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Statistical Report

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Title

Open Observational Study on the Safety of Reminyl® in Patients with Mild to Moderate Alzheimer's Disease

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Results of an Open Observational Study on the Safety of Reminyl® in Patients with Mild to Moderate Alzheimer's Disease

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1. Introduction

The purpose of this multicenter study was to collect safety data on the use of Reminyl® in patients diagnosed with mild to moderate Alzheimer's disease (AD), either as initial treatment or after previous treatment has failed. The study duration was 6 months. In total, the study involved five visits. During visit 1, demographic data was recorded, medical history was taken, vital signs were measured, and lab tests were obtained. MMSE, DAD, NPI, CGI-Caregiver and Cornell scores were first recorded at baseline. Galantamine was prescribed, and a symptoms questionnaire was completed, listing symptoms seen with previous therapeutic treatments. Visits 2, 3, 4, and 5 were scheduled at the end of months 1, 2, 3, and 6, respectively. Every time, the study drug was prescribed again, MMSE, DAD, NPI, CGI-Caregiver and Cornell scores were recorded, adverse events (AEs) were reported, and the symptoms questionnaire was completed. Additional lab tests were obtained during visit 5 (at the end of month 6). Study data were recorded on MS Excel spreadsheets and analyzed using SPSS statistical software. Missing values were not replaced. The results of intention-to-treat (ITT) analyses are presented below. The ITT population comprised all randomized patients, regardless of whether or not they fulfilled inclusion criteria or deviated from study protocol (333 patients). Three of the study participants did not fulfill inclusion criteria (MMSE score). Of these patients, one left the study. There were also 42 patients who discontinued the study prematurely (see Paragraph 3. Number of Evaluable Cases). The data obtained from all these patients were included in the analysis. The techniques used were simple descriptive techniques, t-test for independent and dependent samples, and also chi-square and McNemar's tests where needed. Mixed effects models were used to analyze scale score data (see Paragraph 10 for more details regarding data adjustment).

2. Demographic Data

Participating in the study were 333 patients with mild to moderate dementia of the Alzheimer type, enrolled in 16 centers. Center code numbers, investigators' names, and number of patients by center are shown on Table 1.

Table 1: Number of study participants by center

Center Code Number	**Investigator**	**Number of Patients**
1	Vagenas	20
2	Giatas	30
3	Kontogianni	20
4	Doskas	30
6	Politis	29
7	Sakka	20
8	Fortos	5

9	Varelas	20
10	Gatos	15
11	Makris	20
12	Taskos	4
15	Tsolaki	30
16	Fitsioris	20
21	Oikonomidis	30
22	Rigopoulou	20
25	Papatriantafyllou	20

Of the 333 patients, 137 were men (41.4%) and 194 were women (58.6%). In two cases, the patient's gender was not recorded. Table 2 shows the distribution of men and women, by center:

Table 2: Distribution of men and women by center

Center code number	**Men**	**Women**
1	9 (45%)	11 (55%)
2	13 (43.3%)	17 (56.7%)
3	10 (50%)	10 (50%)
4	15 (50%)	15 (50%)
6	11 (40.7%)	16 (59.3%)
7	9 (45%)	11 (55%)
8	1 (20%)	4 (80%)
9	9 (45%)	11 (55%)
10	8 (53.3%)	7 (46.7%)
11	8 (40%)	12 (60%)
12	1 (25%)	3 (75%)
15	16 (53.3%)	14 (46.7%)
16	9 (45%)	11 (55%)
21	3 (10%)	27 (90%)
22	10 (50%)	10 (50%)
25	5 (25%)	15 (75%)

Age was recorded for 328 patients. As shown in Table 3 below, their mean age was 73.5 years. In general, there was no gender difference in age (mean age difference=0.5 years, t=0.661, p=0.509). Table 4 shows descriptive data of age, by center.

Table 3: Descriptive data of patient age (in years)

N	328
Mean	73.5
Median	74.0
Standard deviation	6.68
Min	55
Max	92

Table 4: Descriptive data of patient age by center (in years)

Center	N	Mean	Median	Standard deviation	Min	Max
1	20	71.1	73.0	6.20	55	78
2	30	75.6	75.0	6.61	62	90
3	20	78.3	79.0	3.95	71	86
4	30	74.5	74.0	6.57	65	89
6	28	72.0	73.0	6.54	59	85
7	17	74.4	76.0	5.50	61	82
8	5	80.6	82.0	9.04	71	92
9	20	74.5	75.0	6.28	62	90
10	15	69.9	65.0	10.37	59	86
11	20	71.9	71.5	5.43	56	82
12	4	75.8	75.5	7.37	67	85
15	29	73.4	75.0	7.10	58	84
16	20	71.5	73.5	4.67	61	81
21	30	71.9	72.0	5.85	61	87
22	20	73.4	72.0	5.94	59	86
25	20	74.1	74.0	7.57	62	88

As can be seen from Tables 2 and 4, the centers were quite homogeneous in terms of patient demographic data With respect to caregiver characteristics, caregivers were mostly women - 226 women (69.5%) vs. 99 men (30.5%). 242 caregivers (78.6%) lived with the patient, while 66 (21.4%) did not. The vast majority of caregivers were closely related to the patient: 162 (48.9%) were spouses, 121 (36.6%) were children, 2 (0.6%) were grandchildren, 14 (4.2%) were siblings, 5 (1.5%) were parents, 2 (0.6%) were nieces/nephews, and 25 (7.6%) were professional caregivers. Typically, caregivers were younger than patients. Descriptive data are presented in Table 5.

Table 5: Descriptive data of caregiver age (in years)

N	309
Mean	59.1
Median	61.0
Standard deviation	14.52
Min	22
Max	91

3. Number of Evaluable Cases

Out of 333 patients, 42 (12.6%) discontinued the study prematurely. 291 patients (87.4%) completed the study. Table 6 shows causes of study discontinuation (in the case of one patient whose last visit was at month 5 and subsequently discontinued, no cause of discontinuation was recorded):

Table 6: Number of patients who discontinued the study prematurely, by cause.

Insufficient efficacy	1
Adverse events	5
Lost to follow-up	31
Other causes	4
Total	41

Of the four patients for whom the cause of discontinuation was categorized under 'Other causes', three were discharged from hospital and one patient died. In two other patients, two causes of study discontinuation were recorded. One patient no longer fulfilled inclusion criteria (original cause of discontinuation was insufficient efficacy); another patient was discharged from hospital (and was lost to follow-up). Table A in the Appendix lists detailed information on cases of early discontinuation, by patient and center.
Table 7 shows the number of patients who discontinued the study at any time point (last recorded visit):

Table 7: Patient's last recorded visit

	1st visit	End of month 1	End of month 2	End of month 3
Discontinued the Study	17	9	4	12
Cumulatively	17	26	30	42
No. of patients remaining in the study	316	307	303	291

Seemingly, the highest number of last recorded visits occurred after the 1st visit. Table 8 shows discontinuations by center:

Table 8: Number of study discontinuations, by center

Center	Number of discontinuations
1	1/20 (5%)
2	2/30 (6.7%)
3	0/20 (0%)
4	7/30 (23.3%)
6	0/29 (0%)
7	0/20 (0%)
8	0/5 (0%)
9	4/20 (20%)
10	8/15 (53.3%)
11	1/20 (5%)
12	0/4 (0%)
15	19/30 (63.3%)
16	0/20 (0%)
21	0/30 (0%)
22	0/20 (0%)
25	0/20 (0%)

Apparently, the highest number of discontinuations occurred in centers 15 (where 19 patients discontinued) and 10 (where 8 patients discontinued).
There is a strong correlation between gender and discontinuation rate. Out of 194 women, 18 discontinued (9.3%); out of 137 men, 24 discontinued (17.5%). The difference was statistically significant (χ^2=4.921, p=0.027). The correlation between discontinuation rates and age was not found to be statistically significant (coefficient of age obtained from logistic regression was -0.14; standard error = 0.025; p=0.580).

4. Dosage

In most patients, medication dosage was increased gradually. The most common doses were 8 mg/day, 16 mg/day, and 24 mg/day. Non-standard (interim) doses were also used infrequently. Table 9 shows basic descriptive data of dosage. Table 10 shows frequency of occurrence and rates of different doses, at each time point of the study.

Table 9: Descriptive data of dosage (mg/day) at each time point of the study

	Baseline-Month 1	Month 1-Month 2	Month 2-Month 3	Month 3-Month 6	After month 6
N	333	308	302	294	289
Mean	11.8	17.3	21.1	22.1	22.4
Median	8.0	16.0	24.0	24.0	24.0
Standard deviation	4.41	3.68	4.16	3.70	3.19
Min	8	8	8	8	16
Max	24	24	24	24	24

Table 10: Frequency of occurrence and rates of dosage (mg/day), at each time point of the study

Dosage (mg/day)	Baseline-Month 1	Month 1-Month 2	Month 2-Month 3	Month 3-Month 6	After month 6
8	185 (55.6%)	11 (3.6%)	6 (2%)	4 (1.4%)	
10				1 (0.3%)	
12		1 (0.3%)			
16	139 (41.7%)	234 (76%)	96 (31.8%)	60 (20.4%)	57 (19.7%)
24	9 (2.7%)	62 (20.1%)	200 (66.2%)	229 (77.9%)	232 (80.3%)

Evidently, the most common doses were: 8 mg/day during the first month of the study, 16 mg/day between months 1 and 2, and 24 mg/day after month 2. Initial dose distributions appeared to be equal in both genders (χ^2=2.632; p=0.268). The correlation between initial dose and age was very weak (r=-0,047; p=0,392). Mean initial dose was not different between patients who eventually discontinued the study and study completers (mean doses were 11.1 mg/day and 11.9 mg/day, respectively; t=-1.138; p=0.256).

5. Medical History - History of Previous Treatments for Alzheimer's Disease - Rationale for the Use of Reminyl - Adverse Events Before Baseline

Out of 333 patients, 113 (33.9%) had no medical history. Of the remaining 220 patients' medical histories, 103 (46.8%) involved a single organ system, 63 (28.6%) involved two organ systems, 30 (13.6%) involved three organ systems, 16 (7.3%) involved four organ systems, 2 (0.9%) involved five organ systems, 5 (2.3%) involved six organ systems and in 1 patient (0.5%) the medical history involved nine organ systems. Table 11 shows the total number of medical conditions (432 events), by organ system, for the 220 patients who reported at least one condition in their medical history.

