CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-169

Medical Review(s)

Review and Evaluation of Clinical Data
Response to Approvable Letter - Labeling

NDA: 21-169

Sponsor: Janssen Research Foundation

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

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

Proposed Dosage: 8-12 mg po BID

Date of the Response to the Approvable Letter: August 31, 2000

Safety Reviewers: Judith A. Racoosin, MD, MPH

Date Review Completed: January 31, 2001

Materials used in the review:
NDA 21-169: Response to the Approvable Letter, paper volumes and electronic submission dated 8/31/00

Indications

No comments.

Contraindications

No comments.

Warnings

Cardiovascular Conditions

The sponsor makes the argument that for common events (such as nausea and vomiting), the comparison of the risk of such events between the slow titration and the rapid titration regimens accurately reflects the differences in frequency of these events and can be attributed to the difference in titration speed. In contrast, the sponsor suggests that the incidence of infrequent events (such as syncope) is more affected by random chance, hence a comparison of the incidence of these events between fast and slow titration studies does not accurately reflect their true incidence. As such, for the infrequent events bradycardia and syncope, the sponsor wants to pool the data from the slow titration study (GAL-USA-10) with the fast titration studies.

In this case, due to different study designs and dose groups, it does not seem prudent to pool the data between the fast and slow titration studies. One issue that would be somewhat obscured by pooling is whether syncope is dose-related. Only GAL-USA-10 had any substantial person time at the lower doses of 4mg BID and 8 mg BID (the 8 mg BID dose is being recommended as the lowest efficacious dose). The sponsor raises the issue that some of the syncopal events that occurred in patients randomized to the higher doses (8 mg BID and 12 mg BID) actually occurred at lower doses during the titration. In their recalculation of the syncope rates, the sponsor has changed the denominator to reflect the fact that every patient randomized to a dose above the starting dose had to pass through each of the lower doses on his or her way to their randomized dose. Even with this recalculation, there is still a dose-response relationship for syncope (placebo 0.7% [2/286]; 4 mg BID 0.4% [3/692]; 8 mg BID 1.3% [7/552]; 12 mg BID 2.2% [6/273]). The fact that patients randomized to higher doses spent substantial portions of the trial at lower doses (one month at each lower dose) leads to the observation that the total person-time spent at the highest dose was substantially less than that at the lower doses. Additionally, the new denominators show that fewer patients were exposed to the highest dose as compared to the lowest doses. Thus, I think it is important that this information be conveyed in the "Cardiovascular Conditions" subsection of the Warnings. See attached labeling for changes to text.

Precautions

The "Information for Patients and Caregivers" subsection should be moved from within the discussion of drug-drug interactions to the beginning of the Precautions section where it will be seen more prominently. A statement should be added to this subsection warning of the potential risk of increased gastrointestinal side effects if the drug is not retitrated after a period of drug interruption. See attached labeling for changes to text.

Adverse Events

Adverse Events Reported in Controlled Trials

The sponsor proposes to say that nausea and vomiting, the most common adverse events, lasted less than a week in most cases, and the majority of the patients only had one episode. The text of the ISS-A in section 8.2.1.1, paragraph 6, states that "65% of the patients with nausea experienced one episode, 22% had two episodes, and 12% had more than two episodes". They go on to say "the duration was usually short, with a reported median duration of 5 to 7 days." The statement that most patients only had one episode is misleading, implying that they will only feel nauseous once; yet the sponsor defines an episode as lasting a median of 5 to 7 days. Therefore, the assurance of only one episode in a majority of patients should be deleted. Furthermore, the labeling states that nausea lasted less than a week in "most" cases, when in reality that was the median length. Thus half the patients' experienced nausea that lasted more than 5-7 days. The labeling should be modified to say the median duration of nausea was 5-7 days. See attached labeling for changes to text.

In Table 3, it is not clear what the rationale is for pooling USA-10 with USA-1, INT-1, and 93-01? Since there were substantial differences in the study designs between USA-10 and the other three studies, it would be more informative to show side by side the placebo and galantamine risks for the three "one week" titration studies with the placebo and galantamine risks for the "four week" titration study. Additionally, the sponsor only included data from the 8 mg BID and 12 mg BID dose groups. However, study 93-01 had an 18 mg/day dose group that falls into the recommended range. Therefore the calculations for the three "one week" titration studies should be repeated to include the data from this dose group.

In my original revisions to the sponsor's proposed labeling, I added a statement in the Adverse Events section regarding the occurrence of renal calculi in four galantamine patients compared to zero placebo patients in the U.S. RCTs. Because the sponsor did not feel this adverse event deserved a "stand alone" paragraph, in their current proposed labeling they have deleted the statement and added "renal calculi" to the listing of "Other Adverse Events Observed During Clinical Trials" under Urinary System disorders. In explanation for this change, the sponsor provided some data to support their contention that the observation is consistent with what would have been observed in the background in this population. First, the sponsor has calculated from the 1993 National Hospital Discharge Survey (NHDS) that the rate of hospitalization with urinary stone as any diagnosis in the age group 65 and older is 2.1/1000 person-years. This compares to the

incidence of renal calculi in the development program (RCT combined with open extension) of 2.8/1000 person-years. Furthermore, the sponsor shows that the likelihood of observing four cases in the galantamine group in the RCTs when two-thirds of the patients are randomized to galantamine is $(0.67)^4$ or 0.2. Thus it would not be rare to observe this distribution of events by chance. Finally, the sponsor argues that three of the four cases are not likely to be drug-related because one of the patients had a remote history of renal calculi, and the other two patients had short exposures to the drug (6 days and 18 days). It is not clear that a short exposure to a drug could not induce renal calculi. In the experience with indinavir, patients passed renal calculi as early as week 1[1]. Based on the sponsor's first two lines of evidence, the comparison to the rate observed in the NHDS, and the probability argument, I think it is reasonable to keep the sponsor's changes regarding renal calculi.

Other Adverse Events Observed During Clinical Trials

In this section, the sponsor proposes to include "all adverse events occurring in approximately 0.1% ..., except for those already listed elsewhere in labeling, WHO terms too general to be informative, or relatively minor events." I have requested that the sponsor explain what is meant by "relatively minor events". Furthermore, the sponsor asserts that the adverse events listed in this section "were observed at a similar frequency in placebo-treated patients in the controlled studies", yet there is no reference to a table to support this statement. I have requested that the sponsor provide such supporting data.

I have added "esophageal perforation" to the Gastrointestinal System Disorders adverse event listing and "low serum glucose' to the Metabolic and Nutritional Disorders listing.

/S/ 1/31/01

Judith A. Racoosin, MD, MPH
Safety Team Leader

[1] Daudon M, et al. Urinary stones in HIV-1 positive patients treated with indinavir. *Lancet* 1997; 349(9061): 1294-5.

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

Review and Evaluation of Clinical Data
SAFETY UPDATE

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 Response to the Approvable Letter: August 31, 2000

Safety Reviewers: Judith A. Racoosin, MD, MPH
Gerard Boehm, MD, MPH

Date Review Completed: January 25, 2001

Materials used in the review:

- NDA 21-169: Response to the Approvable Letter, paper volumes and electronic submission dated 8/31/00
- JRF Response to FDA Request for Clinical/Safety Information, dated 10/2/00
- JRF Response to FDA Request for Clinical/Safety Information, dated 11/28/00
- JRF Response to FDA Request for Information- Clinical, dated 12/21/00 (email)
- JRF Response to FDA Request for Information- GAL-INT-6, dated 1/3/01
- JRF Response to FDA Request for Information- Clinical, dated 1/10/01
- JRF Response to FDA Request for Information- Clinical, dated 1/16/01
- JRF Response to FDA Request for Information- Clinical, dated 1/17/01 (email)

1 Background

1.1 Time period covered

The safety update of the galantamine development program submitted with the response to the approvable letter covers the period from October 1, 1999 through June 30, 2000.

1.2 Studies included in the safety update

1.2.1 Alzheimer's disease- completed

The sponsor completed two studies in patients with Alzheimer's disease during the safety update period. The sponsor provided the full study report for the withdrawal study GAL-USA-11, which is reviewed below (see section 2.1).

GAL-CAN-1 was a study of switching directly from donepezil to galantamine in patients who did not respond to donepezil. This study was discontinued after enrolling 58 patients because nearly 75% of patients experienced adverse events (AEs) related to excessive cholinergic stimulation. Six of the 58 patients discontinued prematurely, one patient experienced syncope, and no patients died.

1.2.2 Alzheimer's disease- ongoing

Table 3 attached to the safety update details the ongoing trials of galantamine in Alzheimer's disease patients. Basically, the ongoing trials are all extensions of the original RCTs as seen in the table below. Additionally, refer to Figure 1 in the Appendix for a pictorial layout of the galantamine trials for Alzheimer's disease over time.

Table 1. Summary of origin of ongoing trials of galantamine in Alzheimer's disease patients

Ongoing trial	Original RCT	Previous extension trials
GAL-USA-9	GAL-USA-3	GAL-USA-6
GAL-USA-12	GAL-USA-10	GAL-USA-11
GAL-USA-17	GAL-USA-16	N/A
GAL-USA-18	N/A	GAL-USA-9, USA-12, USA-17
GAL-INT-8	GAL-INT-1/GAL-INT-2	GAL-INT-3/GAL-INT-7
GAL-INT-13	GAL-INT-1/GAL-INT-2	GAL-INT-8
GAL-IV-503*	GAL 95-05/GAL 95-07	GAL 95-05X/GAL 95-07X

all ongoing trials are JRF-sponsored except GAL-IV-503 which is sponsored by Shire.
N/A- not applicable

1.2.3 Other indications- completed and ongoing

During the safety update period, the sponsor completed four studies of galantamine in other indications. GAL-SWE-2 for obstructive sleep apnea; GAL-IV-201 for chronic fatigue; GAL-IV-201X, an extension to GAL-IV-201, and GAL-IV-202 for fibromyalgia.

