placebo, while the remainder in that group continue to receive active drug; the change in efficacy parameter(s) over a designated period after withdrawal is then compared between those 2 subgroups. In clinical drug trials for Alzheimer's Disease, randomized withdrawal after a period of parallel-arm double-blind treatment has been proposed as a means of distinguishing between a symptomatic effect of a drug and a disease-modifying effect.
- The changes in ADAS-Cog in the Gal 24/placebo group during GAL-USA-11 suggests, together with the results of an earlier withdrawal study, GAL-USA-5, suggest that any improvement in that parameter on galantamine is diminished or lost once that drug is discontinued.

5. Teleconference With Sponsor: 8/15/00

The teleconference was held so that the Division could state its reasons why certain items in the sponsor's earlier draft label (which accompanied the NDA Amendment of 2/25/00) were excluded from the Agency draft that accompanied the approvable letter.

The items discussed and the views conveyed by Dr R. Katz were as follows:

- A statement that galantamine was a nicotinic receptor modulator was excluded as the relevance of that purported function to the clinical effects of the drug was unknown
- A description of the ADCS-ADL results was excluded from the summary of the GAL-USA-10 study for the following reasons*
  - The Division was, in general, reluctant to include the results of secondary efficacy measures in labeling, and in particular if such an intention was not disclosed a priori by the sponsor
  - The results on this measure were confirmed only in a single study
  - With other purported measures of activities of daily living, in other galantamine efficacy studies, the results were inconsistently positive
  - Activities of daily living were already subsumed under the CIBIC-Plus the results of which were described in labeling; a description of the ADCS-ADL results might therefore be redundant
- A description of the Neuropsychiatry Inventory results was also excluded from the summary of the GAL-USA-10 study for the following reasons*
  - The Division was, in general, reluctant to include the results of secondary efficacy measures in labeling, and in particular if such an intention was not disclosed a priori by the sponsor
  - Although nominally statistically significant in GAL-USA-10, the results on the Neuropsychiatry Inventory might not remain statistically significant when adjusted for multiple comparisons
  - The results on this measure were clearly negative (p=0.54) in the GAL-INT-2 study

*It was indicated to the sponsor that a "full disclosure" description of the analysis of measures of activities of daily living and behavior across all studies would not be an acceptable alternative

6. Items In Label Needing Detailed Discussion

6.1 Galantamine As A Nicotinic Receptor Modulator

6.1.1 Sponsor's Arguments In Favor Of Describing This Function

- Galantamine enhances cholinergic neurotransmission by acting directly on nicotinic receptors; it binding to a distinct allosteric site on the nicotinic receptor acting synergistically with acetylcholine to facilitate nicotinic acetylcholinergic receptor activation. It is the most potent agent in a class referred to as allosterically potentiating ligands
- The allosteric potentiating action of galantamine is different from that of classical nicotinic agonists
- Galantamine acts on nicotinic receptors in brain slices from humans as well as rats
- Possible therapeutic benefits of nicotinic enhancement due to galantamine include
  - Since galantamine acts on pre-synaptic as well as post-synaptic nicotinic receptors it could enhance function in other neurotransmitter systems

  - It could increase the number of expressed nicotinic receptors
  - It could protect against beta-amyloid induced neuronal death
- Nicotine and nicotinic agonists enhance cognitive and psychomotor function, and nicotine may be anxiolytic, and several studies indicate that nicotinic enhancement may be a feasible strategy in Alzheimer's Disease. In fact treatment with cholinesterase inhibitors may cause indirect nicotinic enhancement
- Nicotinic receptors are lost in Alzheimer's Disease
- In-vitro and in-vivo animal studies suggest that the effects of galantamine extend beyond cholinesterase inhibition
- Anesthesiologists experienced with classic cholinesterase inhibitors noted that galantamine, in contrast to drugs such as neostigmine, had clinical effects that were consistent with greater nicotinic enhancement and less cholinesterase inhibition. Galantamine has been employed in Europe for the treatment of neuromuscular disorders
- The sponsor has compared galantamine with rivastigmine and donepezil using data from multiple sources
  - human pharmacokinetics
  - human cerebrospinal fluid acetylcholinesterase inhibition
  - brain acetylcholinesterase inhibition on primate and human positron emission tomography

