4.2.9.10 Discussion

In general, galantamine had a small effect on vitals signs when given at low doses (up to 24 mg/day) with a slow, one to two month titration, as seen in Gal USA-10. For example, in Gal USA-10 trial the mean changes for SBP, DBP, and pulse in the galantamine arms were lower than what was reported in the galantamine arms of Gal INT-1 and Gal USA-1 where the titration was 4 weeks.

Most of the studies suggest that a small (2 to 10 mmHg) decrease in SBP and DBP can be expected in patients taking galantamine. The Gal INT-1 study suggested there was a slight dose-related effect of galantamine on SBP. In most circumstances this drop in value was of little clinical importance; however, in some patients it was enough to result in adverse events such as hypotension, syncope, or dizziness. As seen in the many studies, 1-2% of patients taking galantamine experienced a drop in their SBP and DBP large enough to be potentially clinically significant as defined in FDA Table 32. The sponsor's subset analyses of those patients with a drop in their SBP or DBP showed no difference for gender or age.

As expected with an acetylcholinesterase inhibitor, pulse tended to decrease (about two to four bpm) with galantamine use. There did not appear to be a dose-related effect of galantamine on pulse. In the large majority of patients, this drop in value was of little concern. However, in some patients it may become clinically relevant and manifest as bradycardia, chest pain, dizziness etc. As seen in the many studies, one to two percent of patients taking galantamine experienced a drop in their pulse large enough to be potentially clinically significant as defined in FDA Table 32. The sponsor's subset analyses showed no difference for gender or age in most studies.

4.2.10 Weight

This section of the review describes the effect of galantamine on patient weight. For most studies, statistical methods of analysis included descriptive statistics, tabulations of paired t-test across treatments, and outlier findings. In all studies, patients were weighed lightly dressed. In some studies, the sponsor stratified weight loss into four groups; 0 to <7%, 7 to < 15%, 15 to 21%, >21%; however, when describing clinically significant weight loss, the sponsor tended to use a threshold of 10%.

4.2.10.1 Phase II, Shire Gal 93-01/Gal 93-01X

In the Shire Gal 93-01, placebo-controlled, double-blind 12 week study, galantamine was evaluated in three different dosages (6 mg TID, 8 mg TID, 12 mg TID). Investigators recorded weight at screening, week 2, week 4, week 8, and week 12; this weighing schedule contrasted most other studies where patients were weighed only at the beginning and end of the trial. The data in the table below demonstrates no consistent findings with respect to weight change at the various time-points. There was some suggestion of a dose response effect for weight loss.

FDA Table 35. Mean weight by treatment group and time point, Shire Study 93-01

	Placebo	6 mg TID	8 mg TID	12 mg TID
Screening	65.0 kg	65.5 kg	63.4 kg	63.9 kg
Week 2	65.2 kg	65.8 kg	63.3 kg	63.0 kg
Week 6	64.8 kg	65.1 kg	63.5 kg	64.4 kg
Week 12	65.2 kg	65.8 kg	63.3 kg	63.0 kg
Change in mean weight at week 12 from baseline,	+0.2 kg	+0.3 kg	-0.1 kg	-0.9 kg

Source Sponsor's Display 34

Review of premature discontinuation summaries showed that no patient discontinued due to weight loss. While many patients discontinued due to nausea and vomiting,, no pattern of weight loss among these patients was discernable. Weight loss, as a reported adverse event, occurred at a similar rate in all three galantamine treated groups at approximately 2.1%. This was comparable to placebo at 2.3%.

In the small, open-label, extension trial of Gal 93-01X, the overall incidence of weight loss as a reported adverse event, was 9.0% (17 patients) for the first extension. The magnitude of this weight loss rarely exceeded 1 kg. In those patients initially randomized to placebo, the incidence of weight loss as a reported AE was slightly higher than in those patients initially randomized to galantamine (11.6% v. 7.6%). In the second extension 93-01XX, there was little difference in the incidence of weight loss as an AE between patients previously randomized to placebo in Gal 93-01 and those previously randomized to galantamine. No patient in the extensions up to 24 months had severe (as judged by the investigator) weight loss.

4.2.10.2 Shire Gal 95-05/Gal 95-05X

In the original Gal 95-05 trial, investigators did not measure weight except to compare mean body mass index between groups at screening. There were no between group differences at screening.

In the 95-05X extension trial, weight was recorded at week 29 (start of Gal 95-05X) and week 53. Comparison of mean body weight with baseline (start of Gal 95-05) showed a very small statistically significant weight loss at week 29 but not at week 53. The mean change was –0.92 kg at week 29 and –0.42 kg at week 53. Death summaries, adverse event summaries, and discontinuation reports were reviewed. Only two patients (both previously randomized to placebo) discontinued galantamine due to weight concerns. Patient #G0116 discontinued galantamine due to dysphagia, anorexia, weight decrease (-6 kg) and character change. The patient was on galantamine for approximately three weeks when she reported these concerns and was then hospitalized. Review of case report form does not provide any other details regarding hospitalization and course. Patient G0225 was on galantamine for approximately seven weeks when he discontinued treatment due to weight loss (-5 kg) and nausea. The nausea resolved within a week but the weight loss "resolved with residual effects". The investigator did not clarify this in the narrative or case report form.

4.2.10.3 Shire Gal 95-07/Gal 95-07X

In these single-center pilot studies designed to evaluate the tolerability, efficacy, and pharmacokinetics of galantamine 12 mg BID versus galantamine 16 mg BID, investigators measured weight on each visit. There was no placebo arm to these studies. The original Gal 95-07 study demonstrated an decrease in mean body weight of 0.6-0.8 kg in the two dose groups. In the open-label extension trial of Gal 95-07X, the mean body weight decreased 0.2 kg from the study 95-07 baseline.

4.2.10.4 JRF Gal INT-1/ Gal INT-3

In the double-blind, randomized placebo-controlled multi-center study, Gal INT-1, patients were followed over a six month period. This was followed by an open-label, six-month extension in Gal INT-3. Patients were weighed lightly clothed at the start and end of the trials. Between group comparisons of weight change were performed using ANOVA.

There was a statistically significant weight decrease in galantamine-treated patients compared to placebo at six months. In the Gal INT-1 study, the mean weight loss in the combined galantamine-treated patients was -1.4 kg compared with a gain of 0.2 kg in the placebo group. 54(12%) patients in the combined galantamine-treated groups lost greater than seven percent of their body weight compared with ten (4%) patients in the placebo group. Treatment was discontinued due to weight loss in six (1.4%) patients treated with galantamine compared to none for placebo. Approximately six percent of the galantamine-treated patients reported weight loss as an adverse event compared to one-half percent of the placebo-treated group. In this study, the AE weight loss was associated with the AE anorexia in galantamine but not placebo patients. Additionally, the AE weight loss was also seen more often in galantamine but not placebo patients complaining of asthenia as an adverse event. The sponsor's subgroup analysis showed no gender difference for weight loss.

In Gal INT-3, investigators recorded weight at the start and end of the trial. In general, the weight loss seen in this extension study is not as great as seen in the original study. Many of the patients that originally lost weight returned close to their screening weight. The only group that did not return close to their screening weight was those patients that originally received galantamine 16 mg BID. This group had a mean change from screening of -1.3 ± 0.37 kg at the end of the first study and -1.1 ± 0.37 kg at the end of the extension study.

4.2.10.5 JRF Gal USA-1/Gal USA-3/Interim Gal USA-9

In GAL USA-1, weight was measured at the beginning and end of the study with the patient lightly clothed. The overall design was similar to Gal INT-1. Statistical analyses included descriptive statistics, between-group comparisons analyzed using ANOVA, and percent of patients exceeding the clinically important thresholds at each time point.

Similar to INT-1, at the end of six months the galantamine-treated patients had a statistically significant weight loss compared to placebo. The mean weight loss was

approximately 2.25 kg for the galantamine groups compared to a gain of +0.1 kg for the placebo group. From Sponsor's Table 36 it can be summarized that 47(11%) of the galantamine-treated patients lost at least seven percent of their body weight compared to 12(5.6%) in the placebo group. Nine patients in the galantamine-treated groups discontinued due to weight loss compared to none in the placebo groups. Sponsor's analysis identified no risk factors for weight loss such as age or gender. The AE weight loss occurred at an elevated frequency in placebo and galantamine patients reporting the AE anorexia and in galantamine-treated patients reporting the AE asthenia.

In GAL USA-3, investigators measured weight at the final visit of Gal USA-1, month one, month two, month three, and month six. The patients previously exposed to placebo lost a mean of -1.1 kg over the course of the study. According to Sponsor's Figure 2, the majority of this weight loss occurred between the first and second month of galantamine treatment. The patients previously randomized to galantamine and staying on galantamine tended not to lose weight or had a slight increase during the study. This is similar to the experience in Gal INT-3 where the original galantamine-treated patients did not lose additional weight.

In the Interim report of Gal USA-9, there is no statistical difference in weight at the end of the study compared to baseline. This suggests that with continued galantamine treatment most patients did not lose additional weight.

4.2.10.6 JRF Gal USA-16

In this six-week trial designed to assess the cardiovascular safety of galantamine, patients were weighed lightly clothed at the beginning and end of the trial. Even in this short trial, a significant difference in weight loss occurred between placebo and galantamine treated patients. The mean decrease of weight in the galantamine-treated patients was -0.77 kg compared to an increase of approximately +0.34 kg for placebo-treated patients. Only one patient in the placebo and one in the galantamine treated group lost greater than seven percent of their body weight.

4.2.10.7 JRF Gal USA-10

In this large six-month study, designed to assess the effect of slow titration of galantamine, weight was evaluated at screening and the end of the trial. Patients were weighed lightly clothed.

There was a statistically significant weight loss between the galantamine 12 mg BID group compared to placebo. Table 36 below displays the mean change in weight and percentage of patients with a clinically significant weight loss. The differences between galantamine groups suggested a dose-related effect. The 10.9% incidence for weight loss of >7% of body weight in patients treated with galantamine 12 mg BID was consistent with what was seen in Gal USA-1 (12.2%) and Gal INT-1 (7.7%). The AE anorexia was associated with the AE weight loss in both placebo and galantamine patients. The AE asthenia was associated with the AE weight loss in only the placebo group.

FDA Table 36. Evidence of a dose-related weight loss with galantamine, GAL-USA-10

	Placebo	4 mg BID	8 mg BID	12 mg BID
Mean change in weight (kg) (endpoint - screening)	-0.1	-0.5	-0.5	-1.3
Patients losing >7% of baseline body weight (%)	3.5	7.1	6.4	11.0

Source: Sponsor's Table 35 and Table 36.

A review of the sponsor's Annex 3, "Narratives of deaths, adverse events leading to discontinuation, serious adverse events, and adverse events of potentially clinical importance" identified discontinuations for weight loss in one galantamine and no placebo patients. Although only one patient (#A73344) discontinued treatment with galantamine due to weight loss as an AE (the actual amount of weight loss was not reported), several others that discontinued treatment also had significant weight loss. Patient #A73435, on galantamine 8 mg BID, discontinued treatment due to " anorexia, nausea and dizziness" on day 60; a weight measurement three weeks later on a follow up visit revealed a 22% weight loss. Patient #A73785, on galantamine 12 mg BID, discontinued treatment due to "vomiting" on day 77 and had a 10% weight loss as measured at month 3 of treatment. Patient #A73748, on galantamine 8 mg BID, discontinued treatment due to "somnolence and stupor" on day 93 and had a 9% weight loss as measured at month 3 of treatment.

4.2.10.8 JRF Gal INT-2/Gal INT-7

In the flexible-dose three month trial of Gal INT-2, weight was evaluated at the beginning of the trial but not at the end. Approximately 3.8% of the galantamine-treated patients "reported" weight loss compared to no reports in the placebo group. From the Sponsor's Table 29, "Incidence of adverse events leading to treatment discontinuation", four (1.5%) patients in the galantamine-treated group discontinued treatment due to weight loss as compared to none in the placebo group. Otherwise, little information can be discerned from Gal INT-2 regarding weight.