The only ongoing trial of galantamine in non-AD patients is the subgroup of patients being studied in with vascular dementia[1]. GAL-INT-14 is the open-label extension to .

2 Reviews- Studies in Alzheimer's disease

2.1 GAL-INT-11

The purpose of Gal-11 was to gather safety data on a population that had been withdrawn from galantamine treatment. Gal-11 studied subjects who completed Gal-10. At the end of Gal-10, subjects in the placebo, 4mg/bid, and 8mg/bid groups continued the same treatments for an additional 6 weeks, while subjects from the 12mg/bid group were switched to placebo and observed for 6 weeks. The sponsor's Gal-11 study report reviews deaths, serious adverse events (SAEs), discontinuations, common adverse events (AEs), lab results, vital signs, and ECG data. The sponsor makes comparisons across treatment groups in Gal-11 and their mean change analyses generally compare results to baseline, which is defined as the value obtained at the start of study Gal-10, the previous 5 month controlled trial.

In the following paragraphs, treatment groups are identified by listing their randomization group in Gal-10 followed by their treatment in Gal-11. For example, the group treated with galantamine 12mg bid in Gal-10, and then switched to placebo in Gal-11 will be identified as the 12mg bid/placebo group.

2.1.1 Exposure

The sponsor summarized the number of subjects exposed to the different treatments and demonstrated that the treatment groups had similar mean treatment duration during Gal-11. The following table summarizes the number exposed, the mean treatment duration and the total person time of exposure for the four treatment groups in Gal-11 (source Gal-11 study report, pp.55-6).

Table 2. Summary of exposure during Gal-11

Exposure	**Placebo/Placebo**	**4mg bid/4mgbid**	**8mgbid/8mg bid**	**12mgbid/Placebo**
Number exposed	219	104	202	198
Mean treatment duration	43.5 days	42.8 days	44.4 days	43.0 days
Patient years of exposure	26.1	12.2	24.6	23.3

No subjects received their first exposure to galantamine during Gal-11.

[1] GAL-INT-6 is a study of the safety and effectiveness of galantamine in patients with vascular dementia alone and vascular dementia mixed with Alzheimer's disease.

2.1.2 Deaths

The sponsor reported 2 deaths during Gal-11, one in Placebo/Placebo patient (A50858), and the second in a 4mg bid/4mg bid subject (A50689). The placebo patient died of respiratory insufficiency. The death of the 4mg bid/4mg bid subject is summarized below (source: patient narrative data supplied with the Gal-11 study report).

A50689 This 79 year old male completed treatment with galantamine 4mg bid in Gal-10 and was enrolled in Gal-11 where he continued on the same dose. He received galantamine for approximately 5 days in trial Gal-11 when, approximately 1 month prior to death, the subject was discontinued from the study and his other medications (aspirin, isosorbide mononitrate, and atenolol) were discontinued at the request of his wife. The subject was found dead by the staff of the nursing home where he resided and the cause of death was listed as advanced Alzheimer's disease. No autopsy was performed. Adverse events captured during studies Gal-10 and Gal-11 for this subject were aggressive reaction, agitation, confusion, and psychosis.

2.1.3 Serious Adverse Events

The sponsor reported that the SAE risk demonstrated a dose-related trend for the placebo/placebo (2.3%), 4mg bid/4mg bid (2.9%), and 8mg bid/8mg bid (5.4%) groups and that the 12mg bid/placebo group had a SAE risk (4%) slightly less than the 8mg bid/8mg bid group.

There did not appear to be clustering of specific SAEs by treatment group. Falls (n=2), injury (n=3), anemia (n=2), and dementia (n=3), were the only SAEs that occurred in more than one subject. There were no SAEs suggestive of hepatic failure, serious skin reactions, rhabdomyolysis, muscle weakness or aplastic anemia. The sponsor reported a renal failure SAE that I summarize below.

A50387 This 88 year old female completed treatment with galantamine 8mg bid during study Gal-10 and entered Gal-11. She continued treatment with galantamine 8mg bid for 34 additional days, when study drug was stopped during a hospitalization for evaluation of anemia and blood in her stools. She was subsequently diagnosed with colon cancer, which was treated by surgical resection. Her post operative course was complicated by acute renal failure (Cr 4.4mg/dL) which was not detailed, but which occurred 21 days after stopping galantamine. She reportedly recovered from this event.

Sponsor's table 24 listing all SAEs occurring in this study is included in Appendix 1.

2.1.4 Discontinuations due to Adverse Events

The sponsor identified 14 patients who discontinued from Gal-11 for AEs with the following breakdown by treatment group: 1.8% (n=4) placebo/placebo, 1% (n=1) 4mg bid/4mg bid, 2.5% (n=5) 8mg bid/8mg bid, and 2% (n=4) 12mg bid/placebo. There did not appear to be a clustering of specific AEs leading to discontinuation since no AEs led to discontinuation of more than one subject in any of the treatment groups.

There were no AEs leading to discontinuation that were suggestive of hepatic failure, serious skin reactions, rhabdomyolysis, renal failure, muscle weakness, or aplastic anemia. There was an AE of bradycardia that led to discontinuation and that case is summarized below.

A50816 This 71 year old male was treated with galantamine 8 mg bid during Gal-10 and received an additional 23 days of the same treatment during Gal-11 when he was discontinued for bradycardia. At the time of discontinuation, he had a radial pulse of 44 bpm with a blood pressure of 130/80 mm Hg. An ECG showed a heart rate of 43bpm but the narrative did not note the type of arrhythmia. The subject had heart rates of 56bpm, 60bpm, 48bpm, and 64bpm during Gal-10. The subject was hospitalized and had heart rates ranging between 44 to 60 bpm. Work up included cardiac catheterization, which documented borderline narrowing of the LAD, and a thallium stress test, which documented apical ischemia. The subject was diagnosed with sick sinus syndrome and the narrative noted that the bradycardia had not resolved at the time of hospital discharge.

2.1.5 Treatment Emergent Adverse Events

The sponsor indicated that the treatment emergent AE incidence was similar across the Gal-11 treatment groups. The sponsor defined treatment emergent AEs as those AEs that occurred during treatment during Gal-11, occurred during Gal-10 but worsened during Gal-11, or that occurred within three days of termination of the trial medication (source Gal-11 study report, p.56). The treatment emergent AE risk was 54.3% in the placebo/placebo group, 43.3% in the 4mg bid/4mg bid group, 57.9% in the 8mg bid/8mg bid group and 57.6% in the 12mg bid/placebo group.

In assessing treatment emergent AEs, the sponsor listed in table 19 those events occurring in ≥2% of subjects in any of the treatment groups (Table 19, Gal-11 study report). Using table 19, I identified the AEs where the risk was higher in subjects with any exposure to galantamine (4mg bid/4mg bid, 8mg bid/8mg bid, or 12mg bid/Placebo) compared to subjects not exposed (Placebo/Placebo). I also identified events where the risk was ≥1.5 times higher among those withdrawn from galantamine (12mg bid/Placebo) compared to the other treatment groups. Those events are included in the following table.

Table 3. Common Treatment Emergent AEs Where the Risk in Galantamine-Exposed Subjects was greater than in Placebo Subjects or the Risk in Subjects Withdrawn from Galantamine was ≥1.5 times Greater than Other Subjects

AE	Placebo/Placebo	4mg bid/ 4mg bid	8mg bid/ 8mg bid	12mg bid /Placebo
Depression	0	2.9% (n=3)	3.5% (n=7)	3.5% (n=7)
Nervousness	0	1% (n=1)	1% (n=2)	2.5% (n=5)
Anorexia	0.5% (n=1)	1% (n=1)	2.5% (n=5)	2% (n=4)
Gait Abnormal	0.9% (n=2)	1.9% (n=2)	1.5% (n=3)	2% (n=4)
UTI	4.6% (n=10)	4.8% (n=5)	5% (n=10)	7.6% (n=15)
Urinary	0.5% (n=1)	1% (n=1)	1% (n=2)	2.5% (n=5)

Incontinence				
Fall	1.4% (n=3)	3.8% (n=4)	3.5% (n=7)	3.5% (n=7)
Bradycardia	0.5% (n=1)	1.9% (n=2)	2.5% (n=5)	1.5% (n=3)

These results demonstrate that the risks for depression, nervousness, anorexia, gait abnormal, fall, and bradycardia were higher for subjects with any galantamine exposure (including prior but not present exposure) compared to those not exposed to galantamine. In addition, the risks for UTI, urinary incontinence and nervousness were at least 1.5 times higher among subjects withdrawn from galantamine compared to the other treatment groups.

I looked for AEs where withdrawal of galantamine was associated with marked increases or decreases in risk. I calculated incidences for the common AEs for the withdrawal group (12mg bid/Placebo) and placebo group (Placebo/Placebo) in Gal-11 using number of subjects experiencing an event in the numerator and person time in the denominator. I then calculated relative risks by dividing the incidence for the withdrawal group by the incidence in the placebo group. Similarly, I calculated relative risks for the 12mg bid and placebo groups in Gal-10. I then identified the AEs where the relative risk from Gal-11 increased or decreased by at least a factor of 2 when compared to Gal-10. During Gal-10 the 12mg bid group had a higher risk for depression compared to placebo (RR=1.5), and in Gal-11 there were 7 cases of depression in the withdrawal group compared to 0 in the placebo group. During Gal-10 there were similar risks for gait abnormal for the galantamine and placebo groups (RR=1.1) but in Gal-11, the risk for the withdrawal group was more than twice the placebo group (RR=2.3). During Gal-10, the risk for urinary incontinence was similar between treatment groups (RR=1.2), but the relative risk increased during Gal-11 (RR=5.7). The relative risk for bradycardia decreased from 8.8 during Gal-10 to 3.4 during Gal-11. A complete listing of the incidences and relative risks observed in the 12mg bid group and placebo group for Gal-10 and the withdrawal group and placebo group during Gal-11 are provided as an attachment to this review. These comparisons are subject to three limitations: 1) they are based on relatively few events; 2) the person time exposure in Gal-11 was 25% that in Gal-10; 3) patients intolerant of galantamine during initial exposure in Gal-10 would have discontinued prior to Gal-11; thus the Gal-11 study cohort is not strictly comparable to the Gal-10 cohort.

