

35204022	Implausible	NO	Brain lesions likely from a lung primary
35204042	Not implausible	NO	Intraparenchymal bleed, hypertensive crisis
35206021	Implausible	NO	Septicemia, peridiverticular abscess
35207028	Not implausible	NO	Collapsed, resuscitated, ECG with inferior ischemic changes c/w MI, later died
35209002	Implausible	NO	Nine days after an MI developed CP (leg) and died
35211009	Implausible	NO	Evidence of metastatic disease, unknown primary (adenoca)
35213004	Not implausible	NO	Developed renal/hepatic insufficiency and died
35213005	Implausible	NO	Metastatic disease in all cell lines
35213006	Implausible	NO	Weight loss, general decline with anorexia and fatigue
35213007	Implausible	NO	Probable peridiverticular abscess, c/w sepsis and death
35213008	Implausible	NO	Exhibited decline, all meds discontinued, hospice initiated, died after last dose
35502104	Not implausible	YES	Sudden death at dinner table, no autopsy
35507116	Not implausible	YES	Found dead in bathroom, no autopsy
35510117	Not implausible	NO	Suicide, GSW to head
35515108	Not implausible	NO	syncope, ?aspiration, acute respiratory failure, arrested, died, no autopsy
35516101	Not implausible	YES	Sudden death, no autopsy
35518101	Implausible	NO	Passenger in an MVA
35518102	Not implausible	NO	5 days after last dose died of CVA
35521101	Implausible	NO	30 days after last dose died renal insufficiency, circumstances unknown
35524116	Not implausible	NO	CVA unsure of any of details, died 2 days later ?second CVA?
35527101	Implausible	NO	Underlying pelvic malignancy, had not taken much of the drug (spat out tabs)
35528105	Not implausible	NO	Fall, hip fx, THR, post op infection, died from confirmed PE 27 days after last dose
35528106	Implausible	NO	Metastatic colon cancer discovered, died 25 days after
35528126	Not implausible	NO	? Respiratory infection, few details aside from presence of fever/cough

?6 not implausible

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Memorandum

Date: April 21, 1999
To: Russ Katz, M.D.
Acting Director, Division of Neuropharmaceutical
Drug Products
Through: Greg Burkhart, M.D.
Safety Team Leader
From: Gerry Boehm, M.D.
John Feeney, M.D.
Joel Freiman, M.D.

ISI — 4-21-99

Subject: Classification of Deaths in NDA 20-690

We were asked to review the records available for 67 deaths. We were asked to 1) identify the sudden unexplained deaths and 2) identify the deaths in which drug-attribution was implausible.

The records we reviewed were provided by _____ in an April 1, 1999 submission. The records were not blinded as to treatment assignment. They consisted almost entirely of patient narratives without supporting documentation.

Before reviewing the cases, the three of us met and agreed on the following definitions.

Sudden Unexplained Deaths

We considered the following criteria essential to our diagnosis of sudden unexplained death (SUD).

1. If observed, the death occurred within minutes.
2. An obvious medical cause of death was not found. If an autopsy was not performed, an obvious medical cause of death was also not established based on clinical information.
3. Accidental deaths such as drownings, motor vehicle accidents (where the patient was the driver), and falls with immediate death were included.
4. Deaths from gunshot wounds and other violent acts (passenger in a motor vehicle accident) were not included.

Implausible Drug-Attribution

Drug attribution was considered implausible in the following situations.

1. The death occurred > 7 days after cessation of drug. However, if the precipitating cause of death occurred within 7 days of drug cessation, drug attribution was considered plausible even if death was delayed beyond 7 days of drug cessation.
2. The death was due to a gunshot wound or other violent act.
3. The death was due to autopsy-proven CAD with acute MI.
4. The death was due to autopsy-proven pulmonary embolism.
5. The death was due to stroke in the setting of a cardiac risk factor (atrial fibrillation) or with evidence of peripheral vascular disease.
6. The death was due to meningitis.
7. The death was due to subarachnoid hemorrhage.
8. The death occurred in a patient moribund from cancer.

Drug attribution was specifically mentioned as plausible in the following situations.

1. The cause of death was unknown or unclear.
2. Death resulted from suicide.
3. Death resulted from pneumonia or urosepsis.
4. The death was classified as a SUD.
5. The death resulted from complications caused by an accidental fall.

Results: The attached table reflects the results of our review. Thirty-two deaths were considered implausible. Twelve deaths were considered SUDs. A brief rationale for the classification of each case is also included in the table.

~~ISI~~
Gerry Beety, M.D.

~~ISI~~
John Feeney, M.D.

~~ISI~~
Joel Freiman, M.D.

Aricept deaths on disk

Nar #	Pt ID	Plausibility	Sudden	Comments
201_012		I	No	Off study drug almost two weeks before family noted increasing weakness and declining health
X 202_338		NI	Yes	Found on the floor of her bedroom in cardiac arrest, no autopsy
X 202_39		I	No	Died of an apparent MI 9 days after discontinuing medication
X 202_517		NI	Yes	After 218 weeks of study drug she died in bed, no prior symptoms or complaints noted
X 202_57		I	No	Passenger in a single vehicle MVA
X 303_354		I	No	Died 6 months after a diagnosis of lung cancer, off study drug 1-week prior to death
X 303_364		I	No	Narrative describes a gradual decline in functional status, drug stopped 9 days prior to death
X 303_365		I	No	Died 19 weeks after diagnosed with lung cancer (not treated)
X 303_367		I	No	Myeloma treated palliatively, developed apparent CVA, (?hyperviscosity)
X 303_371		I	No	CVA 17 days after stopping drug, Death occurred 34 days after stopping drug
X 303_375		I	No	Death due to autopsy proven pulmonary embolism
X 303_391		NI	Yes	Expired in her sleep, no autopsy
X 303_411		NI	No	Found dead, prior day had difficulty breathing and swallowing, no treatment undertaken
X 303_412		NI	No	Hx of angina, had CP, LMD found him hypotensive, admitted, died next day ?MI
X 303_415		NI	No	Had two MI's, the second one (in ICU) fatal
X 303_423		I	No	Altered mental status, put on multiple meds (antipsychotics, anxiolytics)
X 303_441		I	No	Drug dc'd (for bradycardia) 11 days prior to death
X 303_452		NI	No	Few details, ?embolism to lower legs (no info about workup) died 45d after event
X 303_468		NI	Yes	Found dead outside house by a neighbor
X 303_500		NI	No	Developed sepsis, required ventilatory support, made comfort care and died
X 303_504		NI	No	Deteriorated following a fall (?fall related to drug)
X 303_526		I	No	Died 9 days after last dose (diagnosed with advanced pancreatic/liver cancer)
X 303_331		I	No	Died 30d after last dose, drug was dc'd after admission to NH for agitation, difficulty prov care
X 304_234		I	No	Hit by a car, died from multiple trauma
X 304_320		I	No	V/Q scan demonstrated a PE (actual results not provided)
X 313_488		I	No	Died 18d after stopping drug from a bilat pneumonia (drug stopped for deter condition)
X 313_498		NI	Yes	Found dead next to bed
X 442		I	No	Died 11d after last dose, drug dc'd during admission for abd pain; pt with myelodysplasia
X ADE-301-1392		I	No	Bladder cancer, in hospice at time of death
X ADE-301-95		NI	No	Admitted for GI bleed, renal insufficiency, dc'd to NH, condition deteriorated
X ADE-302-78		NI	Yes	Admitted for CP- w/u neg for MI, dc'd, at home, more CP, died suddenly
X ADE-303-108		NI	Yes	Collapsed in front of family, failed resuscitation efforts
X ADE-303-176-2		NI	No	Acute anterior wall MI
X ADE-303-1962		NI	No	Autopsy revealed hemorrhagic pancreatitis, cholelithiasis, ? common duct, pancreatic duct patent
X ADE-303-209		I	No	Leiomyosarcoma, esophagitis during XRT, aspiration pneumonia death

Aricept deaths on paper

Patient#	Plausibility	Sudden	Comments
λ	I	N	Deterioration in clinical course med d/c'd, died>30d after last dose
	I	N	CVA with hx afib, htn, died 20 after event, can't tell when last dose was given
X	NI	N	Admitted for anemia, hypotension, ?GI bleed, ?sepsis (UTI)
X	I	N	Died from complications of injuries sustained while a passenger in an MVA
	NI	N	Gangrene of lower extremities, ill-described heart disease
X	NI	N	Dx with pneumonia that was not treated per pt wishes
X	I	N	Death more than 7d after last dose
	I	N	Off drug for 23d prior to death, dehydration/pneumonia
X	I	N	Metastatic prostate cancer
	NI	N	CHF/arrest, prior day had fever and diarrhea
λ	NI	N	Anterolateral MI, made comfort care
	NI	N	Cyanosis, dyspnea, lethargy, then death, no autopsy
X	I	N	Death attributed to acute lymphoma
X	NI	N	?CVA not documented, no autopsy
X	I	N	Choked, developed respiratory, heart failure
	I	N	Off drug 11d, developed dyspnea ?renal failure died 33d after last dose
	NI	N	Stopped drug for weight loss/anorexia, progressed off drug, died 12d after last dose
λ	NI	Y	Sudden death, no autopsy
X	NI	N	Developed pneumonia, decided not to treat
X	NI	Y	Found dead
	NI	N	Sx are suggestive of MI but no supporting documentation
	I	N	Admitted for resp fail, MI, renal failure, died in ICU
	NI	Y	Found unresponsive and failed resuscitative attempts
λ	NI	N	Condition deteriorated, developed pneumonia while hospitalized
	NI	Y	Found dead in bed

