1 Background

1.1 Development of Galantamine

An IND was filed for galantamine in the U.S. in 1986. After an investigation of galantamine for the treatment of mild to moderate Alzheimer's disease by was abandoned in 1993, Shire Pharmaceuticals obtained the European development rights for the drug. After a Shire dose-finding study showed promising results in 1995, Janssen Research Foundation (JRF) entered into an agreement with Shire and to develop the drug for the treatment of mild to moderate Alzheimer's disease. An end of Phase II meeting was held with the FDA in October 1996. In addition to launching Phase III trials, JRF performed necessary preclinical and biopharmaceutical studies. During development, dosing was adjusted from a TID to a BID regimen and various titration schedules were investigated. At a pre-NDA meeting held in October 1998, the Division recommended that the total exposure to galantamine be increased and that the cardiovascular safety be investigated further. As such, the NDA was submitted on September 29, 1999[1], with an amendment submitted February 25, 2000 including the results of GAL-USA-10, a large placebo-controlled study using a slow titration schedule, and GAL-USA-16, a smaller placebo-controlled safety study of the cardiovascular effects of the drug.

1.2 Summary of Galantamine's Pharmacokinetics

1.2.1 General

In the original NDA, the recommended treatment regimen for galantamine was 12-16 mg po BID, after dose titration by weekly increments of 4 mg BID. Based on the results of USA-GAL-10, in the February 2000 amendment to the NDA, the recommended treatment regimen was modified to a dose range of 8-12 mg po BID, following dose titration of monthly increments of 4 mg BID. After an oral dose, galantamine is rapidly absorbed, with peak plasma concentrations attained after about one hour; the absolute oral bioavailability is 88.5%. Administration with food delayed Tmax by 1.5 hours and decreased the Cmax by 25%. Eighteen percent of galantamine is protein bound.

In vitro experiments identified that galantamine is predominantly metabolized by the cytochrome P450 3A4 and 2D6 isoenzymes using N-demethylation, O-demethylation, glucuronidation, N-oxidation, and epimerization pathways. Renal clearance accounts for about 25% of the total plasma clearance. One week after a single 4 mg oral dose, 90-97% of the radioactivity was collected in the urine, and the remainder was collected in the feces. Poor and extensive metabolizers did not differ substantially in the amount of radioactive label recovered. Galantamine is a low clearance drug, with a mean steady

[1] The safety cutoff date for the original ISS was 3/31/99.

state volume of distribution of 175 ± 23L and a total body clearance of 29 ± 770 ml/min. Galantamine has a terminal half-life of 7.3 hours.

1.2.2 Special Populations

Clearance was decreased by 25% in patients with moderate hepatic impairment as compared with normals and those with mild hepatic impairment. The AUC increased by 37% and 67% in patients with moderate and severe renal impairment.

Galantamine plasma concentrations are 30-40% higher and the terminal half-life is longer (11 hours) in the elderly as compared to younger healthy subjects. Its clearance is 20% lower in women due to their lower body weight.

1.2.3 Drug Interactions

In vitro studies suggested that galantamine is unlikely to interfere with the metabolism of other drugs. In *in vivo* drug interaction studies performed in healthy subjects, galantamine had no effect on the pharmacokinetic parameters of warfarin or digoxin. Co-administration of galantamine with cimetidine and with erythromycin (each individually) increased galantamine bioavailability about 15% and 10%, respectively, but this was not clinically significant. Co-administration of galantamine with ketoconazole increased galantamine bioavailability about 30%. Co-administration of galantamine with paroxetine increased the AUC of galantamine by 40% at steady state.

1.3 Summary of Galantamine Preclinical Studies

1.3.1 Acute and Chronic Toxicity

Single dose toxicity studies were performed in rats by the oral route, and in mice and dogs by the oral and intravenous routes. Chronic toxicity of oral galantamine preparations was evaluated in 1-, 6-, and 12-month studies in rats and dogs and in 3-month studies in mice. Many of the side effects observed in these studies were related to the cholinergic stimulation expected as a pharmacological effect of galantamine as a reversible acetylcholinesterase inhibitor.

In the single-dose toxicity studies, most of the side effects were expected from increased cholinergic stimulation and occurred in the CNS and gastrointestinal systems. In the repeated-dose toxicity studies, the CNS and gastrointestinal system were also the predominant site of many side effects. Additionally, the sponsor observed myodegeneration in the wall of the stomach and urinary bladder in dogs.

In the 3-month oral gavage study in mice, at a dose of 20 mg/kg (about 30X the maximum recommended human use level), about 60% of the animals died. Some changes in hematological parameters were also noted (decreased WBC in males and decreased hemoglobin in females). In a similar study in rats, there was also some decreased red blood cell indices in females. However, in the rats, substantial mortality was not observed until a dose range of 40-80 mg/kg.

In the 6- and 12-month studies in rats and dogs, mortality began to occur at 8 mg/kg, but more consistently at 32 mg/kg (50X the maximum recommended human use level). Decreases in white blood cells, and lymphocytes in particular, were observed at 12 months. These longer term studies did not identify myodegeneration in the stomach wall, but did note it in the urinary bladder wall.

In 12-month, but not 6-month, studies in dogs, there was evidence of effects on the female reproductive tract at doses of 4 mg/kg and 8 mg/kg. The changes were not completely reversible at 4 weeks post-dosing.

1.3.2 Reproductive Toxicity

The sponsor carried out studies of fertility, developmental toxicity, and pre/post-natal development in rats and rabbits. They did not identify any adverse effect of galantamine on fertility and there were no teratogenic effects of the drug. Embryotoxic effects were only observed at doses that were toxic to the mothers.

A special 6-month endocrinology study was performed in mature female dogs to investigate the effects of galantamine on the female genital tract, in view of the findings of the oral toxicity study. At doses of 1.6 and 8 mg/kg, the dogs had drug and dose-related decreases in weight of the ovaries and hypophysis, but there were no abnormalities in the genital tract, mammary glands, and pituitary glands on microscopic examination. Serum hormone levels were not affected by treatment.

1.3.3 Mutagenicity and Carcinogenicity Studies

Studies in *in vitro* and *in vivo* systems did not show evidence of galantamine as a mutagen. In the transgenic tumor-suppressor-gene P53-deficient mice, galantamine treatment did not produce any neoplastic or non-neoplastic treatment-related changes. In 24-month carcinogenicity studies in mice and rats no increase in incidental or fatal tumors was associated with galantamine treatment.

2 Methods

Several division reviewers worked on the safety review of the galantamine NDA. Dr. Gerard Boehm reviewed the serious adverse events (SAEs), the laboratory data, the ECG data, and the cardiovascular safety study GAL-USA-16. Dr. Kevin Prohaska reviewed the vital signs data. Dr. Michael Sevka reviewed the common adverse events (AEs). Dr. Judith Racoosin reviewed the exposure data, mortality data, discontinuations due to adverse events, phase I safety data, and authored the document, including the review of systems. Because several different reviewers participated in this safety review, I have included their methods section along with their results, rather than present them separately.

The sponsor's approach to the safety review is detailed below.

2.1 The sponsor's data organization and presentation

JRF submitted the NDA on 9/29/99; Table 2-4a of the ISS-A lists the trials included in the original NDA submission and shows the manner in which they were pooled for summarizing in the ISS-O[2]. Subsequently, on 2/25/00, JRF submitted a large amendment to the NDA. Table 2-4b of the ISS-A lists the trials included in the original NDA submission, with the new trials in bold, and shows the manner in which the new and old trials were pooled for summarizing in the ISS-A.

Section 2.3 of the ISS-A lays out the organization of the amendment and identifies the pools of patients for which the sponsor summarized data. The sponsor approached the safety analysis by combining the safety data from all trials in Alzheimer's disease patients, but also by examining the following subgroups: phase II/III placebo-controlled trials; phase II/III uncontrolled, open label, long-term extension trials; phase II/III uncontrolled, open-label, short-term trials; and a double-blind withdrawal trial.

Within the phase II/III placebo-controlled trials, the safety data from trials INT-1, USA-1, and INT-2 were presented in a pooled fashion due to their similar designs, although because INT-2 offered a flexible dose (24mg or 32mg), the results of those dose groups were combined into a "flex dose" column. JRF trial USA-10 was presented separately because of a slower titration schedule and lower peak dose, and JRF trial USA-16 was presented separately due to its shorter duration. The trial data from Shire 93-01 and 95-05 was presented together.

Within the phase II/III uncontrolled trials, the sponsor presented the data from the long-term JRF extensions pooled, and the data from the long term Shire extensions pooled.

Other pools of patients described in the ISS-A are listed in Table 2-4b "Pooling strategy of trial populations in the amendment."

For the four major placebo-controlled trials (USA-1; INT-1; INT-2, USA-10), the protocols excluded patients with neurodegenerative disorders, multi-infarct dementia, or co-existing medical conditions such as epilepsy, active peptic ulcer disease, significant urinary outflow obstruction, clinically significant psychiatric, hepatic, renal, pulmonary, metabolic, endocrine or cardiovascular disease including recent MI or cardiac surgery, unstable angina, CHF, severe valvular disease, uncontrolled HTN, and conduction disturbances potentially resulting in arrhythmia or syncope. Consequently, the sponsor has not characterized the safety profile of galantamine in patients with these co-morbid conditions.

2.2 The sponsor's AE collection methods

The sponsor indicated that in trials INT-1, USA-1, INT-2 and USA-5, AEs were actively solicited whereas only spontaneously reported AEs were recorded in the Shire trials. The

[2] Throughout this document, the integrated summary of safety (ISS) from the original NDA will be referred to as "ISS-O" and the ISS in the amendment will be referred to as "ISS-A".

sponsor also indicated that treatment emergent events were documented in US trials but that this directive was not always followed in international trials so that "all AEs" and not merely treatment emergent events were incorporated into the sponsor's displays in the ISS-O and ISS-A in a conservative effort to capture AEs (ISS-A p.38-39). Although the sponsor stated that where treatment emergent events were specified in the ISS display headings, displays were footnoted to specify that the two types of AEs were combined and displayed together (possibly over estimating AEs), I found no footnotes within the ISS-A to this effect. The sponsor further stated that their estimate of non-treatment-emergent events included in the "all AEs" was minimal for placebo-controlled trials, but no quantitative support was provided for this comment.

The sponsor included common AEs occurring within three days after the end of trial medication, but SAEs were included in the analyses if they occurred within 30 days of the last dose. Events occurring during the double-blind phases but that did not continue into the extension phases were counted only in the double-blind phase. If AEs were present in the original double-blind trial and still ongoing in the extension, they were counted in the "all AE" analysis in the extension trial. For long-term extension trials, treatment emergent events were defined as those beginning during the extension. If an event occurred between trials the event was included in the AE listings but not in the summary by body system. I was unable to find any discussion regarding the number or nature of AEs that occurred between trials.