I reviewed a listing of all Gal-11 verbatim and preferred terms for treatment emergent AEs (10/2/2000 submission) and found no previously unidentified events suspicious for aplastic anemia, acute renal failure, hepatic failure, rhabdomyolysis, or serious skin reactions.

2.1.6 Labs

2.1.6.1 Mean Change

The sponsor reported that their mean change analysis of lab data found no clinically relevant differences among the treatment groups for hematology or chemistry parameters (Gal-11 study report p.70). They referred to Display SAF.LAB.1, for mean lab values. Display SAF.LAB.1 provided the baseline and visit-specific mean values by treatment

group but did not calculate the mean changes from baseline. I reviewed Display SAF.LAB.1 and calculated the mean changes from baseline (start of Gal-10) and from Gal-10 month 5 (the start of Gal-11) for selected lab tests. Those results are included as an attachment to this review. There did not appear to be evidence of treatment-related mean changes for the labs I examined.

2.1.6.2 Outliers

The sponsor's analysis of laboratory outliers did not appear to suggest treatment group-related differences in risk. The sponsor used the same criteria to define laboratory outliers that they used in their NDA analyses. The outlier results from Gal-11 were generally distributed across treatment groups. Increased uric acid was the only lab test with a risk for outliers in the 12mg bid/placebo group that was at least twofold higher than the other treatment groups. For low total protein, high ALT, high GGT, high creatine kinase and platelet count, the risk in one or more galantamine-exposed groups was at least two fold greater than placebo. Those risks are provided below.

Table 4. Outliers with at least 2-fold increased risk in withdrawal group compared to other groups or at least 2-fold increased risk in one or more galantamine group compared to placebo

Lab test	Placebo/Placebo	4mg bid/4mg bid	8mg bid/8mg bid	12mg bid/Placebo
Uric acid ↑	1.4% (n=3)	0	0.5% (n=1)	3% (n=6)
Total protein ↓	0.5% (n=1)	1% (n=1)	2.5% (n=5)	1% (n=2)
ALT ↑	0.9% (n=2)	1.9% (n=2)	1% (n=2)	0.5% (n=1)
GGT ↑	0.9% (n=2)	2.9% (n=3)	0.5% (n=1)	1% (n=2)
Creatine kinase ↑	0	1.9% (n=2)	1.5% (n=3)	0
Platelets ↑	0.5% (n=1)	1.9% (n=2)	1% (n=2)	0
Platelets ↓	0	0.9% (n=1)	1.5% (n=3)	1% (n=2)

Source Gal-11 study report, table 26, p.71.

These comparisons are based on few events per cell and in most cases do not suggest dose response.

2.1.7 Extreme Lab Outliers

The sponsor provided a listing (Annex 4) that included lab results for those subjects with an outlier during Gal-11. I identified subjects that did not have outliers for a particular test during Gal-10 but developed an extreme outlier during Gal-11 for AST, ALT (>3x ULN), total bilirubin (>2.0mg/dL), creatinine (>2.0mg/dL), hemoglobin (<10g/dL), platelets (<100,000/mm^3) and white blood cell count (<3,000/mm^3). Those cases are described below.

Subject A50387, who received galantamine 8mg bid was diagnosed with acute renal failure as described above, had a creatinine that exceeded 2.0mg/dL during Gal-11.

Subject A50224, who received galantamine 4mg bid, had a baseline hemoglobin of 14.2g/dL that declined slowly during Gal-10 and reached a low of 9.8g/dL at the last visit of Gal-11. This subject did not have an outlier for WBC count or platelets and did not experience a serious AE or an AE leading to discontinuation.

Subject A50318, who had a history of chronic anemia, received galantamine 12mg bid during Gal-10 and placebo during Gal-11 had a baseline hemoglobin of 11.2g/dL that declined to 9.7g/dL at month 5.75 of Gal-11. This subject did not have outliers for WBC count or platelets. She discontinued trial Gal-11, after 18 days of treatment with placebo, for myocardial infarction and congestive heart failure.

Subject A50426, who received galantamine 12mg bid during Gal-10 and placebo during Gal-11, had a baseline hemoglobin of 11.7g/dL that declined to 9.7g/dL at the month 6.75 visit of Gal-11. This subject did not have low outliers for WBC count or platelet count and did not have a serious AE or an AE leading to discontinuation.

Subject A50381 who received galantamine 12mg bid during Gal-10 and placebo during Gal-11, developed a low platelet outlier (80,000/mm^3), a decline in hemoglobin from 12.2g/dL at baseline to 10.1g/dL, and an increased WBC count (28.5). This subject was diagnosed with granulocytic leukemia and discontinued from the study.

2.1.8 Vital Signs

2.1.8.1 Mean Change

The sponsor concluded that there were no clinically relevant differences between treatment groups when comparing mean changes from baseline for vital signs. They provided the mean changes from baseline by treatment group for systolic blood pressure, diastolic blood pressure, and pulse in display SAF.VIT.1B. This display supports that the mean changes observed were small and tended to be in the same direction for the galantamine and placebo groups. I provide a summary of these data as an attachment to this review.

2.1.8.2 Outliers

Using the same vital sign outlier criteria that was used in the NDA analyses, the sponsor found no treatment related pattern of outlier risk in Gal-11. The sponsor provided these data in display SAF.VIT.2. This display demonstrates that vital sign outliers were rare in Gal-11 (most frequent was high SBP in 2.1%, n=4 of those exposed to galantamine 8mg bid).

2.1.9 Electrocardiograms

2.1.9.1 Mean Change

The sponsor stated that there were no clinically important ECG changes as a result of withdrawal of galantamine treatment. The sponsor's presentation of ECG data (Display SAF.ECG.1B) included the mean values for each visit and a calculation of mean changes from baseline (start of Gal-10). I used the sponsor's data in Display SAF.ECG.1B to calculate mean change from month 5 (start of Gal-11). In general, the changes from baseline and from the beginning of Gal-11 were of similar magnitude and direction for

the time points examined. There was some suggestion of a greater mean increase in PR interval for the 4mg bid/4mg bid group (5.9msec) and 8mg bid/8mg bid group (4msec) compared to the placebo/placebo group (0.5msec) and the 12mg bid/placebo group (0.3msec) for the month 5.75 change from baseline analysis. I include a table with mean changes for PR interval, QTc (Bazett's) interval, and heart rate as an attachment to this review.

2.1.9.2 Outliers

The sponsor identified subjects with outliers for ventricular rate, PR interval, QRS duration, QT and QTc intervals and concluded that outlier risk was similar across treatment groups. The criteria for these outlier analyses were the same criteria used in the NDA analyses. The sponsor presented these data in table 33 of the Gal-11 study reports. The table suggests that the risk for PR abnormally high (≥210msec) outliers was greater among the galantamine treatment groups (5.6% 4mg bid/4mg bid, 5.7% 8mg bid/8mg bid) compared to the placebo/placebo group (2.6%) and the 12mg/placebo group (2.9%). The risks for the remaining ECG parameter outliers were low and similar magnitude across treatment groups.

2.1.9.3 QTc Evaluation

The sponsor did not find evidence of drug related increase in QTc interval in this study. The sponsor provided tables that described the distribution of QTc intervals by treatment groups using various cutoff values as well as the distribution for increases in QTc by treatment groups. The percentage of patients with a QTc greater than 500msec was similar across treatment groups (placebo/placebo 0.5%, n=1; 4mg bid/4mg bid 2%, n=2; 8mg bid/8mg bid 0.5%, n=1; 12mg bid/placebo 0.5%, n=1). The risk for a prolongation of QTc>60msec was also similar across treatment groups (placebo/placebo 4.4%, n=6; 4mg bid/4mg bid 3.9%, n=2; 8mg bid/8mg bid 2.6%, n=3; 12mg bid/placebo 2.6%, n=3).

2.1.10 Discussion

Gal-11 provided 6 additional weeks of safety data for groups exposed to galantamine 4mg bid and 8mg bid as well as information about a group previously exposed to 12mg bid that was withdrawn from therapy. There was a single death in a galantamine-exposed subject in this study. Review of the death, the serious AEs, and AEs leading to discontinuation did not identify any previously unrecognized types of adverse events. Risks for SAEs and discontinuation due to AEs, and common AEs were similar across treatment groups although there were too few patients studied to be able to assess small differences in risk. The lab, vital sign, and ECG data did not reveal any previously unrecognized drug-related concerns.

2.2 Summary Data from ongoing trials in Alzheimer's disease

For the ongoing extension trials included in the table in section 1.2.2, the sponsor has summarized SAE and cause-specific mortality data in tabular form. The sponsor has also included GAL-INT-6 and its extension GAL-INT-14 in these tables. Since GAL-INT-6 is a double-blind, placebo-controlled trial examining the effects of galantamine in a population with different forms of dementia (vascular and mixed) from that studied in the

original NDA, it is not clear to me why the sponsor has included it in the table with the extension studies. I have requested that the sponsor separate this data out from the extension trials for Alzheimer's disease, which they have done. See section 3.5 below for preliminary safety data from GAL-INT-6.

My comments that follow in section 2.2.1 and 2.2.2 describe the SAEs and deaths from only the extension trials of the original AD trials.

2.2.1 Deaths

2.2.1.1 All-cause Mortality

Because the extension trials are ongoing, and JRF does not have the CRFs in hand, they are unable to provide a specific estimate of the person-time exposure to galantamine in these trials. I asked them to make a rough estimate of what the exposure might be, by varying the rate of discontinuation (including all reasons for discontinuation; e.g., death, adverse event, withdrawal of consent). The table below summarizes the person time exposure estimates calculated by the sponsor, with the corresponding mortality rates based on 42 deaths in the six extension trials.