  Based on these data the sponsor has concluded that acetylcholinesterase inhibition alone is less pronounced with galantamine than with rivastigmine and donepezil and insufficient to explain its efficacy

6.1.2 Reviewer's Comments

- The above arguments do not establish that
  - Nicotinic receptor modulation is relevant to the clinical efficacy of galantamine in Alzheimer's Disease or that
  - Acetylcholinesterase inhibition is less relevant to the clinical efficacy of galantamine as compared with other cholinesterase inhibitors
- If, as the sponsor appears to believe, nicotinic receptor modulation (and nicotinic enhancement) is greater and acetylcholinesterase inhibition less with galantamine, as compared with other cholinesterase inhibitors, it is surprising that "nicotinic" adverse events such as muscle twitching, cramps and muscle weakness are not more common with galantamine than with other cholinesterase inhibitors.

6.2 Inclusion Of Activities Of Daily Living Scale Results In Label

6.2.1 Description Of Activities Of Daily Living Scales That Sponsor Has Included In Label

6.2.1.1 Disability Assessment in Dementia

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

Initiation
Planning and organization
Effective performance
The number of items scored at each level is as follows:
Initiation: 15 items
Planning and organization: 11 items
Effective performance: 20 items
Total: 46 items
Each item is scored as follows
0: not performed in the last 2 weeks
1: performed in the last 2 weeks
Not applicable: no opportunity to perform task in the last 2 weeks
The maximum possible score is 46. Higher scores indicate less disability, while lower scores indicate more disability.

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

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

6.2.2 Sponsor's Motivation For Including Activities Of Daily Living Scales In Label

- Measures of activities of daily living are clinically relevant in supporting the efficacy of galantamine
- The clinical meaningfulness of observed changes in the activities of daily living scales are validated in the presence of concomitant changes in measures of cognitive, behavioral and global function
- Positive results were seen on measures of activities of daily living in clinical trials of galantamine as follows
  - In GAL-USA-10 highly significant results were obtained for both recommended doses of galantamine in comparison with placebo using the ADCS-ADL
  - On a pooled analysis of GAL-USA-1 and GAL-INT-1, a statistically significant positive effect for galantamine 32 mg/day versus placebo was obtained using the Disability Assessment for Dementia. In the individual trials the effect was not statistically significant but a trend towards superiority for the galantamine groups versus the placebo group was seen at both 24 mg/day and 32 mg/day. The mean Disability Assessment for Dementia score for patients continuing on a dose of 24 mg/day in the open-label extension of GAL-USA-1 was unchanged a year later
  - A highly statistically significant superiority of galantamine versus placebo was seen in GAL-INT-2 using the Disability Assessment for Dementia
  - There was a statistically significant superiority for galantamine versus placebo on the Nuremberg Alters-Beobachtungs-Skala (Nuremberg Geriatric Observation Scale)* in GAL 95-05

    * This is a 15-item scale that assesses: instrumental and basic activities of daily living; ability to communicate verbally, in writing or by gesture; hearing; and vision. It may be rated by relatives, nurses, or clinical staff. Each of the 15 items consists of a statement that is rated on a scale from 1 to 3. The scoring system is structured and each score represents a defined level of functioning Higher total scores indicate greater impairment
  - (The time spent by caregivers in assisting patients with their activities of daily living was assessed in GAL-USA-1 and GAL-INT-1). In GAL-INT-1 caregivers of patients who received placebo spent statistically significantly more time assisting with activities of daily living after 6 months as compared with baseline; caregivers of patients who received galantamine spent less time assisting with activities of daily living at 6 months than at baseline
  - Composite responder analyses that included activities of daily living for GAL-USA-1, GAL-INT-1 and GAL-USA-10 always showed statistical significance favoring galantamine

- Inconsistent results on the Disability Assessment for Dementia scale in GAL-INT-1 and GAL-USA-1 (these 2 studies showed a considerable difference in the magnitude of placebo deterioration as opposed to a similar degree of change in the galantamine groups) suggested that this scale was insufficiently sensitive and led to the use of the ADCS-ADL as the measure of activities of daily living in the GAL-USA-10 study.
- The ADCS-ADL scale is sensitive across a wide spectrum of dementia severity, reliable, and validated. It also assesses a comprehensive spectrum of activities of daily living and is less subjective than other measures
- A description of activities of daily living data in the label will be helpful to physicians, especially those in primary care who may not be familiar with the ADAS-Cog and CIBIC-Plus

6.2.3 Reviewer's Comments

- 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 all studies that could be considered positive based on tests of statistical significance, the effect sizes are small. These results are summarized in the following tables. The first table provides the results for all efficacy studies in which measures of activities of daily living were used.

