4.2.6.5.3 Serious Bradycardia

Bradycardia was not a commonly occurring SAE but because of the known effects of cholinesterase inhibitor's on heart rate, I summarized these SAEs. Using the ISS database, I identified 7 galantamine subjects with a bradycardia SAE. Two of the subjects identified with bradycardia, INT-2/A31009 and USA-1/A35147, also had syncopal episodes and were included above. The remaining cases are described below.

95-05/G0125	This 82 year old male developed chest pain which was treated with isosorbide dinitrate. Subsequently, he experienced a syncopal event and heart rate at the time was 53bpm. He completed the RCT and entered the extension and had no bradycardia events recorded.
INT-3/A03401	This 80 year old male developed CHF signs and symptoms 115 days after starting galantamine. He was treated with captopril and lasix. On day 169, he developed atrial flutter and had a ventricular rate of 29-41bpm. The event resolved and he completed the study.
INT-1/A30725	This 83 year old female had an SAE of bradycardia reported but no documentation of a slow heart rate and no description of the event.
INT-1/A30996	This 77 year old male with a history of atrial fibrillation, cardiac insufficiency, diabetes, and depression was treated with theophylline on day 23 for dyspnea. On day 44, he developed bradycardia with a heart rate of 30bpm. This resolved after the discontinuation of the subject's digoxin.
NED-2/A03033	This 27 year old healthy volunteer was hospitalized for second degree AV block and bradycardia that occurred while taking galantamine 12mg bid and digoxin .375mg.

4.2.6.5.4 Serious Weakness

The narratives for weakness SAEs did not describe events of profound global muscular weakness or subjects requiring mechanical ventilation. Using the ISS data sets, I identified SAEs with verbatim terms suggestive of weakness. The majority of these verbatim terms were coded to the preferred term asthenia. I read the narratives and found that the events described either focal weakness in a single limb or a single side of the body, or the events described complaints of weakness without documentation of objective findings in patients with multiple other adverse events occurring at the same time.

4.2.6.5.5 Serious Renal Failure

I identified 3 galantamine subjects who developed an SAE of renal failure. The first subject, USA-1/A35845, had a screening creatinine of 6.1mg/dL, which documented the presence of renal insufficiency prior to exposure to galantamine. A second subject, USA-10/A73018, developed renal failure 8 weeks into the study but was subsequently diagnosed with multiple myeloma which is the most likely cause of this event. The third subject, USA-10/A73226, was a 78 year old female being treated with triamterene and HCTZ for ankle edema. She developed marked reduction in activity, which was considered consistent with early renal failure. The sponsor did not provide lab results from the time of this event. Galantamine was discontinued and the patient was treated with IV fluids.

4.2.6.5.6 Serious Renal Calculi

There were 4 serious renal calculi cases, all in galantamine subjects and all from randomized controlled trials. These cases are summarized below.

USA-1/A35069	This 69 year old male, taking only vitamin C, and with no history of renal calculi was randomized to galantamine 12mg bid, and on day 29 was admitted for renal calculus. The sponsor provided no information about work up for this event. The patient was hospitalized again on day 135 for renal calculi. In both instances, the subject passed the stones and he recovered.
USA-1/A35658	This 75 year old female was randomized to galantamine 16mg bid. Concomitant medications were aspirin, amitriptyline, atenolol, prochlorperazine, and ranitidine. On day 15 of the study, she discontinued for nausea. Fifteen days later, she was hospitalized for renal calculus and underwent cystoscopy and nephrostomy.
USA-10/A732239	This 72 year old male with no history of urinary tract illness was randomized to galantamine 8 mg bid. Concomitant medications were aspirin, captopril, simvistatin, and promethazine. Approximately 5 months into the study he was admitted twice for treatment of renal calculi.
USA-10/A73379	This 78 year old male was randomized to galantamine 12mg/day. Concomitant medications were aspirin, omeprazole, sertraline, simvistatin, zolpidem, ciprofloxacin, and tolterodine. Six days after starting galantamine he was hospitalized for renal calculus and pyelonephritis. He was treated with antibiotics and surgery and completed the trial.

4.2.6.5.7 Serious Skin Rashes

Four galantamine subjects experienced rashes that were SAEs. These cases are summarized below.

95-05/D0410	This 75 year old female, randomized to galantamine 32mg/day, developed nausea and discontinued from the trial. Eight days after discontinuation, she developed a skin rash, subsequently diagnosed as subcorneal pustulosis.
INT-1/A30196	This 72 year old female, randomized to galantamine 24mg/day, discontinued from the trial for deep venous thrombosis. She had a rash at the time that was designated an SAE, but not mentioned in the narrative.
USA-16/A60072	This 74 year old female randomized to galantamine 32mg/day, discontinued from the trial for anemia, thrombocytopenia (subsequently diagnosed with lymphoma) and UTI. She was started on trimethoprim/sulfamethoxazole for her UTI and developed a rash. She then experienced a seizure and was hospitalized.
USA-9/A30281	This 81 year old female taking galantamine in an extension trial, developed worsening hypertension which was treated with captopril, lasix, and potassium. She then developed a rash on her leg, not described, and an infection. Two weeks later, she died of complications of congestive heart failure.

4.2.6.5.8 Serious Pancreatitis

Three galantamine subjects had pancreatitis SAEs. In the first case, subject INT-1/A30378 developed pancreatitis in the setting of cholelithiasis and was also noted to have a mild elevation of hepatic enzymes. In a second case, subject USA-6/A30114 developed pancreatitis 8 days after starting galantamine but the event did not recur with rechallenge. The third case is summarized below.

USA-6/A50135 This 84 year old female who received galantamine during an RCT, continued on galantamine during this extension trial. Concomitant medications were furosemide, ranitidine and sertraline. She developed pancreatitis and was hospitalized. She fell during the hospitalization and fractured her hip. No other details from the hospitalization were available. She was discharged to a rehabilitation facility and lost to follow up.

4.2.7 Common Adverse Events

Data on common AEs was drawn from the seven phase 2/3 placebo-controlled trials, including JRF studies INT-1, USA-1, INT-2, USA-10, and USA-16 and Shire trials 93-01 and 95-05. Please refer to section 2.1.1 for the sponsor's approach to data presentation.

4.2.7.1 Overall frequency of common AEs

ISS-A Table 6-6a displays the common AEs occurring in the JRF trials INT-1, USA-1, and INT-2. Since the original NDA submission, the sponsor has slowed the recommended titration schedule and lowered the maximum dose of galantamine. The table below includes the incidences for common AEs at and above the doses planned for marketing. I have included the placebo column for both the original ISS studies (with the faster titration) and for USA-10 (with the slower titration) because there were important differences in the placebo incidences of some AEs. The AEs nausea, diarrhea, abdominal pain, dyspepsia, anorexia, fatigue, asthenia, dizziness, and headache showed a dose response relationship across placebo, GAL 24 mg, and GAL 32 mg treatment groups.