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^	ADE-303-243
X	ADE-303-250
X	ADE-303-253
X	ADE-303-271
	ADE-304-172
	ADE-304-205
	ADE-304-216

I=implausible
 NI=not implausibl

NI	No	CVA treated at home, subsequently collapsed, not admitted, returned home, died next day
NI	No	Intracerebral hemorrhage
I	No	Stones obstructing CBD, pancreatitis/pus, sepsis, death
I	No	Died 10 mos after dx with metastatic lung cancer, failed chemo
NI	No	13d after d/c'd for tx of Pseud. pneumonia rapidly deteriorated, stopped eating, died 7d later
NI	Yes	Found dead, autopsy myocard hypert, fibrosis, insuff, atherosclerosis, old thrombosis
I	No	Autopsy documented thrombus in the LAD

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Review of Clinical Data

November 11, 1998 Response to NA Action on Rivastigmine

Mortality in the Rivastigmine NDA

NDA: 20-823
Sponsor: Novartis
Drug: Rivastigmine
Route of Administration: Oral
Reviewer: Greg Burkhardt, M.D., M.S.
Review Completion Date: April 27, 1999

151
4-27-99

Summary

On July 7, 1998, the agency concluded that the rivastigmine NDA was not approvable (NA). The basis for the NA action was insufficient evidence to show that rivastigmine was safe for its intended use. While there were specific findings identified during the review of the NDA that raised concern about the safety of rivastigmine, there was no conclusive evidence showing rivastigmine to be unsafe. The NA letter outlined the findings of concern and suggested additional analyses that could resolve the question. On November 11, 1998, Novartis submitted a response to the NA action.

After reviewing this response and considering the findings from the additional analyzes conducted by both the sponsor and myself, I believe the aggregate findings still represent a weak signal of concern that rivastigmine could have a life-threatening risk. The signal stems from a weak association between rivastigmine and mortality in the randomized studies, and a weak association between the highest doses of rivastigmine and mortality in the open experience. In my opinion, it is likely that neither association is attributable to a toxic effect of rivastigmine, but likely attributable to chance or an unrecognized confounding factor(s).

While I have concluded that it is unlikely that the findings in the NDA are attributable to rivastigmine, I think the sponsor should conduct a large simple randomized study of mortality to affirm rivastigmine's safety. Whether such a study should be conducted prior to approval or as a phase 4 commitment, depends upon one's judgement of the degree of uncertainty that exists about its safety compared to that with other drug approvals. If rivastigmine is approved before the data from such a study are available, I recommend

that the mortality experience from the NDA along with the uncertainty in the interpretation of this experience be placed in labeling.

In the remainder of this memorandum, I will review the sponsor's findings and present additional analyses that I have conducted showing the association between rivastigmine use and mortality. In the process, I will explicate the basis for my belief that the signal is weak, but of enough concern to require additional data to affirm the safety of rivastigmine. Finally, I will attempt to frame the arguments for and against approval, approval contingent on a phase 4 commitment to conduct large simple trial focused on mortality.

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Background

During the initial review of the NDA, Dr. Oliva raised concern about rivastigmine safety because of excess mortality with rivastigmine in the phase 3 RCTs. After further analysis of the RCT data, we confirmed that the mortality rate for deaths within 30 days of the last prescribed dose (LPD) was about 2.7 fold ($6/1923 \div 1/868$) greater with rivastigmine than that with placebo.¹ For deaths within 7 days of drug or placebo, there were 3 deaths² on drug and none for placebo.

The apparent increase in mortality with rivastigmine use across the pooled RCT experience was not statistically compelling³ and there was also no specific cause of death that accounted for the increase, although 2 of the 3 deaths within 7 days may have been sudden in nature.⁴ The division considered the numerical increase in mortality as a basis for additional investigation, but not to represent conclusive affirmative evidence of risk since it wasn't statistically compelling and because sudden death is not unexpected in the elderly.

To follow-up the weak association in the RCTs, safety team members and Novartis personnel independently compared mortality rates by dose across the development program's uncontrolled experience, and carefully examined the clinical details of all deaths occurring in the NDA. The objective of the individual case review was to make sure that specific clinical events (aplastic anemia, serious skin rash, hepatic failure, rhabdomyolysis, etc.), were not occurring in association with rivastigmine use. These types of events are rare in most populations and historically have been considered likely to be drug-associated events.

Comparing mortality by dose in uncontrolled studies⁵ is somewhat unusual in an NDA review. The division's reasoning in deciding to proceed with the comparison was as

¹ Reviewers must choose an interval of time after last use that will define deaths and other events for analysis. When considering the acute risk from exposure to a drug, one would ideally select an interval that is only a few days longer than the half-life of the parent or metabolite(s) of interest. Since this information is frequently lacking, particularly for metabolites, reviewers frequently select a 30-day interval and, given enough events of interest, will use selectively shorter intervals of time after last use to make comparisons between groups. Intervals that are too long will add events that can't possibly be related to the acute exposure reducing the power to find attributable events.

² PIDs; 30334018, 35103011, 35215039

³ For deaths within 30 days, the one-tailed Fisher's was 0.31, and for deaths within 7 days, it was 0.33. Results of the two-tailed Fishers were 0.45 and 0.56, respectively.

⁴ Patient 35215039 was diagnosed with prostate cancer shortly before his death. There was limited information on this patient, but the death may have been sudden in nature.

⁵ Other memoranda have described the NDA database in detail, but it may be helpful to briefly review it here particularly since analyses of subsets of the database are an important aspect of the issue. The NDA contained three general categories of data, (1) the RCT data, (2) the RCT extension data, and (3) the "titration" study data. The last category is somewhat misleading in name since rivastigmine is always administered by titration, but so named because these studies used a faster titration phase. Both the RCTs and the "titration" studies had limited experience at 10/12 mg, the highest doses proposed by Novartis for

follows. If we found no association between dose and mortality, then, the numerical increase in mortality in pooled RCT could be ascribed to chance, assuming that the failure to find an association was compelling. The RCTs also contained little experience at highest doses that Novartis was proposing for marketing (10 and 12 mg) so examining the experience at these doses would be prudent.

Of course, comparing mortality by dose level when dose has not been randomly assigned can be problematic. For example, if patients having more severe underlying disease and a corresponding greater probability of death are systematically treated at higher doses than less severely ill patients, then a correlation between increasing mortality and dose would be expected - even if the drug has no risk. Likewise, if more severely ill patients are not treated with higher doses of a drug, be it attributable to tolerance or any other reason, then lower doses can have appear to have greater mortality. This general phenomenon has been referred to as "confounding by indication" in the epidemiological literature. It presents a major difficulty in interpreting the findings from non-randomized comparisons of event occurrence with drugs and other treatments.

Before proceeding with the analysis, we considered the potential for this type of confounding since it could have great impact on the interpretability of the findings. Since cholinesterase inhibitors can have significant cardiovascular effects, it seems reasonable that investigators could choose to systematically limit the dose for patients with underlying cardiovascular disease. However, it also seems reasonable that investigators may use larger doses for patients with greater cognitive dysfunction, particularly in those with no evidence of cardiovascular disease. Thus, as we started the analysis of the open uncontrolled experience, we viewed an absence of a finding between dose and mortality as only having meaning if we were sure it was not due to confounding. Likewise, we knew that any apparent association would be difficult to interpret.

Tables 1-3 are taken from my July 7, 1998 memorandum and show mortality rates by dose in the RCT extensions. Table 4 shows the relative mortality for the experience at 10/12 mg compared to that at lower doses. The mortality with 10/12 mg was greater than with lower doses when considering deaths within 30 days, but strengthened somewhat when focusing on deaths within 7 days of the last prescribed dose (LPD). Somewhat surprisingly, the increase was entirely attributable to that subgroup of patients with prior exposure to rivastigmine in the RCT. Overall, patients assigned placebo in the RCTs accounted for about 27% of the experience at 10/12 mg, so it was unclear as to whether the striking difference in relative mortality when considering prior exposure in the RCTs was a relevant observation or not. I also caution the reader to recall that patients have not been randomized to dose, so that, finding greater mortality with the highest doses does not mean that the drug accounts for the increase.

marketing. In fact, almost 75% of the experience with 10/12 mg was derived from the RCT extensions. For patients assigned placebo in the RCTs, the RCT extensions would provide their first exposure to rivastigmine. Hence, we viewed the RCT extension experience as the most critical part of the data for evaluating the mortality experience with 10 and 12 mg.

Although I haven't shown the data (Table 6 contains the most recent data on the full database), it is also true that when the full dataset was used for a similar analysis, the size of the relative difference was significantly less. In fact, in the "titration" dataset, 10/12 mg had less mortality than that at lower doses. Also, in the RCT extensions, there was no evidence that changes in dosing or that the titration phase was associated with death and there was clearly no early hazard. A preliminary review of the deaths in the RCT extensions did not identify specific clinical events that accounted for the excess. Finally, in a preliminary case-control study conducted by the FDA review team (we did not have all the deaths), the association between dose and mortality strengthened when considering dose per kg body weight.

Thus, I think the view captured by the NA letter was that the NDA contained two findings of concern. First, there was a numerical excess of death on drug compared to placebo in the controlled experience that was not statistically compelling. Secondly, there was an association between the highest doses of rivastigmine and mortality in the open experience with rivastigmine that strengthened when focusing only on the RCT extension dataset.