2.3 The sponsor's AE coding methods

The sponsor indicated (ISS-A p.38-39) that standard definitions for AEs and SAEs as described in the ICH guideline for GCP were used for the collection and reporting of AEs. AE coding was based upon the WHO-ART dictionary. Additionally, the sponsor indicated that AEs were reviewed by the sponsor's clinicians for consistency across trials resulting in the re-coding of certain AEs listed by patient in Annex 7 of the ISS. On June 15, 2000, the sponsor provided by fax their estimate for the number of AEs affected by the re-coding. The sponsor reported that there were 28,168 reports in the AE-Verbatim listing in the ISS of which 340 (1.2%) were re-coded and influenced 279 preferred terms.

Additionally, coding variables were noted in the SAS transport files for AEs that required further clarification by teleconference with the sponsor. A meeting with JRF representatives on June 13, 2000 provided clarification of the following variables and how each was used in the coding process: AE_V ("AE verb." – AE verbatim term); INCLOLD ("AE included term in individual trial" – original coding of certain terms which were later re-coded); AEINCL ("AE included term" – re-coded term included in the ISS); AEPREF ("AE preferred term" – higher hierarchical term for coding AEs). Further, the sponsor specified that in coding events, "syncope" was used to code falls that were accompanied by suspected or witnessed loss of consciousness, whereas falls that were due to loss of balance or coordination were coded as "fall".

3 Data Quality

One quality issue that is ubiquitous in the reporting of adverse events in NDAs is the absence of important details from a narrative summary. Sometimes, a laboratory value is described as abnormal, or as the reason for discontinuation, but the actual value is not given. One example occurred in study GAL-FRA-1, a phase I study of galantamine pharmacokinetics in patients with renal impairment. The study report stated "some out-of-range values for vital signs, electrocardiograms and laboratory parameters were recorded and considered not to be clinically relevant, except for one subject with decrease of platelet count at post-study visit." The actual fall in platelet count was not provided, however. Another example occurred for patient A03057 in INT-3. This patient developed jaundice and discontinued from the trial for this reason. However, the sponsor did not include the elevated LFT values in the discontinuation narrative or in the laboratory dataset. Another common form of missing data is absence of follow-up in a patient who ended the study with an abnormal laboratory finding or clinical event. In a submission dated 4/20/00, the sponsor was able to provide follow-up data on some patients with end-of-study laboratory abnormalities requested by Dr. Boehm.

3.1 Data Audit

In order to ascertain that the data from the case report forms (CRFs) had been reliably entered into the safety database, I examined all CRFs for patients who died. For the JRF trials, I compared the list of AEs in the CRF to those in the CRT (xae.xpt) and I compared the total MMSE score in the CRF to that in the CRT (xmmse.xpt). Because many fewer datasets were included for the Shire trials, I compared demographic data of age, gender, date of birth, height, and weight in the CRF to that in the CRT (demog.xpt).

3.1.1 Comparison of AEs in CRFs to CRTs

The table below shows irregularities I found while auditing CRFs of patients who died during the galantamine trials. In some cases a CRF AE of "death" was replaced in the CRT by the assigned cause of death. In other cases an AE listed in the CRF was not included in the CRT, or an AE appeared in the CRT that was not on the original CRF.

FDA Table 1. Inconsistencies in AE recording identified during the CRF audit

Study	Patient	CRF AE	CRT AE
USA-10	A74374	UTI	
		Death, Cause Unknown	suspected MI
	A73741	death	CHF
	A73944		pulmonary embolism
INT-3	A03081	Sleeplessness* (crossed out)	sleeplessness
	A03123		dehydration
95-05X	B0609		fever
	F0907		Cardiovascular collapse

*the data correction form states under "query" for page 3 that "Subject has been experiencing sleeping problems before the start of the trial. Should this be added to the medical and surgical history?" The answer/comment says "Yes." However, on the next query page, the query states "Agree to add sleeplessness" to the Adverse Events page. As a result, sleeplessness is listed in the CRT as a treatment emergent event when it appears to have been pre-existing.

Many of the inconsistencies that I originally identified were explained by reviewing the sponsor's query forms that accompanied the CRFs. Of the inconsistencies shown in FDA

Table 1 above, some provided more detail for the AE death and almost all the rest are additional AEs listed in the CRT that were not in the CRF. In general there was a good correspondence between the data in the CRFs and that in the CRTs.

3.1.2 Data Presentation

MMSE scores were not available in the INT-3 CRF, so I checked baseline ECG parameters for consistency between the CRF and the CRT. When I did this I found that the baseline ECG parameters listed in INT-3 were those that were recorded at the baseline visit for the preceding placebo-controlled trial (INT-1), NOT those measured on the baseline ECG for the extension study itself (INT-3). Thus, it became apparent that changes from baseline calculated in summary tables were based on the RCT baseline and not the extension baseline.

3.2 Quality of Adverse Event Coding

The sponsor did not include a coding dictionary with the NDA. Therefore the SAS transport files for AEs from the ISS-A was examined for the quality of AE coding. A JMP table was generated by grouping first on the AE preferred term and then on the AE verbatim term, and then sorting on the number of verbatim terms and examining the hierarchical conversion for each grouped verbatim term used to report 10 or more events. In general, there was consistency with regard to hierarchical coding of verbatim terms to preferred terms.

However, there was some discrepancy with regard to the AE "injury". Specifically, planned surgical procedures were coded to the AE preferred term "injury". When Dr. Boehm removed the surgical procedures from the serious "injury" events, he did not find any difference in the risk of actual injuries between the treatment groups.

Another coding inconsistency noted was the same or similar verbatim term assigned across several preferred terms for cardiac rhythm abnormalities. These preferred terms included Arrhythmia, Arrhythmia atrial, Arrhythmia ventricular, AV block, Bradycardia, Bundle branch block, ECG abnormal, ECG abnormal specific, Extrasystoles, Fibrillation atrial, Heart block, QT prolonged, Sick sinus syndrome, Sinoatrial block, Tachycardia, Tachycardia supraventricular, and Tachycardia ventricular. There was no consistent pattern by which verbatims for cardiac rhythm abnormalities were coded to a particular preferred term

Similarly, falls were coded in an inconsistent manner to the following preferred terms: Back pain, Dizziness, Fracture pathologic, Joint dislocation, Orthostatic hypotension, Purpura, and Syncope. Finally, verbatim terms containing spasm or cramp did not appear to be consistently coded to particular preferred terms including Back pain, Cramps legs, Leg pain, Myalgia, Muscle contraction involuntary, and Muscle weakness.

4 Results

4.1 Phase I Studies and short-term uncontrolled studies

The phase I portion of galantamine development included ten single-dose studies, five repeated-dose studies, and seven drug interaction studies. One of the repeated-dose studies, was invalidated due to GCP noncompliance and nonadherence to the protocol.

4.1.1 Safety in single-dose studies

4.1.1.1 Healthy subjects[3]

Among 120 patients treated in seven JRF single-dose studies in healthy patients[4], no patients died and one patient discontinued for treatment deviation. The only SAE occurred in a subject with severe renal insufficiency who was hospitalized for pulmonary edema 12 days after a single 8 mg dose of galantamine in GAL-FRA-1. Fifty-three percent (64/120) of patients reported at least one AE. The AEs reported by at least 5% of patients included dizziness (19%), nausea (14%), headache (13%), diarrhea (8%), and vomiting (6%). A clinically relevant laboratory abnormality of a decrease in platelet count at the post-visit study occurred in one patient in GAL-FRA-1; however, the actual change in platelet count was not described. No clinically relevant ECG or vital sign changes were observed.

Shire conducted two single-dose cross-over trials in healthy patients; RD 256/20408 was a bioequivalence trial enrolling seven patients. No subjects died, no SAEs were reported, and one subject discontinued due to withdrawal of consent. One other subject reported non-severe headache and diarrhea. There were no clinically significant changes in laboratory parameters or vital signs. RD 256/20899 was conducted in 24 healthy elderly subjects in the fasting and fed states. No subjects died and no SAEs were reported. One patient experienced a severe AE of vomiting after drug administration in the fasting state; she discontinued for this AE. Commonly occurring AEs included headache, nausea, vomiting, and tiredness; the AE profiles were similar in quality and frequency between the fasting and fed states.

4.1.1.2 Special populations[5]

GAL-USA-2 was conducted to examine the effect of chronic hepatic insufficiency on galantamine pharmacokinetics. The subjects, who were dosed orally with one 4 mg dose of galantamine, included eight patients with normal hepatic function, eight patients with mild hepatic impairment, eight patients with moderate hepatic impairment, and one patient with severe hepatic impairment. There were no discontinuations due to AEs or

[3] Included in this pool of studies of "healthy" patients is one study in patients with renal impairment and one study in patients with hepatic impairment. The SAE and the clinically significant decrease in platelets each occurred in a patient with severe renal impairment (two different patients).
[4] See the ISS-O table of "Completed Phase I trials in healthy subjects" for details on trial design.
[5] The two studies described individually in this section are included in the pool of studies in healthy subjects described in section 4.1.1.1.

SAEs, and no AEs were rated as severe. No AEs occurred in the nine patients with the moderate and severe hepatic impairment. Overall, 20% of patients reported AEs, with 25% occurring in the normal group and 38% in the mildly impaired group. Headache was reported most commonly, occurring in three patients. There were no clinically relevant changes in laboratory parameters.

GAL-FRA-1 was conducted to examine the effect of chronic renal insufficiency on galantamine pharmacokinetics. The subjects, who were dosed orally with one 8 mg dose of galantamine, included eight patients with normal renal function, eight patients with moderate renal impairment, and nine patients with severe renal impairment. One SAE of pulmonary edema was reported 12 days after dosing in a patient with severe renal insufficiency. Overall, 44% of patients reported AEs, 25% in the normal group, 25% in the moderate group, and 78% in the severely impaired group. Nausea and vomiting were reported most commonly, occurring in five patients each. The only clinical laboratory abnormality was a decrease in platelet count at the post-visit study in one patient with severely impaired renal function. There were no clinically relevant changes in ECG or vital signs.

4.1.2 Safety in repeated-dose studies

4.1.2.1 JRF Trials

There were no deaths or serious AEs in the three JRF repeated-dose trials (FRA-2, NED-4, and NED 5) conducted in healthy subjects (median age 27).

In these three studies, 5% (4/78) of patients discontinued; 3/4 discontinuations were for AEs. According to ISS-A Table 9-2, the AEs leading to discontinuation included one report of fatigue, one report in the respiratory system, one report in the psychiatric system, and one report in the central and peripheral nervous system. When I went back to the actual study reports to identify what the specific AEs were, I had difficulty making that determination because the study reports were quite abbreviated. However, I did determine that there were no discontinuations due to AEs from NED-4, one discontinuation for an AE from FRA-2, and one discontinuation each for the AEs headache and rhinitis from NED-5.