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-USA-1 and GAL-INT-1 (pooled analysis)	Disability Assessment in Dementia	GAL 24: 0.317 GAL 32: 0.043
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 next table summarizes the results for studies in which the ADCS-ADL and Disability Assessment for Dementia were used as measures of activities of daily living

Study	Activities of daily living measure	LS Mean galantamine-placebo treatment difference in change from baseline to Month 6	p-value for galantamine-placebo comparison
GAL-USA-1	Disability Assessment in Dementia	GAL 24: -0.5 GAL 32: 0.7	GAL 24: 0.943 GAL 32: 0.901
GAL-INT-1	Disability Assessment in Dementia	GAL 24: 2.5 GAL 32: 3.8	GAL 24: 0.270 GAL 32: 0.055
GAL-USA-1 and GAL-INT-1 (pooled analysis)	Disability Assessment in Dementia	GAL 24: 1.2 GAL 32: 2.6	GAL 24: 0.317 GAL 32: 0.043
GAL-INT-2	Disability Assessment in Dementia	4.3	0.004
GAL-USA-10	ADCS-ADL	GAL 8: 0.9 GAL 16: 3.5 GAL 24: 2.4	GAL 8: 0.308 GAL 16: < 0.001 GAL 24: 0.003

- The most robust results were seen in the GAL-USA-10 study in which the ADCS-ADL measure was used: in this study, efficacy on this measure was demonstrated at galantamine doses of 16 mg/day and 24 mg/day, both of which are being recommended for use by the sponsor.
  - Although the ADCS-ADL was one of several secondary efficacy measures, the p-values easily adjust for multiplicity to continue to meet the stipulated level of significance required for a positive result.
  - This rating scale does seem to be comprehensive, sensitive, reliable and valid.
  - The scoring system for the ADCS-ADL 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
  - However 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; some support for their being clinically meaningful is provided by the results of the CIBIC-Plus for that study which parallel those for the ADCS-ADL
    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.
  - **More importantly, these results have yet to be reproduced in a second study**
- The results of the Disability Assessment for Dementia are less persuasive
  - Although the scale may have been established to be both valid and appears comprehensive, it may measure the frequency with which a specific item was performed rather than the extent to which that function was impaired; in that regard it is less structured than the ADCS-ADL
  - The results are inconsistently positive at even a nominally statistically significant level ($p < 0.05$) across the 3 studies (GAL-USA-1, GAL-INT-1 and GAL-INT-2) in which it was used: even by such a yardstick it is positive only in the GAL-INT-2 trial
  - It was one of seven secondary efficacy measures in GAL-USA-1 and GAL-INT-1, and one of six secondary efficacy measures in GAL-INT-2
  - Even in the pooled analysis for GAL-INT-1 and GAL-USA-1, nominal statistical significance is achieved only at the 32 mg/day dose which is not being recommended for use; when adjusted for multiple comparisons, the p-value of 0.043 is less impressive.
  - It may also be noteworthy that in the GAL-USA-1 study, based on clinical effect alone, the group which received galantamine 24 mg/day did the same or showed a trend towards worsening as compared with the placebo group
- In the GAL 95-05 study, the nominally significant p-value of 0.032 for the Nuremberg Geriatric Observation Scale may not be as significant once adjusted for multiple comparisons (4 secondary outcome measures were used). It is also again unclear if the small effect size is clinically meaningful. Furthermore, in this study the only galantamine dose group received 32 mg/day in 3 divided doses, which is not the regime that is being currently recommended
- In the GAL 93-01 study, no statistically significant difference was seen between the galantamine and placebo groups on either of 2 measures of activities of daily living, the Progressive Deterioration Scale and the Instrumental Activities of Daily Living Scale.