In the extension trial of Gal INT-7, investigators did not evaluate weight at the initial visit (end of Gal INT-2) but measured weight at the end of the trial (month 12 total). There was a statistically significant weight loss, compared to the beginning of Gal INT-2, for those patients originally randomized to placebo (mean -2 kg) but not for those patients that received galantamine in both trials (mean near zero). Since the investigators did not record weight during the course of the two studies, it is not possible to determine when the weight loss occurred relative to starting galantamine.

4.2.10.9 JRF Gal USA-5/Gal USA-6

These two small studies were the US extensions of Gal INT-2. The USA-5 study was a six week withdrawal study and weight was not evaluated. The USA-6 study was designed to assess safety and efficacy and included evaluation of weight at month 4.5 (visit 2 of Gal USA-5) and month 12 (week 33).

As was seen in other studies, patients newly exposed to galantamine lost an average of about -2 kg of weight but with continued exposure the change in weight became smaller. Overall, six (5.5%) patients in Gal USA-6 had weight loss as a reported adverse event

4.2.10.10 Discussion

As might be expected with acetylcholinesterase inhibitors, weight loss was seen in all studies. On average, galantamine-treated patients lost about 1-2 kg compared with little change or a slight increase in the placebo group. In most of the larger placebo-controlled studies, investigators only measured weight at the beginning and end of the studies, making it difficult to assess the time course of the weight loss. In Gal 93-01, weight was measured frequently, but no particular pattern for weight loss was identified. In the extension study GAL USA-3, weight was also measured frequently; in this case, the data demonstrated that weight loss was the greatest between month one and month two for patients previously randomized to placebo.

In most studies, the majority of patients who experienced weight loss lost < 7% of their body weight. However, as was seen in several studies, as many as 11% of the patients taking galantamine experienced weight loss of seven percent or greater. In the large RCTs, the relative risk of weight loss of >7% of initial body weight was about 2. On rare occasions, the weight loss exceeded 21%.

The weight loss data from Gal USA-10 suggested a dose-related effect of galantamine on weight loss. In Gal USA-10, the mean weight change from baseline for galantamine 12 mg BID (–1.3 kg) was more than double what was seen for galantamine 4 mg BID (–0.5 kg). For placebo, the mean change in weight was –0.1 kg.

The sponsor's subgroup analyses did not identify age or gender as risk factors for weight loss. Likewise, the FDA examination of the large placebo-controlled studies Gal USA-1, Gal USA-10 and Gal INT-1 did not identify gender as a risk factor for weight loss, as seen in FDA Table D, Appendix 1. In most studies, weight loss was not associated with nausea or vomiting as an adverse event. In Gal INT-1, Gal USA-1, and Gal USA-10 there was a consistent association of weight loss with anorexia as a reported AE.

The larger extension trials demonstrated that with continued galantamine use it can be expected that many patients who initially lost weight may regain some weight or at least stop losing weight. In the extension trial of Gal USA-3, the patients previously exposed to placebo lost a mean of -1.1 kg over the course of the study. The patients originally randomized to galantamine who continued on galantamine tended not to lose weight or had a slight increase during the study. This is similar to the experience in Gal INT-3 where the original galantamine-treated patients also tended to regain part of their lost weight.

4.2.11 ECG Data

This section examines the galantamine NDA ECG data and is intended to be included as part of the overall review of galantamine safety. First, I discuss the ECG recording

schedule. Second, I review the comparative findings from placebo-controlled trials. Third, I present findings from uncontrolled trials. In a separate section I review Study 16, a special randomized controlled trial designed to look for galantamine related ECG changes.

4.2.11.1 ECG Recording Schedules

All submitted phase II-III galantamine trials included 12-lead ECG recordings, but the ECG recording schedules varied. I reviewed the individual study reports to determine the ECG recording schedules since the sponsor did not summarize this information in the ISS. The ECG recording schedule in randomized controlled trials USA-1, INT-1, INT-2, USA-10 included screening, baseline, during study and end study ECGs. Study 95-05 required only screening and end study ECGs. Study 93-01 required only baseline ECGs and investigators obtained end study ECGs only if clinically indicated. In the extensions and uncontrolled trials, the ECG recording schedules varied from a single end study recording to ECG recordings throughout the study period.

4.2.11.2 ECG findings from placebo-controlled trials

The following sections identify the placebo-controlled studies contributing data for the sponsor's ISS ECG analyses and the analyses findings.

4.2.11.2.1 Placebo-controlled trials included in and excluded from the sponsor's analyses

In the sponsor's ISS ECG data presentation, they include analyses of pooled data from placebo-controlled trials INT-1, USA-1 and INT-2 and a separate analysis of data from placebo-controlled trial USA-10. The sponsor excluded ECG data from Shire placebo-controlled trials 95-05 and 93-01 in their ISS ECG data review and referred the reader to the individual study reports for results from these trials. Although not stated in the ISS, the sponsor likely excluded data from these trials because ECGs were infrequently performed and therefore were unlikely to provide additional meaningful information.

4.2.11.2.2 Findings from the sponsor's analysis of Placebo-controlled trial data

The following sections present the heart rate, PR interval and QTc interval findings from placebo-controlled trials. Summary tables of these results are included as an appendix to this review.

4.2.11.2.2.1 Heart rate

The sponsor found heart rate decreases in galantamine subjects in placebo-controlled trials. In the pooled analysis the sponsor found mean decreases in heart rate from baseline of 3-4 beats per minute in galantamine subjects compared to 1 beat per minute in placebo subjects (ISS-A Table 6-32a). Also from the pooled analysis the sponsor found an increased incidence of low heart rate outliers among galantamine subjects with 1.4% (n=5) of 24mg subjects and 2% (n=7) of 32mg subjects having low heart rates compared to 0.8% (n=4) of placebo subjects (ISS-A Table 6-32a). In study USA-10, the sponsor reported a mean decrease in heart rate from baseline of 1.8, 3.1, and 3.2 bpm in the 8mg,

12mg, and 24mg galantamine groups, respectively, compared to a mean decrease of 1 bpm in the placebo group. In Study USA-10, the sponsor found no 8mg subjects, 0.4% (n=1) of 16mg subjects and 0.4% (n=1) of 24mg subjects developed a low outlier heart rate compared to 0 placebo subjects. Study USA-10 used a longer titration period and lower galantamine doses than the trials in the pooled analysis and either factor could contribute to the observed differences in outlier results.

4.2.11.2.2.2 PR interval

The sponsor found PR interval lengthening among galantamine subjects from analyses of placebo-controlled data. For the pooled analysis, although the galantamine 24mg/day group had a mean decrease in PR interval from baseline of 0.4ms, the 32mg/day group had a mean increase from baseline of 3.4ms compared to a mean increase of 0.7 ms in the placebo group (ISS-A Table 6-32a). Also for the pooled analysis, 1.9% (n=6) of the 24mg/day group and 4% (n=13) of the 32mg/day group were normal at baseline and developed a PR >210ms compared to 2% (n=11) of placebo group. In study USA-10, the sponsor reported a mean increase in PR interval from baseline of 4.2, 3.0, and 2.7 ms in the 8mg, 12mg, and 24mg galantamine groups, respectively, compared to a mean increase of 2.0ms in the placebo group. Also in study USA-10, 4% of both the 8mg (n=5) and 16mg (n=9) groups and 1.3% (n=3) of the 24mg group developed a PR interval >210ms compared to 2% (n=6) of the placebo group.

4.2.11.2.2.3 QTc interval

The sponsor did not find evidence of QTc prolongation in galantamine subjects from their analysis of placebo-controlled trial data. For both the pooled analysis and the Study USA-10 analysis, there was a mean decrease from baseline for QTc in the galantamine treated groups, range –0.9 to –3.7ms compared to mean increases in the placebo groups, range 0.6 to 0.9ms. The incidence of QTc outliers was similar for the galantamine and placebo treatment groups.

4.2.11.3 ECG Findings from Findings from Uncontrolled trials

The following sections present the sponsor's approach to analyzing ECG data from uncontrolled trials and review the sponsor's findings.

4.2.11.3.1 Sponsor's ECG data presentation for Uncontrolled trials

For short term uncontrolled trials and uncontrolled trials in healthy subjects, the sponsor identified patients experiencing clinically significant events. For the long-term uncontrolled extension trials, the sponsor presented mean changes from baseline for heart rate, and PR and QTc intervals and stratified these results by patient drug assignment during the preceding placebo-controlled trial.

4.2.11.3.2 Clinically significant events from short term uncontrolled trials and uncontrolled trials in healthy subjects

The sponsor identified the following ECG clinically significant events from short term uncontrolled trials and uncontrolled trials in healthy subjects:

- Subject A03014 from trial GAL-BEL-1 developed extrasystoles and continued in the trial.
- Subject 8 from trial 95-07 was hospitalized for chest pain, subsequently diagnosed as reflux esophagitis. This subject had a bundle branch block noted during this event.
- Subject 3033 from trial GAL-NED-2 developed 3° AV block resulting in hospitalization. Heart block occurred during treatment with galantamine and digoxin.

4.2.11.3.3 Mean changes from baseline for heart rate, and PR and QTc intervals in Uncontrolled trials

For the uncontrolled trial ECG data, the sponsor reported heart rate decreases, greater among the subjects randomized to galantamine in the previous RCT, but felt the findings were not clinically significant. The sponsor found increases in the PR interval in the group randomized to galantamine in the previous RCT, but no increase in the group that previously got placebo. Interpretation of these changes must be made in the context of an absence of data from an unexposed group. Tables listing the sponsor's findings are included as an appendix to this review.

4.2.12 GAL-USA-16: Cardiovascular Safety Study

4.2.12.1 Study GAL-USA-16 design and monitoring

GAL-USA-16 was a 6-week placebo-controlled study that investigated the effect of galantamine on heart rate and PR-intervals in Alzheimer's disease subjects. Potential subjects were excluded from the study for the following cardiac conditions:

- a recent myocardial infarction or cardiac surgery
- syncope-associated conditions
- heart rate less than 50 beats per minute
- heart block greater than 1st degree
- severe aortic or mitral valve disease, uncontrolled hypertension, atrial fibrillation, decompensated congestive heart failure
- a pacemaker

There was no restriction on the concomitant medications subjects took although investigators were warned to avoid drugs with anticholinergic effects and other medications including ®-blockers, calcium channel blockers, and digitalis.

Study subjects were randomized to a titrated galantamine regimen (n=70) or placebo (n=69). The galantamine titration regimen was 4mg bid during week 1, 8mg bid in week 2, 12mg bid in weeks 3 and 4, and 16mg bid in weeks 5 and 6 if tolerated. If the 16mg bid dose regimen was not tolerated, investigators were permitted to reduce the dose to

12mg bid within 3 days of beginning the 16mg bid dose. After 3 days, only termination was allowed for those subjects not tolerating the study medication.

Safety monitoring included cardiac, vital signs, adverse event and laboratory monitoring. The cardiac safety monitoring included ECGs and 24 hour Holter monitoring which were performed at baseline, at the end of week 2, at the end of week 4, and at the end of week 6. Premier Research Worldwide measured ECG intervals using a high resolution digitized system and the sponsor analyzed the data (p.31). Adverse events and vital signs were recorded at each visit. Laboratory data were collected at baseline, and weeks 2, 4, and 6.

4.2.12.2 Analyses

The sponsor performed analyses of Holter and ECG data. The sponsor analyzed means and mean changes from baseline for heart rate and PR interval for each of the three 24 hour monitoring periods. In addition the sponsor calculated the mean and mean change from baseline for heart rate and PR interval for each hour of the three study week monitoring periods. The sponsor summarized the clinically significant cardiac arrhythmias and conduction abnormalities identified from Holter data. The sponsor calculated mean heart rates, PR and QT intervals and mean changes from baseline for the ECGs and identified new, study emergent abnormalities.