The most commonly reported AEs (≥ 10% of patients) in the JRF repeated-dose trials were nausea, vomiting, abdominal pain/colic, headache, dizziness, fatigue, rhinitis, and insomnia. About 10% of the nausea and vomiting episodes were considered severe. No occurrences of bradycardia or AV block were reported, but dizziness occurred in 20% of patients and there was one report of syncope. Bilirubinemia, leukopenia, and leukocytosis were each reported in one patient.

4.1.2.2 Shire Trials

There were no deaths or serious AEs in 95-06, the Shire repeated-dose study conducted in healthy elderly subjects (median age 72).

Fourteen percent (4/29) of patients discontinued prematurely from the trial; all were for AEs. Three patients had nausea and discontinued after the first single dose of 10 mg, while one patient had indigestion and influenza-like symptoms and discontinued during the 10 mg TID portion of the study.

The most commonly reported AEs (≥ 10% of patients) in 95-06 were nausea, vomiting, diarrhea, headache, and abnormal dreaming. No episodes of nausea or vomiting were considered severe. Fifty percent of patients reported AEs while on the 15 mg BID dosage compared with 30% taking the 10mg TID dosage. No occurrences of bradycardia, AV block, or syncope were reported, but dizziness occurred in 7% of patients.

4.1.3 Safety in drug interaction studies

There were no deaths in the seven JRF drug interactions trials conducted in healthy subjects (median age 24). One patient taking galantamine and digoxin in NED-2 developed 2nd and 3rd degree heart block, bradycardia, nausea, and anorexia for which he was hospitalized (no further details of this case were available).

In these seven studies, 18% (18/100) of galantamine-treated patients discontinued; 11/18 discontinuations were for AEs. AEs for which at least two patients discontinued included nausea (n=5), syncope (n=2), dizziness (n=2), palpitations (n=2). Seven percent (2/29) of placebo-treated patients discontinued; both were for bradycardia.

The most commonly reported AEs (≥ 10% of patients) in galantamine-treated patients in the JRF drug interaction trials were nausea, abdominal pain/colic, headache, dizziness, and insomnia. About 33% of these nausea and vomiting episodes were considered severe. In the galantamine-treated group, bradycardia and AV block occurred together once (see above) and isolated bradycardia occurred in a second patient; additionally, there were two incidences (7%) of bradycardia in placebo-treated patients. Dizziness occurred in 19% of galantamine-treated patients (one quarter of these considered severe) compared with 3% of placebo patients. There was no difference in the incidence of syncope between the galantamine-treated and placebo-treated groups (3/100 [3%] v. 1/29 [3%]). Leukopenia and leukocytosis were each reported in 2% of galantamine-treated patients (2/100).

4.1.4 Safety in short-term uncontrolled studies

GAL-BEL-1 was a dose-escalation clinical pharmacology trial in 20 patients; patients began at 8 mg/day with weekly increases of 4 mg BID up to a maximum of 48 mg/day. Shire 95-07 was a double-blind uncontrolled dose comparison trial of 12 mg BID to 16 mg BID in 30 patients.

No deaths occurred in either trial. Three patients in BEL-1 had SAEs; one patient had severe chest pain, one patient had severe pneumonia, and one patient had mild extrasystoles[6]. In 95-07, three patients treated with 24 mg/day and one patient treated with 32 mg/day experienced SAEs; they included esophagitis, hospitalization for planned

[6] The sponsor indicates that the reason for classifying the extrasystoles as an SAE is unknown.

plastic surgery, skin cold and clammy, and postural hypotension (in the 32 mg/day patient).

In BEL-1, 15% (3/20) of patients discontinued prematurely for AEs experienced while receiving 32 mg/day of galantamine. Two patients experienced gastrointestinal complaints (nausea, vomiting, abdominal pain) and the third developed pneumonia. In 95-07, 27% (8/30) of patients discontinued prematurely for AEs, four in each dose group. Nausea and malaise were the only AEs for which more than one patient discontinued.

Ninety percent of the patients in BEL-1 reported at least one AE. Anorexia (65%), nausea (50%), abdominal pain (30%), vomiting (20%), diarrhea (20%), headache (15%), UTI (15%), and sweating increased (15%) were reported by greater than 10% of patients. The frequency of AE reporting increased with increasing dose (15% at 8 mg/day up to 63% for 48 mg/day). Eighty-seven percent of the 24 mg/day patients and 100% of 32 mg/day patients in 95-07 reported at least one AE. There was a dose-response relationship for nausea, diarrhea, vomiting, abdominal pain, malaise, dizziness, headache, weight decrease, UTI. Nausea (33%), dizziness (20%), anorexia (13%), and headache (13%) were reported by greater than 10% of patients in the 24 mg/day group. Nausea (53%), dizziness (27%), diarrhea (27%), vomiting (20%), headache (20%), malaise (13%), and UTI (13%) were reported by greater than 10% of patients in the 32 mg/day group.

Forty-seven of the fifty patients enrolled in the two studies had paired laboratory data. The only clinical laboratory abnormality that occurred consistently in the two studies was an increase in glucose in five patients in each study. It is not known whether these patients had underlying disturbances of glucose metabolism, but the sponsor did not consider them clinically significant.

No clinically significant ECG changes developed between endpoint and baseline in the two studies. One patient in BEL-1 developed extrasystoles on day 37 but continued treatment. One 24 mg/day patient in 95-07 sought hospitalization for chest pain on day 57, but on diagnostic work-up was found to have reflux esophagitis.

No clinically significant vital sign changes developed between endpoint and baseline in the two studies. One 32 mg/day patient in 95-07 discontinued from the trial on day 22 for severe postural hypotension. In 95-07, mean weight decreases were observed at the end of double-blind treatment of 0.6 kg and 0.8 kg in the 24 mg/day and 32 mg/day treatment groups, respectively.

4.2 *Phase II/III Studies*

4.2.1 Brief Description of Major Trials

Table 3.2 of the ISS-A illustrates the flow of the overall clinical plan for the galantamine development program. FDA Table 2 below[7] displays the salient features of the large JRF randomized controlled trials included in the galantamine NDA and its amendment.

FDA Table 2. Salient features of the JRF Randomized Controlled Trials

Study #	GAL-USA-1	GAL-INT-1	GAL-INT-2	GAL-USA-10
Design	Randomized, double-blind, placebo-controlled, parallel-group, 3-arm study, comparing 2 doses of galantamine with placebo	Randomized, double-blind, placebo-controlled, parallel-group, 3-arm study, comparing 2 doses of galantamine with placebo	Randomized, double-blind, placebo-controlled, parallel-group, comparison of flexible dose of galantamine with placebo	Randomized, double-blind, placebo-controlled, parallel-group, 4-arm study, comparing 3 doses of galantamine with placebo
Dosage	Galantamine 24 mg/day Galantamine 32 mg/day B.I.D. Dosing	Galantamine 24 mg/day Galantamine 32 mg/day B.I.D. Dosing	Galantamine flexible dose 24 mg/day to 32 mg/day B.I.D. Dosing	Galantamine 8 mg/day Galantamine 16 mg/day Galantamine 24 mg/day B.I.D. Dosing
Duration of double-blind treatment	26 weeks	26 weeks	12 weeks	5 months
Randomized population	Placebo: 213 patients GAL 24: 212 patients GAL 32: 211 patients	Placebo: 215 patients GAL 24: 220 patients GAL 32: 218 patients	Placebo: 125 patients GAL: 261 patients	Placebo: 286 patients GAL 8: 140 patients GAL 16: 279 patients GAL 24: 273 patients
Completers	Placebo: 172 patients GAL 24: 144 patients GAL 32: 122 patients	Placebo: 186 patients GAL 24: 176 patients GAL 32: 163 patients	Placebo: 113 patients GAL: 175 patients	Placebo: 240 patients GAL 8: 108 patients GAL 16: 219 patients GAL 24: 212 patients
Main inclusion criteria	Probable Alzheimer's disease; Mini-Mental Status Examination score: 11-24; ADAS-Cog ≥ 12	Probable Alzheimer's disease; Mini-Mental Status Examination score: 11-24; ADAS-Cog ≥ 12	Probable Alzheimer's disease; Mini-Mental Status Examination score: 11-24; ADAS-Cog ≥ 12	Probable Alzheimer's disease; Mini-Mental Status Examination score: 10-22; ADAS-Cog ≥ 18
Main exclusion criteria	• Neurodegenerative disorders • Cognitive impairment resulting from trauma, hypoxic cerebral damage, vitamin deficiency, infection, cerebral neoplasia, endocrine or metabolic disease, or mental retardation • Multi-infarct dementia or clinically active cerebrovascular disease • Co-existing medical conditions including epilepsy; active psychiatric disease; peptic ulcer disease; clinically significant hepatic, renal, pulmonary, metabolic, or endocrine disturbances; clinically significant urinary outflow obstruction • Clinically significant cardiovascular disease that would be expected to limit a patient's ability to complete a 5 month trial • Approved, experimental, or over-the-counter agents for the treatment of dementia • History of drug or alcohol abuse			

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

Although similar in design to INT-1 and USA-1, USA-10 differed substantively from these trials because it utilized a slower titration schedule. The former two trials increased the galantamine dose by 4 mg BID weekly whereas the latter trial used a monthly interval for increasing the dose (see FDA Table 3[7] below).

FDA Table 3. Titration schedule for USA-10

Group	Run-in Phase	Double-Blind Phase		
		Weeks 1 through 4	Weeks 5 through 8	Weeks 9 through 21

[7] This table is derived in part from summary tables in Dr. Ranjit Mani's efficacy review of galantamine.

Placebo	Placebo	Placebo	Placebo	Placebo
Gal 24	Placebo	8 mg	16 mg	24 mg
Gal 16	Placebo	8 mg	16 mg	16 mg
Gal 8	Placebo	8 mg	8 mg	8 mg

FDA Table 4 below[7] displays the salient features of the Shire randomized controlled trials included in the galantamine NDA.