The findings and their uncertain interpretation formed the basis for the NA action with the NA letter acknowledging the difficulties in interpretation and encouraging the sponsor to further investigate the findings in the NDA. We suggested that the sponsor conduct a careful case-control study of all deaths in the development program and to have a panel of physicians review the deaths to identify those judged to be implausible in their association with drug. A separate analysis of the remaining deaths (not implausible deaths) that were within 7 days of the LPD was recommended as the primary analysis. All of the analyzes should aim to determine the role of patient attributes on the relative difference in mortality for 10/12 mg and lower doses.

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Sponsor's approach to addressing the mortality signal

In a September 3, 1998 memorandum, I reviewed Novartis's plan to conduct a case-control study of all deaths in the development program using the same patient experience that lead to the findings in the NA letter. The difference with prior analyses would be that the case-control study would consider more patient factors in the analysis. Because the same patient experience would be analyzed, we expected the case-control study to reproduce the findings from previous analyses unless there was some patient attribute that explained the relationship between higher doses and mortality – at least when focusing on the same deaths that had been used in the analyses up to the NA letter. The case-control study would also contain new analyses of deaths judged to be not implausible in association with rivastigmine use.

The November 11, 1998 submission addresses the points raised in the NA letter and follows the approach that Novartis proposed prior to the submission. In short, Novartis created risk sets comprised of one death and all controls who could have died at the same length of follow-up as the indexing death for each risk set (matched by time). This approach is well established as approximating a proportional hazards survival analysis. Its advantage is the computational ease with which many time-dependent variables can be addressed and the efficiency gained when randomly sampling controls for additional data collection. Additional matching variables included the study number and domestic status (US or non-US).

Multiple analyzes were conducted on the full NDA dataset, and then separately for the three subsets of data namely the RCTs, the "titration" studies and the RCT extensions. Separate analyzes were also conducted for all deaths within 30 days, for deaths within 7 days, and the deaths judged to be implausible by clinical reviewers. Novartis also considered exposure in a number of ways. In addition to current dose, the maximum dose and cumulative dose were also examined. Many analyzes were also conducted to evaluate the role of some patient factors on the risk estimates. These factors included baseline information on mental status, extent of disability, body weight, laboratory test results, and concurrent medication use. The only on-study patient factors that were evaluated in the analyses were body weight and laboratory tests results. Hence, the analysis may not have been capable of addressing concurrent disease if there was significant change from baseline for very many patients.

To identify deaths within 7 days of the LPD, the sponsor ~~reviewed~~ review the clinical materials for all deaths. The clinical materials consisted of the data from the CRF and the patient narratives that had been blinded to drug and dose. Each reviewer was also asked to identify deaths that could not be related to drug ~~use~~. Each provided a report summarizing their approach and findings.

Overall, I think Novartis's approach was generally consistent with the requests in the NA letter. Since additional data collection beyond the data already in the CRF database was

not employed, Novartis did not sample from the risk sets of all possible controls – they used all controls. Hence, this approach ends up being even more similar to a proportional hazards analysis since there is no sampling of risk sets and differs only in the statistical likelihood used to compute probabilities. The disadvantage of not collecting additional data on underlying disease status other than on body weight and labs after baseline is that if substantial numbers of patients had a change in status or had new diseases diagnosed (new medication started), the analyses could not access the effect of such changes. Given our concern about the potential for confounding by severity of disease from either AD or cardiovascular diseases, we had thought it important to collect such data for a complete analysis.

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Description of Sponsor's Submission

The submission consisted of two sections, the first discussing the findings from the Novartis development team's perspective and the second discussing them from an epidemiological perspective.

Both sections generally take a similar approach in reviewing the findings by focusing on analyses of the full dataset and deaths within 30 days. Appendices within the submission contain a detailed listing of all findings, although they are not all discussed by Novartis. Both sections end by concluding that there is no evidence of an increase in mortality.

An additional submission was also made following an interim meeting with the sponsor and the division. This second submission included an unblinded review of the deaths by _____ and some discussion about the reasoning for focusing on findings from the full dataset. It also discussed why it is preferable to focus on deaths within 30 days as opposed to within 1 week of the LPD. Finally, this additional submission also included the findings from additional case-control analyses that matched patients within 3 kg of baseline weight and then matched by center.

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Additional analyses conducted by FDA personnel

A FDA team (Drs Frieman, Baum, and Feeney) reviewed all 56 deaths to identify those judged to be implausibly related to rivastigmine use. They used the same clinical materials provided to _____, which were blinded to dose. I have included their report in appendix 4. Of note is one of their criteria for implausibility. Any death where the event leading to death or the actual death occurred more than 7 days after the LPD was judged to be implausible. At my request, the FDA team also identified all cases of sudden and unexplained death (SUD) in the first 7 days after the last dose of drug.

I used the FDA team's review findings to compute mortality rates by dose for the not-implausible deaths and SUDs. I also used the dataset provided by the sponsor to conduct a more refined case-control analyses that first matching patients within 3 kg of baseline weight, and then matching by both baseline weight and change in weight during study. In Dr. Oliva's review, he had noted that rivastigmine caused significant weight loss. In a preliminary case-control study of some the deaths included in this analysis, we had observed a stronger association with mortality with dose was adjusted for body weight.

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risk estimates although the confidence intervals are still broad. Based upon my analysis of these data, the unadjusted is now 5.6 (1.3, 25.0) and the adjusted is 7.5 (1.3, 35.0).

Novartis also examined the effect of cumulative exposure and the maximum dose up to that point in time on mortality. Neither was related to death although cumulative exposure was correlated with LPD to some extent. In addition, none of the 20 cases as within 7 days of the LPD had changed the LPD within 30 days of death. This was generally true of most deaths in the NDA – on stable doses at the time of death.

In appendix 2, I have included the findings that Novartis prefers to focus on – those from the full dataset, for deaths within 30 days and comparing to 1-4 mg. Also included is a summary of the findings for the RCT extension dataset when focusing on deaths within 30 days and using 1-4 mg as the comparison group. The “signal” becomes very small when taking this approach and disappears completely in the RCT extension dataset. Of course, this was also true in the person-time analyses.

Novartis's interpretation of the findings

As pointed out by Novartis, the signal is materially weaker when focusing on the full dataset no matter what comparison one conducts – the results of pooling the experience from the RCTs and “titration” studies where 10/12 mg experience had few deaths. In the RCT extensions, there is no signal if one focuses on deaths within 30 days and comparing to 1-4 mg.

These findings are really not that different from those observed prior to the NA letter – from the person-time analyzes. In the response to the NA letter, Novartis makes a number of points about why their approach is reasonable. Again, some of these arguments were made before the NA letter and are not specific to the case-control study.

1) Focusing on deaths within 7 days is arbitrary, and therefore, we should only consider deaths within 30 days.

It is true that the risk estimates are smaller and less compelling when focusing on deaths within 30 days. In the submission, Novartis argues that a 7-day cutoff is arbitrary, and in the interim meeting, Novartis consultants argued that using all deaths within 30 days is analogous to an intent to treat analysis.

First, I agree that any time period following the end of exposure that is systematically applied across a population is, by definition, arbitrary. Ideally, one would want to know when the exposure of interest (parent, metabolites) ends for each patient and then look for events that occurred during exposure if we are interested in acute risk from exposure (usually the case). Alternatively, using too long of an interval after exposure ends to define events of interest will only result in identifying some events that can't be related to the acute exposure from the drug. This misclassification effectively makes it more

difficult to find events that are attributable to the drug (bias towards the null). The exception to this approach is when focusing on events that may not be diagnosed until well after exposure ends, e.g., liver failure.

Second, there is no question that mortality was greater shortly following discontinuation of rivastigmine. In the RCT extension data, there were 35 deaths where the death or the event leading to death was within 30 days of the LPD. Of these 35, 7 occurred while on drug or within the first day of stopping drug, 5 occurred from 2 to 6 days after the LPD, 9 occurred from 7 to 13 days after the LPD, 3 occurred from 14 to 20 days after the LPD, and 4 occurred from 21 to 27 days after the LPD. This breakdown clearly shows that death is more likely shortly after the drug was discontinued.

I should caution the reader that the fact that an event or death is more likely shortly after stopping a drug, does not mean the drug caused the event. Discontinuation of chronically used drugs is frequently related to worsening underlying disease. We have also observed this phenomenon in other NDAs, and specifically in the donepezil NDA, death was more likely shortly following discontinuation.

I also agree with the sponsor that a signal should not be dependent on the exact time period chosen. As shown by the figure in appendix 3, the signal is stronger the closer one gets to the LPD, but it is not dependent on a 7-day definition. Thus, while the 7-day definition is arbitrary, this fact does not account for the increase in the relative difference in mortality between 10/12 mg and lower doses as one focuses on deaths closer to the last use of drug.

2) *The appropriate comparison group is the experience of < 4mg.*

As noted above, the relative difference in mortality between 10/12 mg and lower doses declines in the RCT extension dataset when focusing on deaths within 30 days instead of deaths within 7 days. However, some difference still remains until one also uses the experience at doses of less than 4 mg as the basis for comparison.

As shown in Table 1, there are only 134 person-years of use at less than 4 mg in the RCT extension (all at 2 mg). In my opinion, this is insufficient experience to argue that it is a better comparison. Even if one uses less than 4 mg, a relative increase in mortality with 10/12 mg is still present when focusing on the full database.