Table 5. Mortality rate in galantamine extension trials USA-9,12,17,18 and INT-8,13

Rate of discontinuation	Exposure time in years- total (US and International trials)	Mortality rate (per 100 person-years)
0%	1232	3.4
10%	1108	3.8
20%	985	4.3

The sponsor notes that in the only two year data they have (from USA , the dropout rate was 7.5%; thus the mortality rates based on discontinuation rates of 10% or 20% should be considered conservative. It is likely, however, that the frequency of discontinuation would increase with time as the morbidity and mortality associated with Alzheimer's disease increases. This trend was observed in the CERAD (Consortium to Establish a Registry for Alzheimer's Disease) study, Part XIV, which examined the demographic and clinical predictors of survival in patients with Alzheimer's disease[2]. Over the seven years of follow-up in this study, the proportion of patients lost each year to death or dropout increased stepwise (9% in the first year, 19% in the second year, 25% in the third year, up to 73% in the seventh year). Therefore the estimates projected above may not be too far out of the expected range.

Given the uncertainty of the person-time exposure in the long-term extension trials, is the range of mortality rates of 3.4 - 4.3 per 100 person-years consistent with what has been observed earlier in the development program? In the placebo-controlled trials, the overall placebo mortality rate was 2.2 per 100 person-years compared with 1.7 per 100 person-years for the galantamine treated group. If one looks only in those trials contributing the largest portions of person-time at the range of placebo mortality rates, the range goes

[2] Heyman A, Peterson B, Fillenbaum G, Pieper C. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Part XIV: Demographic and clinical predictors of survival in patients with Alzheimer's disease. *Neurology* 1996; 46:656-60.

from 1.0 (USA-1) up to 3.7 (USA-10) deaths per 100 person-years. Similarly, the range for the galantamine groups range from 1.4 (USA-1) up to 3.0 (USA-10). In the long-term extension trials, the overall mortality rate was 2.8 per 100 person-years in those <12 months in duration and 2.0 per 100 person-years in those >12 months. The mortality rate estimated for the population of Alzheimer's patients still participating in long-term extension trials is probably within the range of that expected for patients with Alzheimer's disease of several years duration. It is hard to be certain, however, because the cohorts of Alzheimer's disease patients observed in populational studies are not as healthy as those participating in a clinical trial population, thus comparing mortality rates between the two groups is not appropriate.

2.2.1.2 Cause-specific Mortality

Table 6 in section 5.2 of the safety update summarizes the cause-specific mortality in the ongoing AD extension trials. The most common causes of death were those that would be expected in an elderly debilitated population including pneumonia, myocardial ischemia, Alzheimer's disease, and cardiac failure. I am unable to calculate rates for these specific causes of death due to the lack of a specific person-time exposure figure (see section 2.2.1.1).

2.2.2 Serious Adverse Events

Table 5 in section 5.1 of the safety update summarizes the frequencies of SAEs that occurred in at least five patients in the ongoing AD extension trials (as well as the two trials in vascular and mixed dementias). The denominator used by the sponsor in the "Total" column appears to be incorrect due to the exclusion of 355 patients in study GAL-USA-18. The correct denominator should be 2922 (2567+355). However, I asked the sponsor to recalculate this table excluding GAL-INT-6 and GAL-INT-14 because of the difference in indications (the latter two trials were conducted in patients with vascular or mixed dementias). The retabulation was submitted on November 28, 2000.

In the six ongoing AD extension trials, the most common SAEs occurred at a similar frequency as compared to the RCTs and earlier extension trials (see ISS Table 5-12c). Given that many of the patients enrolled in the ongoing extensions have been in galantamine trials for two years or more, increased risk of certain SAEs related to the underlying disease (e.g., falls, pneumonia) would be expected. GAL-USA-17, the extension of GAL-USA-16 (a cardiac safety trial), tended to have higher frequencies for many of the common SAEs; however, this was a smaller study.

A review of the narratives for deaths and SAEs occurring between October 1, 1999 and June 30, 2000 did not reveal any reports of fulminant hepatic failure, rhabdomyolysis, or aplastic anemia. One patient in USA-12 reported esophageal perforation after vomiting. Due to concern that this event was drug-related, I requested further information from the sponsor. The sponsor submitted the patient's hospital records as well as answers to my questions regarding her length of galantamine exposure and adverse event profile during the earlier RCT and extension studies.

This 87 year old woman had been taking galantamine for two years and four months at the time of the event. Per the emergency department record, on the morning of the event, the patient had a normal breakfast and was "doing fine". Her family took her to the adult daycare program, as was her routine. Around 10 am she had sudden onset of paleness, diaphoresis, and abdominal pain associated with nausea and vomiting. Her family picked her up and took her to the emergency department. Not entirely consistent with this story is the report by the sponsor that the patient accidentally did not get her galantamine the night prior to the event, and on the morning of the event did not get her galantamine due to not feeling well. Ultimately, the patient had an abdominal CT scan that showed free air in the mediastinum. A surgeon was consulted and she was taken to the operating room with the pre-operative diagnosis of perforated paraesophageal hiatal hernia. During the exploratory laparotomy, the surgeon identified the source of the perforation as an anterior esophageal laceration consistent with Boerhaave's syndrome. The patient underwent surgical repair of the perforation and recovered. She was discharged on hospital day 11, and restarted on galantamine two weeks later. She subsequently has not had recurrence of the nausea and vomiting.

In the original RCT (INT-2), the patient reported the adverse event "stomach virus" lasting 3 days, from days 55 to 57 of the trial. She did not report any other gastrointestinal AEs at the time of initial exposure to galantamine. The patient had not changed any of her concomitant medications prior to the onset of the event. The patient did have some history of swallowing/eating difficulty prior to entering the galantamine trial. According to the hospital admission note, in 1997 she had a Schatzki ring reported and a maximum diameter of the distal esophagus at the ring approximately 8-9 mm (presumably on a barium swallow). A barium swallow performed in 1998 for difficulty initiating swallowing, limited by the patient's ability to cooperate, did not show the Schatzki ring.

Given the patient's history of swallowing difficulty, her long-term treatment with galantamine, and no apparent prolonged interruption in therapy prior to the event, it seems unlikely that this event was related to the galantamine.

3 Reviews- Indications other than Alzheimer's disease

3.1 GAL-SWE-2 (Obstructive Sleep Apnea)

This study was a 27 week double-blind randomized three-way crossover trial in obstructive sleep apnea patients (placebo, galantamine 12 mg q day [GALqd], and galantamine 12 mg BID [GAL BID]) wherein each treatment phase lasted 9 weeks. Fifty-five out of 60 patients were male, and patients ranged in age from 29-68 years with a median age of 52.

No patients died during the trial or within 30 days of the last drug dose. The sponsor stated that four percent of placebo, and six percent of each of the galantamine groups discontinued prematurely due to AEs; however, the sponsor did not provide the specific AEs. In a response to a question about this, the sponsor replied with the details of the

eight discontinuations. Six of the discontinuations occurred within the first period of the study, and the remaining two occurred on the first day of the second period. As a result I corrected the denominators for each of the treatment groups subtracting each of the patients who failed to crossover to those groups. Additionally, both of the patients who discontinued on the first day of the second period had just completed the GAL BID portion of the trial. So the discontinuation rate for AEs, adjusted for the information provided by the sponsor is 3.7% for the placebo and GALqd groups, and 7.1% for the GAL BID group. Of the patients taking galantamine at the time of discontinuation, four of the six discontinued for gastrointestinal AEs. The remaining two patients, both of whom had just completed the GAL BID portion of the trial, had cardiovascular events. One patient suffered a myocardial infarction and one patient developed congestive heart failure.

One serious adverse event (SAE) of myocardial infarction was reported in a GALqd patient; as mentioned above, this patient had just completed the GAL BID portion of the trial. The overall frequency of AEs did not differ between the placebo and the GALqd group (46% v. 49%), but GAL BID patients experienced a higher risk of AEs (67%). As observed in the AD trials, the most common AEs were gastrointestinal complaints, headache, and dizziness.

3.2 GAL-IV-201 (Chronic Fatigue Study)

This was a 16 week randomized placebo-controlled trial in 434 patients with chronic fatigue syndrome. Five treatment groups (placebo, 2.5 mg TID, 5 mg TID, 7.5 mg TID, and 10 mg TID) included 80-90 patients each.
One patient died due to a "non-accidental" overdose of strychnine. Discontinuations due to AEs increased in a dose-related fashion (15% placebo, 14% 2.5 mg TID, 23% 5 mg TID, 24% 7.5 mg TID, and 26% 10 mg TID). When I examined AEs leading to discontinuation, the only body system that appeared to have a dose-related increase was gastrointestinal. The sponsor reported that the "rates of SAE's were low and the occurrence of a particular AE listed as serious was confined to 1 each". In response to further questioning, the sponsor reported that no placebo patients reported SAEs, and there tended to be an increased frequency of SAEs with dose, peaking at 3.5% for the 10 mg TID group. On review of the SAEs, however, most were surgical procedures that were unlikely to be drug-related.

As was observed in the AD trials, patients on the highest dose of galantamine experienced nausea (58% vs. 32%) and vomiting (9.3% vs. 3.7%) more frequently than placebo-treated patients.

3.3 GAL-IV-201X (Extension of GAL-IV-201)

This trial was discontinued after 223 patients had enrolled due to a lack of efficacy of galantamine in chronic fatigue syndrome as demonstrated in GAL-IV-201. Seventeen percent (n=38) of patients discontinued for adverse events; these AEs generally fell into the gastrointestinal system, or appeared to be related to the underlying disease (e.g., sleep disturbances, depression). The overall risk of discontinuation for AE fell within the

range observed in the randomized controlled portion of the trial. I am unable to determine if the AEs were dose-related because the sponsor did not provide information on the distribution of doses taken.