- No statistically significant differences between the galantamine and placebo groups were seen on the allocation of caregiver time survey, in either GAL-USA-1 or GAL-INT-1.
- Note that the method of rating the CIBIC-Plus in the key efficacy studies (GAL-USA-1, GAL-INT-1 and GAL-USA-10) included an assessment of activities of daily living; details of the CIBIC-Plus data are included in the label. Thus the additional description of activities of daily living ratings does not appear warranted
- A listing of measures of activities of daily living that were used in efficacy studies in the label (the sponsor has currently listed but not describe either the scales or results) does not seem to serve a purpose

6.3 Inclusion Of Neuropsychiatry Inventory Results In Label

6.3.1 Description Of Neuropsychiatry Inventory

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

6.3.2 Sponsor's Arguments For Including Neuropsychiatry Inventory Results In Label

- In GAL-USA-10, statistically significant benefits were observed for galantamine in doses of 16 mg/day and 24 mg/day in comparison with placebo on the Neuropsychiatry Inventory total score. In addition the trend was always in favor of galantamine for each individual item of the 10-item scale; for several such items, statistical significance was observed. The strength of these results is supported by the large number of patients in this trial (the largest trial of galantamine performed so far) as well as the positive result for the Neuropsychiatry Inventory ancillary scale (Neuropsychiatry Inventory Caregiver Distress)
- The lack of a statistically significant result on the Neuropsychiatry Inventory in the GAL-INT-2 study, the only other study in which this measure was used may be explained as follows:
  - In GAL-INT-2 patients had baseline Mini-Mental Status Examination scores that were higher and ADAS-Cog scores that were lower than those took part in GAL-USA-10. Behavioral abnormalities tend to emerge late in the course of Alzheimer's Disease and the mean Neuropsychiatry Inventory score at baseline for patients participating in GAL-INT-2 was 6 points better than for a patient participating in GAL-USA-10.
  - GAL-INT-2 was only 3 months in duration and Neuropsychiatry Inventory scores in both the drug and placebo groups were unchanged at the end of the trial; in GAL-USA-10 the separation of the drug and placebo groups on the Neuropsychiatry Inventory occurred only after Month 3. Thus the results in GAL-INT-2 are not unexpected
- The positive results on the Neuropsychiatry Inventory in the GAL-USA-10 study are buttressed by the results on the CIBIC-Plus results across all studies: the method of rating the CIBIC-Plus in the key efficacy studies (GAL-USA-1, GAL-INT-1 and GAL-USA-10) included an assessment of behavioral symptoms.

- A listing of the Neuropsychiatry Inventory as a behavior measure that was used in efficacy studies in the label (as the sponsor has listed this scale but not described either the scale or results) does not seem to serve a purpose

6.3.3 Summary Of Neuropsychiatry Inventory Results

6.3.3.1 GAL-USA-10

The Neuropsychiatry Inventory (Total) results for this study are summarized in the following tables

	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	275	11.0 ±0.67		134	12.9 ±1.23		267	12.4 ±0.77		262	11.9 ±0.83	
Week 4	262	9.5 ±0.63	−1.1 ±0.50	128	13.0 ±1.24	0.2 ±0.78	255	11.4 ±0.72	−0.3 ±0.49	253	11.5 ±0.78	−0.2 ±0.54
Month 3	243	11.5 ±0.83	0.9 ±0.63	117	13.8 ±1.46	2.0 ±1.03	234	10.9 ±0.78	−0.3 ±0.60	228	11.6 ±0.88	−0.2 ±0.72
Month 5	234	13.0 ±0.96	2.3 ±0.74	106	14.5 ±1.59	2.3 ±1.12	211	10.7 ±0.90	−0.1* ±0.76	212	11.8 ±0.96	−0.1* ±0.86

p < 0.05 with Fisher's LSD procedure comparing each galantamine group with placebo

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

6.3.3.2 GAL-INT-2

The results for the total Neuropsychiatry Inventory and total Neuropsychiatry Inventory Distress Score are in the next table. For the total Neuropsychiatry Inventory score the p-value for the galantamine-placebo comparison was 0.546.

