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Adverse events and dropouts in Alzheimer's disease studies: What can we learn?

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Abstract

Background: Interpreting Alzheimer's disease (AD) clinical trial (CT) outcomes is complicated by treatment dropouts and adverse events (AEs). In elderly participants, AE rates, dropouts, and deaths are important considerations as they may undermine the validity of clinical trials. Published discontinuation and safety data are limited.

Methods: Safety data from 1054 placebo-treated participants in IDENTITY and IDENTITY-2, 76-week, Phase 3 AD studies conducted in 31 countries, were pooled, annualized, and summarized overall, by country and age group.

Results: Median age was 74.2 (interquartile range 67.9–79.5) years; 57.4% were female; and median observation time was 63.2 (interquartile range 41.6–77.4) weeks when study drug dosing was halted. Overall annualized rates for discontinuations, discontinuations due to AEs, serious adverse events (SAEs), and deaths were 21.6% (range 19.6%–24.0%), 8.2% (range 8.1%–8.3%), 12.0%, and 1.7%, respectively. AE and discontinuation rates varied by country and age groups. Fall, pneumonia, and atrial fibrillation AEs were more frequent in the oldest age group.

Conclusions: These annualized placebo safety data provide insight into the course of enrolled patients with mild-to-moderate AD, and are useful in planning longer term trials and in monitoring safety.

Keywords: Alzheimer's disease; Safety monitoring; IDENTITY; IDENTITY-2; Epidemiology; Adverse events; Serious adverse events; Discontinuations; Site selection; Clinical trial methods

1. Introduction

Alzheimer's disease (AD) is a slowly progressing neurodegenerative brain disease for which only symptomatic therapies are currently available. These treatments do not affect the underlying neuropathology of AD and neurodegeneration continues unchecked. There is a great need for treatments that can slow synaptic and neuronal loss. Many potentially "disease-modifying" therapies are under development. Studies to demonstrate disease modification through protection of cognition and function need to be ≥18 months in duration [1,2], but studies of this length in an aged population with AD are complicated due to high rates of discontinuation; adverse events (AEs), including treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs); and death [3,4]. Patient age and location of investigative site may affect these rates. Periodic blinded and/or unblinded reviews of AEs, laboratory evaluations, electrocardiograms, and vital signs during ongoing studies are necessary to ensure patient safety by identifying concerns quickly [5–8].

SAEs are a special category of AEs defined by regulatory authorities as AEs that result in death, are immediately life-threatening, result in hospitalization or prolongation of

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hospitalization, result in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or result in a congenital anomaly or birth defect. In addition, an AE may be considered serious by the trial sponsor or investigator in the absence of these criteria if, based on appropriate medical judgment, they could jeopardize the patient/subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, or blood dyscrasias or convulsions that do not result in hospitalization [7].

To effectively interpret these data and identify potential safety signals, comparisons to safety data from a closely matched untreated population are recommended [9,10]. In fact, safety reporting of United States Food and Drug Administration (FDA) Guidance for Investigational New Drug (IND) requires the use of background rates of common AEs in comparator study populations to determine SAEs to be reported in an expedited manner. Instead of requiring reporting of all AEs that are serious, unexpected, and considered related to study drug by the investigator, the FDA now allows more commonly occurring SAEs to be reported only when they occur with greater frequency than expected in the background population [11]. The data reported herein will be helpful in determining background rates of the most common AEs in the mild-to-moderate AD population. Furthermore, unblinded external data safety monitoring boards (DSMBs) can benefit from having background rates of safety data to assess the magnitude of a particular safety concern.

For this purpose, we previously summarized safety data from 5 published 18-month studies of potential disease-modifying AD therapies and from the AD cohort of the Alzheimer's Disease Neuroimaging Initiative (ADNI) [3]. However, the published data had different AE reporting methods, limiting the breadth of data available. Although complete ADNI data were available, they were limited by a somewhat unique population (mainly North American volunteers with mild AD entering an observational study without potential treatment benefit), included a relatively small sample, and were not monitored and verified per Good Clinical Practice standards [3]. Because of these limitations, we proposed using a larger placebo database that contained all safety data for AD patients followed for $\geq$18 months in potential therapeutic trials. Several such placebo databases exist, including the Alzheimer's Disease Cooperative Study (ADCS) pooled placebo database [12] and the Critical Path Institute's Online Data Repository (CODR) [13]. Safety data from the various studies, however, have not yet been merged.

The IDENTITY and IDENTITY-2 (Interrupting Alzheimer's Dementia by Evaluating Treatment of Amyloid Pathology) studies were global, Phase 3, double-blind, randomized trials comparing semagacestat, a γ-secretase inhibitor, and placebo for 76 weeks in patients with mild to moderate AD. In August 2010, semagacestat dosing was stopped after a protocol-specified interim review showed greater and dose-dependent cognitive/functional worsening for semagacestat patients compared with placebo patients. Patients were followed for 7 months after discontinuing semagacestat treatment to further assess safety and determine whether cognitive/functional worsening was reversible [14]. When semagacestat was halted, the studies were fully enrolled with 37.7% of IDENTITY placebo patients and 6.1% of IDENTITY-2 placebo patients having been followed for the full 76 weeks.

In this study, we report discontinuation and AE data from placebo patients in the IDENTITY studies to extend the limited safety literature in AD therapeutic trials, and to compare the findings with other published annualized rates of safety data.

2. Methods

2.1. Studies included in pooled analysis

Study protocols were reviewed and approved by regulatory agencies and institutional review boards, and all patients and caregivers provided written informed consent prior to randomization, according to the Declaration of Helsinki, in 31 countries at 300 sites that participated in the global IDENTITY studies. Enrollment began in April 2008 and was completed in May 2010. The studies were similar in design with the exception of IDENTITY's dose-response design comparing 100 mg/day semagacestat, 140 mg/day semagacestat, and placebo, with a target enrollment of 500 patients per arm. IDENTITY-2 evaluated 140 mg/day semagacestat and placebo with a target enrollment of 550 patients per arm.

Both studies included a delayed-start design from 76 to 88 weeks; data were not included in this study as all patients received semagacestat during this study period. Both trials had identical inclusion criteria and included patients with mild (Mini-Mental State Examination [MMSE] 20–26) to moderate (MMSE 16–19) AD, as defined by the National Institute of Neurological Disorders and Stroke–Alzheimer Disease and Related Disorders (NINCDS/ADRDA) criteria for probable AD [15]. Males and females $\geq$55 years of age were included; females could not be of child-bearing potential. Other causes of dementia or cognitive decline were excluded using a Modified Hachinski Ischemia Scale score of $\leq$4 [16], Geriatric Depression Scale score of $\leq$6 [17], a brain magnetic resonance imaging (MRI) or computed tomography (CT) scan confirmation of no findings inconsistent with diagnosis of AD, and lack of National Institute of Neurological Disorders and Stroke/Association Internationale pour la Recherché et l'Enseignement en Neurosciences (NINDS/AIREN) criteria for vascular dementia [18].

Patients were required to have a reliable caregiver and could not have serious or unstable medical conditions that could interfere with efficacy or safety evaluation or shorten lifespan to $<$2 years. This included a history in the previous 5 years of meningitis, encephalitis, neurosyphilis, and drug