Analysis of Outcome in Retrieved Dropout Patients in a Rivastigmine vs Placebo, 26-Week, Alzheimer Disease Trial

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Background: Treatment with cholinesterase inhibitors improves cognition in patients with Alzheimer disease (AD). In studies designed with a washout period at the end of the study, after treatment with a cholinesterase inhibitor is discontinued, the cognitive benefits of therapy are no longer apparent following washout. The rivastigmine trials discussed in this article were not designed with a posttreatment washout period at the end of the study. Therefore, to evaluate the effect of discontinuing treatment, we analyzed the retrieved dropout (RDO) population.

Objective: To evaluate the change in cognition (at week 26 vs baseline) observed in patients from 3 large clinical trials of AD who prematurely discontinued treatment with placebo or rivastigmine.

Design and Methods: Eligible patients with AD (Mini-Mental State Examination [MMSE] score, 10-26, inclusive) were enrolled in 1 of three 26-week, double-blind, placebo-controlled studies (Novartis US Pivotal [dose-range] Trial, US fixed-dose study, and a Global Pivotal [dose-range] Trial) that compared rivastigmine therapy with placebo. Patients who discontinued study participation (for any reason) (considered to be the RDO population) were encouraged to return for their scheduled week 26 efficacy evaluations. Effects on cognition were assessed using the Alzheimer’s Disease Assessment Scale–Cognitive subscale (ADAS-Cog).

Results: The results for the Novartis US Pivotal Trials and for the 3 studies combined (Novartis studies B352, B351, and B303) are reported. In the US pivotal trial, RDO patients in the 6- to 12-mg/d group had been not receiving the drug (to be called “off drug”) for 102 (57.7) days (mean [SD]) compared with 68 (51.7) days in the RDO placebo group. In these RDO analyses, a statistically significantly greater worsening on the ADAS-Cog mean change score was observed in the placebo group (n=17) compared with the rivastigmine 6- to 12-mg/d group (n=33) at week 26 (MMSE score, −8.2 vs −3.0; P = .009). In the pooled studies, the mean (SD) number of days off treatment was 95 (52.0) days for the rivastigmine 6- to 12-mg/d group and 66 (52.7) days for the placebo group. The RDO analysis also showed a statistically significantly greater decline in cognitive function as measured by the ADAS-Cog mean change score in the placebo group (n=38) compared with the rivastigmine 6- to 12-mg/d group (n=88) at week 26 (MMSE score, −5.69 vs −2.5; P = .004). A significantly greater proportion of patients in the placebo group exhibited at least a 4-point and 7-point worsening in ADAS-Cog scores at week 26 compared with the rivastigmine 6- to 12-mg/d group in both the Novartis US Pivotal Trials (P = .007, P = .009) and the pooled studies (P = .002, P = .017).

Conclusions: After discontinuation of therapy, rivastigmine-treated patients exhibited less deterioration in cognitive function compared with placebo-treated patients. The less severe worsening of cognition after withdrawal of treatment in patients previously treated with rivastigmine suggests an effect on disease progression.

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cluded from the study design. There have since been anec
dotal reports of precipitous decline after stopping
treatment with acetylcholinesterase (AChE) inhibi-
tors, so close evaluation during this period is war-
ranted when using these agents.

Cholinesterase inhibition is the most extensively re-
searched and best-developed therapeutic approach for the
symptomatic treatment of AD, providing clinical ben-
fits presumably through an increase in synaptic acetyl-
choline levels and enhancing cholinergic neurotransmis-
sion. Limited data are available on the effects of ChEIs
after treatment has been terminated in patients with AD.
If the cholinergic inhibition strategy does, indeed, modify
disease progression owing to influence on biological pro-
cesses such as amyloid precursor protein processing, bind-
ing to AChE and butyrylcholinesterase (BuChE) in
plaques, or modification of brain blood flow or metabo-
lism, then with drug withdrawal, rapid deterioration in
cognition to the level observed in the placebo-treated
cohort should not occur, as would be expected if the ef-
effects of the drug were purely symptomatic.