FDA Table 19. Incidence of common AEs in JRF trials at and above the doses planned for marketing

	INT-1 and USA-1*			USA-10		
	Placebo	fast 24 mg	32 mg	Placebo	16 mg	slow 24 mg
	N=553	N=432	N=429	N=286	N=279	N=273
Total n (%) with AE	419 (76%)	379 (89%)	391 (91%)	207 (72%)	207 (74%)	219 (80%)
Gastrointestinal system	**154 (28%)**	**223 (52%)**	**268 (63%)**	**49 (17%)**	**84 (30%)**	**83 (30%)**
Nausea	68 (12%)	162 (38%)	179 (42%)	13 (5%)	37 (13%)	45 (17%)
Vomiting	30 (5%)	89 (21%)	91 (21%)	17 (6%)	34 (12%)	15 (6%)
Diarrhea	50 (9%)	44 (10%)	70 (16%)	4 (1%)	17 (6%)	27 (10%)
Abdominal pain	23 (4%)	34 (8%)	45 (11%)	10 (4%)	10 (4%)	9 (3%)
Dyspepsia	14 (3%)	19 (4%)	26 (6%)	7 (2%)	13 (5%)	15 (6%)
Psychiatric system	**153 (28%)**	**164 (38%)**	**161 (38%)**	**84 (29%)**	**81 (29%)**	**97 (36%)**

Anorexia	16 (3%)	52 (12%)	66 (15%)	9 (3%)	18 (7%)	24 (9%)
Agitation	51 (9%)	32 (7%)	30 (7%)	27 (9%)	28 (10%)	22 (8%)
Depression	27 (5%)	28 (7%)	28 (7%)	16 (6%)	23 (8%)	22 (8%)
Somnolence	15 (3%)	24 (6%)	23 (5%)	6 (2%)	7 (3%)	13 (5%)
Body as a whole - general	**160 (29%)**	**158 (37%)**	**156 (36%)**	**47 (16%)**	**56 (20%)**	**65 (24%)**
Injury	60 (11%)	55 (13%)	45 (11%)	12 (4%)	12 (4%)	16 (6%)
Fatigue	20 (4%)	26 (6%)	33 (8%)	6 (2%)	10 (4%)	13 (5%)
Asthenia	12 (2%)	14 (3%)	25 (6%)	6 (2%)	4 (2%)	8 (1%)
Syncope	6 (1.1%)	6 (1.4%)	13 (3%)	2 (0.7%)	6 (2.2%)	9 (3.3%)
Centr & periph nervous system	**106 (19%)**	**128 (30%)**	**139 (32%)**	**42 (15%)**	**53 (19%)**	**65 (24%)**
Dizziness	40 (7%)	54 (13%)	69 (16%)	10 (4%)	14 (5%)	19 (7%)
Headache	30 (5%)	41 (10%)	49 (11%)	13 (5%)	19 (7%)	13 (5%)
Metabolic and nutritional	**71 (13%)**	**86 (20%)**	**74 (17%)**	**24 (8%)**	**36 (13%)**	**30 (11%)**
Weight decrease	11 (2%)	43 (10%)	37 (9%)	4 (1%)	15 (5%)	13 (5%)
Urinary system	**76 (14%)**	**73 (17%)**	**67 (16%)**	**39 (14%)**	**37 (13%)**	**44 (16%)**
Urinary tract infection	39 (7%)	33 (8%)	31 (7%)	19 (7%)	23 (8%)	22 (8%)
Secondary terms	**37 (7%)**	**21 (5%)**	**36 (8%)**	**23 (8%)**	**25 (9%)**	**22 (8%)**
Fall	28 (5%)	17 (4%)	29 (7%)	14 (5%)	14 (5%)	12 (4%)

*The placebo column also includes placebo patients from INT-2
Source: ISS-A Table 6-6a and 6-6b

4.2.7.2 AEs by study location (US v. non-US)

The sponsor provided Table 6-11a (ISS-A, p.135-36) displaying adverse events of interest between US and non-US patients from the 3 main RCTs (USA-1, INT-1, INT-2). The sponsor defined AEs of interest as those with a possible attributable mode of action and those that were twice the incidence in the all galantamine dose group as in the placebo group (provided there were at least 10 patients in the galantamine group). There was a twofold or greater reporting rate for US placebo patients compared to non-US placebo patients for anorexia, agitation, somnolence, insomnia, pain, chest pain, weight decrease, rhinitis, hypertension, and viral infection suggesting their may be an intrinsic difference in AE reporting by study location.

4.2.7.3 AEs by dosing duration

The sponsor provided ISS-A Tables 6-17a-b and 6-18 (Amended ISS p.146-150) displaying selected adverse events during dose escalation of placebo-controlled trials.

For the three major placebo-controlled trials (USA-1; INT-1; INT-2), the display was separated into weekly periods for the first 4 weeks and then a maintenance period (for >4 weeks). Nausea, diarrhea, vomiting, and anorexia had higher frequencies in the combined galantamine group compared to placebo during each weekly escalation period and this excess continued during maintenance period. Agitation, injury, dizziness, dyspnea and myalgia also had higher risks than placebo during escalation but this did not continue during maintenance. Risks for dysphasia, syncope, weight decrease,

bradycardia, palpitation, and arrhythmia atrial were greater than placebo only during the maintenance phase (>4wks).

In trial USA-10, nausea occurred more frequently in the galantamine group than placebo during each of the 3 months of dose escalation and during the maintenance period (>12wks); syncope, gait abnormal and bradycardia were greater in galantamine as compared with placebo only during maintenance. Although the sponsor has described the trial design for USA-10 as a slow titration, the four arms of the trial represent three final dose levels compared to placebo using a slower titration design compared to other trials. USA-10 did not have direct comparative arms between a slow and fast dose escalation design ending with the final proposed dose of 24mg total daily dose in both escalation arms; thus, the only comparison for slow versus rapid titration at the 24mg total daily dose is across trials. As a result, the true effect of slow titration on galantamine's AE profile is unknown, especially since the relative risk of dose-related AEs such as nausea and vomiting in galantamine compared to placebo patients was not reduced by the prolongation of the titration period.

In the Shire RCTs, nausea and vomiting incidence was also greater than placebo during each of the 4 weekly dose escalation periods and continuing into the maintenance period (>4wks).

4.2.7.4 AEs by severity

The sponsor provided Tables 6-13a-b and 6-14 (ISS-A, pp. 141-142) showing the incidence of AEs judged by the investigator to be severe. Across all placebo-controlled trials, severe nausea (2-4%) and vomiting (1.3-3%) were reported in combined galantamine doses at higher rates than placebo with a small tendency to increase with increasing dose. Slow titration dosing used in USA-10 reported severe rates (nausea - 3.7%; vomiting -1.8%) which were similar to those observed with standard 24mg dosing in the 3 major RCTs (nausea - 3.0%; vomiting -1.6%). Additionally, severe abdominal pain (0.5-1.3%) and anorexia (0.8-1.0%) across galantamine doses were also reported with higher frequency than placebo (abdominal pain – 0%; anorexia 0.2%) in the combined display for the three major RCTs.

4.2.7.5 AEs by age

The sponsor provided Tables 6-23 to 6-24 (ISS-A pp.164-165) displaying the incidence of common AEs by age groups (<75 yrs; ≥75yrs). From these tables relative risks were calculated and those with differential effects by age group were compiled in the table below. Across the major RCTs, the younger group had an elevated risk of asthenia, dyspnea, malaise and hypertension compared to the older group. At the same time, the elderly were at an elevated risk for injury, syncope, headache, and dizziness compared with the younger group.

FDA Table 20. Incidence (%) of selected AEs by age
JRF USA-1, USA-10, INT-1, INT-2

	Placebo		All Galantamine		Relative Risk	
	N=353	N=486	N=758	N=1056		
	<75	>75	<75	>75	<75	>75
Asthenia	0.8	3	3	3	3.8	1.0
Dyspnea	0.3	1.6	1.2	1.6	4.0	1.0
Shire 93-01, 95-05						
	N=199	N=167	N=248	N=225		
Injury	2.5	3	1.6	7	0.6	2.3
Syncope	0.5	1.8	0.4	3.1	0.8	1.7
Malaise	0.5	1.2	1.6	0.9	3.2	0.8
Headache	9	3	7	8	0.8	2.7
Dizziness	3.5	1.8	4	6	1.1	3.3
Hypertension	0.5	3.6	1.6	1.8	3.2	0.5

Source: ISS-A Tables 6-23 and 6-24

4.2.7.6 AEs by gender

The sponsor provided Tables 6-19a-c to 6-20 (ISS-A pp.153-159) displaying common AEs by gender. Table 6-19a appears to be mislabeled; the title identifies the source at JRF placebo-controlled trials, but then lists USA-2 when the sponsor probably meant USA-1. From these tables relative risks were calculated and those with differential effects by gender were compiled in the table below. Across the major RCTs, men had an elevated risk of constipation, abdominal pain, UTI, somnolence, anxiety, and asthenia compared to women. At the same time, women were at an elevated risk for headache, urinary incontinence, and URI compared with men. Men were at an elevated risk of somnolence as compared to women in all four large JRF RCTs.