Table 11: Number of conditions reported in the medical histories during the study, by organ system

Organ system	No. of medical conditions
Allergic/immunologic	4
Cardiovascular	106
Integumentary	4
Ears, nose, and throat (ENT)	21
Endocrine	42
Eyes	25
Gastrointestinal	18
Genitourinary	29
Hematologic	11
Musculoskeletal	33
Neurological	58
Psychiatric	62
Respiratory	7
Other	12
Total	432

Evidently, the most affected system was the cardiovascular, followed by the psychiatric and neurological systems. Mean age was marginally equal for patients with and without a medical history (72.6 years for patients without a medical history vs. 74.0 years for patients with a medical history; t=-1,863; p=0.063). Patient gender was unrelated to medical history.. Of the 194 women, 128 had a medical history (66%); of the 137 men, 91 did (66.4%). The difference was statistically insignificant (χ^2=0.007; p=0.933). Premature discontinuation did not appear to be related to medical history. Of the 113 patients without a medical history, 12 discontinued the study prematurely (10.6%); of the 220 patients with a medical history, 30 did (13.6%). The difference was statistically non significant (χ^2=0.616; p=0.432). The existence of a medical history did not appear to be related to the initial dose (mean initial dose was 11.8 mg/day for patients both without and with a medical history; t=-0,058; p=0,954). The complete medical history of each patient is shown in the Appendix (Table B).

Time from symptoms to diagnosis appeared to be high-variance. Table 12 shows the main descriptives and some selected percentiles. Evidently, the time from symptoms to diagnosis is characterized by fairly high values.

Table 12: Descriptive data of time from symptoms to diagnosis (in months)

N	321
Mean	64.2
Median	52.1
Standard deviation	59.05
Min	0.0
Max	304.0
5%	0.0
15%	8.7
80%	104.3
90%	144.9
95%	196.6

History of previous treatments for Alzheimer's disease included the use of various therapeutic substances, mainly donezepil and rivastigmine. The highest number of patients had been exposed to one type of treatment

(229/317=72.3%). 75 patients had been exposed to two types of treatment (23.7%) 13 patients had been exposed to three types of treatment (4.1%) Table 13 shows the frequency of use of various therapeutic treatments for the disease.

Table 13: Frequency of use of various therapeutic treatments for Alzheimer's disease, before baseline.

Therapeutic substance	Frequency of use
None	16
Non pharmacological	3
Nootropics	47
Ginkgo biloba	1
Memantine	27
Donezepil	194
Rivastigmine	125
Other	21

Prior to treatment initiation with Reminyl, 307 patients (92.2%) had already been treated for Alzheimer's disease with another AChE inhibitor, while in 26 patients (7.8%) Reminyl was the first AChE inhibitor used. Of those who had previously been treated for Alzheimer's disease with another AChE inhibitor, 217 (70.7%) reported non-responsiveness to the previous treatment, 81 (26.4%) reported adverse events related to the previous treatment, and 9 patients (2.9%) reported both. Of the 26 patients who received Reminyl as the first AChE inhibitor, 20 (76.9%) received Reminyl as initial symptomatic treatment with an AChE inhibitor, and 2 (7.7%) were nonresponders to previous symptomatic treatment. For 4 patients (15.4%), no explanation was provided as to why Reminyl was selected as the first AChE inhibitor.
The difference of mean age between patients who received Reminyl as the first AChE inhibitor and those who did not was statistically insignificant (75.0 and 73.4 years, respectively; t=-1,132; p=0,259).
Of the 26 patients who received Reminyl as the first AChE inhibitor, 12 were women (46.2%), and of the remaining 305, 181 were women (59.3%). The difference was statistically non significant (χ^2=0.862; p=0.353). No correlation was observed with study discontinuation. Of the 26 patients who received Reminyl as the first AChE inhibitor, 4 discontinued prematurely (15.4%), and of the 307 who did not, 38 discontinued prematurely (12.4%). The difference was statistically non significant (χ^2=0.197; p=0.657). By contrast, medical history appeared to be strongly correlated. Of the 26 patients who received Reminyl as the first AChE inhibitor, 8 had a medical history (30.8%), while of the 307 who did not, 212 had a medical history (69.1%). The difference was statistically significant (χ^2=15.672; p=0.001). Patients who received Reminyl as the first AChE inhibitor had different mean initial doses than those who had received previous treatments (mean dose 9.9 mg/day vs. 11.9 mg/day; t=2.333; p=0.020).

91 patients had presented adverse events (AEs) with previous treatments; all had been treated for Alzheimer's disease with another AChE inhibitor. Of these, 4 were nonresponders to the previous treatment, 80 reported AEs related to the previous treatment, and 7 reported both non-responsiveness and AEs related to previous treatment. The results below are based on the 307 patients for whom Reminyl was not the first AChE inhibitor. Of the 90 patients who previously presented AEs, 62 were women (68.9%), and of the remaining 215, 119 were women (55.3%). The difference was statistically significant (χ^2=4.821; p=0.028). The mean ages did not differ between patients who had previously developed AEs and those who had not (72.8 and 73.7 years, respectively; t=0.973; p=0.332). The presence of AEs before baseline was found to be related to premature discontinuation. Of the 216 patients who had not presented AEs before baseline (with other treatments), 19 left the study (8.8%); of the 91 patients who had, 19 left (20.9%). The difference was statistically significant (χ^2=8.619; p=0.003). Moreover, the mean initial doses appeared to differ between patients who had previously developed AEs and those who had not (10.3 and 12.6 mg/day, respectively; t=4.334; p=0.001). Finally, there appears to be a marginal correlation between

medical history and previous AEs. Of the 91 patients with previous AEs, 70 had a medical history (76.9%); of the remaining 216 patients, 142 had a medical history (65.7%). The difference was marginally non-significant (χ^2=3.747, p=0.053).
The 91 patients with previous AEs reported 140 AEs in total, which were seen with previous treatments for Alzheimer's disease (see Table 15).

Table 15: AEs seen with previous treatments for Alzheimer's disease

AE	Frequency of occurrence	AE	Frequency of occurrence
Worry	2	Dizziness	8
Anorexia	4	Vertigo	2
Apathy	1	Debility (fatigue, tiredness)	9
Weight loss	2	Headache	7
Instability	2	Abdominal pain	2
Insomnia	4	Cramps	3
Bradycardia	3	Muscular weakness	1
Gastrointestinal upset	4	Nausea	20
Gastric discomfort	2	Acid regurgitation	1
Diarrhea	10	Stomach ache	1
Agitation	4	Low WBC count	1
Dyspepsia	3	Confusion	2
Precordial discomfort	1	Frequent urination	1
Vomiting	22	Lower extremity tremor	1
Epigastralgia	7	Hyperactivity	1
Deterioration of tremor	1	Hypertension	1
Aggression	1	Somnolence	1
Nightmares	1	Hypotension	1
Sweating	1	Hallucinations	2

6. Safety

300 patients (90.1%) did not develop any adverse events (AE) at any time. The remaining 33 patients developed at least one adverse event at some point during the study. Table 16 shows the rates of patients who developed a minimum of one AE at each visit.
As can be seen the number of AEs was generally low. AE occurrence rates were slightly increased at the end of months 1 and 3 of the study. The former rate can be considered at the high end of normal, whereas the latter is high and cannot be attributed to dose increase. Of the 138 patients whose dose was increased between the end of months 2 and 3, only 5 (3.6%) showed a difference in the occurrence of AEs (defined as developing an AE at the end of month 3 if no AE was present at the end of month 2). Of the 154 patients whose dose was not increased between the end of months 2 and 3, 8 (5.2%) showed a difference in the occurrence of AEs. The difference was statistically non significant (χ^2=0.423; p=0.516).

Table 16: Rates of patients who developed at least 1 AE, by visit

End of month 1	End of month 2	End of month 3	End of month 6
14/312 (4.5%)	8/303 (2.6%)	17/295 (5.8%)	6/293 (2%)

Men and women showed the same rates of AEs. Of the 137 men, 11 developed AEs (8%), whereas of the 194 women, 22 developed AEs (11.3%). The difference was statistically non-significant (χ^2=0.981, p=0.322). Of the 220 patients with a medical history, 21 developed AEs (9.5%); of the remaining 113 patients without a medical history, 12 developed AEs (10.6%). The difference was statistically insignificant (χ^2=0.096; p=0.756). Of the 26 patients who received Reminyl as the first AChE inhibitor, 1 patient developed AEs (3.8%); of the remaining 307, 32 developed AEs (10.4%). The difference was statistically insignificant (χ^2=1.161; p=0.281). No difference was seen in mean age between patients who developed AEs and those who did not (73.5 years in both groups; t=0.035; p=0.972). No difference was seen in mean initial dose between patients who developed AEs and those who did not (12.6 and 11.7 mg/day, respectively; t=-1.145; p=0.253).
There appears to be no correlation between AEs seen with previous treatment and the occurrence of AEs with Reminyl. Of the 242 patients who had not developed AEs with previous treatment, 24 (9.9%) developed AEs with the use of Reminyl; of the 91 patients who had developed AEs with previous treatment, 9 developed AEs with Reminyl (9.9%). The difference was statistically insignificant (χ^2=0.0, p=1.0). Focusing on patients for whom Reminyl was not the first AChE inhibitor (given that they alone developed AEs with previous treatments), we also see that the occurrence of AEs with previous treatments is unrelated to the occurrence of AEs with Reminyl. Out of a total of 307 patients, of the 91 who developed AEs on previous treatments 9 developed AEs also on Reminyl (9.9%). Of the remaining 216 patients, 23 developed AEs on Reminyl (10.6%). The difference was statistically insignificant (χ^2=0.039; p=0.843). The correlation between AE occurrence and study discontinuation did not appear to be so strong. Of the 300 patients who did not develop AEs, 35 left the study (11.7%); of the 33 patients who developed AEs, 7 left the study (21.2%). The difference was statistically non-significant (χ^2=2,458; p=0,117).

The 33 patients with AEs developed 60 AEs in total. Table 17 lists AEs and heir frequency of occurrence. The most frequent AEs were nausea and vomiting. Infrequent AEs were episodes of confusion (in one patient with an active history of depression; the causal relationship with Reminyl was characterized as doubtful), aggression (two events in one patient with an active history of depression;
their causal relationship with Reminyl was characterized as probable for one episode and excluded for the other), respiratory infection (characterized by the investigator as unrelated to Reminyl), paranoid ideas (in a patient without relevant history; the causal relationship with Reminyl was characterized as doubtful), and hallucinations (two events in one patient with an active history of depression; their causal relationship with Reminyl was characterized as excluded and doubtful, respectively).