FDA Table 4. Salient features of the Shire Randomized Controlled Trials

Study #	GAL 95-05		GAL 93-01			
Design	Randomized, double-blind, placebo-controlled, parallel-group, 2-arm trial comparing one fixed dose of galantamine with placebo		Randomized, double-blind, placebo-controlled, parallel-arm study			
Dosage	Galantamine 32 mg/day T.I.D. Dosing		Galantamine 18 mg daily Galantamine 24 mg daily Galantamine 36 mg daily TID Dosing			
Duration of double-blind treatment	29 weeks		3 months			
Treatment Groups	Placebo	GAL 32	Placebo	GAL 18	GAL 24	GAL 36
Randomized population	279	275	87	88	56	54
Completers	229	180	73	63	42	28
Main inclusion criteria	Dementia of the Alzheimer's Type (DSM-IV); Probable Alzheimer's Disease; Mini-Mental Status Examination score: 12-24		Probable Alzheimer's disease; Mini-Mental Status Examination score: 13-24			
Main exclusion criteria	• "secondary dementias" resulting from untreated hypothyroidism, hypoparathyroidism, vascular conditions, epilepsy, neurodegenerative disorders, carcinoma, significant psychiatric disease, Korsakoff's syndrome, drug abuse or syphilis • Active peptic ulcer disease • Significant blood dyscrasia, unstable diabetes, or other serious debilitating illness • Taking medications likely to interfere with or confuse the expected actions of galantamine		• Neurodegenerative disorders • Secondary or pseudodementias due to cerebral trauma, hypoxic cerebral damage, vitamin deficiency, infection, cerebral neoplasia, endocrine or metabolic disease, multi-infarct dementia, or cerebral arteritides • Co-existing medical conditions including epilepsy; any neoplasia within two years, significant cardiovascular disease; active psychiatric disease; peptic ulcer disease; clinically significant hepatic or renal impairment, clinically significant urinary outflow obstruction • Patients receiving psychotropic agents, anti-parkinson's drugs, anticonvulsants, cholinergic agents, antiemetics, centrally acting antihypertensives, nootropic agents and cognitive enhancers, other experimental therapeutic agents • History of drug or alcohol abuse			

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

The salient features of the open extension trials are summarized in FDA Table 5 below.

FDA Table 5. Salient features of Shire and JRF open extension trials

Trial #	Source of patients	Prior treatment assignments	Dosage/ Trial Length (titration period)	% Discontinued for any reason
93-01X	93-01	PBO- 69 GAL18- 55 GAL24- 38 GAL36- 26	Variable dose ranging from 18-36 mg/day 9 months, could extend for another 12 months (93-01XX) (4 weeks)	PBO/GAL- 37.7 GAL18/GAL- 29.1 GAL24/GAL- 21.1 GAL36/GAL- 19.2
95-05X	95-05	PBO- 181 GAL- 149	32 mg/day 24 weeks (5 weeks)	PBO/GAL- 24.3 GAL/GAL- 14.1
INT-3	INT-1	PBO- 168 GAL24- 155	24 mg/day 6 months	PBO/GAL- 17.3 GAL24/GAL- 11.0

		GAL32- 146	(3 weeks)	GAL32/GAL- 10.3
USA-3	USA-1	PBO- 135 GAL24- 116 GAL32- 102	24 mg/day 6 months (3 weeks)	PBO/GAL- 36.3 GAL24/GAL- 17.2 GAL32/GAL- 15.7
USA-5	INT-2	PBO- 47 GAL- 71**	24 or 32 mg/day 6 weeks withdrawal trial	PBO/PBO- 12.8 GAL/PBO- 0 GAL/GAL- 3.1
USA-6	USA-5	PBO/PBO- 42 GAL/PBO- 37 GAL/GAL- 31	24 mg/day 33 weeks (3 weeks)	PBO/PBO/GAL- 26.2 GAL/PBO/GAL- 16.2 GAL/GAL/GAL- 12.9
INT-7	INT-2	PBO- 53 GAL- 91	24 mg/day 9 months (3 weeks)	PBO/GAL- 30.2 GAL/GAL- 14.3
USA-9	USA-3	PBO/GAL- 66 GAL/GAL- 161	24 mg/day 24 months*	PBO/GAL/GAL- 25.8 GAL/GAL/GAL- 15.5

*data presented in study report reflects first 12/24 month study duration
**39 of the GAL patients were randomized to withdrawal (placebo) and 32 were randomized to continuing their former GAL dose (16 on 24 mg/day and 16 on 32 mg/day)

4.2.2 Exposure

The study reports for JRF phase II/III trials included a table summarizing exposure by dose group and exposure duration (broken down into weeks and months). The sponsor used the formula *patient years of exposure = (mean treatment duration X N)/365* to calculate person-time exposure. In order to validate these calculations, I used the ADMSUM.xpt from each JRF study to directly sum up the duration of exposure (variable called XRXDUR) by treatment group. In general, the person-years of exposure calculated by the sponsor matched closely to my calculation based on the exposure dataset (within 1%).

There were no individual datasets for the Shire trials, so to calculate the person-time exposure from these trials, I excerpted the data for each Shire trial from the ISS-A ADMSUM.xpt dataset and used the variable XTOTDUR to sum up the exposure by treatment group.

The three tables below summarize the person-time for phase II/III trials by study number and dose group; exposure in randomized controlled trials is summarized in FDA Table 6 and exposure in open extensions is summarized in FDA Tables 7a and 7b. The person-time calculations concur with the totals included in ISS-A Tables 3-1a and 3-1b with the exception of Shire 93-01X and 93-01XX. Both Dr. Jerry Boehm and I have independently calculated the person-time exposure to galantamine in those extension trials as 181.9 years as compared to the sponsor's total of 154.7. Although the patients participating in 93-01XX are flagged in the exposure (ADMSUM) dataset, the person-time for that second extension was not split out from that for 93-01X, so I am unable to determine if the inconsistency in calculated exposure time is derived from one or both studies. We will ask the sponsor to clarify the source of this difference of 27.2 person-years.

FDA Table 6. Person-years of exposure by study and dose group, randomized controlled trials

Study #	PBO	GAL 4BID	GAL 8BID	GAL 6TID	GAL 12BID	GAL 8TID	GAL16 BID	GAL 12TID
93-01	18.4			16.0		11.1		8.1
95-05	138.6						117	
USA-1	95				83		72	
INT-1	101				94		88	
INT-2*	29.9	0.1	0.4		21.9		28.8	0.3
USA-10#	108.3	51.2	102.4		100.7			
USA-16	7.7						7.3	
TOTAL	**498.9**	**51.3**	**102.8**	**16**	**299.6**	**11.1**	**313.1**	**8.4**

*INT-2 used a flexible dosing schedule whereby patients could remain on 24 mg/day or be titrated up to 32 mg/day. The person-time in the table is derived from ADMSUM.xpt because the study report grouped all the GAL person-time together and did not break it down by dose.

#USA-10 utilized a slower titration (4 weeks at each dose) as compared with INT-1, INT-2, and USA-1.

FDA Table 7a. Person-years of exposure by study and dose group, long-term extension trials ≤ 12 months

Study #	PBO-GAL	GAL ≤12 BID-GAL 12BID	GAL >12 BID-GAL 12BID	ANY GAL**-GAL 12BID
93-01X	36.3	55.6	16.4	
95-05X	71.8		63.3	
USA-3	49.9	53.6	47.4	
INT-3	72.1	71	69.9	
USA-6	21.2			39.6
INT-7	30.2			59.6
TOTAL	**281.5**	**180.2**	**197**	**99.2**

*USA-5 was a 6 wk withdrawal study performed to evaluate the potential disease modifying long term effects of galantamine; each of the groups PBO-PBO, GAL-PBO, and GAL-GAL accrued 5 or less person-years during the trial, so it was not included in the table.

**ANY GAL refers to patient groups for whom the original dose group was not indicated in the data table.

FDA Table 7b. Person-years of exposure by study and dose group, long-term extension trials > 12 months

Study #	PBO-GAL-GAL	GAL-GAL-GAL
93-01XX	17.4	28.7
USA-9	59.5	150.7

FDA Table 8 below shows the percentage of patients who were exposed to study drug for at least 5 months in the 5 month RCT USA-10, and for at least 6 months in the RCTs INT-1 and USA-1.

FDA Table 8. Percentage of patients in JRF INT-1, USA-1, and USA-10 who completed the trial, by dose group

Study #	PBO	GAL 4BID	GAL 8BID	GAL 12BID	GAL 12BID "slow"	GAL16 BID
USA-1	78.8			67.5		55.5
INT-1	87.8			78.7		74.6
USA-10#	81.0	78.0	79.0		78.0	

In USA-1 and INT-1, the percentage of patients completing the trial fell with increasing dose. In contrast, about 80% of each galantamine group and the placebo group completed USA-10.

4.2.3 Demographics

ISS-A Tables 4-1a and 4-1b summarized the demographic characteristics of AD patients participating in placebo-controlled and long-term extension trials, respectively. In the RCTs, 36-44% of the trial participants were male. About 60% of participants exceeded age 74 with the exception of INT-1, which only had 42% of participants older than age 74. As a result, INT-1 had the youngest median age at 73, with the median age in the other RCTs ranging up to 78. Greater than 90% of the participants in each study were white. The median weight ranged from 66 to 69 kg. The demographics of the participants in the long-term extension trials did not differ markedly from those of the patients treated in the RCTs.

In the large JRF RCTs INT-1, INT-2, and USA-1, some differences were identified with regard to age distribution and race distribution between non-US and US participants. The non-US patients tended to be younger than the US patients, with about 45% of non-US patients exceeding age 74 compared to >60% of US. This difference in age distribution led to a decrease in median age of non-US patients of about 3 years. Additionally, 98% or more non-US patients were white compared with 90-92% of US patients.

In the large JRF RCTs INT-1, INT-2, USA-1, and USA-10, among the placebo and combined galantamine groups, patients age at diagnosis of probable AD was 74.5 and the years since probable AD diagnosis was 1.1. Patients in the large JRF RCTs had mean baseline MMSE scores around 19 (out of 30), except for those in USA-10 who had a slightly lower mean around 18. The sponsor attributed this slightly worse disease baseline to less stringent inclusion/exclusion criteria in USA-10.

4.2.4 Mortality

I calculated mortality rates for the placebo-controlled JRF and Shire trials by dividing the total number of deaths by the total person-time exposure to drug and placebo. I calculated the person-time directly from the days of exposure to either drug or placebo as specified by the "XRXDUR" variable in the ADMSUM.xpt file for each study.

4.2.4.1 Randomized Controlled Trials

In the ISS-A the sponsor summarized the risk of mortality in two pooled groups of RCTs: the JRF trials and the Shire trials. In the JRF trials, 1.1% of placebo-treated and 0.6% of galantamine-treated patients died. Among the GAL-treated patients, there was no dose-response relationship for mortality. The sponsor attributed 55% (11/20) of deaths to cardiovascular disease, 30% (6/20) to infection, 5% to cerebrovascular disease and 10% to other causes (one death due to choking, one death due to injuries in a car accident). In the Shire trials, 0.5% of placebo-treated and 0.6% of galantamine-treated patients died.

