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Featured Article

A 24-week study to evaluate the effect of rilapladib on cognition and cerebrospinal fluid biomarkers of Alzheimer's disease

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Abstract

Background: The lipoprotein-associated phospholipase A_2 inhibitor (Lp-PLA_2), rilapladib (SB659032), is being evaluated as a potential treatment to slow the progression of Alzheimer's disease (AD).

Methods: One hundred twenty-four subjects with possible mild AD and with neuroimaging evidence of cerebrovascular disease were randomized to placebo or 250-mg rilapladib once daily, for 24 weeks, in addition to stable background acetylcholinesterase inhibitor and/or memantine. The study assessed the safety and tolerability of rilapladib and its effects on cognition, mechanistic, and disease-related biomarkers. Although the overall intent behind the study was to take a broad exploratory view of the data, two primary end points of interest (cerebrospinal fluid [CSF] amyloid beta peptide 1–42 [$A\beta_{1-42}$] and CogState executive function/working memory [EF/WM] composite score at week 24) were prespecified in the analysis plan for inferential statistical analysis.

Results: Rilapladib was well tolerated with no significant safety concerns. A significant difference from placebo was observed for rilapladib on change from baseline in EF/WM (effect size, 0.45; $P = .026$). There was no significant difference between groups on the change from baseline in CSF $A\beta_{1-42}$ ($P = .133$). Preliminary evidence of effects was detected on other mechanistic (albumin quotient) and disease-related biomarkers (tau/P-tau and neurofilament light chain).

Conclusion: These data provide initial evidence supporting Lp-PLA_2 inhibition as a novel treatment for dementia.

Clinical Trial Registration: Clinicaltrials.gov identifier: NCT01428453.

Keywords: Lp-PLA_2; Alzheimer's disease; Cerebrovascular disease; Cognition; Rilapladib; SB659032; Tau; Amyloid-beta peptide; Albumin quotient; Neurofilament light chain; Cerebrospinal fluid; Biomarkers; Small vessel disease

1. Introduction

Rilapladib (SB659032) is a potent and selective inhibitor of the enzyme lipoprotein-associated phospholipase A_2 (Lp-PLA_2). Lp-PLA_2 is a calcium-independent phospholipase A_2 that is actively secreted by monocyte-derived macrophages, T lymphocytes, and mast cells and circulates in plasma as a complex with low-density lipoprotein (LDL) and, to a lesser extent, high-density lipoprotein [1]. A range of studies demonstrate that inhibition of Lp-PLA_2 can reduce peripheral measures of inflammation in nonclinical [2] and clinical studies [3–5]. Based on nonclinical data, rilapladib is not believed to be brain penetrant and has been evaluated previously in subjects with stable atherosclerosis [6].

Lp-PLA_2 has substrate specificity toward oxidized phospholipids, in particular, those containing a polar fatty acid moiety that are generated during the oxidation of LDL

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(oxLDL) and apoptosis [1]. Lp-PLA_2 rapidly cleaves oxidized phosphatidylcholine in tissue, generating proinflammatory lysophosphatidylcholine (lysoPC) and oxidized nonesterified fatty acids. LysoPC has also been demonstrated to be a mediator of inflammatory stress on brain microvascular endothelial cells [7] and to increase the permeability of endothelial cells [8]. Literature supports that oxLDL can be detected in the central nervous system (CNS) after blood-brain barrier (BBB) disruption [9].

In a diabetic mellitus (DM) and hypercholesterolaemic (HC) pig model, treatment with darapladib (another Lp-PLA_2 inhibitor) numerically reduced the extent of immunoglobulin G brain parenchyma penetration suggesting a reduction in BBB leakage and significantly lowered the total amount of brain amyloid beta peptide 1–42 ($A\beta_{1–42}$) deposition compared with untreated DM/HC pigs [10]. Both findings are relevant and potentially linked, through brain Aβ efflux mechanisms at the BBB, to the pathogenesis and progression of Alzheimer's disease (AD) [11,12].