Table 17: Adverse events seen during the study, and their frequency of occurrence

AE	Frequency	AE	Frequency
Anorexia	3	Dizziness	1
Weight loss	1	Vertigo	1
Insomnia	2	Debility, lasting 2 hours	1
Diarrhea	4	Headache	2
Weight reduction	3	Fatigue	2
Vomiting	7	Tiredness	1
Vomiting	3	Respiratory infection	1
Vomiting	1	Muscular weakness	1
Ep. Pain	1	Muscular weakness	1
Episodes of confusion	1	Nausea	14
Epigastralgia	1	Paranoid ideas	1
Epigastric pain	2	Salivation	1
Aggression	2	Hallucinations	2

Table 18 shows the number of patients who developed at least one AE during the course of the study, by center According to the results listed in Table 18, no center appears to have a notably high number of patients with AEs.

Table 18: Number of patients who developed at least one AE, by center

Center	Total number of patients	Number of patients with at least one AE
1	20	1 (5%)
2	30	2 (6.7%)
3	20	0 (0%)
4	30	4 (13.3%)
6	29	0 (0%)
7	20	0 (0%)
8	5	0 (0%)
9	20	2 (10%)
10	15	3 (20%)
11	20	1 (5%)
12	4	0 (0%)
15	30	4 (13.3%)
16	20	5 (25%)
21	30	4 (13.3%)
22	20	2 (10%)
25	20	5 (25%)

Of the 33 patients who developed at least one AE, 17 developed 1 AE (51.5%), 12 developed 2 AEs (36.4%), 1 developed 3 AEs (3%), 2 developed 4 AEs (6%), and 1 patient (3%) developed a total of 8 AEs during the course of the study (Table 19).

Table 19: Numbers of AEs, their frequency of occurrence, and rates

	Frequency of occurrence
No AE	300 (90.1%)
1 AEs	17 (5.1%)
2 AEs	12 (3.6%)
3 AEs	1 (0.3%)
4 AEs	2 (0.6%)
8 AEs	1 (0.3%)

One could maintain that the number of patients who showed at least one AE persistently throughout the study is of particular interest. Thus, 2 patients had at least one AE throughout the study. One patient, who had presented dizziness and unsteady gait on previous treatments (Nootropics, Memantine, Donezepil), developed persistent nausea. Another patient with no history of AEs on previous treatments (Memantine, Rivastigmine), developed in succession: insomnia, weight reduction, fatigue, and anorexia. A third patient developed persistent hallucinations, from baseline to the end of month 3.

The characteristics recorded for each AE were severity, causal relationship with the study drug, etc. Table 20 shows the number of AEs, by severity.

Table 20: Frequency of occurrence and rates of AEs by severity (in two cases of AEs, the relevant information is unavailable).

Severity		
Mild	Moderate	Severe
33 (56.9%)	17 (29.3%)	8 (13.8%)

The 8 AEs characterized as severe were all seen in one patient who discontinued the study after the 1st visit. The 8 severe AEs were: nausea, vomiting, diarrhea, epigastric pain, fatigue, insomnia, muscular weakness, and tiredness. Table 21 lists dose-related strategies for the management of AEs. For the majority of AEs, the most drastic strategy used was dose adjustment.

Table 21: Frequency of occurrence and rates of study drug related strategies for the management of AEs

None	Dose adjustment	Temporary discontinuation	Permanent discontinuation
35 (58.3%)	8 (13.3%)	6 (10%)	11 (18.3%)

Table 22 shows AEs for which concomitant treatments were prescribed.

Table 22: Frequency of concomitant treatment due to AE

No	Yes
53 (88.3%)	7 (11.7%)

Table 23 shows the causal relationship between AEs and the use of Reminyl. Table 24 lists AEs more strongly correlated with the use of Reminyl.

Table 23: Causal relationship between AEs and the study drug

Excluded	Doubtful	Possible	Probable	Definite
2 (3.3%)	6 (10%)	13 (21.7%)	24 (40%)	15 (25%)

Table 24: List of AEs whose causal relationship with Reminyl is characterized as possible or higher (frequencies in parentheses).

Causal relationship with the drug	Number of patients	AEs
Possible	8	Anorexia, Diarrhea, Weight reduction, Vomiting (4), Epigastralgia, Headache, Muscular weakness, Nausea (2), Salivation
Probable	12	Anorexia (2), Weight loss (3), Insomnia, Diarrhea, Vomiting (5), Epigastric pain, Aggression (2), Dizziness, Vertigo, Fatigue, Nausea (6)
Definite	7	Insomnia, Diarrhea (2), Vomiting (2), Epigastric pain (2), Fatigue (2), Muscular weakness, Nausea (5)

Table 25 shows results related to AE outcomes. Table 26 lists all AEs which persisted beyond the visit when they were recorded.

Table 25: Frequency of occurrence and rates of AE outcomes

AE resolved	Persisting	Death due to AE
42 (70%)	18 (30%)	0

Table 26: AEs persisting after they were recorded during visits

Number of patients	List of AEs
9	Anorexia (3), Weight loss (4), Insomnia, Epigastric pain, Vomiting, Aggression, Debility, Headache, Fatigue, Nausea, Salivation, Confusion, Hallucinations

For the 18 AEs characterized as 'persisting' in Table 26, this status applies specifically to the visit during which the AE was recorded. The following AEs, seen in 5 patients, appear to persist beyond the end of the study (shown in parentheses are AE duration, in days, up to the end of the study):
Hallucinations (178), Aggression (4), Nausea (176), Anorexia (87), Weight reduction (94), Epigastric pain (7), Insomnia (144), Fatigue (116), Weight reduction (122), Anorexia (402). Table 27 shows descriptive data of AE duration, excluding these cases.

Table 27: Descriptive data of AE duration (in days, excluding AEs that persisted beyond the end of the study)

N	45 (4 missing)
Mean	9.7
Median	9.0
Standard deviation	7.84
Min	1
Max	39

Table 28 shows AEs reported due to severity.

Table 28: Frequency of AE reporting due to severity

Reported due to severity		
No	Yes (no hospitalization)	Yes (prolonged current hospitalization)
59	0	1

In brief, the majority of AE cases were mild to moderate in severity (86.2%) In most instances (71.6%), either no measures were taken or the dose was adjusted. In a high proportion of AEs (65%), the causal relationship with Reminyl was characterized as probable or higher. In 9 patients, the AEs persisted after the end of the study.
Five patients discontinued the study due to AEs. Of these, three patients developed one AE each (Nausea [2] and Aggression), one patient developed eight AEs (Nausea, Vomiting, Diarrhea, Epigastric pain, Fatigue, Insomnia, Muscular weakness, Tiredness), and one patient developed four AEs (Vomiting, Anorexia, Headache, Weight reduction).
The study protocol also recommended subgroup analysis of safety in patients who received Reminyl as initial treatment with an AChE inhibitor vs. patients who had previously been treated with another AChE inhibitor. However, of the 26 patients who received Reminyl as initial treatment with an AChE inhibitor, only one developed 8 AEs, all of which were categorized as severe and had a duration of 12 days. The patient left the study before visit 2.
Table C in the Appendix provides all AE-related information, by center and patient,

7. Lab Tests

Lab tests included blood counts, biochemical tests and urinalysis. Measurements were obtained at visits 1 and 5. Investigators recorded whether measurements were within normal ranges or not. Table 29 shows the numbers and

rates of patients whose lab test results fell outside of the normal ranges. It also shows p-values from McNemar's tests performed to determine whether these rates were equal at the two time points. There were no differences in the rate of abnormal values between baseline and last visit.

Table 29: Numbers and rates of patients whose lab test results fell outside of the normal ranges. The p-values are from McNemar's tests performed to determine whether these rates were equal at visits 1 and 5.

Blood parameters	Baseline (N=320)	End of month 6 (N=293)	p-value
Hemoglobin	9 (2.8%)	5 (1.7%)	0.453
Hematocrit	10 (3.1%)	6 (2%)	0.453
RBC	2 (0.6%)	2 (0.7%)	1.0
WBC	1 (0.3%)	2 (0.7%)	1.0
Platelet count	1 (0.3%)	0	1.0
Neutrophils	1 (0.3%)	0	1.0
Lymphocytes	0	0	-
Monocytes	0	0	-
Eosinophils	0	0	-
Basophils	0	0	-
Biochemical parameters			
SGOT	5 (1.6%)	1 (0.3%)	0.375
SGPT	2 (0.6%)	1 (0.3%)	1.0
Alkaline phosphatase	0	0	-
GGT	6 (1.9%)	1 (0.3%)	0.219
Creatinine	3 (0.9%)	1 (0.3%)	0.500
Urea	3 (0.9%)	3 (0.9%)	-
Urinalysis			
Blood	2 (0.6%)	3 (1%)	1.0
Glucose	7 (2.2%)	8 (2.7%)	1.0
Proteins	1 (0.3%)	0	1.0

As is evident from the table, a very low proportion of values fell outside normal ranges (according to investigators). The differences in rates between visits 1 and 5 are negligible. In the subgroup of patients for whom Reminyl was the first AChE inhibitor used, there was one case each of abnormal values of SGOT, SGPT and GGT.

8. Vital Signs

The measured vital signs were: heart rate (on supine or standing position), systolic blood pressure and diastolic blood pressure. Table 30 shows the numbers and rates of patients whose measured values fell outside of normal ranges (i.e. heart rate [supine or standing] > 90 beats per minute, systolic blood pressure > 140 mm Hg, and diastolic blood pressure > 90 mm Hg)

Table 30: Numbers and rates of patients whose vital signs fell outside of the normal ranges.

	Heart rate (supine position)	Heart rate (standing position)	Systolic blood pressure	Diastolic blood pressure
Baseline	1/278 (0.4%)	2/278 (0.7%)	70/300 (23.3%)	26/300 (8.7%)
End of month 1	0/255 (0%)	0/265 (0%)	63/281 (22.4%)	19/281 (6.8%)
End of month 2	2/248 (0.8%)	3/254 (1.2%)	52/271 (19.2%)	13/271 (4.8%)
End of month 3	0/247 (0%)	0/246 (0%)	47/265 (17.7%)	6/265 (2.3%)
End of month 6	0/243 (0%)	0/243 (0%)	41/263 (15.6%)	10/263 (3.8%)

The probability of a value falling outside of the normal range is very low for heart rate measurements (in both supine and standing positions), and decreases steadily (in a statistically significant manner) for both systolic and diastolic blood pressure measurements, as can be seen by comparing these probabilities between visits, applying McNemar's test (Table 31).