Rivastigmine is a centrally selective ChEI that dem-
strates brain-region selectivity for the hippocampus and
cortex. In addition to inhibiting AChE, rivastigmine also
inhibits BuChE. Butyrylcholinesterase is an enzyme that,
in healthy subjects, constitutes a small percentage of cho-
linesterase activity in the brain, but in patients with AD,
as the illness progresses, increases to about 30%. It has
been suggested that BuChE may be involved in trans-
forming amyloid deposits from a diffuse to a more com-
 pact neuritic stage, and thus, the enzyme may play a role
in disease progression. In 3 double-blind, placebo-
controlled studies, patients treated with high-dose ri-
vastigmine demonstrated a significant clinical benefit on
all outcome measures, including cognition; global as-
essment of change including behavior; activities of daily
living; and disease severity. A 26-week, double-
blind, placebo-controlled study with a 26-week exten-
sion, in patients with mild to moderately severe AD, sug-
gests that patients initially receiving placebo lost cognitive
function that was not regained after starting rivastig-
mine therapy in the extension phase. The results sug-
gest a possible effect of the drug in delaying disease pro-
gression. Additionally, similar results were seen in a long-
term (52-week) study in patients with advanced disease
(GLOBAL Deterioration Scale score, 5-6) with statistically
significantly better results for rivastigmine-treated pa-
tients compared with patients originally randomized to
placebo (for the first 26 weeks) at follow-up weeks 52,
78, and 104.

For preservation of function vs worsening after dis-
continuing treatment with a ChEI during a study, both ben-
eficial effects from previous therapy on disease progres-
sion and negative effects from drug withdrawal may play
roles. From the long-term experience with ChEIs, it can
be generally concluded that their use delays symptoms and
possibly progression of the disease for 6 to 12 months. It has
been suggested that preserved function during fol-
low-up after early withdrawal of a drug compared with pla-
cebo would be presumptive evidence that the drug is de-
laying disease progression. However, to our knowledge,
formal clinical studies using drug withdrawal design have
not been conducted to provide further evidence for a disease-
modifying activity, primarily owing to ethical concerns about
withdrawing an effective therapy. The objective of this anal-
ysis was to evaluate the change in cognition observed at week
26 in patients who were originally treated with placebo vs
rivastigmine after patients had discontinued these treat-
ments in an AD trial and, subsequently, returned for sched-
uled efficacy evaluations.

STUDY DESIGN

Eligible patients with AD were enrolled in 1 of 3 26-week,
double-blind, placebo-controlled studies (US Pivotal Trial, US
fixed-dose study, or Global Pivotal Trial study) that compared
rivastigmine with placebo. A pooled analysis was conducted
with the combined results from 3 double-blind, placebo-
controlled studies. Investigators remained blinded to patient
treatment groups in the event they discontinued the study early.
Each study had similar inclusionary and exclusionary criteria,
visit schedules, and efficacy outcome measurements. For de-
tails concerning study design and results, refer to previous pub-
llications.

PATIENT POPULATION

The eligibility criteria were generally the same in all studies.
Eligible patients (with a dependable caregiver) were 50 years
old or older, not of childbearing potential, and fulfilled the cri-
teria for dementia of the Alzheimer type, as described in Diag-
nostic and Statistical Manual of Mental Disorders, Fourth Edi-
tion. Patients had probable AD according to the National
Institute of Neurological and Communicative Disorders and
Stroke–Alzheimer’s Disease and Related Disorders Associa-
tion (NINCDS-ADRDA), and their Mini-Mental State Exami-
nation (MMSE) score was between 10 and 26 (both inclusive).
The procedures followed were in compliance with the ethical
standards of the institutional committees on human experi-
mentation and with the Helsinki Declaration of 1964, amended

The Alzheimer’s Disease Assessment Scale–Cognitive sub-
scale (ADAS–Cog) was used to evaluate cognitive function.
Efficacy evaluations (ADAS–Cog score, mean change from base-
line) were completed at baseline, weeks 12, 18, and 26, or within
24 hours of the last dose of study medication in patients who
discontinued treatment early. The retrieved dropout (RDO)
population was analyzed, which included all patients who pre-
maturely discontinued study participation for any reason and
returned for their scheduled week 26 efficacy evaluation.

ANALYSIS PLAN

The results for the US dose-range trial and for the 3 studies with
data pooled are reported. The change from baseline was the pri-
mary efficacy parameter in the analysis. Mean change scores for
ADAS–Cog were calculated as baseline score minus the postbase-
line score. A positive value would indicate an improvement. The
proportion of patients who displayed worsening (any, ≥4 points
and ≥7 points from baseline) was also measured. All compari-
sions to placebo were conducted against a 2-tailed alternative
hypothesis, with P < .05 being considered statistically significant.
For the categorical analyses (improvement and worsening), the Mantel-
Haenszel test was performed. Analyses of the change from base-
line scores were performed in the context of 1-way analysis of
covariance/analysis variance models (ANCOVA/ANOVA) by pool-
ing over centers owing to the small sample size within centers.
The ANCOVA/ANOVA models were also used to correct for the difference in ADAS-Cog scores at baseline.