The sponsor conducted PK analyses to determine the relationship between serum trough galantamine levels and ECG, vital sign, and Holter parameters. The sponsor analyzed the relationship between serum trough concentrations of galantamine and heart rate, PR interval, QRS, and QT_c data captured by ECG and pulse from vital sign measurement. The sponsor also conducted regression analyses to examine the relationship between serum trough levels and various heart rate and PR interval variables from week 6 Holter monitoring.

The sponsor compared the incidence of conduction disturbances and arrhythmias between treatment groups. The sponsor classified patients as having a conduction disturbance if they experienced 2° or 3° heart block. Patients were classified as having an arrhythmia if they experienced one of the following events:

- torsades de pointes
- ventricular fibrillation, sustained ventricular tachycardia, non-sustained ventricular tachycardia.
- Ventricular premature contraction (VPC) was 0 and they had at least 1 occurrence of VPC>=5 on drug,
- VPC was >0 but less than 100 at baseline and there was at least 1 occurrence of VPC>=10 times baseline on drug or
- VPC was >100 at baseline and there was at least one occurrence of VPC>=3 times baseline on drug (p.41).

The sponsor plotted the galantamine trough concentration against whether or not the patient had an arrhythmia or conduction disturbance.

The sponsor analyzed the vital sign and ECG data to identify potentially clinically significant changes. The sponsor used the following pre-specified criteria to identify potentially clinically significant vital sign and ECG findings.

Table 4: Criteria for potentially clinically important changes in vital signs

Parameter	Low	High
Diastolic blood pressure (mm Hg)	decrease of ≥15 mm Hg and value ≤50 mm Hg	increase of ≥15 mm Hg and value ≥105 mm Hg
Systolic blood pressure (mm Hg)	decrease of ≥20 mm Hg and value ≤90 mm Hg	increase of ≥20 mm Hg and value ≥180 mm Hg
Pulse (bpm)	decrease of ≥15 bpm and value <50 bpm	increase of ≥ 15 bpm and value >120 bpm

The same criteria, without the requirement of change, were applied to values at the reference point (Baseline).

Table 5: Criteria for potentially clinically important changes in ECG values

Parameter	Low	High
PR interval (msec)		≥210
QRS duration (msec)	≤50	≥150
QT interval (msec)	≤200	≥500
QTc interval (msec)		≥450
Ventricular rate (bpm)	<50 and change ≤-15	>120 and change ≥15

The same criteria, without the requirement of change, were applied to values at the reference point (Baseline).

4.2.12.3 Results

4.2.12.3.1 General Safety- Deaths, Serious Adverse events, Discontinuations

The sponsor reported that there were no deaths in either study group within 30 days of last dose of medication (one non-cardiac galantamine death >30 days). The serious adverse events were listed in Table 20 on p. 69 of the study report. Galantamine subject A60209, a 78-year-old female was hospitalized for chest pain, considered musculoskeletal upon evaluation. This subject completed the trial and reportedly had an end study ECG demonstrating no clinically significant changes from previous ECGs. There were no serious cardiovascular adverse events listed for galantamine treated subjects. Thirteen percent (9/69) of placebo patients discontinued compared to 23% (16/70) the galantamine group with two of the placebo discontinuations due to adverse events compared to 13 of the galantamine discontinuations. I reviewed the discontinuations due to adverse events in the both treatment groups. The placebo subjects discontinued for diarrhea (A60109) and abnormal hepatic function (A60186). Among the galantamine group, there were two discontinuations for cardiac related events. Subject A60002, a 70 year old female taking benazepril and diltiazem for hypertension developed transient complete heart block 14 days after starting treatment with galantamine. On the day of the recorded heart block, she had nausea and vomiting. The narrative noted this subject had bradycardia and supraventricular tachycardia on her baseline Holter suggesting underlying sick sinus syndrome. Subject A60228 reportedly discontinued for bradycardia and diarrhea. This 71 year old female developed sinus bradycardia (heart rate

56 on ECG, previously had been 72-84) 42 days after beginning treatment with galantamine. None of the other discontinuing subjects had cardiac adverse events recorded during the study and their reasons for discontinuation included a variety of gastrointestinal adverse events such as diarrhea, nausea, anorexia, and vomiting.

4.2.12.4 Results of Holter Monitor Analyses

The following sections present the heart rate, PR interval , and cardiac abnormalities diagnosed from Holter monitoring. I present the heart rate and PR interval data for each by study week monitoring period first, followed by mean data for each hour of each study week monitoring period.

4.2.12.4.1 Holter Heart Rate Results

The sponsor provided an analysis of the mean heart rate data by study week. The table below is copied from the study report and demonstrates the galantamine group had a slower mean heart rate than the placebo group for each study week monitoring period. In addition, the galantamine group had decreases in mean heart rate from baseline for each monitoring period while the placebo group had a decrease at week 2 but increases at weeks 4 and 6.

Table 11: Holter monitor 24-hour mean heart rate (bpm)

	Placebo			Galantamine			Mean difference (95% CI)
Timepoint	n	mean±SE	mean change from baseline±SE	n	mean±SE	mean change from baseline±SE	
Baseline	68	73.7±1.17	–	70	72.1±1.12	–	
Week 2	67	73.6±1.09	-0.1±0.63	65	71.0±1.36	-1.0±0.63	-0.9 (-2.69, 0.84)
Week 4	60	73.8±1.18	0.2±0.63	59	70.7±1.08	-2.1±0.55	-2.3 (-3.95, -0.63)
Week 6	59	74.1±1.17	0.4±0.67	55	70.8±1.22	-1.8±0.74	-2.2 (-4.19, -0.23)

Source: Display SAF.HOL.3

The sponsor also analyzed the data for each hour of the 3 study monitoring periods. The sponsor provided the hourly Holter heart rate data in both graphical (Figures 2-5) and tabular (Display SAF. HOL.1) format. For heart rate, the sponsor provided the minimum, maximum, mean, and mean change from baseline for hourly heart rates for each of the study weeks (baseline, week 2, week 4, and week 6). The following table summarizes that information. While the range of heart rates and range of mean hourly rates were similar between treatment groups, the lower limit of the mean change from baseline range was consistently lower for the galantamine group.

FDA Table 37. Summary of the mean heart rate range, heart rate, and mean heart rate change from baseline range observed by Holter monitoring in study 16

Study Period	Mean heart rate range for individual subjects		Range of mean hourly heart rate		Range of mean hourly heart rate changes from baseline	
	PBO	Gal	PBO	Gal	PBO	Gal
Baseline	41-135	39-129	66-80.1	64-79.3		
Week 2	45-129	42-156	64.9-80	64.7-80.8	-2.3 to 3.6	-7.2 to 3.1

Week 4	41-138	43-120	64.7-80.2	61.8-77.8	-4.4 to 2.7	-8.1 to 1.3
Week 6	39-185	40-127	63.8-81.7	62.1-78.7	-2.8 to 3.7	-8.1 to 1.9

The following data document that galantamine subjects had more mean decreases in heart rate during the monitoring periods. The sponsor calculated the mean heart rate change from baseline for each of the 24 hours of monitoring and plotted these results for weeks 2, 4, and 6. For each treatment group, I totaled the number of hours out of 24 where the mean change in heart rate from baseline was negative. For drugs not affecting heart rate, one would expect that the study drug and placebo groups would have similar numbers of hours where the mean change from baseline was negative. The table below demonstrates the galantamine group had more mean decreases in heart rate from baseline than the placebo group.

FDA Table 28. Number of hours with a mean decrease in heart rate from baseline by treatment group and study week

Study Week	Number of hours out of 24 where the mean change from baseline for heart rate was negative	
	Placebo	Galantamine
Week 2	11	14
Week 4	10	20
Week 6	8	23

4.2.12.4.2 PR Interval Results

The sponsor presented the PR interval data by study week monitoring period. The following table is taken from the study report and demonstrates the galantamine group had a higher mean PR interval for each 24-hour monitoring period compared to placebo. In addition, the PR interval mean change from baseline for was positive for each of the monitoring periods for the galantamine group but was negative for each of the monitoring periods for the placebo group.

Table 12: Holter monitor 24-hour mean PR interval (msec)

	Placebo			Galantamine			Mean difference (95% CI)
Timepoint	n	mean±SE	mean change from baseline±SE	n	mean±SE	mean change from baseline±SE	
Baseline	68	159.4±3.09	--	70	162.8±3.33	--	
Week 2	67	158.8±2.74	-0.8±1.54	65	164.7±3.46	1.9±1.17	2.7 (-1.18, 6.51)
Week 4	60	157.5±2.70	-2.1±1.88	59	162.4±3.67	1.9±1.79	4.0 (-1.11, 9.18)
Week 6	59	159.4±2.57	-0.5±1.91	55	163.6±3.73	4.7±1.88	5.2 (-0.07, 10.57)

Source: Display SAF.HOL.7

The sponsor also analyzed the Holter PR interval data for each hour of the 3 study monitoring periods. The Holter results provide evidence of a galantamine-related

lengthening of PR interval. In the PR interval tables, the sponsor provided the minimum, maximum, mean, and mean change from baseline for PR intervals by study hour for each of the study weeks (baseline, week 2, week 4, and week 6). The following table demonstrates that the range of PR intervals and range of hourly PR intervals were similar for the treatment groups but that the galantamine group consistently had higher upper range limits for PR interval than the placebo group.

FDA Table 39. Summary of the PR interval range, mean PR interval range, and mean PR interval change from baseline range observed by Holter monitoring in study 16

Study Period	PR range for Individual subjects (ms)		Range of Mean Hourly PR (ms) Intervals		Range of Mean Hourly PR Interval changes from baseline	
	PBO	Gal	PBO	Gal	PBO	Gal
Baseline	116-327	109-377	154.3-167.8	155.2-171.6		
Week 2	113-327	120-395	155.3-168.6	157.5-176.3	-2.8 to 4.3	-1.9 to 5.7
Week 4	106-350	109-374	153.1-168.7	153.9-173.4	-6.0 to 6.2	-2.1 to 7.9
Week 6	105-453	86-395	159.1-170.7	157.4-174.1	-5.5 to 4.3	-0.9 to 9.6

The sponsor calculated the mean PR interval change from baseline for each of the 24 hours of monitoring and these results demonstrate that galantamine subjects had more mean increases in PR during the monitoring periods. For each of the three monitoring periods, I totaled the number of hours with no change or an increase in mean PR interval from baseline. For drugs not effecting PR interval, one would expect that the study drug and placebo groups would have similar numbers of hours where the mean PR interval change from baseline was 0 or positive. The table below demonstrates the galantamine group had more mean increases in PR interval than the placebo group.

FDA Table 40. Number of hours with a mean increase in PR interval from baseline by treatment group and study week

Study period	Number of hours out of 24 where the mean change from baseline for PR interval was positive or 0	
	Placebo	Galantamine
Week 2	7	23
Week 4	2	18
Week 6	8	23

4.2.12.4.3 Holter abnormality results

The sponsor's Table 13 below compared the number of new Holter abnormalities, by type of abnormality and treatment group. More galantamine subjects had 1st degree heart block, 3rd degree heart block and pauses >2 seconds than placebo subjects although these events occurred infrequently.