Table 31: Results of comparing (between visits) the probabilities of vital sign measurements falling outside of the normal range. The p-values shown are from applying McNemar's tests.

Visits being compared	Heart rate (supine position)	Heart rate (standing position)	Systolic blood pressure	Diastolic blood pressure
Baseline-End of month 1	1.0	1.0	1.0	1.0
Baseline-End of month 2	0.5	1.0	0.5	1.0
Baseline-End of month 3	1.0	0.153	0.018	0.006
Baseline-End of month 6	0.307	0.045	<0.001	0.011

Tables 32 and 33 are comparable to Tables 30 and 31, but examine the subpopulation of patients for whom Reminyl was the first AChE inhibitor used.

Table 32: Numbers and rates of patients whose vital signs fell outside of the normal ranges (subpopulation: patients who received Reminyl as the first AChE inhibitor)

	Heart rate (supine position)	Heart rate (standing position)	Systolic blood pressure	Diastolic blood pressure
Baseline	0/17 (0%)	1/17 (5.9%)	2/25 (8%)	2/25 (8%)
End of month 1	0/16 (0%)	0/17 (0%)	4/25 (16%)	3/25 (12%)
End of month 2	0/16 (0%)	0/18 (0%)	2/24 (8.3%)	2/24 (8.3%)
End of month 3	0/16 (0%)	0/16 (0%)	3/23 (13%)	1/23 (4.3%)
End of month 6	0/13 (0%)	0/16 (0%)	2/22 (9.1%)	3/22 (13.6%)

Table 33: Results of comparing (between visits) the probabilities of vital sign measurements falling outside of the normal ranges. The p-values shown are from applying McNemar's tests (performed in patients who received Reminyl as the first AChE inhibitor)

Visits being compared	Heart rate (supine position)	Heart rate (standing position)	Systolic blood pressure	Diastolic blood pressure
Baseline-End of month 1	-	-	-	-
Baseline-End of month 2	1.0	1.0	1.0	1.0
Baseline-End of month 3	0.625	1.0	1.0	1.0
Baseline-End of month 6	1.0	1.0	1.0	1.0

Tables 34 and 35 show results from the subpopulation of patients who had received previous treatment with other AChE inhibitors. Due to subpopulation size, these results are comparable to those seen in the entire sample.

Table 34: Numbers and rates of patients whose vital signs fell outside of the normal ranges (subpopulation: patients who had received previous treatment with other AChE inhibitors)

	Heart rate (supine position)	Heart rate (standing position)	Systolic blood pressure	Diastolic blood pressure
Baseline	1/261 (0.4%)	2/261 (0.4%)	68/275 (24.7%)	24/275 (8.7%)
End of month 1	0/239 (0%)	0/248 (0%)	59/256 (23%)	16/256 (6.3%)
End of month 2	2/232 (0.9%)	3/236 (1.3%)	50/247 (20.2%)	11/247 (4.5%)
End of month 3	0/231 (0%)	0/230 (0%)	44/242 (18.2%)	5/242 (2.1%)
End of month 6	0/230 (0%)	0/227 (0%)	39/241 (16.2%)	7/241 (2.9%)

Table 35: Results of comparing (between visits) the probabilities of vital sign measurements falling outside of the normal ranges. The p-values are from McNemar's tests (performed in patients who had received previous treatment with other AChE inhibitors)

Visits being compared	Heart rate (supine position)	Heart rate (standing position)	Systolic blood pressure	Diastolic blood pressure
Baseline-End of month 1	1.0	1.0	1.0	1.0
Baseline-End of month 2	1.0	0.625	1.0	1.0
Baseline-End of month 3	0.728	0.153	0.010	0.005
Baseline-End of month 6	0.210	0.038	<0.001	0.004

9. Co-administered Medications

In total, 189 patients (56.8%) received concomitant treatments for other health issues. However, patients differed in the number of co-administered medications. Table 36 shows the numbers of co-administered medications per patient, and their respective frequency of occurrence and rates.

Table 36: Frequencies of different numbers of co-administered medications received by patients.

Number of co-administered medications per patient	Frequency of occurrence
0	144 (43.2%)
1	76 (22.8%)
2	61 (18.3%)
3	25 (7.5%)
4	17 (5.1%)
5	4 (1.2%)
6	2 (0.6%)
7	2 (0.6%)
8	2 (0.6%)

There appears to be no correlation between the occurrence of AEs before baseline (with the use of previous therapeutic treatments for Alzheimer's disease) and concomitant treatments during the study. Of the 242 patients who had not developed AEs before baseline, 135 received concomitant treatment (55.8%), whereas of the 91 patients who had developed AEs before baseline, 54 received concomitant treatment (28.6%). The difference was statistically non significant (χ^2=0.341; p=0.559).

There is something we need to note about the names and frequencies of co-administered medications used in the study. Some of these medications were impossible to identify, because they were written in illegible handwriting. These medications are recorded in Table 36, but don't necessarily appear in Table 37. Table 37 shows the frequency of occurrence of co-administered medications used by patients during the study.

Table 37: Co-administered medications (by pharmaceutical substance) and their frequency of occurrence

Acenocoumarol	3	Felodipine	1	Mirtazapine	5
Acetylcysteine	2	Ferrous Sulfate	2	Nifedipine	7
Acetylsalicylic Acid	16	Finasteride	6	Nimodipine	2
Alendronate Sodium	5	Fluoxetine Hydrochloride	5	Olanzapine	4
Allopurinol	1	Fluvastatin	1	Omeprazole	2
Amantadine	1	Fluvoxamine	1	Paracetamol + Orphenadrine citrate	1
Amiloride Hydrochloride + Furosemide	4	Folic Acid	1	Paroxetine	4
Amiloride Hydrochloride + Hydrochlorothiazide	1	Fosinopril	3	Perindopril	15
Amitriptyline hydrochloride	1	Furosemide	3	Pindolol	1
Amoxicillin	1	Gabapentin	1	Piracetam	6
Amlodipine	12	Glibenclamide	4	Pramipexole	5
Aniracetam	1	Glibenclamide + Phenformin Hydrochloride	1	Pravastatin Sodium	2
Atenolol	5	Glimepiride	2	Propafenone Hydrochloride	1
Atorvastatin	2	Gliclazide	7	Propranolol	1
Baclofen	1	Glyceryl Trinitrate	3	Propranolol Hydrochloride	1
Betahistine Hydrochloride	1	Hydrochlorothiazide + Amiloride Hydrochloride	3	Quetiapine	12
Betaxolol	1	Indapamide	4	Quinapril	3
Biperiden	1	Insulin Isophane Human Monocomponent Biosynthetic	1	Quinapril Hydrochloride + Hydrochlorothiazide	2
Bromazepam	2	Insulin	7	Rabeprazole	2
Buflomedil	1	Ipratropium	1	Ramipril	6
Buspirone Hydrochloride	2	Irbesartan	3	Ranitidine Hydrochloride	3
Calcitonin	3	Iscover (Clopidogrel)	2	Risperidone	11
Calcium Folinate Pentahydrate	1	Isosorbide Mononitrate	3	Rivastigmine	2
Calcium Salts	10	Lacidipine	1	Rizatriptan	1
Captopril	1	Latanoprost	1	Salbutamol	2
Carvedilol	2	Levodopa + Benserazide Hydrochloride	14	Sertraline	2
Cefepime	1	Levodopa + Carbidopa	6	Simvastatin	5
Cilazapril	4	Levothyroxine Sodium	7	Sertraline	14
Cinnarizine	1	Lisinopril	2	Sulpiride	2
Ciprofloxacin Lactate	1	Loperamide	1	Thiamine Hydrochloride + Pyridoxine Hydrochloride + Cyanocobalamin	2
Citalopram	18	Lorazepam	1	Tiapride	1
Clarithromycin	1	Mebeverine	1	Topiramate (Topamac)	1
Clopidogrel	11	Medigoxin	1	Trimetazidine	2
Diclofenac Sodium	1	Memantine	1	Valsartan	4
Digoxin	5	Metformin Hydrochloride	7	Venlafaxine	4
Enalapril Maleate	3	Metoprolol	3	Vitamin E	2

10. Scale Score Analysis (MMSE, DAD, NPI, CGI-Caregiver, Cornell)

In each visit, patients were assigned scores on the following scales: MMSE, DAD, NPI, CGI-Caregiver, and Cornell. Patients were not assigned scores on all scales at every visit. The main research question here is whether there are differences in scale scores with time (factor name = "TIME") Secondary research questions were whether there are differences in the effects of Reminyl (1) between patients who had developed AEs on previous treatment and those who had not (factor name = "previous AE") (2) between patients who developed AEs during the study and those who did not (factor name = "emergence of AE"), and (3) between patients for whom Reminyl was the first AChE inhibitor used and those for whom it was not (factor name = "first AChE inhibitor").
Data analysis was performed using mixed effects models. Due to the large size of the available sample, an unstructured variance matrix was selected. REML was the method used for parameter estimation. All tests performed to determine the effects of the aforementioned factors are adjusted for the linear effects of age, dose, and different scale scores at baseline.

10.1 Mini-Mental State Examination (MMSE)

Table 38 shows descriptive data of MMSE scores, by visit. As can be observed, the mean MMSE score increased with time, but its standard deviation did not not. The interaction term of time with the factor "first AChE inhibitor" was statistically insignificant ($F=0.818$; $p=0.485$), which suggests that subgroup analysis by "first AChE inhibitor" is not required. The effect of time is similar for both subgroups. Scale scores are influenced both by dose (coefficient of dose=-0.030; $F=6.879$; $p=0.009$) and scale score at baseline (coefficient = 0.986; $F=3039.659$; $p<0.001$); they are not influenced by age (coefficient of age=0.009; $F=0.628$; $p=0.429$). The results listed in Table 39 show that only the effect of time is statistically significant. For patients of the same age, dose and baseline scale score, no differences are seen in the mean MMSE scores between subgroups with and without previous AEs. Similar conclusions can be drawn on the differences in the mean MMSE scores between subgroups (1) of patients who developed AEs during the study vs. those who did not and (2) of patients for whom Reminyl was the first AChE inhibitor vs. those for whom it was not. For patients of the same age, dose and baseline scale score, mean scale scores increase steadily with time.