	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

6.3.4 Reviewer's Comments

- In clinical efficacy studies of galantamine, 2 rating scales for behavior were used: the Neuropsychiatry Inventory and the ADAS-NonCog. A summary of results across studies that used these measures, is in the table below

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

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

- There was no evidence for a statistically significant superiority of galantamine over placebo on the ADAS-NonCog in either of the 2 studies in which it was used
- The evidence for efficacy based on the Neuropsychiatry Inventory was inconsistent across the 2 studies in which it was used; while the GAL-USA-10 study was nominally "positive" the GAL-INT-2 study was "negative"
- 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 (the Neuropsychiatry Inventory was one of six secondary efficacy measures); furthermore the effect size seen is very small and may not be clinically meaningful, unless correlated with the CIBIC-Plus .
- While there was a trend in favor of galantamine on each of the 10 individual components of the Neuropsychiatry Inventory, the multiplicity of such comparisons would clearly have to be taken into consideration in deciding if one or more comparisons were statistically significant. The sponsor has not provided details of these analyses; neither have the results for the Neuropsychiatry Inventory Caregiver Distress score been presented.
- Note that the method of rating the CIBIC-Plus in the key efficacy studies (GAL-USA-1, GAL-INT-1 and GAL-USA-10) included an assessment of behavior; details of the CIBIC-Plus data are included in the label. Thus an additional description of a measure of behavior in the label does not appear warranted
- A listing of the Neuropsychiatry Inventory as a behavior measure that was used in efficacy studies in the label (as the sponsor has currently included such a mention) does not seem warranted

6.4 ADAS-Cog Responder Analysis

6.4.1 Background

Cumulative distribution curves and tables describing ADAS-Cog responder analyses for the 4 key efficacy studies (GAL-INT-1, GAL-USA-1, GAL-INT-2 and GAL-USA-10) were included in the draft label that accompanied the "Approvable" letter. 3 change scores were chosen for these curves and tables: ≥ 7- and ≥ 4-point improvements and No Change

6.4.2 Sponsor's Change To Label

The sponsor has added data for a ≥10 point ADAS-Cog change to the above cumulative distribution curves and tables.

6.4.3 Comments

These changes are acceptable.

6.5 Efficacy Of Galantamine Doses > 16 Mg/Day

6.5.1 Background

The draft label attached to the "Approvable" letter issued by the Agency on 7/29/00 included the following statement in the "Dosing and Administration" section

In the draft label accompanying this resubmission the sponsor has stated the redrafted the above statement as follows

Thus the statement below has been deleted from the sponsor's version of the label attached to this submission

6.5.2 Sponsor's Reasons For Deleting Above Statement From Label

- In GAL-USA-10, the only study in which these doses had been compared, those randomized to the 24 mg/day dose received that dose for 1 month less at endpoint than those randomized to the 16 mg/day dose received their assigned dose. There was thus inadequate time for the mean changes in each of these dose to show separation
- A responder analysis based on the ADAS-Cog data for GAL-USA-10 showed a higher proportion of good responders (≥ 7 or ≥ 10 point improvement) in the 24 mg/day group as compared with the 16 mg/day group. A similar trend was seen between the 32 mg/day and 24 mg/day groups for GAL-USA-1 and GAL-INT-1. Together these data suggest a dose-response relationship. A table showing the responder analysis for GAL-USA-10 (which has been created by me) is below.

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	p-value GAL 24 Vs GAL 16
≥ 0 points	41.8	64.9	65.4	46.5	< 0.001	< 0.001	0.556	0.811
≥ 4 points	19.6	37.0	35.6	25.7	< 0.001	< 0.001	0.266	0.758
≥ 7 points	7.6	22.3	15.9	13.9	< 0.001	< 0.001	0.106	0.080
≥ 10 points	3.6	10.4	7.2	5.9	0.004	0.102	0.378	0.167

- Patients who were treated with galantamine 24 mg/day for 12 months through GAL-USA-1 and its extension GAL-USA-3 showed ADAS-Cog and Disability

Assessment for Dementia scores that were not significantly different from baseline