FDA Table 9 below displays the mortality rates that I calculated for each placebo-controlled trial by treatment group. The rates vary somewhat from trial to trial, but there is no evidence of a substantial difference in the incidence of mortality between the placebo group and the group of all galantamine-treated patients. Additionally, the mortality rates within individual trials do not support a dose-response relationship for mortality. It is difficult to examine a dose-response relationship in a pooling of the RCTs because different studies had different titration schedules and patients randomized to different final doses may have been on the same dose at the time of the event (if it occurred during titration); however, when USA-1 and INT-1 are pooled (study designs were identical), there is no evidence of increasing mortality with increasing dose.[8] The mortality rate in the placebo and all galantamine groups are within the range of the background rate of mortality in patients with Alzheimer's disease.

FDA Table 9. Mortality rates in placebo-controlled trials by trial and treatment group

Trial	Treatment	# of patients	# of deaths	Person-years	Rate (per 100 p-yrs)
USA-1	PBO	213	1	95.1	1.0
	GAL 24	212	1	83.4	1.2
	GAL 32	211	1	72.1	1.4
USA-10	PBO	286	4	108.2	3.7
	GAL 8	140	1	51.2	2.0
	GAL 16	279	3	102.4	2.9
	GAL 24	273	3	100.6	3.0
USA-16	PBO	69	0	7.7	0
	GAL 32	70	0	7.2	0
INT-1	PBO	215	2	100.5	2.0
	GAL 24	220	2	93.5	2.1
	GAL 32	218	0	87.8	0
INT-2	PBO	125	2	29.9	6.7
	GAL*	261	0	51.7	0
93-01	PBO	87	0	18.4	0
	GAL 18	88	1	16.0	6.2
	GAL 24	56	0	11.1	0
	GAL 32	54	0	8.1	0
95-05	PBO	279	2	138.6	1.4
	GAL 32	275	2	117.0	1.7
TOTAL	**PBO**	**1828**	**11**	**498.4**	**2.2**
	GAL- all	**2357**	**14**	**802.1**	**1.7**

*flexible dose (24-32 mg)

[8] The mortality rates by dose group for the pooling of INT-1 and USA-1is 1.5 deaths/100 person years for the placebo group, 1.7 deaths/ 100 person-years for the GAL 24 group, and 0.6 deaths/100 person years for the GAL 32 group.

FDA Table 10 below shows the cause-specific mortality by treatment group. The causes of death were typical of those expected in a group of elderly patients with Alzheimer's disease. The rates of specific causes in the placebo group exceeded or were similar to those in the galantamine group with the exception of sudden death. I should note that often the death narrative for patients who were found dead in a chair or a bed were attributed to myocardial infarction or "natural causes"; however, if there was no autopsy supporting such an assigned cause of death, I assigned a cause of "sudden death". Of the four galantamine patients who died suddenly, one (USA-10, 74304, 8 mg BID) had been off study medication for 24 days and had been suffering worsening psychiatric symptoms of AD, while another one (USA-10, 73741, 8 mg BID) had a 20 pound weight loss accompanied by tachypnea and tachycardia on the day of starting the study medication. One sudden death (USA-10, 73779, 4 mg BID) was somewhat concerning for the possibility of a relationship to study drug; this patient had started on risperidone on the same day he started galantamine, and developed neuroleptic malignant syndrome on study day 46. All medications were discontinued and the patient improved. The patient restarted the study medication (1/2 a tablet) 8 days later and 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". The fourth patient (USA-1, A35383, 12 mg BID) was found dead in a chair on day 164.

The cause of one other death is concerning for a possible relationship to a pharmacological effect of galantamine; Patient 30926 in study INT-1 died after choking on a piece of meat. The patient's family recalled one other episode of difficulty swallowing, but did not recall the patient having other symptoms of muscle weakness. For details on additional specific deaths occurring in the placebo-controlled trials within 30 days of the last dose of medication, see FDA Table A in Appendix 1.

FDA Table 10. Cause-specific mortality in RCTs within 30 days of the last dose

Cause of Death	Placebo		Galantamine	
	N	Rate (per 1000 p-yrs)	N	Rate (per 1000 p-yrs)
Congestive heart failure	2	4.0	0	0.0
Myocardial Infarction	2	4.0	3	3.7
Pneumonia	4	8.0	2	2.5
Aspiration	1	2.0	0	0.0
Other*	0	0.0	2	2.5
Pulmonary Embolism	0	0.0	1	1.2
Stroke	1	2.0	2	2.5
Sudden death	1	2.0	4	5.0

*other includes death due to choking (n=1) and car accident (n=1)

4.2.4.2 Long-term Extension Trials

4.2.4.2.1 Long-term extension trials ≤ 12 months

In the ISS-A, the sponsor summarized the risk of mortality in the JRF and Shire extension trials of less than or equal to 12 months duration. Of the 17 (1.6%) patients that died during or within 30 days of leaving a JRF extension trial (≤ 12 months), 4 (0.9%) were

previously placebo-treated and 13 (1.7%) were previously galantamine-treated patients. Of the 5 (1.0%) patients that died during or within 30 days of leaving a Shire extension trial, 1 (0.4%) was previously placebo-treated and 4 (1.5%) were previously galantamine-treated patients. The sponsor did not try to explain the difference between mortality rates in those two groups and rather explained that the overall higher rates in both groups as compared to the GAL-treated patients in the RCTs was likely due to disease-related factors, including progression of Alzheimer's or co-morbid states.

FDA Table 11a. Mortality rates in long-term extension trials ≤ 12 months by trial and treatment group

Trial	Treatment	# of patients	# of deaths	Person-years	Rate (per 100 p-yrs)
INT-3	pbo/24	167	0	72.1	0.0
	24/24	155	2	70.9	2.8
	32/24	146	1	69.8	1.4
USA-3	pbo/24	135	2	49.9	4.0
	24/24	116	3	53.6	5.6
	32/24	102	3	47.4	6.3
USA-5	pbo/pbo	47	0	5.1	0.0
	gal/pbo	39	0	4.5	0.0
	gal/gal	32	0	3.8	0.0
USA-6	p/p/g	42	1	21.2	4.7
	g/p/g	37	2	21.4	9.3
	g/g/g	31	0	18.2	0.0
INT-7	pbo/24	53	1	30.2	3.3
	24/24	91	2	59.6	3.4
93-01X	Pbo/gal	69	0	36.3	0
	18/gal	55	1	32.2	3.1
	24/gal	38	1	23.4	4.3
	36/gal	26	0	16.4	0
95-05X	Pbo/gal	181	1	71.8	1.4
	Gal/gal	149	2	63.3	3.2
TOTAL		**1711**	**22**	**778.1**	**2.8**
First exposure	**GAL**	**1017**	**17**	**486.3**	**3.5**
	PBO	**694**	**5**	**291.8**	**1.7**

FDA Table 11a above displays the mortality rates that I calculated for each long-term extension trial ≤ 12 months by treatment group based on the exposure data provided in the study reports or in the exposure datasets[9]. The rates vary somewhat from trial to trial, and tend to be higher than those observed in the placebo-controlled trials. This is not an

[9] For study 93-01X, I used the person-time value that was provided by the sponsor because they split out the total for 93-01X from that for 93-01XX. The dataset provided by the sponsor did not allow me to separate out the exposure time for the two trials.

unexpected finding, as Alzheimer's patients' disease tends to worsen over time. However, it is concerning that patients who were treated with galantamine in the RCT portion had a mortality rate double that of patients treated with placebo in the RCT portion.

FDA Table 11b. Cause-specific mortality in long-term extension trials ≤ 12 months within 30 days of the last dose by RCT randomization group

	All Extension Patients		GAL-GAL		PBO-GAL	
	n	Rate/1000 person-years	n	Rate/1000 person-years	n	Rate/1000 person-years
Accident	3	3.6	3	5.6	0	0.0
Stroke	3	3.6	2	3.7	1	3.3
Other*	2	2.4	3	5.6	1	3.3
Myocardial Infarction	1	1.2	1	1.8	0	0.0
Pneumonia	4	4.7	4	7.4	0	0.0
Pulmonary **	2	2.4	2	3.7	0	0.0
Sudden death	5	5.9	2	3.7	3	9.9

*Other for "gal-first" included perforated gastric ulcer (n=1), lung cancer (n=1), end-stage Alzheimer's (n=1); other for "placebo-first" included possible multiple organ failure

** Pulmonary included COPD (n=1) and pulmonary embolus (n=1)

FDA Table 11b above summarizes the cause-specific mortality for patients who died during the long-term extension trials ≤ 12 months. Interestingly, patients who took placebo in the RCT experienced sudden death about three times more frequently than patients who had taken galantamine in the RCT. Patient A50041 was found dead in bed on day 153; patient A03190 died suddenly on day 195 after one day of malaise; and patient C0207 collapsed and died one day after discontinuing from the trial (day 88) for aggression and transferring to a nursing home. Each of the patients had a cardiac history or changes on the ECG suggesting heart disease. The three patients previously treated with galantamine who died after accidents each sustained an intracranial hemorrhage after a fall. Patient A0338 was found at the bottom of the stairs on day 157, unresponsive and hypotensive; during a head CT which revealed a subdural hematoma, the patient coded and could not be resuscitated. On day 118 patient A50051 slipped and fell at home resulting in loss of consciousness; the patient underwent surgery for a large subdural hematoma but developed DIC and died within hours of the surgery. On day 81 patient A50114 had an unobserved fall, but then acted normally for four days; on day 85 the patient complained of a headache, went to sleep, and was later unarousable. A CT scan revealed a massive subdural hematoma that was believed to have resulted from a rebleed into a smaller subacute subdural hematoma suffered four days previously. The patient died the next day due to brain herniation. For details on additional specific deaths occurring in the long-term extension trials within 30 days of the last dose of medication, see FDA Table B in Appendix 1.

4.2.4.2.2 Long-term extension trials >12 months

In the ISS-A, the sponsor summarized the risk of mortality in the JRF and Shire extension trials of > 12 months duration. Of the four (1.8%) patients that died during or within 30 days of leaving USA-9, one (1.5%) was previously placebo-treated and three (1.9%) were previously galantamine-treated patients. The one (2.0%) patient that died during or within

30 days of leaving a Shire extension trial was previously placebo-treated. The mortality rates in USA-9 are comparable to the mortality rates observed with galantamine treatment in the RCTs and shorter-term extensions. The rate in PBO-GAL group in 93-01XX is substantially higher than the PBO-GAL group in 93-01X, but this rate is based on one death and a very small exposure.