Table 38: Descriptive data of total scores on the MMSE scale, by visit

	Baseline	End of month 1	End of month 2	End of month 3	End of month 6
N	333	312	302	295	293
Mean	18.7	19.1	19.5	19.7	19.9
Median	19	20	20	21	21
Standard deviation	4.15	4.20	4.45	4.54	4.64
Min	3	3	2	1	4
Max	27	28	29	28	29
25%	16	16	16	17	16.5
75%	22	22	23	23	23
95%	25	25	25	25.2	26

Table 39: Effects of study factors on MMSE scale scores

Factors	F	p
Time	17.227	<0.001
Previous AE	1.017	0.314
Emergence of AE	0.660	0.417
First AChE inhibitor	0.721	0.396

10.2 Disability Assessment for Dementia (DAD)

Table 40 shows descriptive data of DAD scores, by visit. As can be observed, the mean DAD score increased with time, but its standard deviation did not not. The factor "first AChE inhibitor" was not used, because no data was provided on the DAD scores of patients for whom Reminyl was the first AChE inhibitor. Scale scores are influenced both by dose (coefficient of dose=-0.191; F=4.419; p=0.040) and scale score at baseline (coefficient = 0.939; F=967.465; p<0.001); they are not influenced by age (coefficient of age=0.083; F=1.502; p=0.229). The results listed in Table 41 show that only the effect of time is statistically significant. For patients of the same age, dose and baseline scale score, no differences are seen in the mean DAD scores between subgroups with and without previous AEs. A similar conclusion can be drawn on the differences in the mean DAD scores between patients who developed AEs during the study vs. those who did not. For patients of the same age, dose and baseline scale score, mean scale scores increase with time.

Table 40: Descriptive data of total scores on the DAD scale, by visit

	Baseline	End of month 1	End of month 2	End of month 3	End of month 6
N	49	40	40	40	39
Mean	62.9	70.1	70.8	72.3	73.7
Median	65	74.5	75	76.5	76.0
Standard deviation	20.96	16.09	16.15	15.62	16.20
Min	0	29	27	25	30
Max	90	90	92	92	95
25%	52.5	60.0	64.3	66.5	68.0
75%	80.0	83.0	80.0	81.5	85.0
95%	89.5	88.0	91.9	91.9	94.0

Table 41: Effects of study factors on DAD scale scores

Factors	F	p
Time	5.183	0.004
Previous AE	0.058	0.812
Emergence of AE	0.761	0.389

10.3 Neuropsychiatric Inventory (NPI)

Table 42 shows descriptive data of NPI scores, by visit. As can be observed, the mean NPI score decreased with time, but its standard deviation did not not increase. The interaction term of time with the factor "first AChE inhibitor" was statistically insignificant (F=1.794; p=0.149), which suggests that subgroup analysis by the factor "first AChE inhibitor" is not required. The effect of time is similar for both subgroups. Scale scores are influenced by baseline scale score (coefficient=0.916; F=7205.001, p<0.001); they are not influenced by dose (coefficient of

dose=-0.013; F=0.236; p=0.627) or age (coefficient of age=0.021; F=0.713; p=0.399). The results listed in Table 43 show that only the effect of time is statistically significant. For patients of the same age, dose and baseline scale score, no differences are seen in the mean NPI scores between subgroups with and without previous AEs. Similar conclusions can be drawn on the differences in the mean NPI scores between subgroups (1) of patients who developed AEs during the study vs. those who did not and (2) of patients for whom Reminyl was the first AChE inhibitor vs. those for whom it was not. For patients of the same age, dose and baseline scale score, mean scale scores decrease steadily with time.

Table 42: Descriptive data of total scores on the NPI scale, by visit

	Baseline	End of month 1	End of month 2	End of month 3	End of month 6
N	319	295	285	281	278
Mean	12.6	11.4	10.7	10.3	9.9
Median	8	7	6	6	6
Standard deviation	15.50	14.01	13.5	13.42	13.15
Min	0	0	0	0	0
Max	86	80	74	74	78
25%	2	2	2	1	1
75%	17	15	15	15	14.3
95%	42	38.4	38	37.9	38

Table 43: Effects of study factors on NPI scale scores

Factors	F	p
Time	13.684	<0.001
Previous AE	0.857	0.355
Emergence of AE	0.001	0.979
First AChE inhibitor	1.938	0.165

10.4 CGI Scale

Table 44 shows descriptive data of CGI scores, by visit. As can be observed, the mean CGI score decreased with time, but its standard deviation did not not increase notably. The interaction term of time with the factor "first AChE inhibitor" was statistically insignificant (F=1.503; p=0.214), which suggests that subgroup analysis by the factor "first AChE inhibitor" is not required. The effect of time is similar for both subgroups. Scale scores are influenced by baseline scale score (coefficient=0.932; F=2447.564, p<0.001); they are not influenced by dose (coefficient of dose=-0.002; F=0.231; p=0.631) or age (coefficient of age=0.001; F=0.028; p=0.867). The results listed in Table 45 show that only the effect of time is statistically significant. For patients of the same age, dose and baseline scale score, no differences are seen in the mean CGI scores between subgroups with and without previous AEs. Similar conclusions can be drawn on the differences in the mean CGI scores between subgroups (1) of patients who developed AEs during the study vs. those who did not and (2) of patients for whom Reminyl was the first AChE inhibitor vs. those for whom it was not. For patients of the same age, dose and baseline scale score, mean scale scores decrease with time.

Table 44: Descriptive data of total scores on the CGI scale, by visit

	Baseline	End of month 1	End of month 2	End of month 3	End of month 6
N	329	309	299	294	287
Mean	3.8	3.8	3.7	3.6	3.6
Median	4	4	4	4	4
Standard deviation	1.11	1.13	1.22	1.23	1.21
Min	1	1	1	1	1
Max	7	7	7	7	7
25%	3	3	3	3	3
75%	5	4	4	4	4
95%	6	6	6	6	6

Table 45: Effects of study factors on CGI scale scores

Factors	F	p
Time	6.885	<0.001
Previous AE	0.547	0.460
Emergence of AE	0.026	0.872
First AChE inhibitor	0.291	0.590

10.5 Cornell Scale

Table 46 shows descriptive data of the Cornell scale, by visit. As can be observed, the mean Cornell score decreased with time, and the standard deviation decreased slightly. The interaction term of time with the factor "first AChE inhibitor" was statistically insignificant (F=0.213; p=0.887), which suggests that subgroup analysis by the factor "first AChE inhibitor" is not required. The effect of time is similar for both subgroups. Scale scores are influenced by baseline scale score (coefficient=0.854; F=1230.909, p<0.001); they are not influenced by dose (coefficient of dose=-0.049; F=1.334; p=0.250) or age (coefficient of age=0.026; F=0.749; p=0.390). The results listed in Table 47 show that only the effect of time is statistically significant. For patients of the same age, dose and baseline scale score, no differences are seen in the mean Cornell scores between subgroups with and without previous AEs. Similar conclusions can be drawn on the differences in the mean Cornell scores between subgroups (1) of patients who developed AEs during the study vs. those who did not and (2) of patients for whom Reminyl was the first AChE inhibitor vs. those for whom it was not. For patients of the same age, dose and baseline scale score, mean scale scores decrease steadily with time.

Table 46: Descriptive data of total scores on the Cornell scale, by visit

	Baseline	End of month 1	End of month 2	End of month 3	End of month 6
N	109	81	73	73	77
Mean	7.0	6.8	5.7	5.3	4.6
Median	5	4	3	2	2
Standard deviation	7.74	7.89	7.20	6.53	5.49
Min	0	0	0	0	0
Max	86	80	74	74	78
25%	2	2	2	1	1
75%	17	15	15	15	14.3
95%	42	38.4	38	37.9	38

Table 47: Effects of study factors on Cornell scale scores

Factors	F	p
Time	5.143	0.003
Previous AE	0.227	0.636
Emergence of AE	0.059	0.809
First AChE inhibitor	0.000	0.993

11. Conclusions

The results reported in this paper can be summarized as follows:

- The number of AEs seen during the study was not notably high. 33 patients developed 60 AEs in total. Eight AEs were characterized as severe; all eight were seen in one patient. In 65% of AEs, the causal relationship with Reminyl was characterized as probable or higher. The most relevant AEs were nausea, vomiting, and diarrhea.
- Previous AEs appear to be related to premature discontinuation from the study. Of the patients who had previously developed AEs, 20.9% left the study, vs. 8.8% of those who had not previously developed AEs. By contrast, no correlation was seen between previous AEs and the emergence of AEs during the study. Moreover, no correlation was seen between "first AChE inhibitor" and discontinuation, or between "first AChE inhibitor" and the emergence of AEs. Finally, no correlation was seen between the emergence of AEs during the study and discontinuation. With regard to safety, the emergence of AEs during the study was not influenced by previous AEs, or by the fact that Reminyl was the first AChE inhibitor used. All relevant rates were low.
- The mean scale scores appeared to change with time, for all scales. MMSE and DAD scores increased with time. The mean MMSE score changed from 18.7 at baseline to 19.9 at the last visit. The mean DAD score changed from 22.9 at baseline to 73.7 at the last visit. On the other scales, statistically significant decreases of mean scores were seen. On the NPI scale, the mean score changed from 12.6 at baseline to 9.9 at the last visit, on the CGI scale from 3.8 to 3.6, and on the Cornell scale from 7.0 to 4.6, respectively.

- Dosage was steadily increased throughout the study. The mean dose was increased from 11.8 mg/day at baseline to 22.4 mg/day at the last visit.
- 42 patients (12.6%) discontinued the study prematurely. The main cause was that patients were lost to follow-up (73.8% of noncompleters).