FDA Table 21. Incidence (%) of selected AEs by gender
JRF USA-1, INT-1, and INT-2

	Placebo		All Galantamine		Relative Risk	
	N=223	M=330	N=434	N=688		
	Male	Female	Male	Female	Male	Female
Constipation	2	5	4	4	2.0	0.8
Somnolence	0.9	4	7	5	7.8	1.3
Anxiety	1.8	4	4	3	2.2	0.8
Asthenia	1.3	3	5	4	3.8	1.3
Headache	8	4	8	11	1.0	2.8
JRF USA-10						
	N=108	N=178	N=245	N=447	RR	RR
	Male	Female	Male	Female	Male	Female
Abdominal Pain	0.9	5	2	3	2.2	0.6
Somnolence	0.9	3	3	4	3.3	1.3
UTI	1.9	10	5	10	2.6	1.0
Urinary Incont.	6	1.1	3	3	0.5	2.7

URI	5	1.1	5	4	1.0	3.6

Source: ISS-A Tables 6-19a and 6-19b

4.2.7.7 AEs by race

Over 90% of patients participating in placebo-controlled trials were Caucasian and no more than 5% of any patient treatment group was of another race. Consequently, the sponsor indicated that results of any analyses by race should be interpreted with caution.

As seen in the table below, both the white and "other" race galantamine-treated groups experienced an excess of nausea and dizziness, but the elevated risk appeared to be more marked in the "other" race group.

FDA Table 22. Incidence (%) of selected AEs by race in the JRF RCTs

	Placebo		All Galantamine		RR	RR
	White	Other	White	Other	White	Other
	N=525	N=26	N=1063	N=56		
Nausea	13	4	38	39	2.9	9.8
Dizziness	7	4	14	18	2.0	4.5

Source: ISS-A Table 6-25

4.2.8 Laboratory Data

The sponsor presented laboratory data in several places in their NDA submission. The ISS-O and ISS-A contained the results of various pooled analyses of lab data while the results for individual trials are presented separately in the study reports. Lab data sets for Janssen RCTs USA-1, USA-10, USA-16, INT-1, and INT-2 were submitted separately, by study, in electronic format as SAS transport files. Additional individual lab data sets were provided for the following extension trials: USA-3, USA-5, USA-6, INT-3, and INT-7. The sponsor included lab data for Shire trials 93-01, 93-01X, 95-05, 95-05X, 95-07 and 95-07X pooled with lab data from other trials in ISS data sets. During my review, I also relied on adverse event data sets, trial termination data sets, as well as narrative summaries and CRFs for selected subjects to determine the clinical events associated with the identified lab abnormalities.

4.2.8.1 Sponsor's approach to lab data collection and analysis

Lab testing and schedules varied across protocols but all studies included hematologic and chemistry testing, and many included urinalysis testing. There was no table in the ISS-O or ISS-A summarizing the testing (analytes, schedules) performed across the different studies. Although not specifically mentioned in the protocols, it appeared that a limited number of central labs were used. On p. 32 of the ISS-O, the sponsor described their approach to evaluation of laboratory parameters in their development program. They calculated means and standard errors for lab data and provided pre, within and post-treatment cross tabulations that classified results as above, within, or below normal limits. In addition, they identified subjects with potentially clinically significant laboratory results. Subjects had potentially clinically significant lab results if they did not have a pathological (pre-specified outlier) lab result at baseline, and then had one or more pathological results during the trial. In addition, subjects who had a lab results that met

the criteria for low pathologic at baseline and then had a high pathologic result during the study (or vice versa) were also included as having a potentially clinically significant result. The sponsor's approach to their outlier analyses classified subjects with results above or below the normal limit but not exceeding the pathological limit at baseline as "normal". The cutoff values for non-enzyme pathological lab results (ex. hemoglobin, creatinine, etc.) were based on values identified by Lippert and Lehman, a copy of which is included as an appendix to this review. Enzyme test result (ex. AST, ALT, etc.) pathologic abnormalities were those results that were at least 2x above the upper limit of normal.

4.2.8.2 Sponsor's presentation of lab data

4.2.8.2.1 Animal data

The sponsor summarized findings from animal trials in the ISS-A (pp.322-325). They noted a decrease in WBC count in male mice and a decrease in hemoglobin and red blood cells in female mice in a 3-month oral gavage study at 10 and 20mg/kg doses. In addition they noted in a 12-month study in rats given 32mg/kg, a slight decrease in WBC count and lymphocyte count. There was no mention of changes related to renal or hepatic lab values in the sponsor's summary.

4.2.8.2.2 Studies in Humans

The sponsor's approach to presentation of lab data in the ISS-A was to provide a summary of the risk for potentially clinically significant outliers for lab tests using various data groupings. They provided an analysis that grouped data from all 5 RCTs and presented the outlier lab data from other studies (extensions, uncontrolled) separately (Table 5-31, p.71 ISS-O). They also provided analyses of the lab data from the 3 Janssen RCTs (Table 6-30, p.132, ISS-O) and the 2 Shire RCTs (Table 6-31, p.133, ISS-O) separately. They provided tables of outliers identified during extension trials and stratified the data by the treatment (galantamine or placebo) the subject received in the RCT. I did not find a summary of pooled mean change data for lab tests in the body of the ISS-A. The sponsor referenced supporting display tables that provided mean and median change from baseline for each lab test by visit.

4.2.8.2.2.1 Outliers

In their review of lab data in the ISS, the sponsor noted that there were subjects who experienced potentially clinically significant changes in lab values but that no consistent changes were observed (ISS, p.70). They provided a table summarizing potentially clinically significant laboratory changes for all patients.

For comparative purposes, the sponsor pooled data for the RCTs (INT-1, USA-1, INT-2, 93-01, and 95-05 Table 5-13, p.71, ISS-O). In this pooled analysis, there were 2 lab tests where the risk for outlier was >2x higher on galantamine compared to placebo. For low calcium outlier, the risk for galantamine subjects was 1.4% (21/1454) compared to 0.6% (5/889) for placebo subjects. For high CPK outlier, the risk for galantamine subjects was 1.1% (16/1454) compared to 0.4% (4/889) for placebo. I am uncertain about the accuracy

of the denominator count used in the risk calculations presented in this table. The sponsor used 1,454 as the denominator for the galantamine subjects and 889 as the denominator for the placebo subjects in the RCTs in this table for all of the lab tests. In the course of the lab review, I recognized that lab analytes tested varied across the RCTs. For example, CPK was assayed in trials USA-1 and INT-2, but not in INT-1, 93-01, or 93-05. Therefore, the risks for high CPK outliers in the RCTs should be 1.2% for placebo (4/326) compared to 3.9% for galantamine (16/408).

In addition to the above analysis, the sponsor presented pooled data by dose for the three Janssen RCTs (USA-1, INT-1, and INT-2, Table 6-30 p. 132 ISS-O) separately from the two Shire RCTs (93-01, 95-05, Table 6-31 p. 133 ISS-O). I examined both tables and looked for events occurring more frequently on drug than placebo and then looked for evidence of dose response. In the three Janssen trials, low calcium occurred in 0.9% (5/538) of placebo patients, 1% (4/402) of patients randomized to galantamine 24mg/day, and 1.8% (7/392) of those randomized to 32mg/day. The sponsor did not identify the calcium results for placebo subjects in the Shire trials so comparisons of outliers based on this table were not possible. In the two Janssen trials in which CPK was measured, 1.2% (4/326) of placebo subjects had high CPK outliers compared to 3.6% (7/195) in the 24mg/day galantamine group, and 2.1% (4/187) in the 32mg/day galantamine group. CPK analysis was not performed in the Shire trials. In the three Janssen trials, 0.4% (2/535) of placebo subjects had a low WBC outlier compared to 0.7% (3/401) in the 24mg/day galantamine group and 1.3% (5/393) in the 32mg/day galantamine group. In the 2 Shire trials, 1.2% of placebo subjects had a low WBC outlier compared to 2.7% (2/75) in the 18mg/day group, 2% (1/49) in the 24mg/day group, and 0/246 in the 32mg/day group. The sponsor submitted a table summarizing outlier results for study USA-10 in their 2/29/00 submission (ISS-A Table 6-30b, p.181). This table did not appear to suggest a difference in risk for outliers between treatment groups.