Novartis goes on to argue that comparing 10/12 mg with lower doses is arbitrary. In Table 6, I have listed the person-years at 10/12 mg and that at lower doses by study type. Notice that in the RCTs, there was little experience at 10/12 mg. We knew this fact when this issue began and deliberately focused on 10/12 mg experience outside of the RCTs so that the safety of the highest doses could be evaluated. Thus, in my view, while arbitrary, the grouping is reasonable.

3) *We should ignore the findings*

In my review of the findings from the case-control analysis, I have considered the findings when using the not implausible deaths identified by [redacted]. Novartis argues that because of the discrepancy between [redacted] findings, we should use neither one ([redacted] excluded all the deaths from the RCT extensions).

Based upon my review of [redacted] reports, it seems fairly certain that [redacted] approach was not consistent with the request in the NA letter. In fact, [redacted] used more stringent criteria – attempting to identify deaths related to drug. This is very different from trying to determine those deaths unlikely to be related drug, the approach taken by [redacted]

4) *The mortality rate for placebo in the RCTs is too low.*

It is not possible to know whether the placebo rate is too low or the drug rate is too high. In the two controlled trials in the donepezil NDA, there was 1 death within 30 days of the LPD in 288 person-years of placebo or drug. In the rivastigmine NDA, there was 1 placebo death within 30 days in about 396 person-years of placebo – not that different from the overall donepezil NDA controlled experience.

5) *There is no dose-response in the RCT data.*

I do agree that not finding a clear increase in mortality at 10/12 mg compared to lower doses and placebo must be considered in the overall evaluation of the signal from the RCT extensions. However, the fact that there is no dose-response does not lower the strength of any signal.

6) *There is no signal in the "titration" studies.*

I agree that there is no signal in the titration studies. In fact, the risk estimates are in the opposite direction. While these studies have a higher overall mortality rate than that in the RCTs or RCT extensions, there is no evidence of an early hazard and the deaths are not temporally associated with the faster titration phase. Thus, I generally agree that we must consider the experience at 10/12 mg in the titration studies in the overall evaluation of the experience with rivastigmine. The findings are also not dependent on the experience at 10 mg.

7) *The failure to identify an explanatory event leading to death reduces any signal strength.*

In my view, finding a specific cause that explains a difference in event rates serves to strengthen a signal, not necessarily to weaken it. In fact, when there are a substantial number of background events (as with all-cause mortality and even sudden death in the elderly) it can be difficult to identify specific clinical events. Most NDAs are not designed for formal cause-specific mortality analysis.

8) *The mortality rate in the rivastigmine NDA is less than expected in an AD population.*

External or historical comparisons are not good enough to reduce the concern from an observation that the highest doses have greater mortality or that drug had more mortality than placebo. Patients are carefully selected for clinical trials. It is not surprising that their overall mortality is less than that in the general AD patient population even if rivastigmine causes death.

9) *Given the number of analyzes, it is not surprising to see some findings of concern.*

I generally agree that if one looks at enough subgroups in a dataset, there will appear to be some findings of concern. However, in this case, there is an association between death and 10/12 mg across the full dataset that is stronger in the RCT extension dataset. Thus, I don't think the association or even finding the association was a function of having looked at a lot of subgroups. As I said before, the fact that we have focused on 10/12 mg is not surprising given that the RCTs had very little exposure to such doses.

10) *Matching by center makes the signal go away.*

While this is an interesting finding, its interpretation does not necessarily mean that the drug has no risk. In fact, if only selected centers tended to use higher doses and higher doses carried some risk, then matching by center would eliminate the association. Epidemiologists have referred to such "over matching" as matching on exposure. Matching by center also reduces the pool of control patients so the estimates become more unstable.

11) *Since mortality increases in time and since the dose is titrated over time, the association between 10/12 mg and mortality in the RCT extensions is spurious.*

This same argument was made before the NA letter and has been addressed in several memoranda. It was made again recently at the interim meeting. I will discuss this point in more detail in the next section, but it is clear from the data that such a bias does not exist.

Additional FDA Analyzes

I have included the report by Drs Feeney, Freiman and Boehm in appendix 4. In short, the team found that 36 of the 56 deaths in the NDA could not be excluded on the basis of being implausible in relation to exposure; 21 of 35 from the RCT extensions. Of these 56, 14 were these judged to be sudden and unexplained (SUD) with 9 occurring in the RCT extensions. Of note regarding their methodology is the fact they considered any death as implausible when it more than after 7 days after the LPD unless the event leading to death began within 7 days of the LPD. Thus, the FDA team included time since LPD as a criterion in determining implausibility. This was somewhat different from [redacted] who separately identified deaths within 7 days but then judged all deaths within 30 days according to implausibility.

I reviewed the differences between the findings of the FDA reviewers and [redacted] deaths in the RCT extension dataset. Of the 35 deaths in the extensions, [redacted] considered 16 of these to be within 7 days of the LPD and not implausible. The FDA team classified 14 of these as not-implausible. The FDA also classified 7 additional deaths as being with 7 days and not implausible while [redacted] added 2 others. The 14 deaths they agree on are patients 30304001, 30331002, 35106045, 35102071, 35112014, 35203025, 35213004, 35207028, 35202038, 35203002, 30342006, 30329008, 30425004, and 35203023.

In Table 6, I have used the findings from [redacted] and the FDA team to compute mortality rates across the full database and by study type.⁶ I also included rate ratios (RRs) and 95% confidence limits (CIs) that were estimated using Poisson regression. Again, I remind the reader that standard statistical theory does not apply for non-randomized comparisons between groups. Thus, the statistical findings are helpful descriptively, but can not be used inferentially. The statistical findings will also vary by the methodology used. For example, even though the CIs include 1 for the FDA not implausible deaths in the RCT extension dataset, the p value using a binomial is 0.02. At best, the statistical findings can be used qualitatively to consider the strength of any finding.

⁶ Some comment about the differences between the analysis of the case-control study and the person-time analyses I am going to show here may be helpful to the reader. The strength of the case-control analysis is that it matches patients by time so that the relative differences observed between compared groups (i.e., 10/12 mg compared to lower doses) can not be a function of time. The person-time analyses (poisson regression) also can be used to make relative comparisons. While these will be similar to those observed with the case-control analysis, they may not be as exact. On the other hand, the person-time analysis includes the absolute rate in the population, thus allowing one to know the excess rate that can be attributed to the exposure. The excess rate is very useful in conceptualizing the public health importance of any signal of risk since the same relative difference can result from an event that is generally rare or one that is more frequent. Hence, I use person-time analyses to help frame the interpretation of findings from the case-control analysis.

Examining the findings that are summarized in Table 6 illustrates several key points. First, the mortality pattern in the titration dataset clearly contradicts that in the RCT extension dataset no matter what definition of death is used including SUDs. Obviously, pooling data, as shown at the bottom of the table results in smaller rate ratios across the full database – the preferred approach by Novartis. Across the full dataset, the relative increase in mortality with 10/12 mg compared to lower doses and placebo varied from 1.6 when using FDA deaths to 3.4

There is also strong statistical evidence that the risk estimates from the RCT extension dataset differs from that in the “titration” dataset - what many call interaction or effect modification. To evaluate for interaction, I fit the following 2 models using the epicure software package and specifically the Poisson regression module.

(1) Mortality rate = intercept + study type + dose (10/12 vs lower doses)

(2) Mortality rate = intercept + study type + dose (10/12 vs lower doses) + study type*dose

The first model represents the base model with the second only differing from it in having the interaction term. A likelihood ratio test is then used to quantify the absolute decrease in deviance (conceptually similar to variance) that is attributable to the interaction term in the second model - this change is generally assumed to follow a chi square distribution with 1 degree of freedom.

I fit this model successively for the definitions of death shown in Table 6. In all cases there was strong evidence of statistical interaction (p values for the LRT all less than 0.10). It did not matter whether the RCT dataset was included or not.

Thus, one has to conclude that the “titration” dataset has a different finding when comparing mortality between 10/12 mg and lower doses from that in the RCT extension dataset. However, how to interpret such a difference and what to do about it is not as clear-cut.

In general, epidemiologists seeking to give the best description of the pattern(s) of disease occurrence in a dataset would describe event occurrence separately for each well-defined subgroup across which there were disparate risk estimates. I generally share this view although I also believe that there has to be some evidence or even belief that the delineation produced by the subgrouping has meaning. When describing variation in risk for patients that share some attribute such as age or use of some medication, it is easy to see why such a group may be of interest. In this case, the subgroups are defined by study type which can be a surrogate for some differences in patient attributes (one study enrolls older more severely ill patients, for example) or for study design (one study is short-term

⁷ When considering the experience across the full dataset, I believe it is appropriate to combine the placebo experience with that from doses below 10 mg. Even so the results are not substantially different if placebo is left out, but the rate ratio does decrease to about 1.4.

and not capable of observing a late occurring hazard). Hence, we compared the patients and the protocols used in the "titration" studies to those in the RCT extensions.

I compared the patients at baseline between those in the RCTs and study 355 using data provided in the case-control study. There was no difference in age, gender, body mass, albumin, creatinine, triglycerides, uric acid, mental status, or degree of disability. There was a difference in the percentage of patients reportedly using 2 or more cardiovascular drugs (broad definition) even though the inclusion/exclusion criteria were not that different. Of the 480 patients in study 355, 79% (380/480) used 2 or more CV drugs compared to 4.9 % of patients in the RCTs (136/2551). Likewise, 11.6 percent of patients in study 355 used no CV drugs compared to 62.6% in the RCTs. Novartis also classified each patient as at or not at risk from cardiovascular disease finding a similar percentage between study 355 and the RCTs. However, the results from the classification seem a bit unusual since medication use is strong indicator of underlying disease. In fact, in epidemiological studies, medication use is a good way to identify patients with expected increases in mortality from the underlying diseases treated by those medications.