FDA Table 12. Mortality rates in long-term extension trials > 12 months by trial and treatment group

Trial	Treatment	# of patients	# of deaths	Person-years	Rate (per 100 p-yrs)
USA-9	PBO-GAL-GAL	66	1	59.5	1.7
	GAL-GAL-GAL	161	3	150.7	2.0
93-01XX	PBO-GAL	19	1	17.4	5.7
	GAL-GAL	32	0	28.7	0
TOTAL		**278**	**5**	**256.3**	**2.0**
First exposure	**GAL**	**193**	**3**	**179.4**	**1.7**
	PBO	**85**	**2**	**76.9**	**2.6**

The cause-specific mortality in the long-term extension trials > 12 months was typical of what would be expected in patients with long-standing Alzheimer's disease. In 93-01XX the one death was due to pneumonia. In USA-9, the PBO-GAL-GAL death was due to complications of congestive heart failure (although this was not well-documented) and the other deaths were attributed to CVA (n=2) and sudden death (n=1).

4.2.5 Discontinuations

4.2.5.1 Placebo-controlled trials

The excerpt of ISS-A Table 6-1a below displays the reasons for discontinuation from trial medication in the JRF trials USA-1, INT-1, and INT-2. These three trials had similar titration schedules, beginning with 4 mg BID and increasing by 4 mg BID weekly to a maximal dose of 16 mg BID (32 mg total). The GAL-treated patients in INT-1 and USA-1 were randomized to 24mg or 32 mg, whereas the GAL-treated patients in INT-2 were treated with a "flex dose", being titrated to 24mg or 32mg depending on tolerability.

As can be seen below, about 50% of the placebo patients who discontinued prematurely did so for adverse events compared with about 75% of the GAL-treated patients. There appeared to be a dose-response relationship for discontinuations due to AEs in GAL-treated patients. There was little difference between groups for other reasons for discontinuation.

ISS-A Table 6-1a: Reasons for discontinuation from trial medication by treatment group, JRF trials in original ISS

The excerpt of ISS-A Table 6-1a below displays the reasons for discontinuation from trial medication in the Shire trials 93-01 and 95-05. 93-01 was a phase II trial with a group sequential design utilizing dose groups placebo, 6mg TID, 8 mg TID, and 12 mg TID; the titration periods ranged from 5 days to two weeks. In contrast, 95-05 was a phase III randomized comparison of placebo and 32 mg/day (in three divided doses) of galantamine.

Similar to the JRF trials, about 50% of the placebo patients who discontinued prematurely did so for adverse events compared with about 75% of the GAL-treated patients. There was also a dose-response relationship for discontinuations due to AEs in GAL-treated patients. There was little difference between groups for other reasons for discontinuation.

ISS-A Table 6-1a: Reasons for discontinuation from trial medication by treatment group, Shire trials in original ISS

ISS-A Table 6-1b, seen below, displays the reasons for discontinuation from JRF USA-10. USA-10 differed from USA-1 and INT-1 in that a slow titration schedule was used; all GAL-treated patients were started at 4 mg BID for one month, patients randomized to a total of 16 mg and 24 mg per day were then increased to 8 mg BID, and finally after one month those patients randomized to 24 mg per day were increased to 12 mg BID.

In contrast to the trials described above, the proportions of placebo and All GAL patients discontinuing prematurely for AEs were similar. With the introduction of a slower titration schedule, there is only a slight dose-response relationship for withdrawals due to AEs.

ISS-A Table 6-1b: Reasons for discontinuation from trial medication by treatment group, JRF trial USA-10

ISS-A Figure 3 demonstrates that in the JRF placebo-controlled trials USA-1 and INT-1, most of the discontinuations from the GAL24 and GAL32 groups occurred during the titration period; after the first month, discontinuations occurred at similar rates between the placebo and GAL-treated groups. In comparison, in USA-10 (ISS-A Figure 5), there was little difference in discontinuations between the placebo and GAL-treated groups during the first two months. Around the beginning of month 3, the placebo discontinuations slowed down, whereas discontinuations among GAL-treated patients continued at about the same rate as in the first two months.

4.2.5.1.1 Discontinuations due to AEs

FDA Table 13 below displays the adverse events leading to discontinuation that showed a dose-response relationship. This table is adapted from Tables 6-3a and 6-3b of the ISS-A. The Placebo (10), GAL8, GAL16, and "slow GAL 24"[10] were the dose groups in USA-10, while the Placebo, GAL24, and GAL32 values are pooled from JRF trials USA-1, INT-1, and INT-2. As would be expected from an anticholinesterase inhibitor, gastrointestinal side effects occurred commonly and in a dose-related fashion. However, if one compares the incidence of discontinuation due to nausea, vomiting, and anorexia between the "slow" GAL24 and standard GAL24 treatment groups, these side effects occurred about 50% less often with the slow regimen. Discontinuations due to dizziness and asthenia also occurred less frequently in the "slow" GAL24 group compared with the standard titration.

Discontinuations due to AEs in the Shire placebo-controlled trials (Table 6-4, ISS-O) 93-01 and 95-05 occurred in a similar pattern to the earlier JRF trials (USA-1, INT-1, INT-2). Notably, the 36 mg dose of galantamine received by 54 patients in 93-01 was not well-tolerated; nausea, anorexia, somnolence, fatigue, syncope, headache, and dizziness occurred at a frequency at least double that in the 32 mg dose group.

FDA Table 13. Adverse events leading to discontinuation with a dose-response relationship, JRF trials USA-1, INT-1, INT-2, USA-10

	Placebo	Placebo (10)*	GAL8	GAL16	slow GAL24	GAL24	GAL32
	n=553	n=286	n=140	n=279	n=273	n=432	n=429
Total n (%) discontinued	82 (15%)	46 (16%)	32 (23%)	60 (22%)	61 (22%)	112 (26%)	144 (34%)
Total n (%) dc due to AE	40 (7%)	20 (7%)	9 (6%)	19 (7%)	27 (10%)	80 (19%)	115 (27%)

[10] Slow refers to the slower titration regimen utilized in JRF-USA-10.

Gastrointestinal	12 (2%)	3 (1.0%)	2 (1.4%)	8 (3%)	17 (6%)	52 (12%)	84 (20%)
Nausea	8 (1.4%)	2 (0.7%)	1 (0.7%)	5 (1.8%)	10 (4%)	44 (10%)	69 (16%)
Vomiting	4 (0.7%)	0	0	2 (0.7%)	7 (3%)	23 (5%)	36 (8%)
Anorexia[11]	1 (0.2%)	2 (0.7%)	0	3 (1.1%)	1 (0.4%)	10 (2. 3%)	15 (4%)
Somnolence	1 (0.2%)	1 (0.3%)	0	1 (0.4%)	2 (0.7%)	2 (0.5%)	4 (0.9%)
Confusion	0	0	2 (1.4%)	1 (0.4%)	0	2 (0.5%)	6 (1.4%)
Dizziness	5 (0.9%)	1 (0.3%)	0	5 (1.8%)	2 (0.7%)	6 (1.4%)	12 (3%)
Asthenia	0	1 (0.3%)	0	2 (0.7%)	0	2 (0.5%)	5 (1.2%)
Dyspnea	0	1 (0. 3%)	0	0	0	1 (0.2%)	2 (0.5%)

*Placebo group from USA-10
Source: ISS-A Table 6-3a and 6-3b

Given the known pharmacologic effects of the anticholinesterase inhibitors, one might anticipate a dose-response relationship for discontinuations due to side effects expected in the safety profile. FDA Table 14 displays the frequency of discontinuation due to these side effects in the controlled JRF trials. Aside from some dose relationship with weight decrease in the standard titration studies, there were few occurrences of discontinuations due to AEs potentially expected based on the pharmacological effects of galantamine.

FDA Table 14. Discontinuations due to AEs pharmacologically related to anticholinesterase inhibitors, JRF trials USA-1, INT-1, INT-2, USA-10

	Placebo	Placebo (10)*	GAL8	GAL16	slow GAL24	GAL24	GAL32
	n=553	n=286	n=140	n=279	n=273	n=432	n=429
Weight decrease	0	0	0	0	1(0.4)	9 (2.1%)	6 (1.4%)
Choking	0	0	0	0	0	1 (0.2%)	0
Muscle weakness	0	1 (0.3)	0	0	0	0	0
Bradycardia	0	0	1 (0.7%)	0	0	0	2 (0.5%)
Syncope	2 (0.4%)	0	1 (0.7%)	0	3 (1.1%)	2 (0.5%)	1 (0.2%)

*Placebo group from USA-10

4.2.5.2 Uncontrolled, Open Extension Studies

4.2.5.2.1 Long-term extension studies up to 12 months

The excerpt of ISS-A Table 7-7 below displays the reasons for discontinuation from trial medication in the JRF trials USA-3, INT-3, USA-6, and INT-7. Patients in all four extension trials were dosed with galantamine 12 mg BID. The first two trials were six months in duration, and followed USA-1 and INT-1, respectively. USA-6 enrolled patients from INT-2 who participated in the USA-5 withdrawal trial, and INT-7 enrolled patients directly from INT-2. Patients who received placebo in the RCT are referred to as PBO-GAL, while patients who received galantamine in the RCT are referred to as GAL-GAL. Patients who received galantamine in INT-2, but who were randomized to placebo in INT-5, are referred to as GAL-PBO-GAL (n=37).

FDA Table 15. Discontinuations in long-term extension trials ≤ 12 months

[11] In the galantamine NDA, the AE "anorexia" is grouped into the psychiatric body system.

	JRF USA-3, INT-3, USA-6, INT-7			Shire 93-01X, 95-05X, 95-07X	
	PLA-GAL	GAL-PLA-GAL	GAL-GAL	PLA-GAL	GAL-GAL
	N=398	N=37	N=641	N=250	N=285
Total n discontinued	105 (26%)	6 (16%)	85 (13%)	70 (28%)	52 (18%)
Adverse event	84 (21%)	3 (8%)	58 (9%)	51 (20%)	34 (12%)
Non-compliant	3 (0.8%)	2 (5%)	5 (0.8%)	4 (2%)	1 (0.4%)
Withdrew consent	8 (2%)	1 (3%)	3 (0.5%)	6 (2%)	7 (3%)
Insufficient response	3 (0.8%)	0	1 (0.2%)	1 (0.4%)	0
Subject ineligible	1 (0.3%)	0	1 (0.2%)	0	3 (1%)
Other	6 (1.5%)	0	17 (3%)	8 (3%)	7 (3%)

As can be seen above, most patients who discontinued did so for AEs. Patients who had been treated previously with placebo discontinued about twice as frequently as those who had been treated with galantamine. FDA Table16 below shows the AEs in the JRF and Shire long-term extension trials that occurred in at least 1% of patients in any treatment group. The column for the GAL-PLA-GAL group has been removed for simplicity of presentation because only 3 patients of the 37 discontinued for AEs (pneumonia, disease progression, drug intolerance [without specification of symptom]).