I reviewed the study report summary tables where the sponsor presented the outliers for the individual RCTs. I looked for tests where the outlier risk on drug was at least 1% in the galantamine subjects and the risk was 2 times greater on galantamine compared to placebo for the controlled trials. Those results are included in the following table.

FDA Table 23. RCT outlier comparisons across treatment groups

Study	Lab test	Placebo	Galantamine
95-05	Glucose ↑	1.4% (4/279)	5.8% (16/275)
	Platelets ↑	0.4% (1/279)	2.2% (6/275)
	GGT ↑	0.4% (1/279)	2.2% (6/275)
	ALT ↑	0.8% (2/279)	1.8% (5/275)
	Calcium ↑	0/279	1.1% (3/275)
93-01	None		
USA-1	Potassium ↑	0.5% (1/213)	1.4% (6/423)
INT-1	Chloride ↑	0.5% (1/215)	3% (13/438)
	Potassium ↓	0.5% (1/215)	1.1% (5/438)
INT-2	CPK ↑	(0/125)	1.5% (4/261)
	Total bilirubin ↑	(0/125)	1.5% (4/261)

USA-10	None		
USA-16	Platelets ↑	2.9% (2/70)	1.4% (1/69)
	Platelets ↓	2.9% (2/70)	0

Platelets increased was the only test with a two-fold increased outlier risk among galantamine subjects observed in more than 1 RCT (95-05, USA-16).

For open label and extension trials, the sponsor presented the number and percentage of subjects meeting the clinically significant criteria, but there was no discussion of more extreme outliers. There did not appear to be evidence of notable changes in risk for outliers from extension trials.

4.2.8.2.2.2 Mean change from baseline data

Using the Table Lab2.1.G provided by the sponsor in the ISS-O, I calculated mean change from baseline (endpoint-baseline) for selected lab tests for galantamine and placebo for trials INT-1, and USA-1. This analysis did not appear to reveal any drug related systematic changes in lab values or suggest dose responses. These results are included as in Appendix 3 to this review.

4.2.8.3 FDA lab data analyses

4.2.8.3.1 Methods

In addition to the analyses presented by the sponsor, I conducted several outlier analyses using the JMP statistical software package with the available lab data sets. My approach differed slightly from the approach taken by the sponsor. In my outlier analyses, I first identified those subjects with at least one pre-trial lab measurement (screening, baseline) and at least one measurement during the double blind phase. I then identified the subjects that did not exceed the upper (for high outliers) or lower (for low outliers) limits of normal prior to the study (screening or baseline). From that group, I identified subjects that exceeded the outlier value for a particular test during the study. In most cases, I used the same outlier cutoff (pathologic value) that the sponsor used. In some cases, when I wanted to examine the distribution of outliers further, I used additional more extreme outlier cutoffs. Since the study designs were identical, I combined the data from the randomized controlled trials USA-1 and INT-1. Study USA-10 was another relatively large RCT that was a good source of data for comparison of drug to placebo. Because of differences in design (USA-10 used a longer titration period and lower doses), I present the data from USA-10 separately from INT-1 and USA-1. Although USA-10 randomized to different doses of galantamine, I did not stratify by galantamine dose since I was uncertain about the effect of slow titration on the validity of the analysis. My concern arose from the fact that the titration schedule resulted in all galantamine subjects receiving the same dose during the first month of the study and those randomized to the 2 upper doses receiving the same dose during the first 2 months of the study. Therefore, there was no justification for stratifying by dose for early occurring lab outliers. I did not perform an additional outlier analysis on the data from INT-2 since differences in design (flexible dose) precluded pooling with INT-1 and USA-1 and the sponsor's analysis

suggested consistent findings when compared to the outlier analyses of the other RCTs (see above).

I examined mean change from baseline for selected lab tests. Using the JMP statistical software package and the electronic laboratory datasets, I subtracted the sponsor's designated endpoint lab value from the baseline value for each patient and then calculated the mean change for the placebo group and each galantamine dose group for studies USA-1 and INT-1. Similarly, I calculated the mean change from baseline for selected labs from study USA-10 (galantamine v. placebo). For these analyses, I used the standard international units for the examined analytes.

I analyzed the submitted lab data sets to identify extreme outliers for selected lab tests and then characterized the clinical events surrounding these abnormalities using available data (CRFs, narrative summaries, adverse events data sets, trial termination data sets). The examined tests and outlier cutoffs that I selected were: AST or ALT ≥3xULN; Tbili≥2mg/dL; CPK≥400U/L; Cr≥2.3mg/dL; WBC≤2500; PLT≤60,000; and HGB≤9g/dL. The results of this analysis are summarized below.

4.2.8.3.2 Chemistry RCT Outliers

The following table includes outlier results for selected RCTs.

FDA Table 24. Comparisons of chemistry lab outlier risk from studies USA-1 and INT-1 (pooled), and USA-10

Lab test Pathologic limit	INT-1, USA-1			USA-10	
	Placebo	Gal 12mg BID	Gal 16mg BID	Placebo	Gal
Total bilirubin ≥2.0 mg/dL[+]	(0/400)	(0/385)	(0/384)	(0/268)	(0/647)
AST ≥2x ULN	0.8% (3/395)	0.5% (2/389)	0.8% (3/386)	0.4% (1/250)	0.3% (2/635)
ALT ≥2x ULN	1.0% (4/401)	0.8% (3/382)	1.3% (5/373)	0.8% (2/248)	1% (6/622)
CPK ≥2x ULN[◊]	1.6% (3/192)	1.7% (3/178)	1.2% (2/170)	0.4% (1/252)	0.2% (1/597)
Alkaline Phosphatase ≥2x ULN	0.3% (1/395)	(0/385)	(0/386)		
Creatinine ≥2.3 mg/dL	(0/384)	(0/387)	(0/369)	(0/248)	(0/605)
Uric Acid ≥9.1 mg/dL	0.3% (1/371)	0.6% (2/355)	0.9% (2/343)		
Potassium ≥5.6 mEq/dL ≤3.2 mEq/dL	12% (45/380) 1.0% (4/412)	13% (49/369) 1.5% (6/402)	11% (2/183) 1.3% (5/392)	2.2% (6/268) 0.4% (1/264)	0.9% (6/653) (0/639)
Sodium ≥151 mEq/L ≤126 mEq/L	(0/406) (0/385)	(0/403) 0.3% (1/387)	0.5% (2/391) (0/373)	(0/254) 0.4% (1/255)	0.2% (1/615) (0/640)
Glucose[◊] ≥240 mg/dL* ≤60 mg/dL°	(0/163) 1.5% (3/195)	0.7% (1/152) 2.8% (5/180)	0.7% (1/149) 4.5% (8/177)	(0/209) 1.2% (3/258)	(0/528) 1.7% (11/629)
Calcium ≥10.8 mg/dL[‹]	1.0%(4/411)	2.5% (10/401)	2.0% (8/397)	(0/266)	(0/640)

≤8.2 mg/dL	2.2% (9/416)	1.5% (6/403)	2.0% (8/397)	2.6% (7/266)	2.3% (15/646)
Chloride					
≥112 mEq/L	7% (27/414)	6% (24/401)	8% (30/385)	(0/273)	0.6% (4/661)
≤94 mEq/L	0.2% (1/402)	0.8% (3/394)	0.5% (2/393)	3.3% (9/267)	1.2% (8/655)
Phosphorus◊					
≥5.2 mg/dL	1.0% (2/204)	(0/190)	1.1% (2/186)	0.7% (2/273)	0.6% (4/660)
≤2.0 mg/dL	2.5% (5/200)	1.6% (3/192)	2.2% (4/184)	1.5% (4/271)	0.6% (4/643)
Albumin					
≤2.0 g/dL	(0/192)	0.6% (1/173)	0.6% (1/162)	0.4% (1/244)	0.5% (3/587)

◊ these laboratory assays were not performed in INT-1
+ sponsor used 1.4mg/dL as upper path limit * sponsor used 120mg/dL as upper path limit
° sponsor used 45mg/dL as lower path limit ‹ sponsor used 11.6mg/dL as upper path limit
™ sponsor used 2.7g/dL as lower path limit

There did not appear to be evidence of drug related increased risk for outliers for most of the chemistry tests. Using a cutoff of 60mg/dL, there was a suggestion of a dose response for low glucose in study USA-1 and INT-1. Using a more extreme cutoff (glucose 45mg/dL) as the cutoff there was 1 galantamine subject meeting this outlier criteria from the above three controlled trials (A74001, USA-10). There did not appear to be a difference in risk for high CPK outliers or low calcium outliers in the above analyses.