-

6.5.3 Reviewer's Comments

- In the ADAS-Cog responder analysis for GAL-USA-10 shown above, the proportion and numbers of patients in the ≥ 7 point and ≥ 10 point improvement categories is small; and the differences in these proportions between the 24 mg/day and 16 mg/day groups not statistically significant
- Comparisons of the mean ADAS-Cog change at Month 5 between the 24 mg/day and 16 mg/day groups revealed no statistically significant difference as indicated by the following table

Comparison	ADAS-Cog Mean Change from Baseline at Month 5: Difference Between Treatment Groups. Observed Cases	p-value
GAL 24 vs GAL 8	-1.9	0.007
GAL 16 vs GAL 8	-1.6	0.028
GAL 24 vs GAL 16	-0.3	0.554

- Using pooled ADAS-Cog data, the galantamine 32 mg/day was compared with the 24 mg/day group on the mean ADAS-Cog change from baseline at Month 6 ; 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. Pooled Analysis of GAL-USA-1 and GAL-INT-1	p-value
GAL 32 vs GAL 24	-0.5	0.330

- There is thus inadequate evidence that
  - The 32 mg/day group is superior to the 24 mg/day group
  - The 24 mg/day group is superior to the 16 mg/day group
- The following statement should be re-instated in the label
  "There is no evidence that doses greater than 16 mg/day confer additional benefit"

6.6 Dose Titration Recommended In Label

6.6.1 Background

The draft label that accompanied the "Approvable" letter included the following text in regard to dose titration

6.6.2 Sponsor's Current Text

In the draft label accompanying the current submission, the sponsor's text for the above paragraph reads as follows

6.6.3 Reviewer's Comments

- Note that the section highlighted above in pink in the draft label that accompanied the "Approvable" letter has been deleted in the current version.
- This section should be re-inserted in the label. Increases in dosage from 4 mg b.i.d to 8 mg b.i.d should be made only a minimum of 4 weeks of treatment at the lower dose and only if that dose is well-tolerated.

7. Overall Comments

- The results of the GAL-USA-11 study, together with those of GAL-USA-5 an earlier study, suggest that the small beneficial effects of galantamine recede once the drug is discontinued and that the drug does not have a disease-modifying action.
- No other new efficacy data have been provided with this submission
- Changes that I have made to the sponsor's draft labeling that accompanied this submission include the following (these changes are discussed in detail earlier in this review)
  - Statements that galantamine was a nicotinic receptor modulator was deleted from the Description and Mechanism of Action sections as the relevance of that purported function to the clinical effects of the drug was unknown
  - References to several secondary efficacy measures-the ADCS-ADL, Disability Assessment for Dementia and Neuropsychiatry Inventory-were deleted from the Clinical Trials section for the reasons already discussed at length
  - A statement that there is no evidence that doses of galantamine exceeding 16 mg/day confer additional benefit has been reinstated in the Dosage and Administration section
  - A statement that the starting galantamine dose of 4 mg b.i.d should be continued for a minimum of 4 weeks and increased to 8 mg b.i.d only if the lower dose is well-tolerated has also been re-instated in the label.
- **Based on my review of the efficacy data in the original NDA submission, it may again 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, limited as they are.**
- However, it should again 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; and 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.
- The safety data in this submission are being reviewed separately by Drs Judith Racoosin and Gerald Boehm.

8. Recommendations

As before, 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 resubmission, that the benefits of that drug outweigh the risks**

/S/

Ranjit B. Mani, M.D.
Medical Reviewer

R. Katz, M.D. /S/

rbm 11/29/00
cc:
HFD-120
NDA
Fanari

Review and Evaluation of Clinical Data

NDA	**21169**
Sponsor:	**Janssen**
Drug:	**Galantamine**
Proposed Indication:	**Alzheimer's Disease**
Material Submitted:	**Resubmission/Labeling Review**
Correspondence Date:	**8/31/00**
Date Received / Agency:	**9/5/00**
Date Review Completed	**11/28/00**
Reviewer:	**Ranjit B. Mani, M.D.**

1. Background

This submission contains the sponsor's response to the Agency's approvable letter for galantamine (Reminyl®) dated 7/29/00.

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

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 the original NDA and the amendment, were completed by me on 6/13/00. The safety review of the submission was completed by Drs Judith Racoosin, Jerry Boehm and Kevin Prohaska. Please see these reviews for full details.