Thus, my conclusion after comparing the patients is that the inclusion criteria must of allowed patients with what probably is mild cardiovascular disease into study 355 but not the RCTs. This difference may account for the 2-fold increase in mortality in the "titration" studies. (Using the FDA not implausible deaths, the overall rate in the RCT extensions is 10.6 (21/1986) but 20.6 (9/436) in the "titration" studies.)

However, the fact there may have been greater CV disease in patients enrolled in the "titration" studies, still does not explain why there would not be an increased mortality rate in patients exposed to higher doses, if such doses have risk. It even seems reasonable that patients with some types of CV disease could be at greater risk from a cholinergic.

We also compared the protocols between the RCTs and the "titration" studies. There were some differences. First, the "titration" studies used a faster titration schedule and, second, the "titration" protocols placed less emphasis on achieving higher doses - patients may been more likely to be titrated down in dose. To see if the occurrence of death correlated with the faster titration, we examined the timing of each death. As in the RCT extension deaths, there was no association between recent changes in dose and death. Patients were stable on their current dose at the time of death.

Even if one assumes that there is a late occurring hazard with rivastigmine use, the "titration" study experience is not necessary dismissible. I identified the patients who reached 10 or 12 mg in study 355 (by far the largest of the titration studies). Of the 544 patients entering into this study, 264 were dosed at least once at 12 mg (10 mg was not used in this study). Of these 264, 169 patients were on 12 mg for longer than 30 days, 153 for longer than 60 days and 100 for longer than 180 days. Overall, there was 133 person-years of use at 12 mg in this study with 129 person-years beyond the first 60 days of use and 98 person-years of use beyond the first year at this dose. While it would not be too

surprising to see no deaths given this limited amount of use, it is also true that it is reassuring to some extent, to observe no increase in risk.

Thus, even given the significant statistical evidence that the estimates are different and the suggestion that patients with more CV disease were allowed into the "titration" studies, I do not believe that the experience in the titration dataset is dismissible. Exactly how to incorporate the experience into the overall evaluation is somewhat debatable, but I prefer pooling person-time as opposed to pooling across death strata from the case-control analysis. When pooling across the case-control study, each death contributes the same weight, hence studies that have higher mortality could contribute more information than their experience would dictate. In this case, the titration studies, which have little experience at 10/12 mg contribute more to the full dataset analysis in the case-control study than in the person-time. Thus, I think the best estimate would be to use that from the relative difference in mortality across the full dataset, but basing the pooling on person-time.

A second point that is illustrated by the findings in Table 6 is the significant variation in risk estimates depending on what definition of death is used for the analysis. In the RCT extension dataset, for example, using not implausible deaths suggests about a 8.5 fold increase in mortality in contrast with the findings from using the FDA team's assessment of deaths where is about a 2.5 fold greater mortality. Of course, such variation results from the relatively small number of deaths at doses less than 10 mg – adding or subtracting a few deaths has a great effect on the difference in dose groups. If I use the 14 deaths agreed upon by the FDA team as within 7 days and not implausible, there is about 6 fold greater mortality with 10/12 mg (12 in the 10/12 mg group and 2 were with lower doses). The small number of events in some cells also accounts for why the CIs are fairly wide. In my opinion, the variation in the risk estimates by reviewer speaks even more to inconsistency in the findings than the variation in risk observed in the "titration" dataset.

Finally, from Table 6 it appears that about 50% of the excess in FDA not implausible deaths for 10/12 mg is attributable to an increase in SUDs. Tables 7 and 8 attempt to evaluate this observation in more detail. Table 8 stratifies the experience in the RCT extensions by time since study entry into the extensions. Notice that the SUDs excess in mortality results from deaths occurring well out in extension experience whereas the increase in all-cause is also attributable to a difference occurring relatively early in the study (60-180 days). Thus, in my view, the apparent increase in SUDs is not the explanation for why there was an increase in all-cause mortality.

The 5 patients classified as having SUDs after more than year in the RCT extensions are numbers 30331002, 35112014, 35202038, 35203002, and 35203023. The first 4 of these deaths were fairly typical sudden deaths in elderly patients. All had underlying disease that could account for the death and there was nothing unusual about the death. Patient 3520323 had pancreatic cancer that may have been advanced although the clinical details surrounding the death were limited.

The effect of body weight on risk estimates

In Dr. Racoosin's preliminary case-control study, the relative difference in mortality for higher doses increased when dose was adjusted for body weight. Thus, one of the purposes of the larger and more detailed case-control analysis conducted by Novartis was to examine the role of body weight, both baseline and change during study, on risk estimates. In general, the findings from the case-control study showed that when controlling for body weight the strength of the findings increased.

As pointed out by Novartis, there are difficulties in interpreting the findings after such an analysis. First, low baseline body weight is a predictor of mortality in the rivastigmine dataset independent of dose. I have also observed this association in the donepezil NDA dataset. A second difficulty is the fact that rivastigmine causes decreases in body weight as a function of dose.

These two difficulties essentially mitigate against simply computing risk estimates on a mg per kg basis since body weight is a confounder (lower body weight clearly related to greater exposure and mortality). To address this issue, both the sponsor and myself conducted additional case-control analyses where the control group was matched to the indexing death by baseline weight. There was little change in the magnitude of the risk estimates when compared to unadjusted finding. This would suggest that body weight was not nearly as important as prior analyzes had suggested.

Mortality with Donepezil and Tacrine

To examine the mortality experience observed with donepezil and tacrine, we obtained the data from their respective sponsors, and in the case of tacrine, a completed study report for an analysis of mortality in the 30-week study.

In the phase 2 controlled studies with donepezil (201,203,204,205), there was 1 death within 30 days of the LPD for placebo and none on drug. Overall, there 98 person-years in these studies.

In the two phase 3 RCTs (301 and 302) included in the NDA, there was 1 death within 30 days of the LPD in 954 randomized patients that had about 288 person-years of observation (placebo and drug combined). Of these 954 patients, 763 entered study 303, the extension study for both RCTs, which was similar to the RCT extensions in the rivastigmine.

Table 1 summarizes the mortality experience in study 303 for 5mg and 10 mg experience and there was little variation in mortality by dose when considering deaths within 7 days of the LPD. As shown in table 2, mortality seemed to increase by time, but there was too little experience at 5 mg to make meaningful comparisons between doses.

Table 3 shows the mortality across all phase 3 open-label experience for 10 mg compared to that with lower doses for deaths within 30 and 7 days of the LPD. Table 4 shows the mortality rates based upon FDA review team. There is little difference in mortality for 10 mg compared to that at lower doses. Overall the SUDs rate in the open experience was about 4.4 per 1000 person-years with no difference in the rate by dose. When looking at study 303 separately, there was no difference between 5 and 10 mg for deaths judged to be not implausible by the FDA review team (11.0 vs 12.6). For SUDs, there were 4 SUDs at 10 mg in 1109 PYs of use compared to none at 5 mg in 182 person-years of use. The difference is not statistically compelling with a p value of 0.55.⁸

The experience with tacrine was derived mostly from the 30-week study. Briefly, the sponsor ascertained the vital status up through 30 weeks for all 663 patients included in the study and then conducted a mortality analysis irrespective of the degree of tacrine use. Of the 184 patients assigned placebo 5 died during the 30 interval, a rate of about 5 deaths per 100 person-years. The death rate was lower with 80mg, 120 mg, and 160 mg dose groups and when compared to placebo the hazard ratios were 0.86, 0.74, and 0.42, respectively. Thus, there appears to be a survival advantage with tacrine that is dose-dependent. However, because we know that there was significant dose-dependent patient-dropout, the findings may not be as compelling as they appear since much of the time in high dose group may not have even been on drug. The sponsor also conducted an extended follow-up of the patients following the 30 week interval where dosing was flexible. Mortality also decreased with increasing dose.

While I have not conducted a mortality analysis of the tacrine data, the findings from the 30-week study are at least reassuring. How reassuring the findings actually are would depend on the degree of experience actually on drug in the tacrine dose groups. One interesting observation about the tacrine open experience that was unlike that with donepezil and rivastigmine was that the majority of experience was not at the highest dose. This would suggest that there was a substantial selection process at work and would raise concern that patients making it the highest tacrine dose may have less underlying disease. Thus, in open flexible dosing experience, observing lower mortality at the highest doses may be expected.

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⁸ p value computed using the binomial assuming that the deaths should have distributed according to the person in each compared group.

Discussion

Before discussing my interpretation of the mortality findings in the rivastigmine NDA, it may be helpful to the reader if I first describe my general approach to evaluating evidence, particularly that derived from non-randomized data. Findings from the analysis of non-randomized data in the RCT extensions and "titration" studies are an important aspect of this issue and how to weigh the findings from such data is not straightforward. In fact, there is likely to be substantial variation in interpretation by reviewer reflecting factors like training and experience, but also personnel sentiment.