4.2.8.3.3 Chemistry Mean change from baseline for selected RCTs

The following table provides the mean change from baseline to endpoint for studies USA-1, INT-1 and USA-10.

FDA Table 25. Mean change from baseline for chemistry tests, pooled data from studies USA-1 and INT-1

Lab test	Mean change from baseline		
	Placebo	Galantamine 12mg BID	Galantamine 16mg BID
Total bilirubin	0.0 (n=398)	0.3 (n=381)	0.4 (n=368)
AST	-0.3 (n=398)	0.0 (n=382)	-0.3 (n=373)
ALT	0.1 (n=398)	-0.3(n=382)	-0.2 (n=373)
Alkaline Phos	2.0 (n=399)	5.4 (n=383)	0.8 (n=375)
Creatinine	1.8 (n=399)	0.9 (n=383)	1.5 (n=375)
Uric Acid	2.8 (n=399)	-1.9 (n=383)	1.2 (n=375)
Potassium	0.1 (n=398)	0.0 (n=381)	0.0 (n=373)
CPK*	3.0 (n=187)	38 (n=176)	1.6 (n=170)
Sodium	1.0 (n=399)	0.9 (n=382)	0.7 (n=375)
Glucose*	1.0 (n=187)	0.8 (n=176)	4.1 (n=170)
Calcium	0.0 (n=399)	0.0 (n=383)	0.0 (n=375)
Chloride	-0.4 (n=399)	-0.2 (n=382)	0.1 (n=375)
Cholesterol	0.0 (n=399)	-0.1 (n=383)	-0.1 (n=375)
Phosphorus*	0.0 (n=188)	0.0 (n=177)	0.0 (n=172)
Albumin*	0.7 (n=187)	0.2 (n=176)	0.0 (n=171)

* Not tested in INT-1

The CPK difference noted for the 12mg galantamine group was driven by a subject with an end point result >5,000U/L. When this subject was not included in the analysis, the mean change for this group was 7.4U/L.

FDA Table 26. Mean change from baseline for chemistry tests, USA-10

Lab test	Mean change from baseline	
	Placebo	Galantamine
Total bilirubin	-0.2 (n=264)	-0.3 (n=643)
AST	-0.1 (n=269)	0.4 (n=650)
ALT	-1.4 (n=269)	-0.8(n=650)
Alkaline Phos	-0.1 (n=268)	-0.8 (n=647)
Creatinine	2.8 (n=271)	1.9 (n=654)
Uric Acid	6.8 (n=271)	3.4 (n=654)
Potassium	0.1 (n=267)	0.0 (n=645)
CPK	0.5 (n=269)	3.1 (n=646)
Sodium	-0.5 (n=271)	-0.5 (n=654)
Glucose	0.1 (n=268)	0.1 (n=648)
Calcium	0.0 (n=271)	0.0 (n=654)
Chloride	-0.1 (n=271)	0.1 (n=654)
Cholesterol	0.1 (n=271)	-0.2 (n=654)
Phosphorus	0.0 (n=267)	0.0 (n=645)
Albumin	-0.2 (n=269)	-0.3 (n=650)

For a majority of the tests, the mean changes from baseline were small and were in a similar direction when comparing drug to placebo. In this study, there was a slightly greater increase in CPK for the galantamine subjects.

4.2.8.3.4 Additional analyses of CPK data

As demonstrated above, there did not appear to be consistent evidence of an increased risk of CPK outliers when comparing galantamine subjects to placebo subjects, but there was a suggestion of a small difference in the mean change from baseline data. Therefore, I conducted additional analyses of both outliers, and mean change data for selected controlled trials. The additional analyses of outlier data consisted of examining risks for 2x, 3x, and 4x ULN for CPK for trials USA-1, INT-2, USA-10 and USA-16. I did not find evidence of an increased risk of more extreme outliers in this analysis (see appendix). The additional mean change analyses consisted of looking at the mean change from baseline at each lab collection visit for studies USA-1, INT-2, USA-10, and USA-16. Again there did not appear to be consistent evidence of an increased mean change from baseline in these analyses (see appendix).

4.2.8.3.5 Hematology RCT outliers

The following table presents the low outlier risk for WBC, hemoglobin, and platelet count by treatment group for studies USA-1, INT-1 (combined) and USA-10.

FDA Table 27. Hematology outlier risk for subjects not exceeding normal limit at baseline or screening during study USA-1 and INT-1 combined, and USA-10

Lab test Pathologic limit	USA-1 and INT-1			USA-10	
	Placebo	Gal 12mg BID	Gal 16mg BID	Placebo	Gal
WBC ≤2.8x10E3/mm3	0.5% (2/394)	0.2% (1/406)	0.8% (3/397)	(0/260)	0.2% (1/637)
Hemoglobin ≤11g/dL*	1.1% (4/361)	0.8% (2/367)	1.1% (4/353)	1.2% (3/251)	1.5% (9/607)
Platelets ≤100x10E3/mm3	(0/397)	1.2% (5/408)	0.3% (1/399)	(0/268)	0.3% (2/649)

*Sponsor used ≤ 10g/dL as lower path limit

This analysis did not identify evidence of notable differences in risk for these parameters.

4.2.8.3.6 Hematology mean change from baseline for selected RCTs

The following tables depict mean change data from trials USA-1 and INT-1 (pooled) and for USA-10.

FDA Table 28. Mean change from baseline for hematology tests, pooled data from studies USA-1 and INT-1

Lab test	Mean change from baseline		
	Placebo	Galantamine 12mg BID	Galantamine 16mg BID
Hgb	-0.1 (n=415)	-0.8 (n=401)	-0.6 (n=393)
PLT	1.5 (n=411)	-1.9 (n=399)	-0.9 (n=392)
WBC	0.1 (n=415)	0.1 (n=401)	0.1 (n=393)

FDA Table 29. Mean change from baseline for hematology tests, from study USA-10

Lab test	Mean change from baseline	
	Placebo	Galantamine
Hgb	-0.3 (n=267)	-0.9 (n=644)
PLT	-6.7 (n=265)	-6.7 (n=638)
WBC	-0.2 (n=267)	-0.2 (n=644)

There did not appear to be evidence of a drug-related difference in mean change from baseline from these analyses.

4.2.8.3.7 Analysis of extreme outliers

I examined the data sets for lab results meeting extreme outlier criteria that I selected and described in the methods section above. Although the exact relationship between galantamine and these events is not known, these cases are notable for the observed abnormalities.

4.2.8.3.7.1 Chemistry extreme outliers

I reviewed the submitted lab data sets and identified 2 galantamine subjects who had both increased transaminases ≥3x ULN and a total bilirubin ≥2.0mg/dL. Subject A03168 from extension trial INT-7 had an ALT of 392U/L, an AST of 273U/L, and a total bilirubin of 2.9mg/dL but these results were obtained 5 months after leaving the trial, and after this subject had been diagnosed with a malignant bowel tumor. Subject D0610 from trial 95-

05 (and extension) had an ALT of 246U/L, an AST of 162U/L and a total bilirubin of 2.6mg/dL during week 3 of the RCT. These abnormalities resolved with continued study drug treatment and this subject completed the RCT and extension with no SAEs noted. There were additional subjects with a total bilirubin ≥2mg/dL not associated with increased transaminases and most of these subjects had increased total bilirubin (above ULN) prior to receiving galantamine. None of these subjects had adverse events of hepatitis or liver failure. There were 2 subjects who had increases in transaminases ≥3x ULN at their last visit. When asked about the outcome in these patients, the sponsor reported that the follow up provided by their private physicians documented resolution of these lab abnormalities (4/20/2000 submission).