## RESULTS

### DEMOGRAPHY AND DISPOSITION

Of the 2126 patients enrolled in the 3 double-blind studies, 828 received rivastigmine, 6 to 12 mg/d; 651 received rivastigmine, 1 to 4 mg/d; and 647 received placebo. The mean age of the patients was 73.4 years (age range, 41-95 years) and 59% of patients were female. Of the enrolled 2126 patients, 538 discontinued the study and, of these, 166 constituted the RDO population. The main reason for patient discontinuation in all treatment groups was adverse events. Additionally, more than twice as many patients discontinued from the rivastigmine 6- to 12-mg/d treatment group (38%) compared with 17% in both the rivastigmine 1- to 4-mg/d and placebo treatment groups (Table 1). Baseline ADAS-Cog scores were slightly higher in placebo-treated patients than in rivastigmine-treated patients in both the US study and the pooled data studies. Since patients with more severe AD tend to respond better to treatment, the difference in baseline ADAS-Cog scores was corrected using ANCOVA/ANOVA models in the analysis of the data.

### OFF DRUG FINDINGS

In the US Pivotal (dose-range) Trial, patients in the rivastigmine 6- to 12-mg/d group had not been receiving the drug (or “off drug”) for (mean [SD]) 102 (57.7) days compared with 68 (51.7) days in the placebo group. In the pooled data studies, patients in the rivastigmine 6- to 12-mg/d group had been off drug for 95 (52.0) days compared with 66 (52.7) days for the placebo group.

### ADAS-COG MEAN CHANGE FROM BASELINE SCORE

The results from the US Pivotal (dose-range) Trial showed a statistically significantly greater worsening on the ADAS-Cog mean change score in the placebo group (n = 17) compared with the rivastigmine 6- to 12-mg/d group (n = 33) at week 26 (MMSE score, −8.2 vs −3.0; P = .009) (Table 2). Scores are calculated by subtracting the baseline scores from the postbaseline scores. Therefore, a positive value would indicate an improvement; a negative value would indicate the patient’s cognition was worsening. In the pooled data studies, the RDO analysis also showed a statistically significantly greater decline in cognitive function as measured by the ADAS-Cog mean change score in the placebo group (n = 38) compared with the rivastigmine 6- to 12-mg/d group (n = 88) at week 26 (MMSE score, −5.69 vs −2.5; P = .004). Patients in the rivastigmine 1- to 4-mg/d group also showed less worsening than the placebo-treated patients in both the US Pivotal (dose-range) Trial and the pooled data study analysis when comparing baseline with week 26 ADAS-Cog scores.

### WORSENING FROM BASELINE

A significantly greater percentage of patients in the placebo group exhibited worsening in the ADAS-Cog scores at week 26 compared with the rivastigmine 6- to 12-mg/d group in both the US Pivotal (dose-range) Trial (MMSE score, ≥4-point worsening; placebo 76% vs rivastigmine 6- to 12-mg/d 33%; P = .007) (MMSE score, ≥7-point worsening; placebo 59% vs rivastigmine 6- to 12-mg/d 18%; P = .009) (Table 3) and in the pooled data studies (MMSE score, ≥4-point worsening; placebo 63% vs rivastigmine 6- to 12-mg/d 32%; P = .002)(MMSE score, ≥7-point worsening; placebo 34% vs rivastigmine 6- to 12-mg/d 15%; P = .02). Also, a statistically significantly greater proportion of patients in the placebo group exhibited at least a 4-point worsening in the ADAS-Cog scores at week 26 compared with the rivastigmine 1- to 4-mg/d group in the pooled data studies (MMSE score, ≥4-point worsening; placebo 63% vs rivastigmine 1- to 4-mg/d 38%; P = .04).