The subjective nature of interpreting findings from non-randomized data is directly attributable to the absence of a formal basis to use statistical inference to quantify the degree of unexpectedness observed in non-randomized data. The value of randomization is that it allows the probability of the underlying data to be formally stated. Thus, in making comparisons between groups, p values quantify the degree of unexpectedness for the observed difference assuming that it occurred as a result of randomization (the null). While there are many difficulties in evaluating the findings from randomized studies, they at least start with a maneuver that allows one to know something about the probability of the data, at least initially.

Thus, the question becomes how to evaluate the findings from comparisons made based upon nonrandom assignment to the compared groups, e.g., the dose groups in the RCT extension and "titration" studies in the rivastigmine NDA? My approach has been to view the p values and confidence intervals as quantifying the size of the difference in event rates between compared groups as a function of sample size. Hence, I consider the magnitude of the relative effect (rate ratio) in concert with the size of p value (or width of the confidence interval) for that effect. I generally consider a relative effect of less than 4, even with strong statistical evidence, to be small and one of 10 to be large. I consider a p value that is greater than 0.1 as weak, as modest when it is between 0.01 and 0.1 and strong when less than 0.01.

Obviously, the most compelling signal is one that has a *large* relative effect between compared groups with a *strong* p value. A *large* relative effect with a *weak* p value or wide confidence interval, in my mind, means that more data are generally necessary. Finally, a *small* relative effect with a *strong* p value is not a much more compelling than *small* relative effect that with a *weak* p value.

A reader may find my arbitrary cutoff of 4 to generally define a weak relative effect to be somewhat high since the epidemiological literature clearly supports a lower cutoff. My response to this criticism is that most of the published discussion of how to interpret findings from non-randomized data has been focused on findings from studies of occupational or environmental exposures. While these types of studies must be concerned with many confounding factors, there are no phenomena analogous to "confounding by

indication". Because physicians use information on the health of the patient in selecting treatments and because diseases themselves are associated with untoward events, it is easy to form cohorts of patients exposed to selected drugs (even by dose for the same drug) that have strikingly different morbidity and mortality.

In addition to the size of the effect and its degree of statistical strength, other characteristics of the finding are also important in my judgement of the overall strength of the finding. Patterns of event occurrence that strongly suggest an event attributable to drug, such as an early hazard or a dose response, are compelling findings and elevate a modest effect based upon its size and statistical strength to a strong signal of concern. The specificity of the event of interest is important to overall interpretation of the findings. Events that happen to some extent in the patient population taking the drug of interest make the interpretation of a relative increase in that event more circumspect. Likewise, the reasonableness of the comparison is important. There would, for example, be no basis for comparing mortality between benzyl peroxide users and ACE inhibitor users based upon non-randomized data.

Finally, in describing evidence, I usually take the following approach. I use *weak* to qualify my belief that it is unlikely that the exposure of interest accounts for the findings of concern. I describe a signal as *moderate* when I believe that there is about a 50/50 chance that the exposure accounts for the findings and *strong* when it is likely that the exposure accounts for the findings. This approach attempts to quantify the strength of the signal based upon my belief about the predictive value of the observation. However, I do not have enough experience to know how well it works except in the most general terms. I am pretty certain that a careful review of the epidemiological literature, particularly for pharmacological risk, will show that many weak signals are frequently untrue. Likewise, strong compelling observations are generally embraced as true.⁹

Within this context, let's consider the findings from the rivastigmine NDA. The pooled experience across the phase 3 RCTs suggests a statistically weak association between rivastigmine and increased mortality. Such a finding probably is a common observation during reviews of NDAs, and in fact, we have recently observed similar findings in 2 other NDAs. While 2 of the 3 deaths within a week of the last dose were classified as SUD by the FDA review team, SUD is neither specific nor rare in this population. In the open experience in the donepezil NDA, the SUD rate was about 4 per 1000 person-years. In the physostigmine NDA, in which Dr. Boehm found a dose-response for SUDs in women, the rate in women was about 1 per 100 person-years.

We also examined the entire phase 3 dataset with rivastigmine— primarily attempting to affirm rivastigmine's safety. When pooling the data across the phase 3 database, the degree of increased mortality observed with 10/12 mg compared to lower doses and

⁹ We hardly ever have actual confirmation that large signals are true. In some cases, removal or reduction of exposure had been followed by reduction in event rates and this has been taken as evidence that the observation preceding the intervention was true.

placebo varies from 1.6 fold when using the FDA not implausible deaths to 3.4 fold when using ~~the~~ definition. The findings were inconsistent across the database – strengthening when focusing on the RCT extension dataset but weakening when considering the “~~titration~~” dataset. In fact it is only in the RCT extension dataset when considering ~~the~~, not implausible deaths that the size of the relative effect and the degree of statistical strength begin to suggest a moderate to strong signal. There was no evidence of an early hazard, no compelling dose response and there is no clear clinical event that explains the excess.¹⁰

When focusing on the findings from analysis of SUDs, there was a 2.4 fold increase with 10/12 mg compared to lower doses and placebo that was statistically weaker than with all-cause. As with all-cause mortality the relative difference increased somewhat when focusing only on the RCT extension dataset. When the excess in SUDs was considered along with the excess in all-cause, it was clear that their mortality patterns were disparate enough to preclude pointing to the excess in SUDs as an explanation for the excess in all-cause. In fact, the relative increase in SUDs appeared after long-term use whereas the difference in all-cause was at least partly early in use.¹¹

In summary, my overall interpretation is that there are two weak associations between rivastigmine and mortality that, when taken in the aggregate I interpret as representing a weak signal of concern about rivastigmine’s capacity to cause life-threatening events of an uncertain nature. In short, I consider it likely that factors other than a toxic effect of rivastigmine account for the findings, but I believe that the uncertainty is such that we need the results from a large randomized study to affirm rivastigmine’s safety. I have recommended conducting an additional study not so as because of the strength of the signal, but because of the concern for a fatal event that where the signal suggests an excess risk that is approaching 1 per 100 person-years.

A more difficult question is whether the additional study should be completed before or after approval. I am pretty certain that there would be general consensus about the approval of rivastigmine with a phase 4 commitment, even given a weak signal of concern for life-threatened risk, if the drug had an effect on the course of AD. But it is my understanding from discussions with the clinical team that the efficacy of rivastigmine is similar to that with other drugs in this class - a marginal symptomatic benefit with no evidence to suggest that the disease process is modified. Hence, I think the decision to approve the drug in the face of a weak signal for a life-threatening risk has to be made based upon the degree that one believes the uncertainty about rivastigmine’s safety exceeds the uncertainty with any drug approval, but particularly those drugs intended for the elderly.

¹⁰ In fact, 5 different FDA medical officers have examined the clinical details of the deaths (Drs Burkhart, Knudsen, Oliva, Mani, Freiman, Boehm and Feeney).

¹¹ Historically, few drug-associated events have been recognized that are late occurring. While some have used this as an argument to dismiss late occurring observations, I don’t think that there is much actual denominator based evidence for late occurring events. Thus, the absence of evidence means little when interpreting an observation that appears late.

Let's focus first on the degree of uncertainty that there is for mortality with any new treatment for a disease in an elderly population where survival has not been evaluated as an efficacy endpoint (Alzheimer's Disease (AD) and Parkinson's disease). Of course, if the event leading to death is highly specific and recognizable then careful review will probably identify its occurrence without the need for comparative data. However, if the clinical manifestations of the risk are non-specific resulting in several types of deaths or the event(s) already occurs to some extent in the elderly, it may be difficult to identify the risk without comparative data showing an excess in all-cause or cause-specific mortality.¹² Sudden death, for example, occurs in most elderly populations, hence one may need comparative data to conclude that drug is not causing sudden death.

Indeed, to have substantial statistical evidence that a drug was not causing death in an AD population, the controlled studies will have to be substantially larger than in any NDA I am aware of. Consider the summary findings in Table 6 for the rivastigmine RCT experience and let's assume that it is reasonable to just pool across what appears to be a large amount of controlled experience. As already discussed, there is little statistical power to conclude that the observed excess in mortality observed with rivastigmine is not due to chance. But what if we required that the controlled experience be powered to exclude the possibility that the drug of interest was causing death at a rate of 1 per 100 person-years. My assumption is that most regulatory personnel would find that a drug with this degree of known risk should not be approved - given that it had a marginal beneficial effect.

Let's assume that the background death rate in the population entered into the RCTs is 2 per 100 (similar to that in the donepezil and rivastigmine NDAs), how much experience would it take to find a 1.5 fold increase in mortality (1 extra event per 100 patients per year)? If we require a p value of < 0.05 to have the statistical evidence to conclude that the groups were indeed different, one needs about 900 person-years per group. None of the NDAs in AD have anywhere near this degree of experience.

Similarly, how large would the controlled experience have to be assuming that we found no difference in rates between randomized groups, and we want the upper confidence limit to be less than 1.5? Again assuming that the background rate remains at 2 per 100, we would need slightly more than 2000 person-years per group.

In my view, it is not unreasonable for NDAs for drugs that have a marginal benefit to directly exclude a mortality risk for 1 per 100 person-years. In fact, I don't think it would be too surprising that a cholinergic drug could cause life-threatening events in the elderly since these drugs probably all affect cardiac conduction through their pharmacological action at some dose. In fact, most of the development programs have attempted to find

¹²My general belief is that evaluating events in an elderly population is very difficult and that individual case review will not be that helpful. Thus, I am a proponent of replacing the open experience with large randomized studies that are unblinded and focus on the most serious events.

the doses that show some effect on cognitive function without having other untoward cholinergic effects including those on the cardiovascular and digestive systems.