I found a number of both galantamine and placebo subjects with a CPK ≥400U/L in the lab data sets. Although sometimes reported as an AE, elevated CPK was never listed as a serious AE and was not listed as a reason for discontinuing a trial among galantamine subjects. The CPK elevations did not appear to be associated with symptoms and resolved with continued treatment. One subject had a notable CPK elevation at his last visit (A35155, CPK=5,463U/L). When asked about the outcome of this event the sponsor reported that the patient had a follow up CPK 3 weeks later that was normal and that the reason for the abnormality was not known (4/20/2000 submission).

There were relatively few galantamine subjects with a creatinine ≥ 2.3mg/dL in the submitted data sets. The galantamine subject with the highest creatinine (A35845, Cr=6.1mg/dL) had that result at baseline. For subjects with an increased creatinine during the study, the finding resolved with continued treatment or following discontinuation of study drug. Subject A74150 had a creatinine of 2.5mg/dL at her last visit (baseline = 1.1mg/dL). The sponsor reported that this subject had a follow up creatinine of 1.5mg/dL approximately 1 month later and then a hospitalization 4 months after that for renal insufficiency due to dehydration (4/20/2000 submission).

4.2.8.3.7.2 Hematology extreme outliers

There were occasional galantamine subjects with WBC counts <=2,500/mm^3 during the study, but in general these subjects had low WBC counts at baseline and/or had increases in WBC counts while continuing on galantamine. The lowest WBC count in a galantamine subject (subject A74174 WBC=990/mm^3) appeared to be a lab error. This subject had normal labs one month prior to this result then had the above WBC count along with hemoglobin of 7.8g/dL and a platelet count of 28,000/mm^3 recorded during month 3. When the labs were repeated 4 days later, WBC count was 4,500/mm^3 and hemoglobin was 14.2g/dL (no SAEs, no transfusions recorded).

Subject A73639 (USA-10), an 85 year old female, had a Hgb of 12.5g/dL at baseline. During study week 4 she had a Hgb of 7.9g/dL and during month 3 she had a Hgb of 7g/dL. Her other hematological cell lines were not decreased. She was hospitalized for anemia and transfused 2 units of packed RBCs. Her narrative did not describe her diagnostic work up for this finding. Her NSAID was discontinued and she completed the study and had a final Hgb of 8.9g/dL. Subject A73066 (USA-10), an 85 year old female,

had a Hgb of 14.1g/dL at baseline and 7.4g/dL at month 3. She was hospitalized and transfused 2 units of packed RBCs. A colonoscopy and barium enema both found diverticulosis but the narrative did not document evidence of an acute bleed. This subject was treated with iron replacement and her month 5 hemoglobin was 12.4g/dL. Subject A50173 (USA-3), a 77 year old female had a baseline Hgb of 12.1g/dL and during this extension trial had a Hgb of 7.2 g/dL. She discontinued from this extension trial (family withdrew consent) and her follow up (off drug) Hgb was 11.5g/dL. The sponsor did not provide an explanation for her lab abnormality.

4.2.8.3.8 Urinalysis results

The sponsor provided data sets with the results of urinalyses performed during studies. In the first table, I combined the data from the RCTs INT-1 and USA-1, and in the second table I present the data from trial USA-10. I identified subjects with normal pre-test results (neg or trace for blood, protein, neg for glucose) that became abnormal (>trace for blood and protein, any glucose) during the trial. Those results are provided in the following table.

FDA Table 30. Percentage of patients with urinalysis abnormalities among those normal at baseline, studies INT-1 and USA-1

UA test	Placebo	Gal 12mg BID	Gal 16mg BID
Blood	34% (120/354)	32% (114/356)	30% (103/345)
Glucose	5% (22/404)	9% (37/411)	5% (20/410)
Protein	10% (40/401)	11% (43/408)	10% (40/411)

FDA Table 31. Percentage of patients with urinalysis abnormalities among those normal at baseline, study USA-10

UA test	Placebo	Galantamine
Blood	16% (41/260)	13% (82/623)
Glucose	4% (11/255)	4% (27/640)
Protein	13% (34/262)	15% (94/639)

There did not appear to be a difference in risk for outliers by treatment group for these analytes.

4.2.9 Vital Signs

This section of the review describes the effect of galantamine on systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse. Following this is a discussion of common findings across studies and reviewer's recommendations. For most studies, the sponsor's methods of statistical analysis include descriptive statistics and tabulations of paired t-test across treatments. The sponsor also recorded notable or clinically significant findings. The timing of vital signs measurement with respect to the dosing schedule was not specified by the study protocols.

Since galantamine is an anti-cholinergic compound, adverse events of clinical importance relative to vital signs include syncope, bradycardia, and hypotension. These adverse

events are considered in this review and may be included in the comments. FDA Table 32 summarizes the sponsor's "Criteria for potentially clinically important changes in vital signs" for all studies. These criteria are referred to in discussions regarding changes in SBP, DBP, and pulse. It is important to note that for each parameter there are two thresholds. For example, to meet the criteria for an abnormally high SBP, the change in SBP must be **both** a relative increase of at least 20 mmHg and an absolute value over 180 mmHg.

FDA Table 32. Criteria for potentially clinically important changes in vital signs

Parameter	Abnormally High	Abnormally Low
Systolic BP, mmHg	≥ 180 mmHg and increase of ≥ 20 mmHg vs. Baseline or Initial Visit	≤ 90 mmHg and decrease of ≥ 20 mmHg vs. Baseline or Initial Visit
Diastolic BP, mmHg	≥105 mmHg and increase of ≥ 15 mmHg vs. Baseline or Initial Visit	≤ 50 mmHg and decrease of ≥ 15 mmHg vs. Baseline or Initial Visit
Pulse, bpm	>120 bpm and increase of ≥ 15 bpm vs. Baseline or Initial Visit	< 50 bpm and decrease of ≥ 15 bpm vs. Baseline or Initial Visit

4.2.9.1 Shire Gal 93-01/Shire Gal 93-01X

In the Shire Gal 93-01 study, all randomized patients that took at least one dose of trial medication were included in the analysis of safety. Vital signs were recorded at screening, week 2, week 4, week 8, and at the conclusion of the trial (week 12). No comment was found in the study report as to the method of taking vital signs. Statistical analyses were accomplished by evaluating mean change from treatment baseline.

There were no substantial trends noted in SBP, DBP, and pulse through the course of this trial. In galantamine-treated patients, the mean change for SBP and DBP was less than 2 mmHg. Except for a four beats per minute (bpm) reduction in the mean heart rate for the galantamine 8 mg TID group at week 12, there were no important trends in pulse over the course of this trial. These changes in vital signs did not reach the criteria set in FDA Table 32 for potentially clinically important changes in vital signs.

FDA Table 33 summarizes adverse events for each treatment group that could potentially be related to alterations in vital signs. The one case of syncope in the 12 mg TID galantamine-treated group was mild and not considered related to the trial medication by the investigator, whereas the one case of syncope in the placebo group was considered possibly related to trial medication by the investigator. A total of five galantamine-treated patients discontinued due to dizziness (Sponsor's Table 20); two from the 6 mg TID galantamine group, one from the 8 mg TID galantamine group, and two from the 12 mg galantamine group. This represents a 2.5% incidence of syncope leading to discontinuation in galantamine-treated patients. Only one placebo-treated patient discontinued treatment due to dizziness. No galantamine-treated patient discontinued due to hypotension (Sponsor's Display 30). Review of Selected Adverse Event Summaries showed that one patient (#000036) on 6 mg TID of galantamine experienced bradycardia which in this case was described as a decrease to 58 bpm from a baseline of 66 bpm.