Appendix

Table A: Patients who discontinued the study prematurely by cause and center (the time of last recorded visit is also listed):

Center	Patient Code	Cause	Time of last recorded visit
1	1014	Lost to follow-up	End of month 3
2	2003	Lost to follow-up	End of month 3
2	2014	Insufficient efficacy - the patient no longer fulfilled criteria	End of month 2
4	4015	Lost to follow-up	End of month 2
4	4017	Lost to follow-up	End of month 1
4	4020	Lost to follow-up	End of month 1
4	4025	Lost to follow-up	End of month 1
4	4028	Adverse events	End of month 1
4	4029	Lost to follow-up	End of month 3
4	4030	Adverse events	End of month 2
9	9005	Lost to follow-up	End of month 3
9	9010	Lost to follow-up	End of month 3
9	9011	Lost to follow-up	First visit
9	9017	Lost to follow-up	End of month 3
10	10001	Lost to follow-up - Discharged from hospital	End of month 3
10	10002	Discharged from hospital	First visit
10	10003	Adverse events	End of month 1
10	10004	Discharged from hospital	End of month 3
10	10005	Adverse events	End of month 3
10	10006	Discharged from hospital	End of month 2
10	10007	Death	End of month 3
10	10012		End of month 5
11	11012	Adverse events	End of month 1
15	15001	Lost to follow-up	First visit
15	15002	Lost to follow-up	First visit
15	15005	Lost to follow-up	End of month 3
15	15007	Lost to follow-up	First visit
15	15008	Lost to follow-up	First visit
15	15009	Lost to follow-up	End of month 1
15	15011	Lost to follow-up	First visit
15	15012	Lost to follow-up	First visit
15	15014	Lost to follow-up	End of month 1
15	15015	Lost to follow-up	First visit
15	15016	Lost to follow-up	First visit
15	15017	Lost to follow-up	First visit
15	15018	Lost to follow-up	First visit
15	15019	Lost to follow-up	First visit
15	15020	Lost to follow-up	First visit
15	15021	Lost to follow-up	First visit
15	15026	Lost to follow-up	End of month 1
15	15028	Lost to follow-up	First visit
15	15029	Lost to follow-up	First visit

Table B: Medical history, by center and patient

Center	Patient code	Organ system	Active	Comment
1	1003	Cardiovascular	Yes	Hypertension
	1003	Eyes	Yes	Early-stage cataract
	1004	Gastrointestinal	No	Cholecystectomy 10 years ago
	1004	Neurological	No	Transient CVA one year ago
	1005	Hematologic	No	Iron deficiency anemia
	1006	Musculoskeletal	No	Left femur fracture, treated surgically
	1009	Cardiovascular	Yes	Hypertension
	1009	Eyes	Yes	Glaucoma
	1010	Endocrine	Yes	Diabetes mellitus
	1011	Cardiovascular	Yes	Tachycardia
	1011	Hematologic	Yes	Thalassemia trait
	1014	Musculoskeletal	No	(Right) femoral head, treated surgically
	1016	Cardiovascular	No	Transient CVA in 2003
	1016	Eyes	No	Bilateral cataract, treated surgically
	1017	Endocrine	Yes	Diabetes mellitus
	1020	Cardiovascular	Yes	Labile hypertension
2	2001	Hematologic	No	Myelodysplastic Syndrome
	2002	Endocrine	Yes	Diabetes mellitus
	2002	Neurological	No	CVA
	2003	Cardiovascular	Yes	Hypertension
	2003	Psychiatric	No	Depression
	04	Psychiatric	Yes	Depression
	05	Cardiovascular	Yes	Hypertension
	05	Musculoskeletal	Yes	Arthritis
	05	Psychiatric	No	Depression
	2006	Cardiovascular	Yes	Hypertension
	2007	Psychiatric	Yes	Depression
	2008	Psychiatric	Yes	Organic psychosyndrome
	2009	Psychiatric	Yes	Depression
	2010	Psychiatric	No	Organic psychosyndrome
	2011	Neurological	No	CVA
	2011	Psychiatric	Yes	Depression
	2012	Cardiovascular	Yes	Coronary disease
	2013	Neurological	Yes	Parkinson's disease
	2013	Psychiatric	Yes	Depression
	2014	Gastrointestinal	No	Large intestine CA, treated surgically
	2014	Urinary	No	Prostate CA (radiation therapy)
	2014	Neurological	No	CVA
	2014	Psychiatric	No	Organic psychosyndrome
	2015	Neurological	Yes	Parkinson's disease
	2015	Psychiatric	Yes	Depression
	2016	Psychiatric	No	Organic psychosyndrome
	2016	Psychiatric	No	Depression
	2017	Endocrine	Yes	Diabetes mellitus
	2017	Neurological	Yes	Parkinson's disease
	2018	Cardiovascular	Yes	Hypertension
	2018	Endocrine	Yes	Diabetes mellitus
	2018	Neurological	Yes	Parkinson's disease
	2018	Other	Yes	Hyperuricemia
	2019	Musculoskeletal	Yes	Lower back pain
	2019	Neurological	Yes	Parkinson's disease
	2019	Psychiatric	No	Depression
	2020	Cardiovascular	Yes	Hyperlipidemia
	2020	Endocrine	Yes	Diabetes mellitus

	2020	Urinary	No	Chronic renal failure
	2020	Neurological	No	Paraplegia
	2021	Endocrine	Yes	Diabetes mellitus
	2021	Neurological	Yes	Cerebral small vessel ischemic disease
	2021	Psychiatric	Yes	Depression
	2022	Psychiatric	No	Depression
	2023	Psychiatric	Yes	Depression
	2024	Neurological	No	Organic psychosyndrome
	2024	Psychiatric	Yes	Depression
	2025	Neurological	Yes	
	2026	Neurological	Yes	Osteoporosis
	2027	Neurological	No	CVA hemiparesis
	2027	Psychiatric	No	Organic psychosyndrome
	2028	Neurological	Yes	Parkinson's disease
	2028	Psychiatric	No	Depression
	2029	Neurological	No	CVA
3	3002	Cardiovascular	Yes	Hypertension
	3002	Urinary	Yes	Polycystic kidney disease
	3002	Neurological	Yes	Extrapyramidal tremor
	3002	Psychiatric	Yes	Anxiety/Dysthymia
	3005	Neurological	Yes	Extrapyramidal syndrome
	3008	Cardiovascular	Yes	Hypertension
	3008	Neurological	Yes	Extrapyramidal syndrome
	3008	Psychiatric	Yes	Depression
	3010	Psychiatric	Yes	Depression
	3011	Neurological	Yes	Extrapyramidal syndrome
	3013	Cardiovascular	Yes	Hypertension
	3013	Neurological	Yes	Extrapyramidal syndrome
	3015	Cardiovascular	Yes	Hypertension
	3017	Endocrine	Yes	Diabetes mellitus
	3017	Neurological	Yes	Extrapyramidal syndrome
	3018	Psychiatric	Yes	Neuropsychiatric symptoms
	3020	Neurological	Yes	Extrapyramidal syndrome
4	4004	Cardiovascular	Yes	Arterial hypertension
	4009	Cardiovascular	Yes	Hypertension
	4010	Cardiovascular	Yes	Hypertension
	4011	Cardiovascular	No	Arterial Hypertension
	4011	Neurological	Yes	Parkinson's disease
	4013	Neurological	Yes	Parkinson's disease
	4014	Neurological	Yes	Extrapyramidal syndrome
	4015	Cardiovascular	Yes	Arterial Hypertension
	4015	Gastrointestinal	Yes	Gastritis
	4016	Cardiovascular	Yes	Arterial Hypertension
	4016	Endocrine	Yes	Diabetes mellitus
	4017	Cardiovascular	Yes	Arterial Hypertension
	4017	Gastrointestinal	Yes	Gastritis
	4017	Urinary	Yes	Prostatic hypertrophy
	4017	Respiratory	Yes	Asthma
	4018	Cardiovascular	Yes	Atrial fibrillation
	4018	Eyes	Yes	Cataract
	4018	Urinary	Yes	Incontinence
	4019	Neurological	No	Upper extremity tremor
	4020	Musculoskeletal	Yes	Dislocated shoulder
	4024	Eyes	Yes	Cataract
	4027	Psychiatric	Yes	Depression
6	6001	Psychiatric	No	Depression
	6002	Hematologic	No	Anemia
	6005	Cardiovascular	No	Hypertension
	6006	Neurological	No	Parkinsonian features
	6006	Psychiatric	No	Depression
	6009	Cardiovascular	No	Bypass

	6011	Cardiovascular	Yes	Hypertension
	6011	Musculoskeletal	Yes	Osteoporosis
	6012	Cardiovascular	Yes	Hypertension
	6012	Other	Yes	Hypercholesterolemia
	6014	Musculoskeletal	Yes	Osteoporosis
	6015	Cardiovascular	Yes	Angina pectoris
	6016	Cardiovascular	No	Right carotid blockage, treated surgically
	6019	Cardiovascular	No	Myocardial infarction
	6019	Neurological	Yes	Extrapyramidal
	6020	Neurological	Yes	Extrapyramidal
	6020	Other	Yes	Hypercholesterolemia / Hyperuricemia
	6022	Endocrine	Yes	Thyroiditis
	6023	Cardiovascular	Yes	Hypertension
	6023	Other	Yes	Hypercholesterolemia
	6028	Cardiovascular	Yes	Coronary disease
7	7001	Cardiovascular	Yes	Hypertension
	7001	Endocrine	Yes	Diabetes mellitus
	7002	Cardiovascular	Yes	Hypertension
	7002	Eyes	Yes	Hyperopia
	7003	ENT	No	Vocal cord CA, treated surgically in 1997
	7003	Urinary	Yes	Malignant prostatic hypertrophy
	7005	Urinary	No	Urinary bladder lithiasis
	7005	Urinary	No	Transurethral prostatectomy
	7007	Cardiovascular	Yes	Hypertension
	7008	Cardiovascular	Yes	Hypertension
	7008	Musculoskeletal	Yes	Osteoporosis
	7009	Cardiovascular	Yes	Hypertension
	7009	Endocrine	Yes	Thyroid nodules
	7009	Psychiatric	Yes	Depression
	7010	Cardiovascular	Yes	Coronary disease
	7010	Endocrine	Yes	Diabetes mellitus
	7010	Neurological	Yes	Transient ischemic attacks
	7011	Gastrointestinal	Yes	Colitis
	7012	Cardiovascular	Yes	Hypertension
	7012	Musculoskeletal	Yes	Osteoporosis
	7013	ENT	Yes	Hearing loss
	7014	Cardiovascular	Yes	Bradycardia
	7015	Urinary	No	Prostatectomy, 3 years ago
	7016	Other	Yes	Left hip fracture 04
	7017	Urinary	Yes	Prostatic hypertrophy
	7018	Cardiovascular	Yes	Hypertension
	7018	Musculoskeletal	Yes	Joint pain
	7019	Cardiovascular	Yes	Hypertension
	7019	Musculoskeletal	Yes	Lower back pain
	7019	Psychiatric	Yes	Dysthymia
8	8002	Cardiovascular	No	Mild heart failure/hypertension
	8002	Eyes	No	Bilateral cataract, treated surgically
	8002	Musculoskeletal	Yes	Osteoporosis
	8003	Cardiovascular	Yes	Hypertension
	8003	Eyes	No	Bilateral cataract, treated surgically
	8003	Urinary	Yes	Mild prostatic hyperthrophy
	8003	Hematologic	Yes	Thalassemia trait
	8005	Eyes	Yes	Left eye cataract, treated surgically
	8005	Musculoskeletal	Yes	Degenerative knee arthropathy
	8005	Neurological	No	Transient ischemic stroke
9	9001	Psychiatric	Yes	Paranoid ideas
	9002	Cardiovascular	Yes	Hypertension
	9004	Cardiovascular	Yes	Hypertension
	9004	Urinary	Yes	Dysuria
	9005	Hematologic	Yes	Anemia
	9008	Hematologic	Yes	Dysuria
	9008	Psychiatric	Yes	Psychotic manifestations

