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Featured Articles

Coalition Against Major Diseases/European Medicines Agency biomarker qualification of hippocampal volume for enrichment of clinical trials in predementia stages of Alzheimer's disease

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Abstract

Background: Regulatory qualification of a biomarker for a defined context of use provides scientifically robust assurances to sponsors and regulators that accelerate appropriate adoption of biomarkers into drug development.

Methods: The Coalition Against Major Diseases submitted a dossier to the Scientific Advice Working Party of the European Medicines Agency requesting a qualification opinion on the use of hippocampal volume as a biomarker for enriching clinical trials in subjects with mild cognitive impairment, incorporating a scientific rationale, a literature review and a de novo analysis of Alzheimer's Disease Neuroimaging Initiative data.

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Results: The literature review and de novo analysis were consistent with the proposed context of use, and the Committee for Medicinal Products for Human Use released an opinion in November 2011.
Conclusions: We summarize the scientific rationale and the data that supported the first qualification of an imaging biomarker by the European Medicines Agency.

Keywords: Alzheimer's disease; Hippocampal volume; Mild cognitive impairment; Alzheimer's Disease Neuroimaging Initiative

1. Introduction

Decreased hippocampal volume (HCV) is one of the best established biomarkers used in research studies to stage the progression of Alzheimer's disease (AD) pathology in the brain of patients across the spectrum of the disease [1,2]. A supporting body of literature over approximately 20 years indicates that changes in HCV are most rapid around the onset of dementia [1,3], and there is substantial evidence that reductions in HCV occur at prodromal phases before the development of clinical dementia [2]. It is therefore considered that HCV represents a biomarker that could be used to enrich clinical trials with individuals who are not yet clinically demented but are likely to progress rapidly.

Scientific assessment of the potential for use of biomarkers in clinical trials can be advanced in a structured fashion through the process of biomarker qualification, a process recently introduced by regulatory agencies including the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA). Regulatory qualification of a biomarker for a defined context of use provides scientifically robust assurances to sponsors and regulators that accelerate appropriate adoption of biomarkers into drug development and clinical practice. Such assurances saves time and money by removing the burden of proof on each individual sponsor to provide data to regulatory agencies on biomarker performance and validation.

In the European Union, the EMA, based in London, is the central regulatory agency that reviews new medicinal products. The evaluation is the responsibility of the Committee for Medicinal Products for Human Use (CHMP), which established a Scientific Advice Working Party (SAWP) as one of its supporting Committees to provide scientific advice to applicants.

In additional to the SAWP providing independent expert advice to sponsors seeking marketing authorization, it also runs the qualification of novel methodologies procedure [4], established by the EMA in 2008, which can result in one of two possible outcomes: (*i*) CHMP qualification *advice* based on the evaluation of the scientific rationale and on preliminary data submitted, relevant to the development of future protocols and methods for further method development toward qualification; and (*ii*) CHMP qualification *opinion* based on the assessment of submitted data, relevant to the acceptability of a specific use of the proposed method (e.g., use of a novel methodology or an imaging method) in a research and development context (nonclinical or clinical studies). After publication of a draft qualification opinion, the CHMP evaluation is open to scientific scrutiny and public comment to ensure that adopted opinions are broadly accepted within the community.

The Coalition Against Major Diseases (CAMD) is one of seven precompetitive consortia of the Critical Path Institute created to deliver on the US FDA's Critical Path Initiative [5] to accelerate the development of therapies for AD and Parkinson's disease by generating the best methods and tools for evaluating drug efficacy, expediting clinical trials, and streamlining review by regulatory agencies [6].

In April 2011, CAMD submitted a dossier to the SAWP requesting a qualification opinion on the use of HCV as a biomarker for enrichment in AD trials in the predementia or prodromal phase. SAWP responded with a list of discussion points and questions in May 2011. CAMD submitted a formal written response to several of the questions and then met with SAWP representatives during a face-to-face meeting in June 2011 to respond to the remaining questions. At this meeting, SAWP posed several additional questions and, in August 2011, CAMD submitted a formal written response to these questions. In September 2011, SAWP approved and CHMP adopted the qualification opinion on the use of HCV as a candidate biomarker for AD for release for public consultation. The consultation period ended on November 1, 2011, and the opinion was adopted by CHMP on November 17, 2011 [7].

This article summarizes the content of the data submitted to the EMA, the discussion process between CAMD and the EMA to address outstanding questions and concerns of the EMA, and the resulting qualification opinion.

2. Rationale for seeking qualification of HCV

Advances in the understanding of AD pathophysiology show that the onset of pathology begins decades before the onset of clinical symptoms [8]. Early treatment of AD is thought to offer the best opportunity for effective intervention [9]. For this to be demonstrated, clinical trials must be performed using participants affected during an early phase of the disease process (e.g., predementia). Clinical criteria exist for a prodromal disease stage defined as amnestic mild cognitive impairment (MCI), characterized by objective memory deficits but the absence of frank