Based on these and the other reviews of the above application, an "Approvable" letter was issued on 7/29/00. Please refer to that letter for full details. The letter included the following:

- Draft labeling, revised by the Agency, and containing several "Notes to Sponsor" requesting further revisions or clarifications
- Requests for information and additional analyses pertaining to the safety review
- Requests for information in regard to several toxicology studies, and for specific histopathological examinations in Phase 4
- Requests for information pertaining to Chemistry, Manufacturing and Controls
- A request to adopt a specific dissolution methodology for all galantamine tablets

This review is confined to specific items in the draft label listed below. A more detailed discussion of individual items in the label is in my formal review of the resubmission which is in a separate document

Description
Clinical Pharmacology: Mechanism of Action and Clinical Trials
Indications and Usage
Dosage and Administration

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

Doses in Special Populations

7. Comments

7.1 Description And Mechanism Of Action

References to the nicotinic receptor modulating action of galantamine in the sponsor's draft label enclosed in the resubmission have been deleted because there is no evidence that the clinical efficacy of galantamine is related to such action

7.2 Clinical Trials

- Although the sponsor has listed the ADCS-ADL, Disability Assessment for Dementia, and Neuropsychiatry Inventory as secondary efficacy measures in the package insert, no description of these scales or of the results on these measures in individual trials has not been provided
  I have deleted all references to these measures from the label. A detailed discussion of the reasons for doing so is in the main review. In summary
  - All were secondary efficacy measures; none were designated in advance as being intended for inclusion in the label
  - Assessments of both activities of daily living and behavior were already components of the CIBIC-Plus
  - Although the results on the ADCS-ADL in the GAL-USA-10 study were robust, they have not been reproduced in a second study
  - The results on the Disability Assessment for Dementia were inconsistent across studies and the scale may measure the frequency with which a specific function is impaired rather than the severity of impairment
  - The results on the Neuropsychiatry Inventory were inconsistent across studies; even in the GAL-USA-10 study where they were nominally statistically significant for both the 24 mg/day and 16 mg/day dose groups, they were no longer so when adjusted for multiple comparisons
- The sponsor has made additions to the ADAS-Cog responder analyses described in the label which contains cumulative distribution curves and tables for specific ADAS-Cog change scores. The version of the draft label that accompanied the "Approvable" letter had figures and tables for all 4 key efficacy studies describing the percentages of patients in each treatment group achieving the following levels of change in ADAS-Cog score: $\geq$ 7-, and $\geq$ 4 points and No Change. The version of the draft label included in this submission contains cumulative distribution figures and tables for all 4 key

efficacy studies that also includes percentages of patient improving ≥ 10 points on the ADAS-Cog

7.3 Indications And Usage

I have not made any alterations to the text of the sponsor's draft label. The wording of this section is identical to that in the draft label that accompanied the approvable letter.

7.4 Dosage And Administration

- I have re-inserted the following statement in the label

  "There is no evidence that doses greater than 16 mg/day confer additional benefit"

  The detailed reasons for re-inserting this statement are in the main review. In summary, there is no evidence that a galantamine dose of 24 mg/day is more effective than one of 16 mg/day
- I have also re-inserted a statement that the starting dose of 4 mg b.i.d should be increased to 8 mg b.i.d only after a minimum of 4 weeks of treatment at the lower dose and only if that dose is well-tolerated; such an approach appears to be more prudent.

Ranjit B. Mani, M.D.
Medical Reviewer

R. Katz, M.D.

rbm 11/28/00
cc:
HFD-120
NDA 21169
Fanari

Review and Evaluation of Clinical Data
NDA Safety Review

NDA: 21-169

Sponsor: Janssen Research Foundation

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

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

Proposed Dosage: 8-12 mg po BID

Date of the NDA Submission: September 29, 1999

Safety Reviewers: Judith A. Racoosin, MD, MPH
Gerard Boehm, MD, MPH
Kevin Prohaska, MD
Michael Sevka, MD

Author: Judith A. Racoosin, MD, MPH

Date Review Completed: July 13, 2000

Materials used in the review:

NDA 21-169: electronic submission dated 9-29-99
Amendment to the NDA dated 2-25-00
Amendment to the NDA dated 4-20-00