	9010	Urinary	Yes	Dysuria
	9010	Neurological	Yes	Parkinson's disease
	9011	Cardiovascular	Yes	Hypertension
	9012	Cardiovascular	Yes	Hypertension
	9012	Urinary	Yes	Dysuria
	9012	Psychiatric	Yes	COPD
	9013	Hematologic	Yes	Anemia
	9013	Psychiatric	Yes	Extrapyramidal syndrome
	9014	Cardiovascular	Yes	Hypertension
	9014	Musculoskeletal	Yes	Osteoporosis
	9015	Endocrine	Yes	Diabetes mellitus
	9015	Urinary	Yes	Prostatic hypertrophy
	9016	Cardiovascular	Yes	Hypertension
	9016	Urinary	Yes	Prostatic hypertrophy
	9017	Cardiovascular	Yes	Hypertension
	9017	Musculoskeletal	Yes	Osteoporosis
	9018	Cardiovascular	Yes	Hypertension
	9018	Psychiatric	Yes	Psychotic manifestations
	9018	Other	Yes	CVA
	9019	Hematologic	Yes	Anemia
	9019	Psychiatric	Yes	Depression
	9020	Respiratory	Yes	COPD
10	10001	Urinary	Yes	Prostate
	10003	Cardiovascular	Yes	Cardiovascular
	10003	Eyes	Yes	Glaucoma
	10003	Gastrointestinal	Yes	Stomach ulcer
	10003	Hematologic	Yes	Diabetic vasculopathy
	10003	Neurological	Yes	Dementia
	10003	Psychiatric	Yes	Depression
	10004	Neurological	Yes	Paraplegia
	10005	Cardiovascular	Yes	Hypertension
	10005	Endocrine	Yes	Thyroid issues
	10005	Neurological	Yes	Generalized dementia
	10006	Cardiovascular	Yes	Heart failure, hypertension
	10006	Endocrine	Yes	Diabetes mellitus
	10006	Neurological	Yes	Poor circulation
	10006	Psychiatric	Yes	Depression
	10007	Cardiovascular	Yes	Heart failure, hypertension
	10007	Endocrine	Yes	Diabetes mellitus
	10007	Hematologic	Yes	Coagulation disturbances, arrhythmia
	10007	Neurological	Yes	Generalized atherosclerosis
	10008	Endocrine	Yes	Diabetes mellitus
	10008	Neurological	Yes	Generalized vasculopathy
	10009	Neurological	Yes	Unsteady gait
	10011	Cardiovascular	Yes	Heart failure
11	11004	Cardiovascular	Yes	Hypertension
	11004	Neurological	Yes	Memory disturbances, Parkinson's disease
	11017	Cardiovascular	Yes	Arterial Hypertension, under treatment
12	12002	Endocrine	Yes	Diabetes mellitus
15	15001	Cardiovascular	Yes	Hypertension
	15001	Musculoskeletal	Yes	Osteoarthritis
	15002	Cardiovascular	Yes	Hypertension
	15002	Endocrine	Yes	Diabetes Mellitus, controlled
	15002	Musculoskeletal	No	Arthritis
	15003	Cardiovascular	Yes	Hypertension
	15004	Allergies	No	Eczema in 1973
	15004	Cardiovascular	No	Bypass in 1977
	15004	Integumentary	No	Itchy skin
	15004	ENT	No	Sinusitis
	15004	Hematologic	No	Anemia
	15004	Neurological	No	CVA
	15005	Allergies	No	Allergy to strawberries

	15005	ENT	No	Hearing loss (right-sided)
	15005	Psychiatric	Yes	Depression
	15006	ENT	No	Hearing loss (left-sided)
	15006	Eyes	No	Left eye cataract
	15006	Musculoskeletal	No	Osteoporosis
	15007	Endocrine	Yes	Hypothyroidism
	15007	Psychiatric	Yes	Depression
	15008	Cardiovascular	No	Abdominal aorta aneurysm
	15008	Urinary	No	Frequent urination
	15008	Neurological	No	CVA
	15008	Psychiatric	No	Depression
	15012	Endocrine	No	Prostatic hyperplasia
	15013	Urinary	No	Total removal
	15013	Musculoskeletal	No	Osteoporosis
	15015	Cardiovascular	No	Bypass in 1999
	15015	Endocrine	No	Diabetes Mellitus, controlled
	15017	Integumentary	No	Eczema
	15018	ENT	No	Hearing loss
	15018	Endocrine	No	Thyroiditis
	15019	Cardiovascular	No	Atrial fibrillation and angina pectoris
	15021	Eyes	No	Mild cataract
	15022	ENT	Yes	Hearing loss
	15023	Cardiovascular	No	Bypass in 2000
	15024	Eyes	No	Cataract - glaucoma
	15024	Gastrointestinal	No	Ulcer
	15024	Urinary	No	Prostatectomy
	15026	Integumentary	No	Systemic lupus erythematosus
	15026	ENT	No	Septum
	15026	Eyes	No	Bilateral cataract
	15027	Allergies	No	Common cold
	15028	Cardiovascular	No	Hypertension
	15029	Psychiatric	No	Depression
16	16001	Psychiatric	Yes	Insomnia
	16002	Neurological	No	CVA (1992) - Left Hemiparesis
	16003	Cardiovascular	Yes	Coronary disease
	16003	Urinary	No	Prostatic hypertrophy, treated surgically
	16003	Neurological	No	CVA
	16003	Psychiatric	Yes	Depression
	16003	Other	Yes	DM
	16004	Gastrointestinal	Yes	IBS
	16004	Neurological	Yes	CVA, 20 days ago
	16004	Psychiatric	No	Depression in 1998
	16004	Respiratory	Yes	Chronic bronchitis
	16005	Cardiovascular	Yes	Arterial hypertension
	16005	Other	Yes	Lumbar spondylosis
	16006	Cardiovascular	Yes	Arterial Hypertension
	16006	Eyes	No	Cataract, treated surgically
	16006	Musculoskeletal	Yes	Knee osteoarthritis - Lumbar spondylosis
	16006	Neurological	No	Previous CVA
	16006	Psychiatric	Yes	Mild depression
	16007	ENT	No	Hearing loss (right-sided)
	16007	Neurological	No	Transient CVAs
	16007	Psychiatric	Yes	Neurotic syndrome
	16008	Endocrine	No	Goitre
	16008	Urinary	Yes	Prostatic hypertrophy
	16009	Cardiovascular	Yes	Arterial Hypertension
	16009	ENT	No	Tinnitus - Dizziness
	16009	Musculoskeletal	Yes	Low back pain and sciatica
	16009	Neurological	Yes	Hand sensory deficit
	16010	Psychiatric	No	Insomnia - Anxiety syndrome
	16011	Cardiovascular	Yes	Arterial Hypertension
	16011	ENT	No	Tinnitus

	16011	Neurological	No	Previous CVA
	16012	Endocrine	Yes	Hypercholesterolemia
	16012	Gastrointestinal	No	Previous duodenal ulcer
	16012	Psychiatric	Yes	Sleep disturbances
	16013	Cardiovascular	Yes	Arterial Hypertension
	16013	Endocrine	Yes	Diabetes Mellitus
	16014	Neurological	Yes	Parkinson's disease
	16016	ENT	No	Tinnitus - Dizziness
	16016	Endocrine	Yes	Hypercholesterolemia
	16016	Eyes	No	Right eye cataract, treated surgically
	16017	Cardiovascular	Yes	Arterial Hypertension
	16017	Urinary	Yes	Prostatic hypertrophy, treated surgically
	16017	Neurological	No	Previous CVA
	16019	Endocrine	Yes	Hypercholesterolemia
	16019	Gastrointestinal	No	Duodenal ulcer
	16019	Neurological	Yes	Essential tremor, upper limb
	16020	Cardiovascular	Yes	Arterial Hypertension
21	21001	Cardiovascular	Yes	Angina pectoris
	21001	Endocrine	Yes	Diabetes Mellitus
	21002	Cardiovascular	Yes	Coronary disease
	21002	Endocrine	Yes	Diabetes Mellitus
	21002	Gastrointestinal	Yes	Cholecystectomy
	21002	Respiratory	Yes	Bronchial asthma
	21003	ENT	Yes	Hearing loss
	21003	Endocrine	Yes	Hypothyroidism
	21003	Eyes	Yes	Myopia
	21003	Urinary	No	Total hysterectomy 1982
	21003	Musculoskeletal	Yes	Osteoporosis
	21003	Psychiatric	Yes	Depression
	21004	Cardiovascular	Yes	Arterial Hypertension
	21004	Endocrine	Yes	Diabetes Mellitus
	21004	Eyes	Yes	Cataract
	21004	Neurological	Yes	Dementia
	21005	Cardiovascular	No	Arrhythmia
	21005	Eyes	No	Right eye cataract, treated surgically
	21005	Urinary	Yes	Mild incontinence
	21005	Musculoskeletal	Yes	Bone pain osteoporosis
	21006	ENT	Yes	Hearing loss
	21006	Endocrine	Yes	Hypothyroidism
	21006	Urinary	No	Ovarian cyst, 1992
	21006	Musculoskeletal	Yes	Osteoporosis
	21007	Musculoskeletal	Yes	Osteoporosis
	21008	ENT	Yes	Hearing loss
	21008	Eyes	Yes	Glaucoma
	21008	Gastrointestinal	No	Pancreatitis
	21009	Psychiatric	Yes	Organic psychosyndrome .
	21010	Eyes	Yes	Cataract
	21010	Gastrointestinal	Yes	Dyspepsia
	21010	Respiratory	Yes	Dyspnea
	21011	Cardiovascular	Yes	Arterial Hypertension
	21011	Endocrine	Yes	Diabetes Mellitus, Hyperlipidemia
	21011	Psychiatric	Yes	Organic psychosyndrome
	21012	Cardiovascular	Yes	Arterial Hypertension
	21012	Endocrine	Yes	Diabetes Mellitus, Hyperlipidemia
	21012	Psychiatric	Yes	Organic psychosyndrome
	21013	Musculoskeletal	Yes	Osteoporosis
	21014	Allergies	No	Detergents
	21014	Musculoskeletal	Yes	Osteoporosis
	21014	Neurological	Yes	Alzheimer's disease
	21015	Cardiovascular	Yes	Arterial Hypertension
	21015	ENT	Yes	Hearing loss
	21015	Endocrine	Yes	Diabetes Mellitus