FDA Table 33. Frequency of selected adverse events related to changes in pulse and blood pressure, Shire Study 93-01

	Placebo*	Gal 6mg*	Gal 8mg*	Gal 12mg*
Dizziness	3(3.4%)	4(4.5%)	2(3.6%)	4(7.4%)[#]
Syncope	1(1.1%)	0(0.0%)	0(0.0%)	1(1.9%)
Hypotension	0(0.0%)	0(0.0%)	1(1.8%)	0(0.0%)
Bradycardia	0(0.0%)	1(1.1%)	0(0.0%)	0(0.0%)

Adapted from Sponsor's Study 93-01 Display 23
*All doses were administered TID
[#]One patient had an AE of dizziness reported as serious

In the Shire Gal 93-01X extension trial vital signs were measured at month 3 (initial visit), week 16/18 (titration period), month 6, month 9 and month 12. For the second extension trial 93-01XX (n=51), vital signs were measured at month 18 and month 24. Descriptive statistics were used to analyze vital signs mean changes from baseline (start of Gal 93-01) and initial visit (start of Gal 93-01X). There were no comments found during my review as to the method of taking vital signs. The overall incidence of potentially clinically important changes in SBP, DBP, and pulse was low. There were no patients with an abnormally low pulse compared to the initial visit.

4.2.9.2 Shire-Gal 95-05/95-05X

In the Shire Gal 95-05 study, all randomized patients who took at least one dose of trial medication were included in the analysis of safety. The investigator recorded vital signs at each visit: week 0,2,5,11,17,23,29. There was no comment found in the review as to the method of taking vital signs.

Galantamine did not appear to cause any clinically relevant effects on vital signs when compared to placebo. With the exception of dizziness, a review of all adverse events showed very few events that might be attributed to a change in vital signs. Dizziness was reported as an adverse event more than twice as often for patients taking galantamine 32 mg/day than for placebo (5.5% v. 2.2%). Sponsor's Annex 3 (Narratives for deaths, other serious adverse events and adverse events leading to discontinuation) shows that two patients on galantamine dropped out due to syncope and one due to faintness. In each treatment group, three patients discontinued prematurely due to dizziness.

In the Gal 95-05X extension trial, safety was further looked at over an additional 24 weeks. Investigators checked vital signs with each visit. Overall, there were no treatment trends in SBP and DBP. However, pulse rate did decrease on average approximately three bpm at 53 weeks. Most of this decrease in pulse was seen in patients that were originally randomized to placebo. In the patients originally randomized to galantamine 32 mg/day, the mean pulse rate actually increased one bpm in the extension.

4.2.9.3 Shire 95-07/95-07X

In the uncontrolled Shire 95-07 study (n=30) all randomized patients that took at least one dose of trial medication were included in the analysis of safety. Vital signs were done at screening, baseline, week 2, week 4, week 8, week 16, at any premature discontinuation time and 4 to 8 weeks after final dose. The investigators recorded SBP, DBP and pulse rates in the sitting position after a five-minute rest. Vital signs for 95-07

and 95-07X are found in Sponsor's Display 65. In 95-07, endpoint DBP tended to be about 5 mmHg lower than baseline and endpoint pulse was about 5 bpm lower than baseline. A similar decrease in pulse occurred in 95-07X. A review of Sponsor's Display 66, "Summary of clinically significant changes in vital signs," showed very few events where the vital signs exceeded the criteria for abnormally high and abnormally low measurements.

A review of Sponsor's Annex 3, "Narratives of deaths, other serious adverse events and adverse events leading to withdrawal" identified two patients who prematurely discontinued due adverse events that may have been related to changes in vital signs. Patient # 000023 experienced dizziness after 22 days on galantamine 32 mg, however recorded vital signs were normal throughout the study. Patient #000030 experienced an adverse event of postural hypotension after 22 days of being on galantamine and required six hours of hospital observation. The medication was discontinued and she returned to normal without any residual effects. Patient #000004 reported mild syncope on galantamine but was able to continue with the trial; her recorded vital signs were also normal throughout the study.

4.2.9.4 JRF Gal INT-1/Gal INT-3

In this large double-blind study of six months duration, investigators measured the vital signs in the sitting position after a five-minute rest at each visit. All randomized patients that took at least one dose of trial medication were included in the analysis of safety (n=438). This study was followed by Gal INT-3, a six month open label extension study (n=469) with vital signs measured at month one, month two, month three, and month six.

4.2.9.4.1 Systolic Blood Pressure

In Gal INT-1, SBP tended to decrease more with galantamine use than with placebo. This difference became statistically significant at variable times without showing any evidence of a pattern for galantamine 12 mg BID or galantamine 16 mg BID. The sponsor, using the criteria seen in FDA Table 32, did not deem this decrease from baseline (-10 mmHg) clinically relevant. There did seem to be a small dose-related increase in the proportion of patients meeting the criteria for potentially clinically important reduction in their SBP. One patient (0.5%) on placebo and no patients on galantamine 12 mg BID met the criteria compared with four (2.0%) in the galantamine 16 mg BID group.

In the Gal INT-3 study, SBP trended downward with a mean drop of 2.4 mmHg at month six for all patients originally randomized to galantamine. In the patients originally randomized to placebo, the mean drop was 2.1 mmHg at month six. As found in the Sponsor Table 4-33, only 0.7% of the patients met the criteria for clinically important reduction in their SBP.

4.2.9.4.2 Diastolic Blood Pressure

In Gal INT-1, DBP tended to decrease more with galantamine use than with placebo. This difference was slight at week 3 but became larger at month 4 for both galantamine

groups. This decrease (-5.3 mmHg) compared to baseline was not considered clinically relevant using the sponsor's criteria seen in FDA Table 32. There was no dose-response relationship for the proportion of patients with a clinically abnormally low DBP.

In the Gal INT-3 study, mean DBP also trended downward. However, as seen in Sponsor's Table 4-33, only about 0.5% of the patients experienced a potentially clinically important reduction in their DBP. The incidence of syncope in the Gal INT-3 was 1.9%. This incidence was similar to the 2.0% incidence of syncope in the galantamine-treated arm of the original Gal INT-1.

4.2.9.4.3 Pulse

The criteria for potentially clinically important abnormally high pulse were not met by any patient in the three treatment groups.

In Gal INT-1, pulse decreased more with galantamine use than with placebo. This difference became statistically significant at variable times for galantamine 12 mg BID and galantamine 16 mg BID. For both galantamine groups, the maximum decrease seen was -2.6 bpm from baseline at month six. The number of patients who developed a potentially clinically important decrease in pulse did not correlate with dose (placebo [0.9%] v. gal 12 mg BID [1.9%] v. gal 16 mg BID [0%]). However, there was a dose-response relationship for bradycardia as an AE (placebo [0.5%] v. gal 12 mg BID [1.8%] v. gal 16 mg BID [2.8%]). Two patients from galantamine 16 mg BID discontinued treatment due to bradycardia as an adverse event as compared with no patients in the other two treatment groups.

Pulse did trend downward in Gal INT-3 and 3(0.6%) patients met the criteria (FDA Table 32) for potentially clinically important decrease. In Gal INT-3, the incidence of bradycardia as an adverse event was 6.2%, which was substantially higher than the original Gal INT-1 study. Stricter reporting criteria may account for the difference. Reporting bradycardia as an adverse event was emphasized by the sponsor and was automatic whenever the heart rate was below 50 bpm on any ECG. Bradycardia reported spontaneously was only 1.5%, which is similar to the incidence seen in Gal INT-1. The patients in Gal INT-3 experiencing bradycardia for the first time showed no relationship to original randomization group from Gal INT-1.

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

In this large placebo-controlled, double-blind study, vital signs were measured at screening, baseline, week 3, month 2, month 3, month 4, month 5 and month 6. Investigators measured SBP, DBP, and pulse after five-minute rest in the sitting position only. All randomized patients that took at least one dose of trial medication were included in the analysis of safety (n=423). This study was followed by a six month open-label extension trial (Gal USA-3, n=353) where vital signs were measured at each visit in the same manner as the original study. Also included in this section is a review of the Interim Report on the 24 month open-label extension trial, Gal USA-9 (n=227) which followed GAL USA-3.