Eight patients reported SAEs, but the sponsor did not report what dose the patients were taking at the time of the SAE. One patient with a history of GI bleed and concurrent NSAID use suffered a GI bleed. Another patient was admitted to the hospital for work-up of abdominal pain; no final diagnosis was reported. One patient who was weaned off antidepressants in order to participate in the trial reported serious depression.

One patient was diagnosed with non-Hodgkin's lymphoma; the information available for this patient indicates that after 16 weeks of double-blind treatment (5 mg TID) and 56 weeks of open-label treatment, a swollen gland was noticed at a routine clinic visit[3]. A biopsy of the gland was performed (no pathology report provided), and a CT scan revealed a "probably benign inflammatory process". She was subsequently hospitalized for worsening fatigue and fever. Laboratory tests performed around this time revealed leukopenia, anemia, and a substantially elevated sedimentation rate. On examination the patient had splenomegaly. No information regarding treatment was provided; however, a notation in the patient's chart three months later indicated that the patient "felt much better and has not felt so well in years". This last statement suggests that this patient being treated for chronic fatigue syndrome may have had an undetected lymphoma for some time. Although the patient had about 1.5 years of galantamine exposure, it appears unlikely that the galantamine played a role in the patient's lymphoma.

The remaining four patients reporting SAEs underwent surgical procedures not likely related to drug exposure.

The sponsor did not present any information regarding common AEs.

3.4 GAL-IV-202 (Fibromyalgia Study)

This was a 16 week randomized placebo-controlled trial in 70 patients (35 placebo, 35 galantamine) with fibromyalgia. Over eight weeks, patients were titrated to doses of galantamine up to 35 mg/day or a maximum tolerated dose and then maintained at that dose for eight weeks.

The sponsor reports that the study is concluded, but the data is still blinded. In response to additional questioning, the sponsor stated that the study was now completed and provided unblinded data for discontinuations due to AEs and SAEs. Five placebo patients and one galantamine patient discontinued due to AEs. One placebo patient reported an SAE. The sponsor did not report any deaths.

From the blinded AE data, the most commonly reported AEs were gastrointestinal complaints, headache, and pain.

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[3] There is some discrepancy in the sponsor's records as to when this routine clinic visit occurred. One source said July 99, another source said April 1999.

3.5 GAL-INT-6

GAL-INT-6 is a phase 3, multicenter, 6-month double-blind placebo-controlled trial to assess the safety and efficacy of galantamine in patients with vascular or mixed dementias, followed by a 6 month open extension. In their original safety update, the sponsor pooled blinded data from GAL-INT-6 with the data from the Alzheimer's disease extension trials. Because this trial examined the efficacy and safety of galantamine in a population of patients that likely has a different set of comorbidities from those with Alzheimer's disease alone, I requested that the sponsor present this data separately. By the time the sponsor responded to my request, the trial had been completed, so additional unblinded safety data was available.

Of the patients randomized in GAL-INT-6, 196 took placebo and 396 took galantamine. Seven placebo patients (3.6%) and nine galantamine patients (2.3%) died during the trial or within 30 days of the last drug dose. The sponsor did not provide the frequency of discontinuation due to AEs for each of the treatment groups; however, 25.5% of placebo and 19.2% of galantamine patients reported SAEs. SAEs which were reported by at least 1% of the galantamine patients and occurred at a frequency at least twofold that of placebo are seen in the following table.

Table 6. SAEs occurring in at least 1% of patients and at a frequency at least 2x placebo, GAL-INT-6

Preferred term	Placebo (n=196)	Galantamine (n=396)
Chest pain	0	4 (1%)
Confusion	0	4 (1%)
Headache	0	5 (1.3%)

The sponsor did not provide any data regarding the frequency of common adverse events.

4 Discussion

The galantamine safety update included two main sources of new data: extension trials of the original RCTs for Alzheimer's disease and trials in non-Alzheimer's disease indications. Review of the deaths and serious AEs for the Alzheimer's disease extension trials revealed one new event of concern, a non-fatal episode of esophageal rupture in a patient taking galantamine for two years and four months. Review of the hospital records and additional information provided by the sponsor suggested that it was unlikely that this event was drug-related.

A review of the deaths, discontinuations for AEs, and SAEs in the trials for non-Alzheimer's disease indications did not identify any previously unrecognized types of adverse events.

/S/

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Safety Team Leader

5 Appendix Contents

GAL-USA-11

- Sponsor's Table 24, Serious Adverse Events
- Mean change Lab Data
- Mean change vital sign data
- Mean change ECG data
- Comparison of Incidences and Relative risks for Common AEs in the 12mg bid and placebo groups for Gal-10, and the withdrawal (12mg bid/placebo) and placebo groups during Gal-11

Figure 1
Flowchart of the overall clinical plan for galantamine Alzheimer's disease trials

Table 24: Incidence of all serious treatment-emergent adverse events other than death: number (%) of patient

WHO system-organ class WHO-preferred term	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 serious TEAEs	5 (2.3%)	3 (2.9%)	11 (5.4%)	8 (4.0%)
Secondary terms				
Fall	0	0	2 (1.0%)	1 (0.5%)
Medication error	0	0	0	1 (0.5%)
Surgical intervention	0	0	1 (0.5%)	0
Body as a whole - general disorders				
Back pain	1 (0.5%)	0	0	1 (0.5%)
Drug level increased	1 (0.5%)	0	0	0
Injury	0	1 (1.0%)	2 (1.0%)	0
Syncope	0	0	1 (0.5%)	0
Cardiovascular disorders, general				
Cardiac failure	0	0	0	1 (0.5%)
Centr & periph nervous system disorders				
Dysphonia	0	0	0	1 (0.5%)
Convulsions	1 (0.5%)	0	0	0
Dementia	3 (1.4%)	0	0	0
Dizziness	1 (0.5%)	0	0	0
Gastro-intestinal system disorders				
Gastritis	0	0	0	1 (0.5%)
Diarrhea	0	0	1 (0.5%)	0
Gastroenteritis	0	0	1 (0.5%)	0
GI hemorrhage	0	0	1 (0.5%)	0
Myo endo pericardial & valve disorders				
Myocardial infarction	0	0	0	1 (0.5%)
Neoplasm				
Leukaemia granulocytic	0	0	0	1 (0.5%)
Colon carcinoma	0	0	1 (0.5%)	0
Resistance mechanism disorders				
Infection viral	0	0	0	1 (0.5%)
Sepsis	1 (0.5%)	0	0	0
Respiratory system disorders				
Pneumonia	0	0	1 (0.5%)	1 (0.5%)
Chronic obstruct airways disease	1 (0.5%)	0	0	0
Pulmonary infiltration	0	0	1 (0.5%)	0
Respiratory insufficiency	1 (0.5%)	0	0	0
Heart rate and rhythm disorders				
Palpitation	0	0	1 (0.5%)	0
Metabolic and nutritional disorders				
Dehydration	1 (0.5%)	0	0	0
Psychiatric disorders				
Aggressive reaction	1 (0.5%)	0	0	0
Agitation	1 (0.5%)	0	0	0
Confusion	1 (0.5%)	0	0	0
Somnolence	1 (0.5%)	0	0	0

Mean change from baseline (start of Gal-10), and M5 (start of Gal 11) for Selected Lab Results

Lab test	Change from baseline (start Gal 10)		Change from M5 (start Gal 11)	
	M 5.75	M 6.5	M 5.75	M 6.5
Hemoglobin (g/dL)				
Placebo/Placebo	-0.1	-0.5	-0.1	-0.1
4mg bid/4mg bid	-0.1	-0.1	-0.1	-0.1
8mg bid/8mg bid	-0.1	-0.2	-0.1	-0.1
12mg bid/Placebo	-0.4	-0.3	-0.2	-0.1
WBC				
Placebo/Placebo	-0.2	0.0	-0.1	0.2
4mg bid/4mg bid	-0.2	0.0	-0.1	0.1
8mg bid/8mg bid	-0.1	0.0	-0.3	-0.2
12mg bid/Placebo	-0.2	0.1	0.0	-0.2
Platelets				
Placebo/Placebo	-9.9	-6.9	-5.7	1.9
4mg bid/4mg bid	-7.0	-1.9	-10.6	-4.9
8mg bid/8mg bid	-8.5	-10.6	8.2	6.9
12mg bid/Placebo	-7.8	-4.9	-0.8	-0.8
Sodium				
Placebo/Placebo	-0.7	-0.7	-0.3	-0.3
4mg bid/4mg bid	-0.4	-0.4	0.4	0.3
8mg bid/8mg bid	-0.6	-0.5	-0.1	0.1
12mg bid/Placebo	-1.0	-0.6	-0.5	-0.1
Potassium				
Placebo/Placebo	0.0	0.0	0.0	0.0
4mg bid/4mg bid	0.0	0.1	-0.1	0.0
8mg bid/8mg bid	0.0	0.1	-0.1	0.0
12mg bid/Placebo	0.0	0.0	0.0	-0.1
Glucose(mg/dL)				
Placebo/Placebo	3.6	0.0	5.4	1.8
4mg bid/4mg bid	3.6	5.4	-1.8	0.0
8mg bid/8mg bid	3.6	0.0	1.8	-1.8
12mg bid/Placebo	0.0	1.8	-1.8	-1.8
AST				
Placebo/Placebo	-0.5	-0.7	-0.1	-0.1
4mg bid/4mg bid	0.1	1.2	-0.3	0.8
8mg bid/8mg bid	0	0.1	0.3	0
12mg bid/Placebo	0.3	0	-0.4	-0.4
ALT				
Placebo/Placebo	-1.9	-2.0	1.2	0.7
4mg bid/4mg bid	-0.3	2.0	-0.5	0.6

8mg bid/8mg bid	-0.7	-1.1	0.3	0.6
12mg bid/Placebo	-1.1	-1.2	-0.3	-0.4
CPK				
Placebo/Placebo	3.7	1.9	1.9	-0.8
4mg bid/4mg bid	-0.2	12.6	2.1	17.4
8mg bid/8mg bid	1.7	-2.1	-1.3	-3.9
12mg bid/Placebo	-3.8	-4.8	-11.9	-12.8

Creatinine (mg/dL), and Total bilirubin (mg/dL) had no change for any of the cells.