FDA Table 16. Discontinuations due to common AEs in the long-term extension trials (that occurred in at least 1% of patients in any treatment group

	JRF long-term extensions		Shire long-term extensions	
	PLA-GAL	GAL-GAL	PLA-GAL	GAL-GAL
	N=398	N=641	N=250	N=285
Total n (%) discontinued	105 (26%)	85 (13%)	70 (28%)	52 (18%)
Total n (%) dc due to AE	84 (21%)	58 (9%)	51 (20%)	34 (12%)
Gastrointestinal system	52 (13%)	15 (2.3%)	27 (11%)	5 (1.8%)
Nausea	39 (10%)	5 (0.8%)	15 (6%)	3 (1.1%)
Vomiting	20 (5%)	1 (0.2%)	12 (5%)	1 (0.4%)
Diarrhea	4 (1.0%)	1 (0.2%)	2 (0.8%)	0
Abdominal pain	2 (0.5%)	5 (0.8%)	4 (1.6%)	0
Psychiatric system	30 (8%)	13 (2.0%)	22 (9%)	12 (4%)
Anorexia	13 (3%)	1 (0.2%)	7 (3%)	3 (1.1%)
Confusion	5 (1.3%)	4 (0.6%)	5 (2%)	2 (0.7%)
Somnolence	5 (1.3%)	3 (0.5%)	4 (1.6%)	1 (0.4%)
Agitation	4 (1.0%)	3 (0.5%)	5 (2%)	6 (2%)
Hallucination	4 (1.0%)	1 (0.2%)	1 (0.4%)	1 (0.4%)
Body as a whole	14 (4%)	12 (1.9%)	6 (2.4%)	2 (0.7%)
Syncope	1 (0.3%)	3 (0.5%)	0	1 (0.4%)
Asthenia	3 (0.8%)	0	1 (0.4%)	0
Malaise	1 (0.3%)	0	3 (1.2%)	0
Centr & periph nervous system	18 (5%)	12 (1.9%)	9 (4%)	9 (3%)
Dizziness	11 (3%)	2 (0.3%)	2 (0.7%)	1 (0.4%)
Headache	8 (2.0%)	2 (0.3%)	3 (1.2%)	0
Gait abnormal	0	3 (0.5%)	0	0
	1 (0.3%)	0	1 (0.4%)	3 (1.1%)
Metabolic/nutritional disorders	4 (1.0%)	4 (0.6%)	8 (3%)	2 (0.7%)

Weight decrease	4 (1.0%)	2 (0.3%)	7 (2.8%)	1 (0.4%)
Heart rate & rhythm disorders	0	8 (1.2%)	0	0
Bradycardia	0	5 (0.8%)	0	0
Vascular (extracardiac) disorders	1 (0.3%)	6 (0.9%)	0	4 (1.4%)
Cerebrovascular disorder	0	2 (0.3%)	0	4 (1.4%)

Source: ISS-A Table 7-8

In the PLA-GAL group, the risk for discontinuation due to gastrointestinal AEs, psychiatric AEs, asthenia, malaise, dizziness, headache, and weight loss was substantially higher than that in the GAL-GAL group. In contrast, discontinuations for AEs related to the cardiac and vascular systems occurred more frequently among patients who had been originally randomized to galantamine.

4.2.5.2.2 Long-term extension studies greater than 12 months

This group of studies includes USA-9 (a 12 month extension enrolling patients who completed USA-3 and USA-6) and 93-01XX (a 12 month extension enrolling patients who completed 93-01X). The interim study report of USA-9 included in the NDA supplement only provided data on the patients who previously completed USA-3. Despite the fact that the patients enrolling in USA-9 and 93-01XX had been exposed to galantamine for at least 6 months at the time of enrollment, about a twofold difference in the frequency of discontinuation for AEs persisted between the patients originally randomized to placebo and those to galantamine.

FDA Table 17. Frequency of discontinuation due to AE in long-term extension trials > 12 months

Study	PLA-GAL	GAL-GAL
USA-9	10.6% (7/66)	5.6% (9/161)
93-01XX	26.1% (18/69)	14.3% (17/119)

The excess of discontinuations in the PLA-GAL group came predominantly from AEs in the gastrointestinal and psychiatric systems. In 93-01XX, the difference was also driven by an excess of discontinuations due to the AE "weight decrease".

4.2.6 Serious Adverse Events

The following sections review the sponsor's presentation of SAEs, starting with the overall presentation, followed by the placebo-controlled trials presentation, and the uncontrolled trials presentations.

4.2.6.1 Sponsor's Methods for Serious Adverse Event Review and Presentation

In the ISS-A, the sponsor provided their methods for examining SAEs. The sponsor included all SAEs occurring during or within 30 days of discontinuing a trial. The sponsor used an ICH standard definition for SAEs (ISS-A, p.37). The ICH referenced document defines an SAE as an untoward occurrence at any dose that results in death, is life threatening, requires inpatient hospitalization or prolongs hospitalization, results in persistent or significant disability/incapacity or is a congenital anomaly or birth defect.

The sponsor deviated from the ICH definition in that they presented deaths separately from their SAE presentations.

The sponsor presented SAE information in several places in the ISS-A. Section 5.5 provided an overall summary of SAE information. The sponsor presented SAE information from placebo-controlled trials in section 6.5. The sponsor presented SAE information from repeated dose uncontrolled trials in Alzheimer patients, from repeated dose uncontrolled trials in healthy subjects, and from single dose uncontrolled trials in sections 7, 9, and 10, respectively.

4.2.6.2 ISS-A Overall SAE Presentation

As part of their overall review of SAEs, the sponsor presented ISS-A Table 5-12c, which demonstrates that for each of the included groupings of trials, the SAE risk for galantamine subjects was 12%. ISS-A Table 5-12c also demonstrates that for the pooled placebo-controlled trials, the overall SAE risk for galantamine subjects, 12% (270/2287) was similar to the SAE risk for placebo subjects, 11% (130/1205). In trials USA-5 and USA-16, two 6-week trials not included in ISS-A Table 5-12c, the SAE risk for galantamine subjects was lower at 3% and 6% respectively and in other trials not included in ISS-A Table 5-12c, the SAE risk ranged between 10-21%.

Table 5-12c: Incidence of serious adverse events in patients, combined trials—Amendment

Source: Displays SAE.1J, 1E and 1G
Ordered by decreasing overall incidence of SAEs in 93-01, 95-05, INT-1, USA-1, INT-2 and USA-10 (pooled data)
Serious adverse events could be reported up to 30 days post-treatment

Serious injury, syncope, vomiting, nausea, fall agitation and pneumonia adverse events occurred in at least 1% of galantamine treated patients in one or more of the trial groupings from ISS-A Table 5-12c. In the pooled placebo-controlled trials in ISS-A Table 5-12c, the risk for serious syncope, vomiting and nausea among galantamine subjects was at least 1% and two times the risk observed in placebo subjects.

4.2.6.3 ISS-A SAE Presentation for Placebo-controlled Trials

The sponsor demonstrated similar overall SAE risks for galantamine and placebo groups, and across galantamine dose groups in the placebo-controlled trials. In ISS-A Table 6-

28a, the sponsor pooled SAE data from placebo-controlled trials INT-1, INT-2 and USA-1 and separately pooled SAE data for trials 95-05 and 93-01. The overall SAE risk for galantamine subjects in trials INT-1, INT-2 and USA-1 was 12% (139/1122) compared to 10% (56/553) for placebo subjects. Within these same trials the SAE risk for 24mg dose galantamine group was 13% (57/432), compared to 14% (60/429) for the 32mg galantamine dose group and 8% (22/261) for the flexible dose group. For trials 93-01 and 95-05, the overall SAE risk for galantamine subjects was 11% (50/473) compared to 10% (37/366) for placebo subjects. Within these trials, the SAE risk for the 18mg galantamine group was 6% (5/88) compared to 15% (40/275) in the 32mg group and 9% (5/54) in the 36mg group. ISS-A Table 6-28b presented separately the overall SAE risk data for placebo-controlled trials USA-10 and USA-16. In trial USA-10, 11% (73/692) of galantamine subjects experienced SAEs compared to 9% (27/286) of placebo subjects. The overall SAE risk was 10% (14/140), 9% (25/279), and 13% (34/273) for the 8mg, 16mg and 24mg galantamine dose groups, respectively. In study USA-16, the SAE risk was 6% (4/70) in the galantamine group compared to 3% (2/69) in the placebo group.

Despite similar overall SAE risks, the sponsor identified several individual SAEs with higher risks among galantamine subjects compared to placebo subjects. The sponsor summarized individual SAE risks in ISS-A Tables 6-29a and 6-29b, using the same trial groupings described above.

In trials INT-1, INT-2 and USA-1, serious nausea, vomiting, and syncope occurred in at least 1% in the galantamine group and was at least twice as common compared to the placebo group. The risks for serious nausea and vomiting were 1.2% (14/1122 each) in the galantamine group compared to 0.2% (1/553 each) in the placebo group. Within these studies there was a higher percentage of 24mg galantamine subjects with serious nausea (2%, 9/432) and vomiting (1.6%, 7/432) compared to 32mg subjects (0.7%, 3/429 each). Conversely, for serious syncope, the risk was 0.5% (2/432) for the 24mg galantamine group compared to 1.9% (8/429) for the 32mg group.

In trials 93-01 and 95-05, vomiting and nausea were the only SAEs occurring in at least 1% of the galantamine group and at least twice as frequently compared to the placebo group. Among galantamine subjects the risk for serious vomiting was 2% (10/473) and the risk for serious nausea was 1.7% (8/473), while no placebo subjects developed serious vomiting or nausea. The risk for serious vomiting was 3% (3/88) in the 18mg group compared to 1.1% (3/275) and 7% (4/54) in the 32mg and 36mg groups respectively. The risk for serious nausea was 3% (3/88) in the 18mg group compared to 1.5% (4/275) and 1.9% (1/54) in the 32mg and 36mg groups, respectively. In studies 93-01 and 95-05, serious syncope occurred in 0.8% (4/473) of galantamine subjects compared to 0.5% (2/366) of placebo subjects. While there were no serious syncope cases in the 18mg or 24mg groups, 1.1% (3/275) of the 32mg subjects and 1.9% (1/54) of the 36mg subjects experienced serious syncope.

In trial USA-10, syncope was the only SAE occurring in at least 1% of the galantamine group and was at least twice as common compared to placebo. Serious syncope occurred in 1.4% (10/692) of galantamine subjects compared to 0.7% (4/286) of placebo subjects.