	21015	Eyes	Yes	Left eye cataract
	21015	Gastrointestinal	Yes	Pancreatitis
	21015	Urinary	No	Fibroids, treated surgically in 1984
	21015	Musculoskeletal	Yes	Osteoporosis
	21015	Psychiatric	Yes	Organic Psychosyndrome
	21015	Other	Yes	Carotid artery disease
	21016	Cardiovascular	Yes	Arterial hypertension
	21016	ENT	Yes	Hearing loss
	21016	Eyes	No	Right eye cataract
	21016	Urinary	No	Total hysterectomy 10 years ago
	21016	Musculoskeletal	Yes	Osteoarthritis
	21016	Neurological	Yes	Possible Alzheimer's disease
	21018	Cardiovascular	No	Arrhythmia
	21018	ENT	Yes	Hearing loss
	21018	Endocrine	Yes	Diabetes Mellitus
	21018	Eyes	Yes	Cataract
	21018	Musculoskeletal	Yes	Osteoporosis
	21018	Neurological	Yes	Possible Alzheimer's disease
	21019	Cardiovascular	Yes	Arterial Hypertension
	21020	Musculoskeletal	Yes	Osteoporosis
	21022	Integumentary	Yes	Dermatitis
	21022	ENT	Yes	Hearing loss
	21022	Neurological	Yes	Parkinson's disease
	21023	Cardiovascular	Yes	Arterial Hypertension
	21025	Cardiovascular	Yes	Angioplasty, Arterial hypertension, Coronary disease
	21025	Gastrointestinal	No	Duodenal ulcer
	21026	ENT	Yes	Deafness (left-sided)
	21026	Eyes	Yes	Cataract
	21026	Respiratory	Yes	Chronic bronchitis
	21027	Cardiovascular	Yes	Arterial Hypertension
	21028	Cardiovascular	Yes	Arterial Hypertension
	21029	Cardiovascular	Yes	Vascular disease
	21030	Cardiovascular	Yes	Arterial Hypertension
22	22002	Cardiovascular	Yes	Hypertension
	22002	Urinary	No	Prostatic hypertrophy
	22003	Cardiovascular	Yes	Arterial Hypertension
	204	Endocrine	Yes	Diabetes Mellitus
	205	Cardiovascular	Yes	Arterial Hypertension
	205	Musculoskeletal	Yes	Osteoporosis
	22006	Cardiovascular	No	Bypass surgery
	22006	Psychiatric	Yes	Depression
	22007	Psychiatric	Yes	Depression
	22008	Psychiatric	Yes	Depression
	22009	Psychiatric	No	Depression
	22010	Gastrointestinal	No	Bowel CA, treated surgically
	22011	Neurological	Yes	Extrapyramidal syndrome
	22012	Psychiatric	Yes	Depression
	22015	Cardiovascular	Yes	Mild heart failure
	22015	Psychiatric	Yes	Organic psychosyndrome
25	25001	Cardiovascular	Yes	Hypertension
	25002	Cardiovascular	Yes	Hypertension
	25002	Neurological	Yes	Migraines
	25003	Cardiovascular	Yes	Hypertension
	25004	Cardiovascular	Yes	Cardiac arrhythmia
	25004	Psychiatric	Yes	Mood
	25005	Psychiatric	Yes	Depression
	25006	Endocrine	Yes	Diabetes Mellitus
	25007	Musculoskeletal	Yes	Osteoporosis
	25008	Cardiovascular	No	Arrhythmia - Hypertension
	25009	Cardiovascular	Yes	Arterial Hypertension
	25011	Cardiovascular	Yes	Arterial Hypertension
	25013	Gastrointestinal	No	Stomach CA

	25013	Psychiatric	Yes	Depression
	25014	Cardiovascular	Yes	Hypertension
	25014	Endocrine	Yes	Diabetes Mellitus
	25018	Cardiovascular	Yes	Hypertension
	25019	Cardiovascular	Yes	Hypertension

Table C: List of Adverse Events by center and patient

Patient Code	AE	Start	End	Severity	Reminyl-related Actions	Treatment for AE	Causal relationship with Reminyl	Outcome	Reported as SAE
1007	Diarrhea	12/09/04	12/18/04	Mild	None	No	Definite	Recovery from AE	No
2008	Respiratory infection	01/07/05	1/19/05	Moderate	Temp. discont.	Yes	Excluded	Recovery from AE	Yes (with extended hosp.)
2009	Hallucinations	01/25/05		Mild	None	No	Excluded	Persisting	No
2009	Hallucinations	01/25/05	07/22/05	Mild	None	Yes	Doubtful	Recovery from AE	No
4002	Diarrhea	10/27/04	11/03/04	Mild	None	Yes	Probable	Recovery from AE	No
4024	Nausea	05/29/05	06/01/05	Mild	None	No	Probable	Recovery from AE	No
4024	Vomiting	05/29/05	05/30/05	Mild	None	No	Probable	Recovery from AE	No
4028	Nausea	03/26/05	03/28/05	Mild	None	No	Probable	Recovery from AE	No
4030	Nausea	05/01/05	05/12/05	Moderate	Perm. discont.	No	Definite	Recovery from AE	No
9007	Paranoid ideas	12/01/04	12/17/04	Mild	None	Yes	Doubtful	Recovery from AE	No
9015	Salivation	12/10/04	01/05/05	Mild	None	No	Possible	Persisting	No
10003	Aggression	10/16/04	10/20/04	Mild	Dose adjustment	Yes	Probable	Recovery from AE	No
10003	Aggression	11/13/04		Moderate	Dose adjustment	Yes	Probable	Persisting	No
10005	Vomiting	01/04/05	01/08/05	Moderate	Temp. discont.	No	Possible	Persisting	No
10005	Anorexia	01/01/05	02/05/05	Moderate	Temp. discont.	No	Possible	Persisting	No
10005	Headache	01/06/05	01/08/05	Moderate	Temp. discont.	No	Possible	Persisting	No
10005	Weight reduction	12/28/04	02/05/05	Moderate	Temp. discont.	No	Possible	Persisting	No
10011	Nausea	01/22/05		Mild	None	No	Doubtful	Persisting	No
11012	Nausea	01/19/05	01/31/05	Severe	Perm. discont.	No	Definite	Recovery from AE	No
11012	Vomiting	01/19/05	01/31/05	Severe	Perm. discont.	No	Definite	Recovery from AE	No
11012	Diarrhea	01/19/05	01/31/05	Severe	Perm. discont.	No	Definite	Recovery from AE	No
11012	Epigastric pain	01/19/05	01/31/05	Severe	Perm. discont.	No	Definite	Recovery from AE	No
11012	Fatigue	01/19/05	01/31/05	Severe	Perm. discont.	No	Definite	Recovery from AE	No

11012	Insomnia	01/19/05	01/31/05	Severe	Perm. discont.	No	Definite	Recovery from AE	No
11012	Muscular weakness	01/19/05	01/31/05	Severe	Perm. discont.	No	Definite	Recovery from AE	No
11012	Tiredness	01/19/05	01/31/05	Severe	Perm. discont.	No	Definite	Recovery from AE	No
15005	Episodes of confusion	01/20/05			None	No	Doubtful	Persisting	No
15005	Debility	01/20/05			None	No	Doubtful	Persisting	No
15009	Nausea	01/13/05	01/16/05	Moderate	Perm. discont.	No	Definite	Recovery from AE	No
15022	Weight loss	03/01/05		Moderate	Temp. discont.	No	Probable	Persisting	No
15025	Vomiting	06/03/05	06/04/05	Moderate	Perm. discont.	No	Definite	Recovery from AE	No
16006	Nausea	03/10/05	03/13/05	Mild	None	No	Possible	Recovery from AE	No
16009	Vomiting	03/12/05	03/13/05	Mild	None	No	Possible	Recovery from AE	No
16016	Dizziness	03/10/05	03/17/05	Mild	None	No	Probable	Recovery from AE	No
16016	Vertigo	03/10/05	03/17/05	Mild	None	No	Probable	Recovery from AE	No
16018	Epigastralgia	03/22/05	03/29/05	Moderate	None	No	Possible	Recovery from AE	No
16020	Vomiting	07/12/05	07/16/05	Mild	Dose adjustment	No	Possible	Recovery from AE	No
21001	Headache	11/09/04	11/11/04	Mild	None	No	Doubtful	Recovery from AE	No
21004	Diarrhea	12/9/04	12/13/04	Mild	Dose adjustment	No	Possible	Recovery from AE	No
21015	Epigastric pain	03/11/05	03/15/05	Moderate	Dose adjustment	No	Definite	Recovery from AE	No
21015	Nausea	03/10/05	03/15/05	Mild	Dose adjustment	No	Definite	Recovery from AE	No
21027	Nausea	12/30/04	01/17/05	Moderate	Dose adjustment	No	Probable	Recovery from AE	No
21027	Vomiting	01/08/05	01/17/05	Moderate	Dose adjustment	Yes	Probable	Recovery from AE	No
22014	Anorexia	04/26/05		Mild	None	No	Probable	Persisting	No
22014	Weight reduction	04/19/05		Mild	None	No	Probable	Persisting	No
22014	Epigastric pain	07/15/05		Mild	None	No	Probable	Persisting	No
22015	Insomnia	11/28/04		Mild	None	No	Probable	Persisting	No
22015	Fatigue	12/26/04		Moderate	None	No	Probable	Persisting	No
22015	Weight reduction	12/20/04		Mild	None	No	Probable	Persisting	No
22015	Anorexia	3/15/04		Mild	None	No	Probable	Persisting	No
25001	Nausea	10/19/04		Mild	None	No	Definite	Recovery from AE	No
25005	Nausea	01/10/05	01/20/05	Mild	None	No	Probable	Recovery from AE	No
25005	Vomiting	01/10/05	01/20/05	Mild	None	No	Probable	Recovery from AE	No
25006	Nausea	01/17/05	01/25/05	Mild	None	No	Probable	Recovery from AE	No

25006	Vomiting	1/17/05	01/25/05	Mild	None	No	Probable	Recovery from AE	No
25010	Nausea	01/13/05	01/25/05	Mild	None	No	Probable	Recovery from AE	No
25010	Vomiting	01/13/05	01/25/05	Mild	None	No	Probable	Recovery from AE	No
25012	Nausea	01/22/05	02/02/05	Moderate	None	No	Possible	Recovery from AE	No
25012	Vomiting	01/22/05	02/02/05	Moderate	None	No	Possible	Recovery from AE	No