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Mean change from baseline (start of Gal-10), and M5 (start of Gal 11) for Selected Vital Sign Results

Vital Sign	Change from baseline (start Gal 10)		Change from M5 (start Gal 11)	
	M 5.75	M 6.5	M 5.75	M 6.5
Systolic BP				
Placebo/Placebo	-2.1	-2.8	-0.9	-1.7
4mg bid/4mg bid	-5.1	-3.6	-1.4	0.1
8mg bid/8mg bid	-3.3	-1.2	-1.2	0.8
12mg bid/Placebo	-6.1	-4.9	-3.9	-2.4
Diastolic BP				
Placebo/Placebo	-1.3	-1.7	-0.1	-0.6
4mg bid/4mg bid	-2.5	-2.6	-0.6	-0.5
8mg bid/8mg bid	-0.9	-1.5	-0.3	-0.8
12mg bid/Placebo	-2.4	-3.0	-0.5	-1.1
Pulse				
Placebo/Placebo	-1.4	-1.1	-0.4	0.1
4mg bid/4mg bid	-1.6	-2.0	0.4	0.2
8mg bid/8mg bid	-2.7	-1.9	-1.2	-0.5
12mg bid/Placebo	-1.7	-0.8	1.5	2.2
Weight (kg)				
Placebo/Placebo	-0.1	-0.3	0.7	0.1
4mg bid/4mg bid	-0.8	-0.8	-0.5	-0.2
8mg bid/8mg bid	-0.3	-1.0	0.1	0.4
12mg bid/Placebo	-1.3	-1.1	0	0.4

Mean change from baseline (start of Gal-10), and M5 (start of Gal 11) for Selected ECG Parameters

ECG Parameter	Change from baseline (start Gal 10)		Change from M5 (start Gal 11)	
	M 5.75	M 6.5	M 5.75	M 6.5
PR Interval				
Placebo/Placebo	0.5	1.7	-1.3	-0.1
4mg bid/4mg bid	5.9	1.5	0.9	-3.8
8mg bid/8mg bid	4.0	0.4	0.3	-2.8
12mg bid/Placebo	0.3	-0.6	-1.9	-2.7
QTc (Bazett's)				
Placebo/Placebo	0.1	-1.6	-0.5	-1.2
4mg bid/4mg bid	-4.6	-2.7	-2.8	0
8mg bid/8mg bid	-2.5	-3.2	-1.1	-2.1
12mg bid/Placebo	-2.5	-3.1	-0.7	-1.1
Heart Rate				
Placebo/Placebo	-1	-1.6	0.2	0
4mg bid/4mg bid	-2.5	-1.7	-0.5	0.6
8mg bid/8mg bid	-2.8	-3.2	0.5	0
12mg bid/Placebo	-1.3	-0.6	1.9	2.5

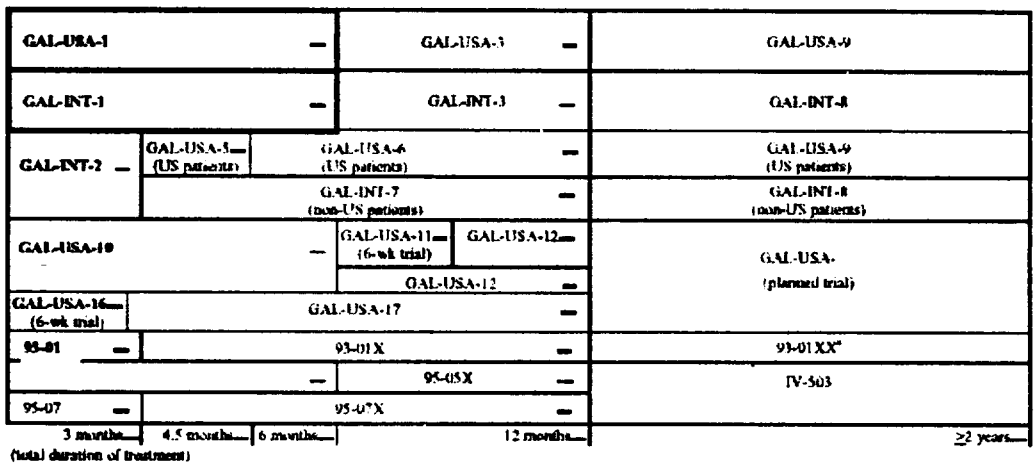
Comparison of Incidences and Relative risks for Common AEs in the 12mg bid and placebo groups for Gal-10, and the withdrawal (12mg bid/placebo) and placebo groups during Gal-11

	Gal-10 AE incidence per 100 person years		RR	Gal-11 AE incidence per 100 person years		RR
Adverse Event	12mg bid (101 PY)	Placebo (108 PY)		12mg bid/Placebo (23 PY)	Placebo (26 PY)	
Agitation	21.8 (n=22)	25 (n=27)	0.9	43.5 (n=10)	34.6 (n=9)	1.3
Confusion	5.9 (n=6)	8.3 (n=9)	0.7	39.1 (n=9)	30.8 (n=8)	1.3
Depression	21.8 (n=22)	14.8 (n=16)	1.5	30.4 (n=7)	0	-
Insomnia	11.9 (n=12)	6.5 (n=7)	1.8	26.1 (n=6)	15.4 (n=4)	1.7
Nervousness	6.9 (n=7)	4.6 (n=5)	1.5	21.7 (n=5)	0	-
Somnolence	12.9 (n=13)	5.6 (n=6)	2.3	21.7 (n=5)	11.5 (n=3)	1.9
Anorexia	23.8 (n=24)	8.3 (n=5)	2.9	17.4 (n=4)	3.8 (n=1)	4.6
Anxiety	6.9 (n=7)	9.3 (n=10)	0.7	8.7 (n=2)	11.5 (n=3)	0.8
Tremor	4.0 (n=4)	5.6 (n=6)	0.7	21.7 (n=5)	19.2 (n=5)	1.1
Gait abnormal	3.0 (n=3)	2.8 (n=3)	1.1	17.4 (n=4)	7.7 (n=2)	2.3
Dizziness	18.8 (n=19)	9.3 (n=10)	2.0	13.0 (n=3)	15.4 (n=4)	0.9
Headache	12.9 (n=13)	12.0 (n=13)	1.1	4.3 (n=1)	7.7 (n=2)	0.6
Urinary Tract Infect	21.8 (n=22)	17.6 (n=19)	1.2	65.2 (n=15)	38.5 (n=10)	1.7
Urinary Incontinence	8.9 (n=9)	7.4 (n=8)	1.2	21.7 (n=5)	3.8 (n=1)	5.7
Hematuria	6.9 (n=7)	3.7 (n=4)	1.9	17.4 (n=4)	11.5 (n=3)	1.5
Injury	15.8 (n=16)	11.1 (n=12)	1.4	26.1 (n=6)	23.1 (n=6)	1.1
Edema Peripheral	6.9 (n=7)	6.5 (n=7)	1.1	17.4 (n=4)	11.5 (n=3)	1.5
Fatigue	12.9 (n=13)	5.6 (n=6)	2.3	8.7 (n=2)	3.8 (n=1)	2.3
Diarrhea	14.9 (n=15)	15.7 (n=16)	0.9	13.0 (n=3)	15.4 (n=4)	0.8
Nausea	44.6 (n=45)	12.0 (n=13)	3.7	13.0 (n=3)	3.8 (n=1)	3.4
Constipation	5.9 (n=6)	11.1 (n=13)	0.5	8.7 (n=2)	11.5 (n=3)	0.8
Edema Dependent	5.0 (n=5)	5.6 (n=6)	0.9	21.7 (n=5)	19.2 (n=5)	1.1
Hypertension	8.9 (n=9)	11.1 (n=12)	0.8	17.4 (n=4)	15.4 (n=4)	1.1
Fall	11.9 (n=12)	13.0 (n=14)	0.9	30.4 (n=7)	11.5 (n=3)	2.6
Surgical Intervention	5.0 (n=5)	4.6 (n=5)	1.1	0	0	-
Bradycardia	7.9 (n=8)	0.9 (n=1)	8.8	13.0 (n=3)	3.8 (n=1)	3.4

Person time and number of adverse events for study Gal-10 were obtained from the Gal-10 study report.

Figure1. Flowchart of Alzheimer's studies in the galantamine development program

Table 3-2: Flow chart of the overall clinical plan and treatment exposure for the 8 double-blind trials and their extensions



Placebo-controlled trials are bolded. In addition, the two JRF 6-month, double-blind, placebo-controlled trials are outlined in bold.
* 93-01XX was actually an amendment to protocol 93-01X, not a separate trial.
b Patients who completed GAL-USA-9 have also been included
New placebo-controlled trials USA-10 and USA-16 and their extensions have been included
Duration of treatment not completely to scale.

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Review and Evaluation of Clinical Data
Response to Approvable Letter

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 Response to the Approvable Letter: August 31, 2000

Safety Reviewers: Judith A. Racoosin, MD, MPH 1/25/01
Gerard Boehm, MD, MPH

Date Review Completed: January 22, 2001

Materials used in the review:

- NDA 21-169: Response to the Approvable Letter, paper volumes and electronic submission dated 8/31/00
- JRF Response to FDA Request for Information- Clinical, dated 10/12/00
- JRF Response to FDA Request for Clarification-Question 7, dated 11/15/00 (email)
- JRF Response to FDA Request for Information- Clinical, dated 1/19/01 (email)

Question 1

Please explain the discrepancy in the person-time exposure by treatment group in 93-01X and 93-01XX between the study report and the ISS-A (amendment dated February 25, 2000) admsum.xpt dataset.