Table 13: New abnormalities detected with Holter monitor at any time after baseline during the trial

	Placebo	Galantamine
Number patients (%) with Holter data	68	67
Any abnormality	36 (53%)	33 (49%)
• First degree block	4 (6%)	6 (9%)
• Second degree block[a]	4 (6%)	4 (6%)
• Third degree block[a]	0 (0%)	2 (3%)
• Pauses>2 seconds	5 (7%)	8 (12%)
• Torsades de pointes	0 (0%)	0 (0%)
• Atrial fibrillation/flutter	1 (1%)	1 (1%)
• Ventricular fibrillation/flutter	0 (0%)	0 (0%)
• Supraventricular tachycardia	21 (31%)	14 (21%)
• Sustained ventricular tachycardia	0 (0%)	0 (0%)
• Nonsustained ventricular tachycardia	1 (1%)	1 (1%)
• Ventricular ectopy proarrythmia	16 (24%)	11 (16%)

Patients could have more than one abnormality.

a: Patient A60114 was coded in the database as having both 2nd and 3rd degree blocks. The cardiologist determined that 2nd degree block was the appropriate code for all events.

Source: Display SAF.HOL.9A

4.2.12.5 Results of ECG Analyses

4.2.12.5.1 ECG Heart rate and interval results

The sponsor reported that there were no statistically significant changes in heart rate, mean change from baseline, or ECG intervals at week 2 or week 4 (p.75). Sponsor's table SAF.ECG 1B listed the mean changes from baseline for heart rate and PR interval and these were small in magnitude and similar between treatment groups. The sponsor reported a slight decrease in mean change from baseline for QT and QTc intervals in galantamine subjects at week 6 (USA-16 Table 27, p. 76).

4.2.12.5.2 ECG potentially important changes

Using the criteria listed in the methods section above, the sponsor identified the potentially important ECG values at any time (Table 28, p. 76). Aside from cases where there was one event in the galantamine group and none in the placebo group (i.e. high QRS, high ventricular rate) there were no notable differences in risk between treatment groups for these events.

4.2.12.5.3 ECG new abnormalities

Diffuse repolarization abnormalities and rare atrial extrasystoles were the new ECG findings occurring in more than 1% of galantamine subjects and more than twice as frequently in the galantamine group compared to the placebo group. Sponsor's Table 26 identifies all new ECG abnormalities by treatment group and is provided below.

Table 26: New abnormalities detected on ECG at any time after baseline during the trial

	Placebo N=69	Galantamine N=70
Number (%) patients with ECG data after baseline	68	68
Any abnormality	16 (24%)	17 (25%)
• Aspecific repolarization abn/certain	4 (6%)	4 (6%)
• Atrial ES/bigeminy	0	1 (1%)
• Atrial ES/frequent	0	1 (1%)
• Atrial ES/rare	1 (1%)	4 (6%)
• AV 1	3 (4%)	4 (6%)
• Left ant fascicular BL/possible	1 (1%)	0
• LVH/certain	1 (1%)	0
• Repolarization abnormalities/diffuse	1 (1%)	5 (7%)
• Repolarization abnormalities/lateral	3 (4%)	2 (3%)
• Sinus bradycardia	2 (3%)	2 (3%)
• Sinus tachycardia	0	1 (1%)
• Transmural/sep/old/certain	0	2 (3%)
• Ventricular ES/couplets	1 (1%)	0
• Ventricular ES/frequent	1 (1%)	1 (1%)
• Ventricular ES/rare	3 (4%)	4 (6%)
• Ventricular ES/unifocal	1 (1%)	0

ES=extrasystoles

4.2.12.5.4 PK/PD analyses

The sponsor reported that the data support linear kinetics for the galantamine dose range of 8 to 16mg bid. The following table summarizes the results of the sponsor's PK analyses of ECG and vital sign data.

Display PKPD.11: Results of linear regression between parameters of interest and galantamine trough plasma concentrations at steady state

Interval Time	Parameter	Corresponding Display	N	Intercept Estimate	Slope Estimate	Slope p-value (T-test)
Pooled Data (Weeks 2, 4, and 6)	ECG Heart rate (bpm)	PKPD.1	151			
	PR interval (msec)	PKPD.2	151			
	QRS interval (msec)	PKPD.3	151			
	QTcB interval (msec)	PKPD.4	151			
	Vital sign heart rate (bpm)	PKPD.5	151			
	Change from baseline in ECG Heart rate (bpm)	PKPD.6	151			
	Change from baseline in PR interval (msec)	PKPD.7	151			
	Change from baseline in QRS interval (msec)	PKPD.8	151			
	Change from baseline in QTcB interval (msec)	PKPD.9	151			
	Change from baseline in vital sign heart rate (bpm)	PKPD.10	151			

* Significant at the 5% alpha level.

Note: Only trough concentrations considered to be at steady-state are included in this linear regression analysis.

The statistical significance of the apparent relationship between trough concentration and vital sign heart rate depended on the inclusion of data from 2 outliers that might not have been trough concentrations (p.81).

The sponsor reported no apparent relationship between galantamine trough plasma concentration at steady state and various Holter measurements at week 6. The sponsor examined the relationship between galantamine trough plasma concentration and heart rate from the 24th hour, and heart rate mean, minimum, maximum, and mean change from baseline over the 24-hour period. The sponsor reported no association between galantamine trough concentration and these heart rate variables. Similarly, the sponsor examined the relationship between galantamine trough plasma concentration and PR interval data from the 24th hour and PR interval mean, minimum, maximum and mean change from baseline over the 24-hour period. The sponsor reported that there was no apparent trend between the PR interval values and galantamine trough concentrations during week 6.

The sponsor provided the trough galantamine concentration for a subject experiencing second degree heart block during week 6 monitoring. This subject's trough concentration (ng/mL) was below the group mean (64.4ng/mL) for galantamine trough concentration. Another galantamine subject had a conduction disturbance at week 6 but did not have a galantamine plasma level for that visit. Similarly, the sponsor provided the trough galantamine concentrations for subjects experiencing arrhythmias during week 6 monitoring. The sponsor reported that similar trough concentrations were observed between galantamine subjects experiencing arrhythmias and those who did not (p.83).

4.2.12.5.5 Sponsor's Interpretation of Results

On p. 86 of the study report, the sponsor acknowledged an average decrease from baseline heart rate of 2 beats per minute at weeks 4 and 6 and based on the magnitude of this change, considered this finding to have no clinical significance. In addition, the sponsor found no subjects meeting the criteria for clinically significant changes in heart rate at any time point for either treatment group. The sponsor also acknowledged that the changes in PR intervals were predominantly positive among galantamine subjects and negative among placebo subjects. Again, based on the magnitude of change, the sponsor considered the findings to have no clinical significance.

4.2.12.6 FDA Heart Rate and PR Interval Outlier Analyses

I examined the Holter monitor data sets provided by the sponsor using the JMP© statistical software package to further characterize differences in risk for heart rate decrease outliers and PR interval increase outliers, by treatment group and gender. I present the results of these analyses in the following sections.

4.2.12.6.1 Heart Rate

I identified 68 placebo and 67 galantamine subjects with Holter data for baseline and at least one study visit. I then selected and removed subjects who had a heart rate <50 at any of the 24-hour measurements at baseline (n=9 placebo, n=11 galantamine subjects). This left 59 placebo subjects and 56 galantamine subjects for the heart rate analyses. From this group, I identified those with one or more recorded heart rates of ≤45bpm and those with one or more decreases in heart rate from baseline of at least 20bpm, 30bpm, and 40bpm for any of their 24 hourly measurements during the study treatment period. I also stratified these subjects by sex to look for risk differences. The results are included in the following table.

FDA Table 41. Examination of heart rate outliers identified from the Holter data set from Study 16

Outlier Cutoff	Placebo (n=59)	Galantamine (n=56)	Relative Risk
Heart Rate <45	**3% (2/59)**	**5% (3/56)**	**1.7**
Male	5% (1/21)	(0/21)	0
Female	3% (1/38)	9% (3/35)	3
↓HR≥20bpm from BL	**78% (46/59)**	**88% (49/56)**	**1.1**
Male	71% (15/21)	86% (18/21)	1.2
Female	82% (31/38)	89% (31/35)	1.1
↓HR≥30bpm from BL	**37% (22/59)**	**50% (28/56)**	**1.4**
Male	33% (7/21)	52% (11/21)	1.6
Female	39% (15/38)	49% (17/35)	1.3
↓HR≥40bpm from BL	**12% (7/59)**	**23% (13/56)**	**1.9**
Male	5% (1/21)	29% (6/21)	5.8
Female	16% (6/38)	20% (7/35)	1.3

This analysis demonstrates a slightly increased risk for having a heart rate less than 45bpm and for having decreases in HR from baseline outliers. In general the relative risks were similar when stratified by sex.

4.2.12.6.2 PR Interval

I used a similar approach to analyze the PR interval Holter data to the one I used for the heart rate data. After identifying and removing subjects with a PR interval value >200msec at baseline there were 62 placebo and 59 galantamine subjects remaining. From this group I identified those with one or more PR intervals >200msec, >220msec, and >240msec at any of the hourly measurements during the study. I also identified the subjects with an increase in PR interval >40msec, >45msec, and >50msec compared to baseline. I stratified these subjects by sex and looked for risk differences. The results are included in the following table.

FDA Table 42. Examination of PR interval outliers identified in the Holter data set, Study 16

Outlier Cutoff	Placebo (n=62)	Galantamine (n=59)	Relative Risk
PR>200msec	**6% (4/62)**	**8% (5/59)**	**1.3**
Male	8% (2/26)	10% (2/20)	1.3
Female	6% (2/36)	8% (3/39)	1.3

PR>220msec	**3% (2/62)**	**7% (4/59)**	**2.3**
Male	4% (1/26)	10% (2/20)	2.5
Female	3% (1/36)	5% (2/39)	1.7
PR>240msec	**3% (2/62)**	**3% (2/59)**	**1.0**
Male	4% (1/26)	10% (2/20)	2.5
Female	3% (1/36)	(0/39)	0
↑PR≥40msec from BL	**16% (10/62)**	**25% (15/59)**	**1.6**
Male	15% (4/26)	25% (5/20)	1.7
Female	17% (6/36)	26% (10/39)	1.5
↑PR≥45msec from BL	**10% (6/62)**	**12% (7/59)**	**1.2**
Male	12% (3/26)	20% (4/20)	1.7
Female	8% (3/36)	8% (3/39)	1.0
↑PR≥50msec from BL	**10% (6/62)**	**12% (7/59)**	**1.2**
Male	4% (1/26)	15% (3/20)	3.8
Female	6% (2/36)	8% (3/39)	1.3

There did not appear to be large differences in risk for these outliers in this study. The relative risks seem greater among galantamine treated males than females, although there were relatively few subjects and few events in each cell after stratifying by gender.

5 Review of Systems

5.1 Mortality

In the JRF RCTs, 1.1% of the placebo-treated patients died compared with 0.6% of the galantamine-treated patients. In the Shire RCTs, 0.5% of the placebo-treated patients died compared with 0.6% of the galantamine-treated patients. Because of the substantial number of discontinuation in the trials, I examined the mortality rates in the trials utilizing person-time exposure, which corrects for differences in attrition between the two study arms. In all seven RCTs combined, the mortality rate in the placebo group exceeded that in the galantamine group by 30% (2.2 v. 1.7 deaths per 100 person-years).

FDA Table 43. Mortality rates from RCTs (per 100 person-years) in recently reviewed NDAs for Alzheimer's disease

	Placebo	Active Drug
Rivastigmine	0.72	0.72
Metrifonate	1.24	1.42
Physostigmine*	0.42	0.85
Galantamine	2.2	1.7

*only deaths within 7 days of last dose were included as compared with 30 days for rivastigmine and metrifonate

Making comparisons of event rates across NDAs is inherently precarious due to differences in study design and study population. Given that caveat, the mortality rates in the galantamine RCTs are within the range of those seen in other recently reviewed NDAs for Alzheimer's disease.