4.2.9.5.1 Systolic Blood Pressure

In Gal USA-1, SBP trended downwards over the course of the trial in all groups. Over the six month trial, the mean decrease in SBP for the two galantamine-treated groups was approximately 3 mmHg compared to a mean fall of approximately 6 mmHg for the placebo-treated group. Two patients (1%) in the placebo group, two (1%) patients in the galantamine 12 BID group, and no patients in the galantamine 16 BID group met the "abnormally low" threshold for clinically significant changes in SBP.

In the extension trial of GAL USA-3, all patients continued on galantamine 24 mg/day for an additional six months. As was seen in Gal INT-3, SBP tended to decrease slightly over the course of the trial but this decrease met the criteria for potentially clinically important changes in vital signs in only two (0.6%) patients. In the Interim Report of GAL USA-9, no patients experienced a decrease in SBP large enough to meet the criteria of potentially clinically important changes in vital signs.

4.2.9.5.2 Diastolic Blood Pressure

As seen in sponsor's Display 52 (Gal USA-1), DBP also trended downward but the change was small (-3 to -4 mmHg) and on average did not reach threshold for potentially clinically important changes seen in FDA Table 32. However, there was a dose-response relationship for "abnormally low" DBP (placebo [1%] v. gal 12 mg BID [3%] v. gal 16 mg BID [4.2%]).

In the Gal USA-3 extension trial, DBP also trended downward (mean change at endpoint of –2.4) but at an overall lower frequency than in Gal USA-1. In Gal USA-3, seven (2.1%) patients met the criteria for potentially clinically important decrease in DBP. In the Gal USA-9 Interim Report only one (0.5%) patient had a reduction in DBP large enough to meet the criteria.

4.2.9.5.3 Pulse

As with the other vital sign parameters, pulse rate trended downward during the GAL USA-1 trial with the actively treated groups and was of low magnitude (mean difference of <4 bpm). The incidence of potentially clinically important change for pulse was 1% (2 patients) in the placebo group compared with 1% (2 patients) in the Galantamine 12 mg BID group and 2.1% (4 patients) in the Galantamine 16 mg BID group. This might suggest that there is a slight dose effect in regards to a decrease in pulse. Similarly, there was an elevated risk for the AE bradycardia in the galantamine groups (placebo 0.9% v. GAL 12 bid 2.8% v. GAL 16 bid 2.8%), with one patient in the galantamine 16 mg BID group reporting bradycardia as an SAE. This one patient (A35147) required hospitalization due to syncope reported as secondary to bradycardia.

In the Gal USA-3 extension trial, pulse also trended downward with an overall incidence of 1.5% of the patients meeting the criteria for potentially clinically important drop in pulse. Of the five extension patients who met these criteria, three were originally

randomized to placebo. In the Gal USA-9 Interim report, two (0.9%) patients met the criteria.

4.2.9.6 JRF Gal USA-16

In this trial of 139 patients of six weeks duration, the goal and design was to investigate the cardiovascular effects of galantamine during titration and after a 6 week treatment period with galantamine. Galantamine was dosed to the maximum tolerated daily dose, up to 32 mg daily. This examination of drug effect on cardiovascular function included the use of Holter monitors and ECGs at baseline, week 2, week 4, and week 6.

No patients in either group had a drop in SBP large enough to meet the criteria for potentially clinically important changes. One (1.5%) galantamine-treated patient and no placebo-treated patients experienced a potentially clinically important drop in their DBP. Patient A60185 had a 20 mmHg drop in DBP (from 70 to 50) but did not experience an AE that could be related to the change in DBP.

The effect of galantamine on heart rate, PR interval, and QT interval are discussed in detail in a section 4.2.12.3 of this document.

4.2.9.7 JRF Gal USA-10

In this placebo-controlled study, lower dosages of galantamine (4, 8, and 12 mg BID) and a slower titration regimen (4 weeks at each dose) than had been used in GAL USA-1 and GAL INT-1 were evaluated for efficacy and safety. All randomized patients that took at least one dose of trial medication were included in the analyses of safety (n=592 Investigators measured pulse and blood pressure in the sitting position after a five-minute rest at screening, week 1, week 4, week 13 and week 21.

Review of Sponsor's Table 34, "Incidence of potentially clinically important vital sign changes", showed no consistent trends in SBP, DBP, or pulse. Vital sign analysis across each time-point showed no significant difference in the minimum/maximum or end-point values for any of these vital signs. The greatest mean change in SBP seen in galantamine-treated patients was approximately -4 mmHg, compared to -2.4 mmHg for placebo. For DBP, the greatest mean change was -2 mmHg compared to -1.3 for placebo. Across all galantamine treated groups, the mean change from baseline in pulse ranged from –1.4 to –3.1 bpm, compared to –0.9 bpm for placebo.

The AEs bradycardia, dizziness, and syncope each showed some degree of dose-relatedness with galantamine treatment as seen in FDA Table 32. This relationship was not present for the AE hypotension.

FDA Table 34. Frequency of selected adverse events related to changes in pulse and blood pressure, JRF Study GAL-USA-10

	Placebo	4 mg Gal BID	8 mg Gal BID	12 mg Gal BID
Bradycardia	1 (0.3%)	5 (3.6%)	7 (2.5%)	8 (2.9%)
Dizziness	10 (3.5%)	7 (5.0%)	15 (5.4%)	19 (7.0%)
Hypotension	1 (0.3%)	0	1 (0.4%)	1 (0.4%)
Syncope	2 (0.7%)	2 (1.4%)	5 (1.8%)	9 (3.3%)

4.2.9.8 JRF Gal INT-2/Gal INT-7

In the flexible dose study of Gal INT-2, investigators measured vital signs in the seated position after five-minute rest at each visit through month three. All randomized patients that took at least one dose of trial medication were included in the analysis of safety (n=261).

As seen in other studies, the mean SBP and DBP dropped one to two mmHg over the course of the study, however these differences were not significant at month three. In contrast to other galantamine studies, sponsor's FDA Table 32 shows an excess of galantamine patients with a potentially clinically significant elevation in their SBP (2.2% v. 0.9%).

Pulse dropped (two bpm) over the course of the study and did meet statistical significance at month three compared to baseline. No patient had a drop in pulse large enough to meet the threshold for potentially clinically significant change. During GAL INT-2, only one patient discontinued treatment with galantamine due to bradycardia. The incidence of syncope was similar for galantamine-treated patients and placebo.

In the extension trial of Gal INT-7 (n=144), vital signs were evaluated frequently and in the same manner as in Gal INT-2. The investigators followed patients out to 12 months. Systolic blood pressure did not show any significant change during this study. No patient in either group experienced an abnormally low SBP. Statistical significance for a drop in DBP and pulse were met at variable times throughout the study. These changes were small (-2.7 mmHg at month six, -4.2 bpm at month 12) and did not meet the threshold for "potentially clinically significant changes in vital signs". Of those patients randomized to galantamine in Gal INT-2, two had an abnormally low DBP and one patient had an abnormally low pulse. This was similar to the results seen in Gal INT-2. In those patients previously randomized to placebo, there were no occurrences of "abnormally low" SBP, DBP, or pulse.

4.2.9.9 JRF Gal USA-5/Gal USA-6

During the Gal USA-5 withdrawal study, 71 patients treated with galantamine in GAL INT-2 were randomized to placebo (n=39) or continuation of galantamine (n=32). Additionally, 47 patients previously randomized to placebo stayed on placebo. The sponsor compared vital signs from the end of Gal INT-2 with the end of Gal USA-5 (week six). The investigators collected data in a similar manner as previous studies. None of the very small changes in vital signs was statistically significant.

In the small Gal USA-6 extension trial (n=110), vital signs were collected at month 4.5 (end of USA-5), month six and month 12. Very few patients had alterations in their vital signs large enough to meet the criteria for potentially clinically significant changes.