The sponsor's response to Question #1 centers around a difference in person-time between the value 154.1, reported in the ISS-A, and the value 154.5, reported in the trial report. This difference of 0.4 person-years was not the inconsistency that I was addressing in Question #1. Rather, when I calculated the person-time from the admsum.xpt file, I came up with a total of 181.9 person-years.

In the admsum.xpt dataset, there are 577 rows that correspond to the extension trials of 93-01 (i.e. 93-01X and 93-01XX). When I grouped these 577 rows by "phase" and "treat", 188 unique patients had "phase=treatment" and "treat=galantamine". I then summed up the "XTOTDUR" and "XRXDUR" person-days for each of the "randgrp" strata and converted them to person-years. See the results in the table below.

RANDGRP	N Rows	XRXDUR Days	XRXDUR Years	XTOTDUR Days	XTOTDUR Years
18 MG/DAY-GAL	55	23137	63.4	23137	63.4
24 MG/DAY-GAL	38	13949	38.2	13949	38.2
36 MG/DAY-GAL	26	9700	26.6	9700	26.6
PLA-GAL	69	19616	53.7	19616	53.7

The table shows that the person-years exposure calculated by either "XTOTDUR" or "XRXDUR" produces the same values. The sum total of exposure in the extension trials of study 93-01 equals 181.9.

Given this description of how I came up with 181.9 person-years, I asked the sponsor to explain how they got 154.1 person-years from the same data. In a "Response to FDA Request for Information- Clinical", dated 10/12/00, the sponsor provided an explanation for the difference between our person-time totals. The variable XRXDUR or XTOTDUR of the "admsum" dataset for trial 93-01+EXT also included the exposure duration of the proceeding double-blind trial, 93-01. As such, my result of 181.9 person-years included the exposure from the extension trials 93-01X and 93-01XX plus the exposure of the patients from 93-01 who subsequently entered the extensions. When the exposure from 93-01 of 27.8 years is subtracted from the total exposure of 181.9 years, the sponsor's total of 154.1 years is the result.

Question 2

We have determined that in the extension trials of ≤ 12 months in duration, there is a twofold mortality excess in patients originally randomized to galantamine as compared to those originally randomized to placebo. One possible explanation for this finding is confounding by indication. Please compare the severity of illness of the GAL-GAL patients as compared to the PLA-GAL patients at the time of entry into the first long-term extension by examining concomitant medications, co-morbid conditions, and AEs experienced during the RCT to investigate this possibility. If confounding by indication is not supported by the data, please put forth an explanation for the difference in mortality described above.

The sponsor's response to Question 2 begins with their contention that the twofold excess risk of death in the GAL-GAL group could be due to random variation. Their contention is based on the following approach: in the <= 12 month open-label extension trials, 63% of the person-time was observed in the GAL-GAL group. If one assumes that death is not related to drug exposure, then the mortality risk should be proportional to the person-time exposure. Based on this assumption, of the 24 deaths in the six <= 12 month open-label extension trials, 15 would be expected (0.63*24) in the galantamine-treated group. By binomial probability, the chance of observing 18 or more deaths when 15 are expected is .16. Hence, the sponsor asserts that it would not be rare to observe this distribution of deaths at random.

The sponsor includes two additional analyses of mortality rates for the six <= 12 month open-label extension trials. When they include **only deaths** occurring during treatment or within 7 days of the last drug dose, there was no difference in mortality rate between the PLA-GAL (.014/ person-year) and GAL-GAL groups (.015/person year). When they included **deaths resulting from AEs** that occurred during treatment or within 7 days of the last drug dose, the mortality rate in the GAL-GAL (.029/ person-year) group exceeded that in the PLA-GAL (.018/ person-year) group by 50%.

Despite the fact that the sponsor attributed the mortality difference between the PLA-GAL and GAL-GAL groups to random chance, they still conceded that in three of the six <= 12 month open-label extension trials (INT-3, 95-05X, and 93-01X), there was an excess mortality rate in the GAL-GAL group. In order to look for confounding by indication, the sponsor examined AEs and concomitant medications used during the RCT portion of the trial to look for differences between the two groups. Other than the gastrointestinal AEs expected to occur with galantamine exposure, the sponsor did not identify any difference in AE occurrence or concomitant medication use between the two groups.

For the studies where it was available (95-05X and INT-3), baseline information regarding age, ADAS-COG, and duration of Alzheimer's disease prior to diagnosis was examined for the two groups. The sponsor did not explain why those baseline variables were not available for 93-01X. The sponsor asserts that differences in baseline status of the two groups support the presence of confounding by indication in 95-05X and INT-3. The baseline data on age and ADAS-COG (European version) for 95-05X shows that the

GAL-GAL group had a mean and median age two years older than the PLA-GAL group, as well as lower mean ADAS-COG score by 3 points. This data seems consistent with the sponsor's suggestion that these findings support the presence of confounding by indication in 95-05X. In INT-3, however, there is no important age difference between the two groups (0.4 years) and the difference in ADAS-COG score is 1.7 points. Additionally, there was no important difference between the two groups in time since diagnosis at baseline (.06 years). This data does not support the contention of confounding by indication for study INT-3.

The sponsor makes a separate argument that the GAL-GAL group still has an overall lower mortality rate than would be predicted by a model for AD-related mortality based on a real life population[1]. The factors used in the model include age, duration of illness, gender, cognitive scores, and presence of extrapyramidal symptoms. As the sponsor recognizes (2nd paragraph, page 4), though, this model does not factor in comorbidities. It is well known that clinical trials exclude patients with illnesses other than the disease being studied. As such, even if the model reflects the characteristics of the clinical trial population, the fact that the study participants are largely free from comorbidities is not factored in. Based on exclusion criteria for cardiovascular and other serious illness, we would expect the mortality rate of the clinical trial population to be lower than a similar population in the "real world".

The remainder of the sponsor's response to Question 2 makes four points:

1. The mortality rate in the placebo group (.042/person-year) of a large trial for another JRF Alzheimer's drug that enrolled a comparable population to galantamine was comparable to the mortality rate in the galantamine group (.036/person year).
2. An independent panel of experts concluded that no clear relationship between the administration of galantamine and mortality could be established for the deaths that occurred during the galantamine development program.
3. Mortality rates from the >12 month open-label extension trials did not show a difference between GAL-GAL and GAL-PLA groups.
4. Mortality did not differ between the galantamine and placebo treated groups in the RCT portions of the development program.

Discussion

Much of the sponsor's response to Question 2 did not directly address the question that was posed. Of the part that was pertinent to the question, the sponsor showed evidence for confounding by indication in study 95-05X, but not in study INT-3. No evidence was provided for study 93-01X. The sponsor's argument that it would not be rare for 18 deaths to occur in the GAL-GAL group when 15 would be expected seems reasonable. Furthermore, the observation that the excess mortality rate in the GAL-GAL group compared to the PLA-GAL group in the <12 month extension trials did not persist in the

[1] Stern Y, Tang M, Albert M, et al. Predicting time to nursing home care and death in individuals with Alzheimer's disease. *JAMA* 1997; 277:806-12.

> 12 months extension trials lowers the concern that cumulative galantamine exposure confers a mortality risk.

Question 3

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

In their response, the sponsor submitted two tables, one that provided comparisons of the risks for surgical procedures, diagnostic procedures, and hospitalizations not specified and a second table that provided the risks for injury as depicted in the NDA and after re-coding so that only accidental injuries were considered. In addition, the sponsor's second table provided separately the risks for injuries that were serious adverse events, and injuries that led to discontinuation by treatment group.

There appeared to be little difference in risk between treatment groups for surgical procedures, diagnostic procedures, and hospitalizations not specified. After re-coding, the risk for injury among galantamine treated subjects (5%, 111/1860) was similar to the risk in placebo subjects (4%, 45/834) in the pooled randomized controlled trials. After re-coding, the injury risks in the open label extensions were similar (7%, 75/1076 in USA-3+INT-3+USA-6+INT7 and 4% 23/535 in 93-01X+95-05X+95-07X) to the injury risk in the galantamine treated subjects in the RCTs. There was no difference in the injury SAEs between the galantamine and placebo subjects in the RCTs or in the open label extensions (1% in all groups). There was a slight excess of injuries leading to discontinuation in the galantamine group (0.3%, 6/2287) compared to placebo (0.1%, 1/1205) based on few events.

After re-coding only accidental injuries to the preferred term "injury", there was no evidence of a difference in risk between the galantamine and placebo treated groups in the controlled trials. There was no notable difference in risk between treatment groups for surgical procedure, diagnostic procedure or hospitalization not specified when these events were considered separately.

Question 4

On review we observed several instances in which the same or similar verbatim terms were coded to several different AE preferred terms describing cardiac abnormalities. These terms included arrhythmia, arrhythmia atrial, arrhythmia ventricular, AV block, bradycardia, bundle branch block, ECG abnormal, ECG abnormal specific, extrasystoles, fibrillation atrial, heart block, QT prolonged, sick sinus syndrome, sinoatrial block, tachycardia, tachycardia supraventricular, and

tachycardia ventricular. Please reexamine all AE verbatim terms coded to these preferred terms and reclassify them in a consistent manner to the most appropriate preferred term. Following reclassification, please recalculate new incidences for these events across treatment groups and studies.

In their response, the sponsor explained that their coding approach in the NDA involved grouping AE verbatim terms under "included" terms and then grouping related "included" terms under preferred terms. They maintained that related verbatim terms may have been grouped under different "included" terms, but that when these "included" terms were grouped under preferred terms, most of the AEs were appropriately combined. The sponsor did admit that they found some inconsistencies in the coding for the preferred term "ECG abnormal". The sponsor re-coded the cardiovascular events for the controlled trials 93-01, 95-05, INT-1, INT-2, USA-1, and USA-10.