In the long-term extension studies ≤ 12 months, the all-cause mortality rate for the whole study population was 2.8 deaths per 100 person-years; subsequently, in the >12 month extensions, the rate was 2.0 deaths per 100 person-years. If one considers the long-term

extension experience in total, the rate was 2.6 deaths per 100 person-years (27 deaths/1034 person-years). The background rate of mortality in patients with Alzheimer's disease increases with longer duration of disease, therefore it is not unexpected that the mortality rate increased moderately during the extension trials. The more concerning aspect is the two-fold difference in mortality rate in the long-term extension studies ≤ 12 months between those patients originally randomized to placebo and those to galantamine (1.6 v. 3.1 deaths per 100 person-years)[12]. Some of the excess of deaths occurring in the GAL-GAL group in the extension studies were attributed to causes that would be expected to occur in an aging Alzheimer's disease population. For example, pneumonia was the cause of death for four GAL-GAL patients and no PBO-GAL patients (7.4 v. 0.0 deaths per 1000 person-years). Intracranial hemorrhage after fall was another common cause of death in patients originally randomized to galantamine. Three GAL-GAL patients and no PBO-GAL patients died of head injuries incurred after falls (5.6 v. 0.0 deaths per 1000 person-years). This excess is consistent with the observation of an increased risk of the SAE "fall" in the GAL-GAL group of both the JRF and Shire extension trials.

The difference in mortality rates between the GAL-GAL and PBO-GAL groups could possibly be explained by confounding by indication. NDA data for the cholinesterase inhibitors has given some indication that sicker Alzheimer's patients have a higher tolerance to increased cholinergic stimulation, allowing them to remain on the medications. At the same time, patients intolerant of the drug's cholinergic side effects would likely discontinue during the RCT portion. Additionally, sicker patients may not be able to clearly express their symptoms, giving the impression of improved tolerance. Thus sicker patients who tolerated the drug in the RCT would be preferentially entering long-term extensions, and perhaps be dying at an elevated rate as compared to previously galantamine naïve patients. We will ask the sponsor to evaluate the degree of illness of the GAL-GAL patients as compared to the PBO-GAL patients at the time of entry into the first long-term extension to investigate the possibility of confounding by indication.

If this difference in mortality rates between the GAL-GAL and PBO-GAL groups was real, one would have to hypothesize that galantamine has some cumulative toxicity. It is not immediately clear how a cumulative toxicity would demonstrate itself clinically; especially in view of the variety of causes of death observed in the extension trials.

When cause-specific mortality was examined in the RCTs, the most marked difference between galantamine and placebo was the elevated rate of sudden death in the galantamine group (5.0 v. 2.0 deaths per 1000 person-years). This pattern was mirrored in the cause-specific mortality assessment in the long-term extension trials (≤ 12 months) where patients with their first exposure to galantamine (those originally randomized to placebo) had an elevated rate of sudden death compared with those previously exposed to

[12] When the additional experience in the long-term extension studies > 12 months is added in, there is still an excess rate in the GAL-GAL group as compared to the PBO-GAL group, although it is not as marked (3.0 v. 1.9 deaths/100 person-years). One could argue that the lessening of the difference in mortality rates between the two groups with the addition of more person-time experience is that patients intolerant of the increased cholinergic stimulation have died or discontinued.

galantamine (9.9 v. 3.7 deaths per 1000 person-years). The concern is that sudden death is resulting from some effect of galantamine on the cardiovascular conduction system. Of course, sudden death and cardiac conduction system abnormalities are occurring at some background rate in these elderly patients as is evidenced by the placebo group in the RCTs, so it is ultimately difficult to separate out the effect of the drug over and above the background.

One piece of data from the long-term extension trials (≤ 12 months) that is not consistent with finding of increased risk of sudden death in newly galantamine-exposed patients is the observation that discontinuations due to heart rate and rhythm AEs, specifically bradycardia, occurred more frequently in patients who had been originally randomized to galantamine. Thus if one suspected that the mechanism for sudden death was related to galantamine-induced cardiac conduction disorders, one would expect that discontinuations for such AEs would follow a similar pattern (occur at a higher risk in the newly exposed patients).

5.2 Cardiovascular system

5.2.1 Heart rate and rhythm

As part of its pharmacological effects, galantamine increases vagal tone, potentially slowing the heart rate and prolonging conduction through the atrioventricular node.

5.2.1.1 Bradycardia

Study GAL-USA-16 was randomized, placebo-controlled investigation of the effect of galantamine on cardiac conduction. Holter monitoring was performed at baseline, end of week 2 (16 mg/day), end of week 4 (24 mg/day), and end of week 6 (32 mg/day). Examination of Holter monitor data showed that galantamine-treated patients had a mean decrease in HR of 2 bpm at weeks 4 and 6 compared with an minimal increase in HR in the placebo-treated patients. Additionally, the galantamine group had an excess in the number of hours out of 24 during which they had a mean decrease in heart rate.

The review of heart rate vital sign data from the RCTs showed decreases in pulse in the 2-4 bpm range. ECG data from the JRF RCTs showed a mean decrease in heart rate of 3-4 bpm in the galantamine group compared to a decrease of 1 bpm in the placebo group. These findings were consistent with the changes in heart rate identified on Holter monitor in study USA-16.

ISS-A Table 8-1b summarized the frequency of the AE bradycardia in all the phase II/III trials included in the amendment. In all of the RCTs, the incidence of the AE bradycardia was 2-3% and exceeded the risk in the placebo group by 2-10 times. In the JRF extension trials, the risk of the AE bradycardia was around 4-5%, while it was slightly less frequent in the Shire extension trials 1.3-2%.

In the JRF RCTs there were few discontinuations for bradycardia, and no suggestion of a dose-response relationship. In the JRF long-term extensions (≤ 12 months) there were

also few discontinuations for bradycardia, however, of the five (0.8%) that did occur, all were in previously galantamine-treated patients.

Bradycardia was not a commonly occurring SAE. Seven cases were described in the ISS-A database; digoxin was a concomitant medication in at least three of the seven cases, including one healthy patient who was participating in a drug interaction study of digoxin and galantamine. Although the data from that study did not suggest an effect of galantamine on digoxin pharmacokinetics, we will ask the sponsor to look at the clinical data that bears on the possibility of an additive effect of these two drugs on atrioventricular conduction.

5.2.1.2 AV block

The detection of atrioventricular (AV) block, like bradycardia, requires an intervention (in this case, an ECG) to be performed. As a result, the patient usually has to have some intercurrent event that leads them to seek out medical evaluation. In contrast, a study like USA-16, with uniform recording of Holter monitoring at baseline and subsequent two week intervals (each at a higher dose), had the opportunity to detect asymptomatic AV block in an unbiased manner. Although the absolute number of heart block episodes in USA-16 was low, galantamine-treated patients had a 50% increased risk of first degree AV block (9% v. 6%). Galantamine-treated patients also had a small excess of episodes of third degree AV block (3% v. 0%); one of these patient discontinued prematurely from the trial. There was no difference between treatment groups for second degree AV block. The risk of a >2 second pause was 70% higher in the galantamine-treated group (12% v. 7%).

The Holter data for the PR interval supported the findings described above; galantamine prolonged the PR interval in a dose-related fashion, up to 5 msec at the 32 mg/day dose (week 6) as compared to the placebo group (which had a small mean decrease in the PR interval). Consistent with the mean changes from baseline for the PR interval, the galantamine group had an excess in the number of hours out of 24 during which they had a mean increase in PR interval.

Consistent with the findings of USA-16 with regard to PR prolongation and first degree AV block, there was an excess of the AE first degree AV block in galantamine-treated patients in the other RCTs, although this did not appear to be dose-related. The PR interval data from ECGs performed in the JRF RCTs showed some evidence for prolonged PR at the 32 mg/day dose compared to placebo, but there was little difference between the placebo and 24 mg/day dose group for percent of outliers and mean change from baseline.

In USA-1, a 16 mg BID patient and a placebo patient each reported third degree AV block; both events were reported as a SAE.

5.2.1.3 QT interval

ECG data from the JRF RCTs did not show any evidence of QTc interval prolongation in outlier or mean change from baseline analyses.

5.2.2 Syncope

The review of SBP and DBP in the RCTs showed that in the galantamine group, there was a decrease in both parameters over the course of the trials in the range of 2-10 mmHg. About 2% of galantamine patients reached the criteria for clinically relevant fall in SBP or DBP.

As shown in ISS-A Table 8-1b, in the RCTs, syncope was reported about twice as often in the galantamine group as in the placebo group. This excess was not eliminated by the slower titration schedule and lower doses used in USA-10, as evidenced by the excess risk of syncope in the galantamine group (3% v. 0.7%). In the JRF long-term extensions (≤ 12 months), about 1-2% of patients continued to report syncope.

In the large JRF RCTs, discontinuation due to syncope was relatively infrequent, but did occur about twice as often in the galantamine group as compared to the placebo group; however, there was no dose-response relationship. Discontinuation due to syncope in the long-term extensions (≤ 12 months) occurred slightly more often in the GAL-GAL group as compared with the PBO-GAL group.

Syncope was a commonly reported SAE and occurred twice as frequently in the galantamine group as compared with the placebo in the six RCTs (1.2% v. 0.6%). In USA-10 there was a dose-response relationship for syncope as an SAE (PBO=0.7%, 8 mg/day=0.7%, 16 mg/day=1.4%, 24 mg/day=1.8%). The risk of serious syncope decreased in the long-term extensions to a range of 0.2-0.6%. Four cases of syncope were suspicious for a cardiac etiology as detailed in section 4.2.6.5.2.

5.3 Gastrointestinal system

5.3.1 Nausea and vomiting

Gastrointestinal side effects of nausea and vomiting are commonly associated with the class of acetylcholinesterase inhibitors. In the single-dose and repeated-dose Phase I studies in healthy subjects, nausea was one of the most commonly reported AEs. Among the small number of discontinuations in these studies, nausea and/or vomiting were the most common reasons for discontinuation.

In the JRF RCTS, nausea was the most commonly reported AE (38% of "fast 24 mg", 42% of 32 mg), even in USA-10 which utilized a slower titration schedule and a lower maximum dose (17% of "slow 24 mg"). There was a dose-response relationship for the AE nausea, but not for the AE vomiting (although there was an excess of this AE in the galantamine-treated groups). In the long-term extensions (≤ 12 months), nausea and vomiting continued to be reported commonly, with the risk in previous placebo patients about twice that in previous galantamine patients (nausea: 31% v. 15%; vomiting: 15% v. 6%).

In the JRF RCTs, there was a dose-response relationship for discontinuations due to nausea and vomiting (each considered individually). The absolute risk of nausea or vomiting in the "slow" 24 mg group was half that in the "fast" 24 mg group (nausea: 12% v. 6%, vomiting: 10% v. 4%,), but the relative risk compared to the placebo group was similar (about 6x for nausea). In the long-term extensions (≤ 12 months), the risk of discontinuation due to nausea and vomiting in the GAL-GAL group dropped to the level of the placebo group in the RCTs, while the PBO-GAL group had a risk on the order of the galantamine group in the RCTS. This would not be unexpected, as the former placebo group would be experiencing their first exposure to increased cholinergic tone, while the former galantamine group would have developed some tolerance (and those sensitive in the RCT would have already discontinued).

In the RCTs, nausea and vomiting as SAEs occurred in 1-1.2% of galantamine-treated patients compared with 0.2% of placebo patients. There was no dose-response relationship for SAEs for nausea and vomiting. About 1% of patients continued to have nausea and vomiting SAEs in the long-term extension trials (≤ 12 months). Not unexpectedly, patients in these trials originally randomized to placebo had a risk of the SAE nausea that was twice the risk in the group originally randomized to galantamine. Sometimes the events nausea and vomiting were labeled serious because they occurred at the same time as an event that required hospitalization (e.g., syncope).

One case of esophageal rupture was reported in a patient in 93-01X, but it occurred 18 days after the drug was discontinued.

5.3.2 Liver

Dr. Boehm's review of laboratory data did not identify any differences between treatment groups in the frequency of outliers for total bilirubin, ALT, AST, or alkaline phosphatase in INT-1, USA-1, and USA-10. The mean change from baseline analysis did not identify any substantial differences between treatment groups for ALT, AST, or alkaline phosphatase. In studies INT-1 and USA-1, patients in the galantamine 24 mg and 32 mg groups had increases in total bilirubin of 0.3 and 0.4 mg/dl, respectively, compared with no change in the placebo group. However, USA-10 did not show any difference in mean change from baseline between placebo and galantamine groups.