The risk of serious syncope by dose group was 0.7% (1/140), 1.4% (4/279) and 1.8% (5/273) for the 8mg, 16mg and 24mg dose groups, respectively. Serious vomiting occurred in 0.4% (3/692) and serious nausea occurred in 0.3% (2/692) of galantamine subjects compared to 0.3% (1/286, each) of placebo subjects (Source: USA-10 study report, p.98).

In the electronic data sets for these trials, there were no serious cases of hepatic failure, aplastic anemia, or rhabdomyolysis. There were 3 serious cases of renal failure, 4 cases of renal calculi, 3 serious skin rashes and 1 case of pancreatitis. The renal failure, renal calculi, rash and pancreatitis cases are reviewed below.

4.2.6.4 ISS SAE Presentation for Uncontrolled Trials

The sponsor grouped SAE data from the uncontrolled trials into the following 3 separate categories:

- short term repeated dose uncontrolled trials GAL-BEL-1, GAL-BEL-3, and 95-07
- long term extension trials up to 12 months GAL-USA-3, GAL-INT-3, GAL-USA-6, GAL-INT-7 (Janssen trials), 93-01X, 95-05X, and 95-07X (Shire trials)
- long term extension trials greater than 12 months GAL-USA-9, 93-01XX

The following sections follow the sponsor's presentation, which used the grouping detailed above.

4.2.6.4.1 Short term repeated dose uncontrolled trials

The sponsor identified 3 subjects from trial GAL-BEL-1, and 4 subjects from trial 95-07 that had serious adverse events. There were no serious nausea or vomiting, and no serious syncope reported for these subjects. In the electronic data sets for these trials there were no serious rashes, aplastic anemia, renal failure, hepatic failure, pancreatitis, renal calculi, or rhabdomyolysis.

4.2.6.4.2 Long term extension trials up to 12 months

Overall SAE risk in long term extension trials up to 12 months was similar to the SAE risk in galantamine subjects from the preceding placebo-controlled trials. The sponsor reported that 11% (174/1611) of the subjects enrolled in long term extension trials up to 12 months experienced one or more SAEs. The risk was consistent when comparing Shire extension trials (12%, 62/535) to the Janssen trials (10%, 112/1076). In the preceding placebo-controlled trials, the overall SAE risk for galantamine subjects 11-12%.

The sponsor found similar incidences of overall serious adverse events and after grouping patients by the treatment received during the preceding controlled trials. Subjects who received placebo during a placebo-controlled trial, and then entered an extension were grouped as PLA-GAL patients. Subjects who received galantamine during a placebo-controlled trial and then entered an extension were grouped as GAL-GAL subjects. For

PLA-GAL subjects, the overall SAE risk was 11% (74/648) compared to 10% (96/926) for GAL-GAL subjects.

Despite similar overall SAE risks between groups, the risks for nausea, vomiting, agitation, aggressive reaction, injury, dehydration, pneumonia, and fall, and neoplasm appeared to differ between the PLA-GAL group and the GAL-GAL group. In ISS-A Table 7-24 (Janssen trials) and ISS-A 7-25 (Shire trials), the sponsor presented SAE risks for events occurring in more than 5 subjects. In the following table, I have summarized the events where there were there was at least a two-fold difference in SAE risk between the treatment groupings from either table.

FDA Table 18. SAE risks for events with at least a two-fold difference between treatment groups in the Janssen or Shire extension trials up to 12 months

Event	Janssen /Shire	PLA-GAL	GAL-GAL
Vomiting	Janssen	0.8% (3/398)	0.6% (4/641)
	Shire	1.6% (4/250)	0.4% (1/285)
Nausea	Janssen	1.3% (5/398)	(0/641)
	Shire	1.6% (4/250)	0.7% (2/285)
Agitation	Janssen	0.3% (1/398)	0.6% (4/641)
	Shire	1.6% (4/250)	0.7% (2/285)
Aggressive Reaction	Janssen	< 5 subjects in either group	
	Shire	2% (5/250)	0.4% (1/285)
Chest pain	Janssen	0.3% (1/398)	0.8% (5/641)
	Shire	< 5 subjects in either group	
Injury	Janssen	1.5% (6/398)	2% (13/641)
	Shire	1.6% (4/250)	3.2% (9/285)
Dehydration	Janssen	0.3% (1/398)	0.8% (5/641)
	Shire	< 5 subjects in either group	
Pneumonia	Janssen	0.8% (3/398)	1.4% (9/641)
	Shire	< 5 subjects in either group	
Fall	Janssen	0.5% (2/398)	1.1% (7/641)
	Shire	(0/250)	2.1% (6/285)
Neoplasm	Janssen	0.5% (2/398)	1.1% (7/641)
	Shire	< 5 subjects in either group	

The table depicts a higher risk for vomiting and nausea in the PLA-GAL group that was consistent in both the Janssen and Shire trials. There was a consistently higher risk for injury and fall in the GAL-GAL group in both the Janssen and Shire trials. For the remaining events, the difference in risk was reversed for the PLA-GAL and GAL-GAL groups in the Janssen trials compared to the Shire trials.

In the electronic data sets for these trials, there were no serious cases of renal failure, hepatic failure, aplastic anemia, rhabdomyolysis, renal calculi or skin rashes in the uncontrolled trials up to 12 months. There were two patients with serious pancreatitis in these trials and the cases are reviewed below.

4.2.6.4.3 Long term extension trials greater than 12 months

Twenty-one percent (47/127) of subjects in USA-9, and 14% (7/51) of subjects in 93-01XX developed SAEs, risks higher than observed in the other groupings of uncontrolled

trials. When the overall risk for trial USA-9 was stratified by treatment in the preceding RCT, the risk for the PLA-GAL group was 29% (19/66) compared to 17% (28/161) for the GAL-GAL group. No SAE occurred in more than 6 subjects in either trial. Fall, injury, and pneumonia were the three SAEs occurring in more than 3 subjects in either trial.

In the electronic data sets for these trials, there were no serious cases of renal failure, hepatic failure, aplastic anemia, rhabdomyolysis, renal calculi or pancreatitis. One subject developed a serious skin rash and that case is described below.

4.2.6.5 Review of Selected SAEs

In the following sections, I describe SAEs potentially related to galantamine's known pharmacological properties such as nausea, vomiting, syncope, bradycardia, and weakness as well as events of interest with any new drug such as renal failure, renal calculi, skin rashes, and pancreatitis. Using narrative summaries, CRFs, study reports, and electronic data sets, I have attempted to characterize these events, acknowledging that for infrequent events, the ability to assess drug relatedness is limited.

4.2.6.5.1 Serious Nausea and Vomiting

Nausea and vomiting were consistently among the most commonly reported SAEs and occurred more than twice as frequently among galantamine exposed subjects in the RCTs. I discuss these events together because as one might suppose, they frequently occurred simultaneously. In the ISS-A database, for the 36 galantamine subjects with serious nausea, 22 also had vomiting recognized as an SAE (ISS-A electronic data set).

There did not appear to be a dose-response relationship for serious nausea and vomiting, and these events were not limited to initiation of therapy. As discussed above, in trials INT-1, INT-2, and USA-1, the risk of serious nausea and vomiting were higher in the 24mg group (2% and 1.6% respectively) than in the 32mg group (0.7% for both). The risk from Shire RCTs did not suggest a dose response (data presented above). Although some of the nausea and vomiting SAEs were reported within the first weeks of therapy, there were events reported months after first exposure.

I read the narratives for serious nausea and vomiting for trials INT-1, INT-2, USA-1, USA-10, INT-3, and USA-3 in an attempt to summarize what occurred. In most cases, the narratives did not characterize nausea or vomiting with respect to timing since last dose or whether it was constant or intermittent. I found that nausea and vomiting SAEs were not necessarily the only events occurring in a patient at the time of an SAE. If one or more criteria for an SAE were met, it appeared that all of the AEs occurring at that time were reported as SAEs. In some cases, nausea and vomiting occurred with another event that met the criteria for an SAE. For example a subject hospitalized for syncope who also experienced nausea and vomiting had all three adverse events listed as SAEs. There were cases where the narrative suggested that nausea and vomiting were the primary events and in some of those cases patients were hospitalized for sequelae such as

dehydration. I searched for esophageal rupture cases as potential serious sequelae of vomiting. I found one patient (9301X/000138) who developed esophageal rupture but the case occurred 18 days after discontinuation of treatment so the relationship between galantamine and this event is difficult to establish.

4.2.6.5.2 Serious Syncope

Syncope was among the more commonly reported SAEs and occurred more frequently among galantamine subjects than placebo subjects in the RCTs. As detailed above, there appeared to be a dose-response relationship for serious syncope in the RCTs.

Generally, the narratives provided little information about diagnostic evaluations, although the work up for syncope may have been limited in these elderly patients with Alzheimer's disease. The reports did not appear to describe a single type of event. There were syncopal events that occurred in the setting of other adverse events such as infectious processes, GI bleeds, or dehydration or in patients taking other medications including antihypertensives, or α blockers. Other syncopal events occurred without documented prior illness and in some of the cases, a cardiac etiology was implicated. The following cases of syncope were suspicious for a cardiac etiology.

> Subject INT-2/A31009, a 73 year old female, experienced syncope during the fourth week of titration, associated with sinus bradycardia (HR=30bpm) and vomiting. During subsequent monitoring she had a 5 second episode of sinus arrest recorded on telemetry. Study medication was discontinued. The sponsor suggested myocardial ischemia, paroxetine, or galantamine may have been responsible for this event.

> Subject USA-1/A35147 a 79 year old female with a history of 1st degree AV block and atrial fibrillation, taking digoxin, diltiazem and fosinopril, experienced a syncopal episode on day 178 that was associated with bradycardia (not quantified) requiring an external pacemaker. The patient refused a permanent pacemaker and was discharged to home. She completed the study.

> Subject USA-10/A73042 an 84 year old female experienced a syncopal episode after 41 days of treatment. She experienced hypertension after the first day of treatment and was initially treated with valsartan and then switched to amlodipine. Later during the study, galantamine was held prior to cataract surgery. On the day galantamine was re-started, the patient had a syncopal episode. The syncope was described as vasodepressor and during the hospitalization the subject had a seizure attributed to hypertension and was diagnosed with mild aortic stenosis and mild peripheral vascular disease. She was subsequently diagnosed with sick sinus syndrome and had a pacemaker inserted. The subject restarted the study medication but developed lethargy, which led to discontinuation from the trial.

I found another syncope case with a cardiac etiology listed as sick sinus syndrome.

> Subject USA-1/A30056, an 84 year old female with a history of tachycardia treated with metoprolol, experienced a syncopal episode during week 3. She was hospitalized and had 3rd degree heart block noted on monitoring. She was diagnosed with sick sinus syndrome and had a permanent pacemaker inserted. She discontinued from the study during week 5 for nausea, vomiting, fatigue, and malaise.