The problem with trying to exclude this degree of risk for a drug intended for the elderly is that one needs comparative data since death is a relatively common event. Thus, in my opinion, all the AD NDAs that I have seen to date are vastly underpowered to find meaningful effects on mortality, and I don't think we can rely on individual case review to exclude risk.

With donepezil in particular, the NDA was much smaller than the rivastigmine NDA. Thus, not only did we have limited comparative data for detecting mortality differences, but there was limited power to find other events of interest. This latter point deserves some comment since we should also consider the degree of uncertainty that there is in most NDAs for events that are life threatening but not necessary fatal.

In fact, much of the NDA safety review is concerned with events like fulminant hepatic failure, rhabdomyolysis, etc. Within this context, there is significant experience with rivastigmine suggesting that the drug does not cause these types of events. Since there are about 3000 person-years of experience in the rivastigmine NDA, we could cap these risks as no greater than 1 per 1000 patients per year. Overall, there appears to be least 4-5 times more experience in the rivastigmine NDA than in the donepezil NDA. Thus, I think there is less uncertainty about rivastigmine for many events than in most NDAs, and in particular, with donepezil.

An argument to require the completion of the large simple trial before approval focuses on the fact that there is a weak signal of concern for a drug that has been shown to have a marginal symptomatic benefit when similar products are already on the market without such a signal. The fact that we may not have as much evidence to affirm the safety of the marketed products as we would like does not mean that we approve a product with even a weak signal of concern for a serious event. The key to this argument then becomes defining exactly what is a weak signal of concern – certainly numerical differences between drug and placebo for serious events are observed in most NDAs, and some could consider these weak signals of concern. The regulatory burden for delineating exactly what constitutes a signal seems greater with this argument since holding up approval is quite a bit different than requiring more data after approval. Certainly, as the threshold for defining signals is lowered, the difference between small NDAs without signals and large ones with weak signals becomes less and less.

In my view, this sort of argument is more difficult to make since I don't think the degree of uncertainty with rivastigmine is that much different from that present with other approvals. In fact, for many events, we have a great deal more experience with rivastigmine. One could argue, I suppose, that sponsor's of marketed cholinergics and those under IND be required to conduct studies similar to that needed for rivastigmine while Novartis completes the study for rivastigmine before its approval.

In conclusion, I view the evidence in the rivastigmine NDA as consistent with a weak signal of concern that rivastigmine could have a life-threatening risk. While I think it is unlikely that rivastigmine use accounts of the excess mortality in the RCTs or the association between mortality and use of 10/12 mg across the full database, a randomized study comparing several doses of rivastigmine with several doses of donepezil should be conducted to affirm the safety of rivastigmine.

Greg Burkhart, M.D., M.S.
Safety Team Leader
Neuropharmacological Drug Products

HFD-120/Levin/Burkhart/Mani/Katz

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Appendix I. Mortality with Rivastigmine**Table 1. Mortality rates by current dose in the RCT extension dataset**

Dose	PYs	<u>Deaths Within 7 Days of LPD</u>		<u>Deaths Within 30 Days of LPD</u>	
		Counts	Rate	Counts	Rate
2	134	1	7.5	3	22.4
4	221	1	4.5	2	9.0
6	355	1	2.8	4	11.3
8	285	3	10.5	3	10.5
10	231	2	8.7	5	21.7
12	760	12	15.8	18	23.7

Rates are deaths per 1000 person years (PYRs)

PYs, person-years; LPD, last prescribed dose

Table 2. Mortality rates by current dose in the RCT extension dataset for patients who were assigned drug in the preceding RCT

Dose	PYRs	<u>Deaths Within 7 Days</u>		<u>Deaths Within 30 Days</u>	
		Counts	Rate	Counts	Rate
2	78	0	0.0	0	0.0
4	132	0	0.0	0	0.0
6	222	1	4.5	4	18.0
8	194	1	5.2	1	5.2
10	168	2	11.9	4	23.9
12	552	9	16.3	13	23.6

Rates are deaths per 1000 person years (PYRs)

PYs, person-years; LPD, last prescribed dose

Table 3. Mortality rates by current dose in the RCT extension dataset for patients assigned placebo in the preceding RCT

Dose	PYRs	<u>Deaths Within 7 Days</u>		<u>Deaths Within 30 Days</u>	
		Counts	Rate	Counts	Rate
2	56	1	17.9	3	53.6
4	89	1	11.2	2	22.4
6	133	0	0.0	0	0.0
8	91	2	21.9	2	21.9
10	63	0	0.0	1	15.9
12	208	3	14.4	5	24.0

Rates are deaths per 1000 person years (PYRs)

PYs, person-years; LPD, last prescribed dose

Table 4. Adjusted rate ratios for 10-12 mg compared to lower doses in the RCT extension dataset

	Adjusted RR	95% CI
All Extension Patients		
Deaths within 30 days	1.8	0.9,3.6
Deaths within 7 days	2.2	0.9,5.8
Extension Patients with Drug in RCT		
Deaths within 30 days	2.7	1.0,7.5
Deaths within 7 days	4.4	1.0,19.9
Extension Patients with Placebo in RCT		
Deaths within 30 days	1.0	0.3,3.0
Deaths within 7 days	0.9	0.2,4.1

Adjusted for age, sex and time since study entry

Table 5. Relative All-Cause Mortality in the RCT Extension Dataset for 10 and 12 mg Compared to Lower Doses

	Relative Mortality	95% CI
Deaths within 7 Days		
Unadjusted	2.7	1.0,7.5
Adjusted	3.5	1.0,9.8
Deaths within 7 Days; Implausible Excluded		
Unadjusted	2.3	0.9,5.8
Adjusted	2.9	1.1,7.7
Deaths within 30 Days		
Unadjusted	1.7	0.9,3.5
Adjusted	2.1	1.0,4.4

*Adjusted for age, gender, baseline CVD, baseline GDS, baseline weight, and prior exposure in RCTs

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ON ORIGINAL**

Memorandum

Date: March 23, 1999
To: Russ Katz, M.D.
Acting Director, Division of Neuropharmacological
Drug Products
Through: Greg Burkhart, M.D. *151*
Safety Team Leader *11/79*
From: Gerry Boehm, M.D.
John Feeney, M.D.
Joel Freiman, M.D.

Subject: Classification of Deaths in NDA 20-823

We were asked to review the records available for 56 deaths. We were asked to 1) identify the sudden unexplained deaths and 2) identify the deaths in which drug-attribution was implausible.

The records we reviewed were provided by Novartis in a February 26, 1999 submission (7 volumes). The records were blinded as to treatment assignment. They contained patient narratives, serious adverse event case report forms, hospital records, and death certificates where available.

Before reviewing the cases, the three of us met and agreed on the following definitions.

Sudden Unexplained Deaths

We considered the following criteria essential to our diagnosis of sudden unexplained death (SUD).

1. If observed, the death occurred within minutes.
2. An obvious medical cause of death was not found. If an autopsy was not performed, an obvious medical cause of death was also not established based on clinical information.
3. Accidental deaths such as drownings, motor vehicle accidents (where the patient was the driver), and falls with immediate death were included.
4. Deaths from gunshot wounds and other violent acts (passenger in a motor vehicle accident) were not included.

Implausible Drug-Attribution

Drug attribution was considered implausible in the following situations.

1. The death occurred > 7 days after cessation of drug. However, if the precipitating cause of death occurred within 7 days of drug cessation, drug attribution was considered plausible even if death was delayed beyond 7 days of drug cessation.
2. The death was due to a gunshot wound or other violent act.
3. The death was due to autopsy-proven CAD with acute MI.
4. The death was due to autopsy-proven pulmonary embolism.
5. The death was due to stroke in the setting of a cardiac risk factor (atrial fibrillation) or with evidence of peripheral vascular disease.
6. The death was due to meningitis.
7. The death was due to subarachnoid hemorrhage.
8. The death occurred in a patient moribund from cancer.

Drug attribution was specifically mentioned as plausible in the following situations.

1. The cause of death was unknown or unclear.
2. Death resulted from suicide.
3. Death resulted from pneumonia or urosepsis.
4. The death was classified as a SUD.
5. The death resulted from complications caused by an accidental fall.

Results: The attached table reflects the results of our review. Twenty deaths were considered implausible. Fourteen deaths were considered SUDs. A brief rationale for the classification of each case is also included in the table.

^m
Gerry Boehm, M.D.

John Feeney, M.D./

Joel Freiman, M.D.