Two galantamine-treated patients in the safety database had a concomitant 3x increase in transaminase and total bilirubin > 2 mg/dl. One patient had the measurement taken five months after discontinuing from the trial and after the patient had been diagnosed with a malignant bowel tumor. The other patient had their elevations identified during week 3 of the RCT, but the LFT abnormalities resolved while the patient continued treatment.

Two galantamine-treated patients in the safety database developed jaundice during study INT-3. After six months of galantamine in INT-1, patient A03057 suffered a fall and hip fracture on day 34 of INT-3 at which time he was noticed to be jaundiced. He was

discontinued from the trial at this time for elevated LFTs[13]; valproic acid (started some time prior to the trial) was also discontinued. After six months of galantamine in INT-1, patient A03362 developed jaundice on day 99 of INT-3; laboratory tests revealed moderately elevated transaminases (4-7X ULN) and elevated alkaline phosphatase and GGT (2-7X ULN). The LFTs normalized within one week, but subsequently the patient was diagnosed with gallstones. An ERCP/sphincterotomy was performed, but this procedure was complicated by rupture of the duodenal wall three days post-procedure. The patient discontinued from the treatment at this time.

There were no cases of acute fulminant liver failure or hospitalized non-viral hepatitis in the ISS-A database. Patient B0406 in 95-05X was reported to have the AE "hepatic failure" yet it was evaluated as mild and not serious and began on the day the patient (placebo in 95-05) started in the long-term extension (the patient subsequently discontinued on day 21 of the extension due to vomiting).

5.3.3 Pancreatitis

There were two cases of serious pancreatitis in galantamine patients that was not associated with gallstones. One case had a negative rechallenge and the other patient's course was not well-described. As I've described earlier with other adverse events, the pertinent laboratory data for this patient was not included in the narrative.

5.3.4 Other gastrointestinal illness

The overall incidence of the AEs "peptic ulcer", "gastric ulcer hemorrhagic", and "gastric hemorrhage" was low and little difference was seen between the galantamine and placebo groups. The risks of these AEs did not increase with prolonged exposure in the extensions.

5.4 Renal system

5.4.1 Renal function

There was no study in which the frequency of outlier creatinine values in the galantamine group exceeded that in the placebo group. When considering only patients with normal baseline renal function, no patient in INT-1, USA-1, or USA-10 developed an outlier creatinine value >2.3. The mean change from baseline analysis based on the sponsor's ISS-A table Lab2.1.G did not identify any systematic change in creatinine values across treatment groups.

The urinalysis data for INT-1, USA-1, and USA-10 showed no evidence of a difference in new-onset proteinuria between treatment groups.

Three SAEs of "renal failure" were reported in the ISS-A database. One patient had substantial preexisting renal insufficiency, and one patient who developed renal failure eight weeks into the trial was subsequently diagnosed with multiple myeloma. The third

[13] The LFT values were not provided in the narrative or the dataset.

patient discontinued from the trial for renal failure, but no laboratory values were provided in the narrative to indicate the severity of the SAE.

5.4.2 Renal calculi

Four galantamine patients and no placebo patients had SAEs for renal calculi during the RCTs (all US cases). Two patients were reported to have had no history of kidney stones and information on past history of stone disease was not included for the other two patients. Diagnosis of renal calculi was made on day 6, day 29 (with another episode on day 135), day 30, and 5 months. The patient diagnosed on day 30 had discontinued from the trial for nausea on day 15.

Renal calculus disease usually presents in early to mid adulthood, so presentation of new disease in these elderly patients is unusual. Of the four cases, two reported no history of stone disease. An additional unusual aspect of the cases is the relatively early onset following initiation of galantamine. Review of the literature describing the well-recognized syndrome of indinavir-associated renal calculi suggests that patients experienced renal colic or passed stones anywhere from week 1 to week 20 in one study[14] and between weeks 13-47 in another study[15]. Clearly, this is evidence from a different drug used in a different patient population, but it does suggest that stone formation could occur over a matter of a few weeks to months.

In the urinalysis data from studies USA-1, INT-1, and USA-10, there was no excess of new-onset hematuria (as measured by dipstick) in the galantamine-treated patients as compared with placebo patients.

5.4.3 Electrolytes

The outlier and mean change from baseline analyses did not reveal any differences between the galantamine and placebo groups for high or low potassium, sodium, or chloride.

5.5 Musculoskeletal system

5.5.1 Muscle weakness

In the galantamine NDA, the sponsor considered for analysis sixteen World Health Organization (WHO) preferred terms considered to be possibly indicative of, or related to, the incidence of muscle weakness. These terms included muscle weakness, fatigue, asthenia, malaise, abnormal gait, paralysis, ataxia, fall, speech disorder, dysphonia, dyspnea, dysphagia, choking, myalgia, hypokinesia, and involuntary muscle contractions. These terms were chosen by the sponsor in an attempt to capture any case of weakness potentially attributable to the mode of action of galantamine.

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

[15] Kopp JB, et al. Crystalluria and urinary tract abnormalities associated with indinavir. *Annals of Internal Medicine* 1997; 127(2): 119-25.

The sponsor's effort to capture any case of weakness potentially attributable to the mode of action of galantamine by examining reports of 16 AE preferred terms related to muscle weakness did not identify any cases of neuromuscular weakness most prominently involving proximal and/or axial and/or respiratory muscles. The AE "muscle weakness" was more common in patients treated with the study drug as compared to placebo-treated patients (0.6% vs. 0.1%), but specific cases of muscle weakness were generally localized to one side or to the legs.

My review of the serious AEs reported in galantamine studies included in the ISS-O identified 39 events in the body as a whole, musculoskeletal, central and peripheral nervous system, and respiratory system with preferred terms that could potentially be related to muscle weakness; however, none of these events fit a pattern of weakness most prominently involving proximal and/or axial and/or respiratory muscles. Additionally, of 43 discontinuations for AEs relating to weakness, none fit this pattern of weakness. Finally, my review of non-serious AEs relating to neck complaints or weakness symptoms did not identify any patients with a constellation of symptoms that fit a pattern of weakness most prominently involving proximal and/or axial and/or respiratory muscles.

Of 21 deaths occurring within 30 days of galantamine treatment in the ISS-O, seven had some symptom relating to weakness. None of these seven patients fit a pattern of weakness most prominently involving proximal and/or axial and/or respiratory muscles. One patient (INT-1/A30926), however, had an autopsy documenting death from choking on a piece of meat. The patient's family members reported one other recent occurrence of the patient having difficulty swallowing, but they did not recall any associated symptoms of weakness.

The review described above was performed prior to the submission of the 2/25/00 amendment. Dr. Boehm reviewed the SAEs of weakness submitted for the entire NDA including the amendment and did not identify any patients with a pattern of weakness most prominently involving proximal and/or axial and/or respiratory muscles.

5.5.2 CPK

In the sponsor's analysis, one trial (INT-2) showed a difference in outliers for CPK elevation in the galantamine group (1.5% v. 0%). Dr. Boehm's outlier analysis of CPK in USA-1 and USA-10 (CPK was not measured in INT-1), based only on patients with a normal baseline value did not identify any excess of CPK outliers (>2x ULN) in the galantamine-treated patients. Dr. Boehm's mean change from baseline analysis in USA-1, showed a substantially higher change from baseline for the GAL 24 mg/day group, but this value was driven by one patient with an endpoint value greater than 5000. The mean change from baseline analysis in

USA-10 showed only a minimally higher increase in CPK in the galantamine group compared to the placebo group

Due to some indication of a differential increase in CPK in the galantamine compared to the placebo group, Dr. Boehm performed additional outlier and mean change from baseline analyses in USA-1, INT-2, USA-10, and USA-16; these analyses did not identify a higher risk of more extreme outliers or a consistently increased mean change from baseline in the galantamine-treated patients. These additional analyses are included in Appendix 3.

There were no clinical episodes of rhabdomyolysis reported in the ISS-A safety database. There were some reports of increased CPK as AEs, but never as an SAE. One patient in USA-1 (A35155) had an endpoint CPK value of 5,463 U/L. Follow-up information provided by the sponsor indicated the patient had a subsequent measurement within normal limits three weeks later, but did not have an explanation for the high value at the end of the study.

5.6 Falls and Injuries

While reviewing the SAEs, Dr. Boehm discovered that verbatim terms for surgical procedures had been coded to the preferred term "injury". When he removed the surgical procedure terms, he found no difference in the risk for the SAE "injury".

The sponsor specifically spelled out in their methods section that care was taken to exclude syncopal episodes with change in consciousness from the preferred term "fall". Thus "fall" referred to loss of balance or coordination. In the large JRF RCTs, about 4-5% of patients in all groups reported the AE "fall". The risk in the GAL 32 mg group was slightly higher at 7%. There was no difference between treatment groups for discontinuations due to falls in the large JRF RCTs. In the large RCTs, there was no difference between treatment groups for the SAE "fall". The overall risk increased slightly in the long-term extension trials (≤ 12 months).

Clearly, falls in this population can have significant associated morbidity and mortality. As described in the discussion of mortality, three patients in the GAL-GAL group in the long-term extension (≤ 12 months) died of intracranial bleeding sustained in falls.

5.7 Hematological system

Dr. Boehm's outlier and mean change from baseline analyses did not identify any differences between treatment groups for WBC, platelets, or hemoglobin.

Three galantamine patients had extreme falls in hemoglobin during their exposure. Two patients were hospitalized and transfused and completed the study. The third patient, in an extension, discontinued from the trial. None of the narratives described the patients' work-ups for the drop in hemoglobin (if there was one).

No cases of aplastic anemia were observed during the galantamine development program.

5.8 Metabolic and endocrine systems

5.8.1 Weight loss

Weight loss of 1-2 kg was observed in the galantamine-treated patients in the RCTS compared with no change or a slight increase in placebo patients. In 93-01 and USA-10, there was a dose-response relationship for weight loss (see FDA Tables 35 and 36). USA-10 also showed a dose-response for percentage of patients losing >7% of baseline weight; 11% of patients in the "slow" 24 mg group met that criteria as compared with 3.5% of placebo patients. Some patients seemed to be more sensitive to the gastrointestinal effects of the drug, leading to substantial weight loss; however, in contrast to physostigmine, we were unable to identify a gender effect. As would be expected, patients who experienced the AE "anorexia" had a substantially higher risk of reporting the AE "weight loss"; generally this held true in both the placebo and galantamine groups.

5.8.2 Glucose metabolism

5.8.2.1 Hyperglycemia

The sponsor identified one study (95-05) in which there was an excess of outliers for glucose increase (5.8% v. 1.4%); however, the cutoff used by the sponsor was very conservative (120 mg/dl). Neither Dr. Boehm's outlier analysis (using a cutoff of 240 mg/dl) nor his mean change from baseline analysis identified any important difference between the treatment groups in USA-1 and USA-10 for glucose increase. There were no extreme outliers for glucose increase.

The urinalysis data for INT-1, USA-1, and USA-10 showed no evidence of a difference in new-onset glycosuria between treatment groups.

In the Shire RCTs, the AE "hyperglycemia" was reported about twice as often in the combined galantamine group compared with the placebo group; all the reports of hyperglycemia in the galantamine group were at the 32 mg/day dose.