### IMPROVEMENT FROM BASELINE

A greater percentage of patients in both the rivastigmine 6- to 12-mg/d, and 1- to 4-mg/d groups exhibited any improvement in the ADAS-Cog scores at week 26 vs

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**Table 1. Patient Disposition**

<table>
<thead>
<tr>
<th>Variable</th>
<th>US Pivotal (Dose-Range) Trial</th>
<th>Placebo-Treated Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients randomized</td>
<td>231</td>
<td>233</td>
</tr>
<tr>
<td>No. of patients who discontinued treatment</td>
<td>82 (35)</td>
<td>34 (15)</td>
</tr>
<tr>
<td>Reasons for discontinuation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>67 (29)</td>
<td>19 (8)</td>
</tr>
<tr>
<td>Death</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>Withdrawal of consent</td>
<td>9 (4)</td>
<td>10 (4)</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>5 (2)</td>
<td>5 (2)</td>
</tr>
</tbody>
</table>

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*Data are given as number (percentage) of patients. For the pooled data studies, high dosing groups include those who received rivastigmine, 6 to 12 mg/d; those who received a fixed dose of 6 mg/d; and those who received 9 mg/d. For the pooled data studies, low dosing groups include those who received rivastigmine, 1 to 4 mg/d and those who received a fixed dose of 3 mg/d (adapted from Exelon New Drug Application).
There was statistically significantly less cognitive decline noted in the rivastigmine-treated patients compared with placebo after therapy had been discontinued. These results suggest a possible "structural effect" of rivastigmine treatment in patients with AD (Figure 1). This effect has been hypothesized previously in the "withdrawal maneuver" comparing putative disease-modifying agents with placebo (Figure 2). The results suggest a possible beneficial residual effect of rivastigmine after therapy has been discontinued. The mean change from baseline ADAS-Cog score at week 26 for the RDO populations from both the US Pivotal (dose-range) Trial and pooled data studies demonstrated significantly less decline in cognition for the rivastigmine 6- to 12-mg/d group compared with the placebo group. Patients treated with rivastigmine, 6 to 12 mg/d, also demonstrated significantly less worsening from baseline, both 4-point or more and 7-point or more worsening, as measured by the ADAS-Cog compared with patients treated with placebo. These data suggest that the effect of rivastigmine may be greater than merely symptomatic, providing a beneficial delay in progression in some patients. The persisting improvements are in agreement with a previously proposed disease modification effect also suggested with use of other ChEIs. To our knowledge, this is the first report of its kind to use RDO data to show a potential clinical beneficial effect to disease progression in AD. Previous animal studies have suggested
that long-term administration of ChEIs might protect cholinergic neurons. Possible neuroprotective effects might also be explained by the drug’s effect at the cholinergic synapse, maintaining concentrations of AChE and possibly protecting against neurodegeneration in neuronal systems that receive cholinergic innervation. Another possible explanation for the increase in effect on cognition in patients with AD observed with rivastigmine therapy may be the ability of the agent to increase cerebral blood flow. It has been suggested that decreased cerebral blood flow may precede and or contribute to neuronal degeneration in AD.

Other mechanisms of action by which rivastigmine may affect disease progression include effects on amyloid precursor protein and or β-amyloid metabolism, and/or possible inhibition of both AChE and BuChE at nonsynaptic locations, such as plaques and/or neurofibrillary tangles. There is some evidence suggesting that BuChE may be involved in the transformation of amyloid precursor protein to β-amyloid proteins that deposit and eventually compose the core of plaques. The amount of BuChE activity associated with amyloid plaques increases about 5- to 6-fold in the brains of individuals with dementia compared with control subjects without dementia. Cholinesterase inhibitors may also interfere with disease progression by promoting soluble amyloid precursor protein release (a potential neuroprotective protein), as demonstrated in rat brain and recently confirmed in neuroblastoma cells.

There are limitations to this data set. Retrieved dropout data cannot be assumed as a random sample from the discontinued patients. Out of all discontinued patients, less than 33% of them had RDO data in the pooled studies (<40% in the US Pivotal [dose-range] Trial). Also, the reasons for study discontinuation are not entirely random. Somewhat more patients discontinued from the rivastigmine-treated group than the placebo group apparently related to dose-dependent adverse effects, although the implications, if any, on these data analyses are unclear.

In both RDO analyses (US Pivotal [dose-range] Trial and pooled data studies), patients treated with rivastigmine, 6 to 12 mg/d, were typically receiving the drug for somewhat shorter periods compared with placebo-treated patients. However, receiving rivastigmine for a shorter time, if it influenced the results, would be expected to diminish differences between the rivastigmine- and placebo-treated groups. Nevertheless, significant differences favoring the rivastigmine-treated groups were present at week 26. A caveat would be the overall short length of observation, which limits definitive conclusions. Potential effects of rivastigmine and the other ChEIs on AD progression need to be further investigated in longer-term trials.

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REFERENCES