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Spreadsheet for the exelon blinded review of deaths

Patient number	Assessment of implausibility	SUD	Comments
30334018	Not implausible	YES	Found dead in bed, no autopsy
30409003	Not Implausible	NO	Died from GI bleed that was not completely worked up due to underlying malignancy
P 30411001	Not Implausible	NO	Fell, leg fx, pin inserted, developed pneumonia, PE, died
P Ext 30302004	Not Implausible	NO	Fell, hip fx, hip replacement, infected prosthesis, died from sepsis ✓
D Ext 30304001	Not implausible	NO	developed worsening CHF, then viib, asystole, death ✓
D Ext 30305010	Not implausible	NO	Recent ?respiratory infection not well described ✓
D Ext 30312016	Not implausible	NO	Fell, fx hip, died from ?PE ✓
P Ext 30329008	Not implausible	YES	Got out of bed, collapsed, became SOB, LOC, death ✓
D Ext 30331002	Not implausible	YES	Post hip fx, died at home but cause of death unclear, sudden ✓
P Ext 30342006	Not implausible	YES	Died while walking ✓
D Ext 30411003	Not implausible	NO	Chest infection ✓
P Ext 304425004	Not implausible	YES	Sudden death, no autopsy ✓
P Ext 30431015	Not implausible	NO	Fell, fx hip, pinned, re-pinned due to misalignment, developed UTI, sepsis, death ✓
35103011	Not implausible	NO	Nausea, vomiting, anorexia -d/c'd drug, next day dx with prostate CA, died 3d later
35105003	Not implausible	NO	Left frontal lobe bleed
35215039	Not implausible	YES	Sudden death, heard falling to floor EMS called CHB no autopsy
D Ext 35102071	Not implausible	YES	LOC sudden death failed resuscitation, no info to support MI (reported cause)
P Ext 35106045	Not implausible	NO	hospitalized for abd pain, hematemesis, ileus, ?diverticulitis and died next day ✓
D Ext 35111049	Not implausible	NO	?infection, neg CXR, neg urine ?blood, +fever, sl inc WBC, ?resp failure ✓
D Ext 351112014	Not implausible	YES	Hx of AAA, died suddenly, but no autopsy ✓
D Ext 32502038	Not implausible	YES	Found dead in bed ✓
D Ext 35203002	Not implausible	YES	Died 3 days after hosp discharge, treated for chest congestion, dyspnea, weakness ✓
P Ext 35203023	Not implausible	YES	Found dead in bed ✓
D Ext 35203025	Not implausible	NO	No hx CAD, inferior wall MI, died 3 days later ✓

WJF

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PEXT	35204022	Implausible	NO	Brain lesions, likely from a long primary
DEXT	35204042	Not implausible	NO	Intraparenchymal bleed, hypertensive crisis
PEXT	35207028	Not implausible	NO	Collapsed, resuscitated, ECG with inferior ischemic changes c/w MI, later died
DEXT	35213004	Not implausible	NO	Developed renal/hepatic insufficiency and died
PEXT				
DEXT				
PEXT				
DEXT				
PEXT				
	-35502104	Not implausible	YES	Sudden death at dinner table, no autopsy
	-35507116	Not implausible	YES	Found dead in bathroom, no autopsy
	-35510117	Not implausible	NO	Suicide, GSW to head
	-35515108	Not implausible	NO	syncope, ?aspiration, acute respiratory failure, arrested, died, no autopsy
	-35516101	Not implausible	YES	Sudden death, no autopsy
	-35518102	Not implausible	NO	5 days after last dose died of CVA
	-35524116	Not implausible	NO	CVA unsure of any of details, died 2 days later ?second CVA?
	35528105	Not implausible	NO	Fall, hip fx, THR, post op infection, died from confirmed PE 27 days after last dose
	-35528128	Not implausible	NO	? Respiratory infection, few details aside from presence of fever/cough

5 SUD From DEXT ~~6~~ 15 not Impl.
 4 SUD From PEXT 6 not Imp.
 2 SUD From RCTs 6 not Imp
 3 SUDs Titration 9 not Imp
 14 36

Memorandum

Date: April 21, 1999
To: Russ Katz, M.D.
Acting Director, Division of Neuropharmacological
Drug Products
Through: Greg Burkhart, M.D.
Safety Team Leader
From: Gerry Boehm, M.D.
John Feeney, M.D.
Joel Freiman, M.D.

ISI 1-21-99

Subject: Classification of Deaths in NDA 20-690

We were asked to review the records available for 67 deaths. We were asked to 1) identify the sudden unexplained deaths and 2) identify the deaths in which drug-attribution was implausible.

The records we reviewed were provided ~~in~~ in an April 1, 1999 submission. The records were not blinded as to treatment assignment. They consisted almost entirely of patient narratives without supporting documentation.

Before reviewing the cases, the three of us met and agreed on the following definitions.

Sudden Unexplained Deaths

We considered the following criteria essential to our diagnosis of sudden unexplained death (SUD).

1. If observed, the death occurred within minutes.
2. An obvious medical cause of death was not found. If an autopsy was not performed, an obvious medical cause of death was also not established based on clinical information.
3. Accidental deaths such as drownings, motor vehicle accidents (where the patient was the driver), and falls with immediate death were included.
4. Deaths from gunshot wounds and other violent acts (passenger in a motor vehicle accident) were not included.

Implausible Drug-Attribution

Drug attribution was considered implausible in the following situations.

1. The death occurred > 7 days after cessation of drug. However, if the precipitating cause of death occurred within 7 days of drug cessation, drug attribution was considered plausible even if death was delayed beyond 7 days of drug cessation.
2. The death was due to a gunshot wound or other violent act.
3. The death was due to autopsy-proven CAD with acute MI.
4. The death was due to autopsy-proven pulmonary embolism.
5. The death was due to stroke in the setting of a cardiac risk factor (atrial fibrillation) or with evidence of peripheral vascular disease.
6. The death was due to meningitis.
7. The death was due to subarachnoid hemorrhage.
8. The death occurred in a patient moribund from cancer.

Drug attribution was specifically mentioned as plausible in the following situations.

1. The cause of death was unknown or unclear.
2. Death resulted from suicide.
3. Death resulted from pneumonia or urosepsis.
4. The death was classified as a SUD.
5. The death resulted from complications caused by an accidental fall.

Results: The attached table reflects the results of our review. Thirty-two deaths were considered implausible. Twelve deaths were considered SUDs. A brief rationale for the classification of each case is also included in the table.

ISI
Gerry Boehm, M.D.

ISI
John Feeney, M.D.

ISI
Joel Erdman, M.D.

Aricept deaths on disk

Nar #	Pt ID	Plausibility	Sudden	Comments
201_012		I	No	Off study drug almost two weeks before family noted increasing weakness and declining health
202_338		NI	Yes	Found on the floor of her bedroom in cardiac arrest, no autopsy
202_39		I	No	Died of an apparent MI 9 days after discontinuing medication
202_517		NI	Yes	After 218 weeks of study drug she died in bed, no prior symptoms or complaints noted
202_57		I	No	Passenger in a single vehicle MVA
303_354		I	No	Died 6 months after a diagnosis of lung cancer, off study drug 1-week prior to death
303_364		I	No	Narrative describes a gradual decline in functional status, drug stopped 9 days prior to death
303_365		I	No	Died 19 weeks after diagnosed with lung cancer (not treated)
303_367		I	No	Myeloma treated palliatively, developed apparent CVA, (?hyperviscosity)
303_371		I	No	CVA 17 days after stopping drug, Death occurred 34 days after stopping drug
303_375		I	No	Death due to autopsy proven pulmonary embolism
303_391		NI	Yes	Expired in her sleep, no autopsy
303_411		NI	No	Found dead, prior day had difficulty breathing and swallowing, no treatment undertaken
303_412		NI	No	Hx of angina, had CP, LMD found him hypotensive, admitted, died next day ?MI
303_415		NI	No	Had two MI's, the second one (in ICU) fatal
303_423		I	No	Altered mental status, put on multiple meds (antipsychotics, anxiolytics)
303_441		I	No	Drug dc'd (for bradycardia) 11 days prior to death
303_452		NI	No	Few details, ?embolism to lower legs (no info about workup) died 45d after event
303_468		NI	Yes	Found dead outside house by a neighbor
303_500		NI	No	Developed sepsis, required ventilatory support, made comfort care and died
303_504		NI	No	Deteriorated following a fall (?fall related to drug)
303_526		I	No	Died 9 days after last dose (diagnosed with advanced pancreatic/liver cancer)
303_331		I	No	Died 30d after last dose, drug was d/c'd after admission to NH for agitation, difficulty prov care
304_234		I	No	Hit by a car, died from multiple trauma
304_320		I	No	V/Q scan demonstrated a PE (actual results not provided)
313_488		I	No	Died 18d after stopping drug from a bilat pneumonia (drug stopped for deter condition)
313_498		NI	Yes	Found dead next to bed
442		I	No	Died 11d after last dose, drug dc'd during admission for abd pain; pt with myelodysplasia
ADE-301-1392		I	No	Bladder cancer, in hospice at time of death
ADE-301-95		NI	No	Admitted for GI bleed, renal insufficiency, d/c'd to NH, condition deteriorated
ADE-302-78		NI	Yes	Admitted for CP- w/u neg for MI, d/c'd, at home, more CP, died suddenly
ADE-303-108		NI	Yes	Collapsed in front of family, failed resuscitation efforts
ADE-303-176-2		NI	No	Acute anterior wall MI
ADE-303-1962		NI	No	Autopsy revealed hemorrhagic pancreatitis, cholelithiasis, ? common duct, pancreatic duct patent
ADE-303-209		I	No	Leiomyosarcoma, esophagitis, during XRT, aspiration pneumonia death

X	ADE-303-243	NI	No	CVA treated at home, subsequently collapsed, not admitted, returned home, died next day
X	ADE-303-250	NI	No	Intracerebral hemorrhage
X	ADE-303-253	I	No	Stones obstructing CBD, pancreatitis/pus, sepsis, death
X	ADE-303-271	I	No	Died 10 mos after dx with metastatic lung cancer, failed chemo
	ADE-304-172	NI	No	13d after d/c'd for tx of Pseud. pneumonia rapidly deteriorated, stopped eating, died 7d later
	ADE-304-205	NI	Yes	Found dead, autopsy myocard hypert, fibrosis, insuff, atherosclerosis, old thrombosis
	ADE-304-216	I	No	Autopsy documented thrombus in the LAD

I=implausible

NI=not implausible

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