After re-coding, the changes in risk for the cardiovascular AEs were minor and did not result in any substantial alterations in understanding of galantamine's cardiovascular risk profile. The sponsor provided a listing of the results of their re-coding, which appeared appropriate. Table 1 summarizes the cardiovascular AE risks following the sponsor's re-coding.

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Cardiovascular AE risks in studies 93-01, 95-05, INT-1, INT-2, USA-1, and USA-10 following re-coding

AE	PBO	8mg/day	16mg/day	18mg/day	24mg/day	24mg/day*	32mg/day	36mg/day	Flex dose
Bradycardia	0.6% (7)	3.6% (5)	2.5% (7)	1.1% (1)	1.6% (8)	2.9% (8)	2.1% (15)	0	1.9% (5)
Extrasystoles	0.6% (7)	0.7% (1)	1.4% (4)	0	1.8% (9)	0.4% (1)	0.7% (5)	0	0.8% (2)
Palpitation	0.2% (3)	0	0	0	0.8% (4)	0.4% (1)	0.4% (3)	3.7% (2)	1.5% (4)
Bundle branch block	0.5% (6)	1.4% (2)	0.7% (2)	0	0.4% (2)	0.7% (2)	0.4% (3)	0	0.8% (2)
AV block	0.2% (3)	0	0	0	1% (5)	0	0.7% (5)	0	0.8% (2)
Atrial Fib	0.5% (6)	0	0	0	0.4% (2)	1.8% (5)	0.6% (4)	0	0
Tachycardia	0.7% (8)	0.7% (1)	0.7% (2)	0	1% (5)	0	0.3% (2)	1.9% (1)	0
Arrhythmia	0.2% (2)	0.7% (1)	0.7% (2)	0	0.2% (1)	0.7% (2)	0.3% (2)	0	0
QT prolonged	0.1% (1)	0	0.7% (2)	0	0	0.4% (1)	0.3% (2)	0	0.8% (2)
Arrhythmia atrial	0.1% (1)	0	0.7% (2)	0	0.2% (1)	0.4% (1)	0.1% (1)	0.1% (1)	0
Arrhythmia ventricular	0.3% (4)	0	0.4% (1)	0	0	0.7% (2)	0.1% (1)	0	0.4% (1)
Sick sinus syndrome	0.1% (1)	0	0	0	0	0.4% (1)	0.1% (1)	0	0.4% (1)
T wave inversion	0.2% (2)	0	0	0	0.4% (2)	0.4% (1)	0	0	0
Tachycardia supraventric	0.2% (3)	0	0.7% (2)	0	0	0.4% (1)	0	0	0
Heart block	0.2% (2)	0	0	0	0	0.4% (1)	0	0	0
Cardiac arrest	0.1% (1)	0	0	0	0	0	0	0	0

* slow titration

Question 5

Please explain how the incidence of falls was calculated given that verbatim terms describing falls were coded to a variety of AE preferred terms including the following: back pain, dizziness, fracture pathologic, joint dislocation, orthostatic hypotension, purpura, and syncope.

In response, the sponsor reclassified fall terms and demonstrated no change in the risk for fall AEs compared to the NDA submission. The sponsor reviewed their original coding and reclassified any verbatim terms that described falls to the preferred term fall. This reclassification resulted in identification of 25 new fall preferred term AEs occurring in 13 galantamine-treated patients. The sponsor provided a table that summarized the risk of fall AEs following reclassification. The relatively small number of patients whose fall AE was identified by the reclassification did not change the risk for fall in the galantamine subjects in the controlled trials (5% [109/2287]). As such, the difference in risk compared to placebo-treated subjects (4% [47/1205]) did not change. The sponsor documented that the risk for falls in the open label trials (5% [57/1076] USA-3+INT-3+USA-6+INT-7; 3% [16/535] 93-01X+95-05X+95-07X) also did not change following reclassification.

Question 6

All verbatim terms containing spasm or cramp should be examined for appropriate assignment to such preferred terms as back pain, cramps legs, leg pain, myalgia, muscle contraction involuntary, and muscle weakness. Following reclassification, please recalculate new incidences for these events across treatment groups and studies.

In their response, the sponsor employed a new coding approach where verbatim terms with anatomical descriptions indicating that the spasm or cramp was distal to the hip were coded as cramps legs and those not distal to the hip or with no anatomical description were coded as myalgia. The two exceptions to this rule were for neck muscle spasm or cervical spasm verbatim terms, which were re-coded to the preferred term dystonia. The sponsor provided the risks following re-coding and the NDA risks for the preferred terms cramps legs, myalgia, and dystonia.

Re-coding of the cramps and spasm verbatim terms had negligible impact on the AE risks for cramps legs, myalgia and dystonia. Following re-coding, there was a slightly increased risk for cramps legs compared to the NDA results in both the galantamine group (re-coded 1.1%, n=26, NDA 0.7%, n=16) and the placebo group (re-coded 0.3%, n=4, NDA 0.1%, n=1). The changes in AE risks following re-coding were minor for cramps legs in the open label studies and for the preferred terms dystonia and myalgia in the controlled trials and open label studies.

Question 7

Please review the clinical histories of patients who had glucose measurements less than 60 mg/dl or who had AEs or SAEs of hypoglycemia to try to identify risk

factors. Additionally, please look for hypoglycemia outliers using cutoffs of 75 mg/dl, 60 mg/dl, and 45 mg/dl in groups stratified by use of medical therapy for diabetes (e.g. all users vs. non-users).

The review of the galantamine NDA identified a dose-response relationship in USA-1 for patients with glucose < 60 mg/dl (placebo 1.5%, GAL 12 BID 2.8%, GAL 16 BID 4.5%). Low serum glucose levels are concerning in this population because patients with dementia may have an impaired ability to communicate symptoms of hypoglycemia.

Serum glucose measurements

The sponsor reviewed the galantamine NDA safety database and identified 110 patients with a serum glucose measurement <60 mg/dl or with an AE for hypoglycemia. In a review of the medical histories of the patients who had a serum glucose level <60 mg/dl, the sponsor did not identify any specific disease or pattern of disorders that emerged as a risk factor for hypoglycemia.

Within the RCTs of 3-6 months duration in which serum glucose was measured (USA-1, USA-. INT- , 61 patients were identified as having serum glucose measurements below 60 mg/dl. In 30 patients, the low serum glucose was treatment emergent. In the table below, the frequency of patients with a serum glucose measurement below 60 mg/dl is broken out by dose.

Frequency of serum glucose measurements <60 mg/dl by dose, USA-1, USA-10, INT-2

Dose	Cases/number exposed	Percent	Median glucose measurement
Placebo	14/624	2.2	*
4 mg BID	4/140	2.8	53.5
8 mg BID	3/279	1.1	57
12 mg BID	8/485	1.6	56
16 mg BID	8/211	3.8	53
Flex dose (12-16 mg BID)	7/261	2.7	58

*data not requested from sponsor

Two of the above 30 patients had more than one serum glucose measurement below 60 mg/dl during the trial. Patient A34007 had low measurements on the 8mg BID and 12 mg BID doses, and Patient A73039 had two low measurements on the 12 mg BID dose.

During my initial NDA review, I had a question of what effect concomitant medical therapy for diabetes would have on the incidence of hypoglycemia. As requested, the sponsor broke down the data with the cutoffs of ≤ 75 mg/dl, ≤ 60 mg/dl, and ≤ 45 mg/dl, stratified by use of medical therapy for diabetes, as seen in the table below. For non-users of diabetic medical therapy, the risk of a low serum glucose measurement was similar between placebo and galantamine-treated groups at all cut-off thresholds. However, for users of diabetic medical therapy there was an excess of low serum glucose measurements in the galantamine group compared with the placebo group at each cut-off.

Glucose (mg/dl)	Galantamine (n=1376)		Placebo (n=624)	
	User N=63	Non-user N=1313	User N=37	Non-user N=587
≤ 75	11 (17%)	263 (20%)	2 (5%)	126 (21%)
≤ 60	4 (6%)	43 (3%)	0	14 (2.4%)
≤ 45	1 (2%)	1 (0.1%)	0	0

Hypoglycemia Adverse Events

The sponsor also reviewed the medical history of the 13 patients who had an AE of hypoglycemia reported. Five of the patients had a diagnosis of diabetes. Four patients had a second AE reported for hypoglycemia during the open-label extension; one of these patients had a history of diabetes.

Two of the 13 patients had AEs that were deemed "serious". One patient's report of a serious AE for hypoglycemia came 19 days after the patient discontinued from the trial due to withdrawal of consent; the patient was hospitalized for syncope and hypoglycemia but when the sponsor reviewed the available hospital record, there was no glucose measurement lower than 111 mg/dl recorded. The other serious hypoglycemia AE occurred 63 days into the trial when the patient was found hypotensive, dehydrated, and hypoglycemic (glucose 54 mg/dl). The patient was discontinued due to withdrawal of consent and discharged home under hospice care.

Discussion

After examining the frequency of low serum glucose in the three 3-6 month RCTs in which glucose was measured, I did not find a dose-response relationship for serum glucose measurements ≤ 60 mg/dl, although the risk was highest at the highest tested dose. Further, an examination of the median low glucose measurements that were observed in each dose group did not reveal substantially lower glucose levels at the higher doses. If there is a slightly higher risk of hypoglycemia at 16 mg BID compared to the background, it is unlikely that patients will be exposed to this dose as the proposed galantamine labeling states that doses above 12 mg BID do not have superior efficacy.

It is not clear what to make of the excess risk of hypoglycemia in the galantamine-treated users of diabetic medical therapy compared to the placebo-treated users of diabetic medical therapy. Users of diabetic medical therapy account for only 5% of the participants in the galantamine double-blind RCTs, so the observation made in this small subpopulation may be reflective of chance. On one hand, one might expect more episodes of hypoglycemia among users of diabetic medical therapy because Alzheimer's patients' oral intake may not match well with the hypoglycemic effects of their medication; alternatively, users of diabetic medical therapy might be expected to have fewer episodes of hypoglycemia due to their general state of running a high serum glucose.