5.8.2.2 Hypoglycemia

Dr. Boehm's outlier analysis identified a dose-response relationship in USA-1 for patients with glucose < 60 mg/dl. Glucose levels of this degree are concerning in this population that may have an impaired ability to communicate symptoms of hypoglycemia. The hypoglycemia that was observed may be related to decreased food intake in diabetic patients on sulfonylureas or insulin who are suffering from treatment-related nausea, vomiting, and anorexia. We will ask the sponsor to review the clinical histories of patients who had glucose measurements less than 60 mg/dl or who had AEs of hypoglycemia to try to identify risk factors. It would also be reasonable to look for

hypoglycemia outliers among all patients on therapy for diabetes. If this group is at risk for hypoglycemia, it may warrant a precaution in the labeling.

5.9 Dermatological system

Four galantamine and no placebo patients experienced SAEs of rash; however none of the case descriptions supported a strong association between the galantamine exposure and the SAE. Two patients had new medications added in the interim between the initiation of galantamine and the development of rash and a third patient had no serious rash described in the narrative that focused on a discontinuation for a deep vein thrombosis.

Galantamine therapy did appear to be associated with the common AE "sweating increased". In the JRF RCTs in the ISS-O, there was a near doubling of galantamine patients with this AE compared to placebo (2.4% v. 1.3%). In USA-16, 6% of galantamine patients reported this AE compared to 0% of placebo patients. This AE was also reported by 3% of galantamine-treated healthy subjects in the drug interaction trials.

5.10 Central Nervous System

5.10.1 Seizure

Seizure is recognized as a side effect of acetylcholinesterase inhibitors, however, it also occurs in Alzheimer's patients spontaneously. There was no evidence in the galantamine development program of a difference in the occurrence of seizure between treatment groups.

5.10.2 Dizziness

Dizziness was a commonly reported AE in Phase I single-dose, repeated-dose, and drug interaction studies in healthy patients. In the original JRF RCTs, there was a dose-response relationship for the AE dizziness; this persisted in USA-10, but was not as marked. In the Shire RCTs, the relative risk of dizziness in elderly (75 or older) galantamine-treated patients compared to elderly placebo patients was three times that for patients younger than 75.

In the original JRF RCTs there was a dose-response relationship for discontinuations due to dizziness; however, this relationship was not observed in GAL-USA-10. In long-term extension trials < 12 months, there was a substantial excess of discontinuations due to dizziness for the PLA-GAL group compared to the GAL-GAL group.

5.10.3 Headache

Headache was a commonly reported AE in Phase I single-dose, repeated-dose, and drug interaction studies in healthy patients. In the original JRF RCTs there was a dose-response relationship for the AE headache, but this was not observed in USA-10. In the Shire RCTs, the relative risk of headache in elderly (75 or older) galantamine-treated patients compared to elderly placebo patients was more than three times that for patients younger than 75.

In the original JRF RCTs there was an excess of discontinuations for headache in the galantamine group. In long-term extension trials < 12 months, there was a substantial excess of discontinuations due to headache for the PLA-GAL group compared to the GAL-GAL group.

5.10.4 Psychiatric side effects

Insomnia was reported as a common side effect (>10%) in the Phase I repeated-dose and drug interaction studies in healthy patients.

Although somnolence and agitation were reported commonly as AEs, there was little difference in the frequencies between the treatment groups. Interestingly, though, in the JRF RCTs, there was a dose-response relationship for discontinuations due to somnolence. This was also observed for the AE "confusion". In both the JRF and Shire long-term extension trials < 12 months, there was a substantial excess of discontinuations due to somnolence and confusion for the PLA-GAL group compared to the GAL-GAL group. In only the JRF long-term extension trials < 12 months, was there an excess of discontinuations due to agitation and hallucination for the PLA-GAL group compared to the GAL-GAL group.

In the four large JRF RCTs, the relative risk of somnolence in galantamine-treated men compared to placebo-treated men was 2-6X that for women and the relative risk of anxiety in galantamine-treated men compared to placebo-treated men was 3X that for women.

In the RCTs there was no excess of SAEs for agitation in the galantamine group.

6 Discussion

The safety profile of galantamine is consistent with that expected for a drug that causes increased cholinergic stimulation. In a predictable way, the drug slows heart rate and prolongs conduction through the atrioventricular node. It also lowers systolic and diastolic blood pressure to a mild degree.

In this highly screened elderly population, all syncope and syncope reported as serious occurred in a drug-related manner. Although there was no overall difference in mortality between drug and placebo in the RCTs, there was an excess of sudden deaths in galantamine-treated patients. Thus the healthiest of Alzheimer's patients appeared to suffer morbidity and mortality related to the cardiovascular side effects of the drugs. One can only presuppose that an unscreened population of Alzheimer's patients will have a wider spectrum of pre-existing cardiac disease, likely raising the risk of an untoward effect on the cardiac conduction system.

Currently, marketed acetylcholinesterase inhibitors for the symptomatic treatment of Alzheimer's disease carry a precaution for patients that are prone to problems with bradycardia, such as those with sick sinus syndrome and those taking negative chronotropic medications. However, postmarketing surveillance of these drugs indicates that adverse events related to bradycardia and heart block are not limited to those patients

with known risk factors for cardiac conduction disorders. These events likely reflect the presence of undiagnosed disease of the cardiac conduction system, which is common in the elderly population. Therefore, medical providers should presume that all patients are at risk for potential heart rate and rhythm adverse events related to the cardiovascular effects of galantamine.

At the doses and titration schedule intended for marketing there was still a dose-response relationship for discontinuations due to nausea and vomiting. A dose-response relationship also persisted for the AEs nausea, vomiting, and anorexia. There was still an excess of the AE "weight decrease" in the galantamine group. Although the absolute risks of the gastrointestinal side effects associated with increased cholinergic stimulation were lessened by the adoption of a lower maximum dose and slower initial titration schedule, these dose-related risks were not eliminated and the risks relative to placebo were not altered. The frequencies of the AEs nausea, vomiting, and anorexia are consistent with those described in the Aricept labeling.

Aside from the expected cholinomimetic pharmacological effects, the safety review identified only a few additional safety concerns. The development of renal calculi as an AE will have to be followed should the drug be marketed. The occurrence of hypoglycemia needs to be evaluated further in diabetic patients in the safety database who were suffering gastrointestinal side effects.

7 Requests for the sponsor

7.1 Exposure

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

7.2 Mortality

One possible explanation for the twofold mortality excess in patients originally randomized to galantamine as compared to those originally randomized to placebo in the long-term extension < 12 months would be confounding by indication. Please compare the severity of illness of the GAL-GAL patients as compared to the PBO-GAL patients at the time of entry into the first long-term extension by examining concomitant medications, co-morbid conditions, and adverse events experienced during the RCT to investigate this possibility. If confounding by indication is not supported by the data, please provide an explanation for the difference in mortality described above.

7.3 Common AEs

Among the preferred AE terms are several to which any one verbatim term might be subsumed. The following preferred AE terms are examples describing cardiac abnormalities: 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, Tachycardia ventricular. All verbatim terms subsumed to these preferred terms should be reexamined and

reclassified in a consistent manner to the most appropriate preferred term, since in several instances the same or similar verbatim term are noted to be subsumed across several preferred terms[16]. Following reclassification, new incidence for these events should be calculated.

Similarly, 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.

Finally, the verbatim terms subsumed to the following preferred terms should be examined to capture all falls: Back pain, Dizziness, Fracture pathologic, Joint dislocation, Orthostatic hypotension, Purpura, Syncope.

7.4 Laboratory Data

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

7.5 Drug Interactions

In the RCTS, please examine the frequency of heart rate and rhythm AEs among patients taking both digoxin and galantamine, digoxin alone, galantamine alone, and neither drug. Please also perform mean change from baseline and outlier analyses for heart rate as measured on vital signs and ECG and for PR interval as measured on ECG for the groups designated above.

[16] Please be sure to separate out bundle branch block and fascicular hemiblocks (indicating an intraventricular conduction delay) from blocks occurring at the AV or SA nodes.

8 Appendices

8.1 Appendix 1: Supplementary FDA Reviewer Tables

FDA Table A. Deaths occurring in placebo-controlled trials within 30 days of the last dose

Trial	Patient ID	Treatment Group	Cause of Death	Description
GAL-INT-1	A30770	Placebo	Pneumonia	87 yo F suffered hip fracture on day 86 of tx; hospitalized on day 116 for dehydration and pneumonia; drug discontinued and patient died two days later
	A30921	Placebo	Pneumonia	73 yo M with history of TB, was hospitalized on day 7 for fever and pneumonia; drug discontinued on day 10 and patient died 19 days later
	A30926	GAL12 BID	Choking	71 yo F with multiple hospitalizations during the trial for urinary incontinence, agitation, confusion, delirium, and fall all prior to day 50 experienced an episode of choking on a piece of meat on day 100 and subsequently died; choking as the cause of death was confirmed by autopsy. The patient's family recalled one other episode of difficulty swallowing, but did not recall the patient having other symptoms of muscle weakness
	A30932	GAL12 BID	Intracerebral hemorrhage	74yo F with history of HTN developed fatigue and apathy on day 127 and lost consciousness on day 130, leading to drug discontinuation; she was diagnosed with an intracerebral hemorrhage and died 5 days later
GAL-INT-2	A31136	Placebo	Aspiration/ Myocardial infarction	78yo F with no known significant medical history was found choking and cyanotic by her caregiver on day 46; after CPR she was initially stabilized then died the next day. The death certificate listed cardiac arrest, MI, and aspiration as causes of death, but no autopsy was performed
	A40024	Placebo	Myocardial Infarction	73 yo M experienced dizziness and syncope on day 42; in the ED he was diagnosed with an MI; he died that day. An autopsy revealed death due to MI complicated by ventricular rupture and hemopericardium
GAL-USA-1	A35555	Placebo	CHF, Aspiration pneumonia	89 yo M with hx of asthma and atrial fibrillation was admitted for CHF on day 157; the patient developed aspiration pneumonia and died 12 days later.
	A35383	GAL12 BID	Sudden death	65 yo M with hx of esophagitis and dyspepsia during the trial was found dead in a chair on day 164; no autopsy was performed and the death was attributed to an MI because the

				patient's baseline and subsequent ECGs showed a right bundle branch block
	A35772	GAL16 BID	Myocardial Infarction	76 yo F with hx of DM, HTN, obesity, and sinus bradycardia experienced chest pain on day 87, followed by respiratory distress. The patient was unable to be resuscitated. Her ECGs during the study revealed bradycardia and some non-specific T wave changes
GAL-USA-10	A73175	Placebo	CHF	68 yo M with hx of CABG and atrial arrhythmia, was admitted to the hospital on day 6 for tx of atrial flutter and had medication discontinued day 11 for persistent atrial arrhythmia. Pt requested comfort care only, and died 7 days later; death was attributed to heart failure. Autopsy performed but not available.
	A73553	Placebo	Peri-operative myocardial infarction	79 yo M diagnosed with esophageal carcinoma during the run-in period had esophagectomy 18 days after the end of therapy (total 155 days); patient died of a peri-operative MI the same day
	A73595	Placebo	Pneumonia	85 yo M with hx of asthma and distant MI developed severe pneumonia on day 41 complicated by CHF; patient died the following day of severe pneumonia
	A74374	Placebo	Sudden death	89 yo F with history of chronic stable angina and pacemaker placement was found dead in bed on day 87; no autopsy was done.
	A73779	GAL4 BID	Sudden death	75 yo M started risperidone for agitation and hallucinations the same day he started study medication; he was hospitalized for the treatment of neuroleptic malignant syndrome on day 46 of treatment and all medications were discontinued. The patient restarted the study medication (1/2 a tablet) 8 days later; about 5.5 hours after taking the dose the patient was found dead in a chair. An autopsy only found that the patient aspirated; the cause of death was attributed to "natural causes".
	A73402	GAL8 BID	Pneumonia	79 yo M with chronic inflammatory demyelinating polyneuropathy was hospitalized and intubated for presumed aspiration pneumonia on day 130. He improved and was extubated after 6 days, but one day later redeveloped dyspnea. He was not reintubated per family wishes and he died on day 137.
	A73741	GAL8 BID	Sudden death	63 yo M was noted to have recent weight loss of 20 lbs, tachycardia, and tachypnea on the day he started study medication. On day 6, while temporarily staying in a nursing home while his wife was out of town, he was found dead in bed one hour after speaking to his wife on the phone. A pathological examination of the brain was planned, but no results were