Age-related cerebrovascular dysfunction, and associated cerebrovascular disease (CVD), plays an important role in the initiation and progression of AD [13–15]. Cerebral small vessel disease (SVD) is a CVD subtype that is associated with a high proportion of AD cases [16–18]. The associated pathologic changes in the parenchymal small arteries and arterioles (e.g., arteriolosclerotic changes such as fibrinoid necrosis, lipohylinosis, microatheroma, and microaneurysms) extend to the endothelial barriers of the small vessels and capillaries (i.e., the BBB) resulting in permeability changes and extravasation of plasma components into the vessel walls and brain parenchyma [19]. Postmortem analyses of AD brain tissue have demonstrated changes to the microvasculature through the presence of extravasated serum proteins, such as albumin and immunoglobulin [20–23], as well as white matter lesions and the widespread deposition of cerebral amyloid angiopathy, with associated microbleeds; all of which may contribute to decline in vascular integrity and function [19]. These observations, together with the findings from the nonclinical models, informed on the choice of AD subjects with neuroimaging evidence of CVD (e.g., white matter lesions and/or lacunes, typical of SVD) in the present study.

In summary, it is hypothesized that rilapladib will peripherally reduce the production of proinflammatory and toxic mediators, thereby restoring BBB integrity and reducing its permeability. Resultant, or downstream, effects may include reduced levels of neuroinflammation/toxicity and reductions in CNS Aβ, either through a reduction in influx or a restoration of efflux mechanisms.

The present study was designed to investigate the extent to which the mechanisms observed in preclinical models are present in subjects with AD and CVD and whether any downstream impact on neurodegenerative biomarkers or cognition could be detected over a 24-week treatment period.

2. Methods

2.1. Study design

This exploratory study was a randomized, double-blind, placebo-controlled, parallel group, repeat dose study to evaluate the effect of rilapladib on biomarkers related to the pathogenesis and progression of AD and cognitive function. Subjects were randomized to either 250 mg of rilapladib or placebo once daily for 24 weeks in addition to their stable background therapy (i.e., acetylcholinesterase inhibitor [AChEI] and/or memantine). Study duration was 30 weeks comprising 4-week screening, 24-week treatment period, and 2-week follow-up. The study was conducted at 24 sites in Germany, Spain, Italy, Sweden, Bulgaria, and Canada.

The study was conducted in accordance with the *International Conference on Harmonization Good Clinical Practice guidelines* and the ethical principles that are outlined in the *Declaration of Helsinki 2008*. The protocol was reviewed and approved by ethics committees or institutional review boards at each institution.

2.2. Subjects

Eligible subjects were 50–80 years inclusive and met National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for possible AD [24]. Subjects had radiological (magnetic resonance imaging [MRI] or computed tomography [CT]) evidence of significant CVD, assessed within the last 12 months, by meeting at least one of the criteria in the following:

MRI evidence: White matter lesions: extending caps, irregular halo, diffusely confluent hyperintensities, or extensive white matter changes.
CT evidence: Extensive periventricular and deep white matter lesions: patchy or diffuse symmetrical areas of low attenuation (intermediate density between normal white matter and cerebrospinal fluid [CSF]), with ill-defined margins extending to the centrum semiovale, and at least one lacunar infarct.
MRI or CT evidence: Lacunar cases: multiple lacunes (e.g., >5) in the deep gray matter.

Subjects were required to have a Mini-Mental Status Examination score of 20–26 at screening, a Clinical Dementia Rating of 0.5 or 1.0, and a documented history of $\geq$6-month AChEI therapy, with two months at a stable dose.

Exclusion criteria included significant psychiatric illness; history/evidence of another cause of dementia; history of seizures; abnormal findings that would preclude participation; treatment with monoamine oxidase inhibitors, conventional antipsychotics, an investigational drug or treatment with a potential for interaction with rilapladib. See Supplementary Materials for further details.