				available. CHF was put on the patient's death certificate, but he had no history of heart disease.
	A74304	GAL8 BID	Sudden death	77 yo M treated with study medication for 21 days discontinued because of family withdrawing consent; 8 days later, pt reported increased hallucinations, delusions, and insomnia and 16 days later the patient had a witnessed respiratory arrest at home and did not respond to resuscitation; the death was attributed to "possible MI".
	A73044	GAL12 BID	Accident	80 yo F wandered into roadway on day 33 of treatment, was struck by a car and died
	A73704	GAL12 BID	Pneumonia	74 yo M developed rapidly progressive Alzheimer's disease around day 57; study drug was stopped day 77; he was hospitalized 2 days later after a fall and treated with antipsychotics for increasingly combative behavior. He was also treated with antibiotics for a pneumonia and UTI and was noted to have hyperbilirubinemia. He was transferred to a nursing home after nine days and died there 7 days later. Pneumonia was listed as the cause of death.
	A73944	GAL12 BID	Pulmonary embolism	83 yo F with chronic NSAID use and a history of a Mallory-Weiss tear presented with nausea and hematemesis on day 147; study medication was stopped. The patient was hospitalized, an EGD showed a small actively bleeding gastric ulcer, and she was treated with packed RBCs, fluids, and an H2 blocker. After 4 days the patient was transferred to a nursing home where she died 8 days later. An autopsy revealed a pulmonary embolism to be the cause of death.
93-01	000125	GAL6 TID	Myocardial infarction	80 yo F with a pacemaker presented on day 72 with abdominal pain and constipation; diagnosed with UTI. Later that day, the patient "collapsed" and died in the hospital; the death was attributed to an MI although no autopsy was performed.
95-05	A0813	Placebo	Pneumonia	78 yo F died of pneumonia on day 143
	D0408	Placebo	CVA	88 yo F suffered a CVA on day 17; medication was discontinued. The patient's condition worsened and she died 23 days later.
	A0808	GAL 32 free base/day	CVA	79 yo F suffered a CVA on day 106 and died in her sleep in respite care on day 116
	G0504	GAL 32 free base/day	Myocardial infarction	74 yo M with a history of DM and CAD suffered a heart attack on day 122 and died.

FDA Table B. Deaths occurring in long-term extension trials ≤ 12 months within 30 days of the last dose

Trial	Patient ID	Treatment Group	Cause of Death	Description
GAL-INT-3	A03123	GAL24-GAL24	Pneumonia	75 yo M developed pneumonia and had a syncopal episode 67 days into the extension trial; study medication was stopped on day 80 when the patient became dehydrated. The patient died 3 days later of pneumonia.
	A03351	GAL24-GAL24	Pneumonia	73 yo M was diagnosed with Lewy Body disease 81 days into the extension trial because of the new development of agitation and hallucinations. On day 91 his study medication was discontinued due to the new diagnosis. 21 days later the patient developed pneumonia, and died of this infection 7 days later.
	A03388	GAL32-GAL24	Head injury after a fall	84 yo F with a history of a syncopal episode 26 days into the extension trial was found unresponsive, hypotensive, and hypothermic at the bottom of a flight of stairs on day 157. A CT scan revealed multiple occipital cerebral contusions and a subdural hematoma; during the CT the patient coded and could not be resuscitated.
GAL-USA-3	A50041	PLA-GAL24	Sudden death	78 yo F with history of ECG changes that suggested past MI was found dead in bed on day 153 of the extension. Her only recent illness had been a URI treated with antibiotics on day 132.
	A50223	PLA-GAL24	CVA	73 yo F was treated for 182 days in the extension trial; the patient's caregiver discontinued the study medication secondary to the patient's worsening Alzheimer's disease; the patient had a CVA the following day and died 18 days later.
	A50052	GAL24-GAL24	COPD	82 yo F with history of COPD had multiple hospitalizations for COPD exacerbation during the first few months of the extension trial. Around day 131 the patient was hospitalized with a pneumonia. Her condition slowly deteriorated and the study drug was discontinued on day 157. She died of COPD 18 days later.
	A50147	GAL24-GAL24	Pneumonia	75 yo M was treated for 176 days in the extension trial; over a one week period he had decreased po intake and lethargy; he was admitted with hyponatremia, dehydration, renal failure, and pneumonia; the patient died the following day.

	A50253	GAL24-GAL24	CVA	78 yo M was treated for 186 days in the extension trial; the patient's study medication was discontinued due to worsening agitation and falls; the patient was hospitalized the next day for a pneumonia and worsening CHF and eventually stabilized. However, he had a CVA on the day of transfer to a nursing home 18 days after drug discontinuation and died.
	A50011	GAL32-GAL24	Sudden death	88 yo F with hx of 2 mild MI and left bundle branch block had borderline prolongation of the QT interval at baseline which persisted during the trial. Around day 160, the patient became short of breath, was diagnosed with a bronchitis, and treated with antibiotics. An ECG that day was reportedly within normal limits. On day 166, the patient collapsed in the bathroom and was unable to be resuscitated; her death was attributed to an MI.
	A50051	GAL32-GAL24	Subdural hematoma secondary to fall	79 yo F treated in extension trial for 118 days slipped and fell at home resulting in loss of consciousness; the patient was found on head CT to have a large subdural hematoma with mass effect and shift; the patient developed DIC during the craniotomy and evacuation and died within hours of the surgery.
	A50114	GAL32-GAL24	Intracranial hemorrhage	77 yo F suffered an unobserved fall on day 81 of the extension trial; the patient had a bruise on her lip but otherwise acted normally until 4 days later when she complained of a headache, went to sleep and was later unarousable. A head CT revealed an acute left-sided massive subdural hematoma with marked mass effect and both subfalcine and transtentorial herniation. It was suspected that the patient had a rebleed into a smaller subacute subdural 4 days previously.
GAL-INT-7	A03190	PLA-GAL24	Sudden death	87 yo F with a history of angina, HTN, and DM died suddenly after one day of malaise on day 195 of the extension trial.
	A03099	GAL24-GAL24	Perforated gastric ulcer	76 yo M on chronic NSAID therapy discontinued from the extension trial on day 144 due to GI bleeding from a perforated gastric ulcer; he died five days later due to cardiovascular complications
	A03179	GAL24-GAL24	Myocardial infarction	78 yo M with history of cerebrovascular disease discontinued study medication on day 153 of the extension trial due to the development of severe chest pain; the

				patient suffered a severe MI and died three days later.
GAL-USA-6	A30116	PLA-PLA-GAL24	Unknown	77 yo F with cachexia and remote history of colon cancer was noted to suddenly deteriorate significantly about 5 months after entering the USA-6 extension trial. Worsening cachexia and strong odor were noted and the patient died on day 162. The cause of death was listed as multiple organ failure but no autopsy was performed.
	A30047	GAL-PLA-GAL24	Pneumonia	83 yo F with history of hip fracture and aspiration pneumonia early in the USA-6 extension trial recovered but developed pneumonia again 6 months later on day 237. Study medication was discontinued and the patient died 8 days later.
	A30055	GAL-PLA-GAL24	Unknown	85 yo M with history of prolonged QT on galantamine therapy in INT-2, but also while on placebo in USA-5, developed hallucinations about 3 months after restarting galantamine in the USA-6 extension trial. After a month of worsening of Alzheimer's disease symptoms, the patient was discontinued from study medication on day 130. His death 22 days later in a nursing home was attributed to end-stage senile dementia.
93-01X	0291	GAL18-GAL	CVA	71 yo M experienced a CVA on day 178 of the extension trial; the study medication was discontinued on day 182 secondary to the CVA; the patient died 20 days later.
	0137	GAL24-GAL	Lung cancer	75 yo M stopped study medication on day 260 for an unknown reason. Two days later the patient developed pleurisy. Two weeks later the patient was diagnosed with lung cancer and he died two days after that.
95-05X	C0207	PLA-GAL32	Sudden death	73 yo M with history of MI was discontinued from the extension trial on day 88 due to worsening aggression and transfer to nursing home. The patient collapsed the next day and died; no autopsy was performed but the death was attributed to an MI.
	B0609	GAL32-GAL32	Pulmonary embolism	82 yo F with history of PE during placebo-controlled trial 95-05 was discontinued from extension trial on day 75 due to a protocol violation. 27 days later the patient died suddenly; an autopsy revealed PE as the cause of death
	F0907	GAL32-GAL32	Sudden	67 yo F developed severe speech

			death	disorder and apraxia during placebo-controlled 95-05; four months into the extension trial, the patient developed anorexia and discontinued her study medication on an unknown day (sometime between day 103 and day 133). On day 130 of the extension, the patient developed a "severe extrapyramidal disorder" and oculomotor nerve paralysis. Sixteen days later the patient died suddenly; the death was believed to be cardiovascular in origin. (Note: the investigator listed the treatment stop date as the day of death because the exact date could not be ascertained.)

FDA Table C. Deaths occurring in long-term extension trials > 12 months within 30 days of the last dose

Trial	Patient ID	Treatment Group	Cause of Death	Description
GAL-USA-9	A30281	PBO-GAL-GAL	Congestive heart failure	83 yo F discontinued from treatment on day 265 for a severe leg rash and skin infection. Nine days later the patient developed severe vomiting and the following day died due to complications of congestive heart failure. The patient had a history of MI and CABG, but a history of CHF was not mentioned. No description of any terminal hospitalization was included, so it is not clear whether the CHF was related to sepsis or some sequelae of the leg infection.
	A30018	GAL-GAL-GAL	Sudden death	76 yo F entered GAL-USA-9 and died of a cardiac arrest 27 days later. The patient had a pacemaker for an "irregular" heart rate and evidence of an old MI on ECG. No details were provided regarding the circumstances of the cardiac arrest. The patient was noted to have low potassium measurements during the earlier trials
	A30082	GAL-GAL-GAL	CVA	83 yo F experienced a R middle cerebral artery CVA and small basal ganglia hemorrhage on day 195 and galantamine was discontinued the following day. The patient died 10 days later due to the stroke.
	A30183	GAL-GAL-GAL	CVA	89 yo M experienced a TIA on day 352 and suffered a massive CVA on day 354. Two days later the patient discontinued galantamine and he died 6 days later.

93-01XX	0255	PBO-GAL	Pneumonia	65 yo F discontinued from treatment on day 505 for bowel obstruction. Nine days later the patient was diagnosed with an MI and five days after that she developed pneumonia. The patient died of pneumonia 21 days after discontinuing from the trial

FDA Table D. Incidence of the adverse event "weight loss" by gender in three large JRF randomized controlled trials

		Female		Male	
		Incidence	Relative Risk	Incidence	Relative Risk
Gal INT-1	Placebo	1 (0.7%)	-	0	-
	12 mg BID	11 (7.9%)	11.3	6 (7.4%)	*
	16 mg BID	6 (4.3%)	8.6	5 (6.2%)	*
Gal USA-1	Placebo	8 (6.1%)	-	2 (2.4%)	*
	12 mg BID	16 (11.5%)	1.9	10 (13.7%)	5.7
	16 mg BID	22 (17.7%)	2.9	8 (9.2%)	3.8
Gal USA-10	Placebo	2 (1.1%)	-	2 (1.8%)	-
	4 mg BID	2 (2.2%)	2.0	0	0.0
	8 mg BID	11 (6.3%)	5.7	4 (3.8%)	2.1
	12 mg BID	8 (4.4%)	4.0	5 (5.5%)	3.1

Derived from Sponsor's Data Set GALXAE2_P2 by Trial, CRFID, AEPREF, RNDGRP, and SEX using JMP.
*Cannot divide by zero