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A Randomized Phase 2 Study of an Anti–Amyloid β Monoclonal Antibody in Geographic Atrophy Secondary to Age-Related Macular Degeneration

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Purpose: To investigate the efficacy of intravenous GSK933776, a humanized monoclonal antibody directed against the N-terminal amino acids of amyloid β, for the treatment of geographic atrophy (GA) in age-related macular degeneration (AMD).

Design: Prospective, randomized, placebo-controlled, double-masked, multicenter phase 2 clinical trial.

Participants: Patients with GA secondary to AMD, a visual acuity score of at least 35 letters, and GA with a total area of 1.9 to 17 mm^2 were enrolled.

Methods: Participants were monitored monthly for 4 months during an observation period to determine the rate of GA enlargement in the study eye. After the observation period, randomization was performed into 1 of 4 treatment arms (GSK933776 at 3, 6, and 15 mg/kg/month and placebo). At each monthly visit over 18 months, participants underwent visual acuity testing under normal luminance and low-luminance conditions. Ocular imaging included color fundus photography, fundus autofluorescence, fluorescein angiography, and spectral-domain OCT.

Main Outcome Measure: Enlargement in the area of GA measured from color fundus photographs with reference to fundus autofluorescence images.

Results: A total of 191 participants were randomized into the study, with 139 (73%) fulfilling the efficacy population criteria. Over 18 months, GSK933776 did not reduce the rate of GA enlargement relative to placebo. Overall, there were no consistent meaningful differences relative to placebo in any of the visual function measures. There was a correlation between the low-luminance visual acuity (LLVA) deficit at baseline and the rate of GA enlargement. Genetic variations in complement factor I (*CFI*) gene did not correlate with GA progression. No ocular serious adverse events considered related to the GSK933776 treatment were identified, and a similar number of nonocular serious adverse events were reported across all treatment groups.

Conclusions: Intravenous amyloid β inhibition with GSK933776 did not slow the rate of GA enlargement compared with placebo, and no clinically meaningful differences relative to placebo were observed in visual function testing over 18 months. The LLVA deficit was associated with faster GA enlargement; however, no correlation was shown between genetic variations in the *CFI* gene and the rate of GA enlargement. *Ophthalmology Retina 2018;■:1–13 © 2018 Published by Elsevier Inc. on behalf of the American Academy of Ophthalmology*

Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in the developed world among individuals older than 50 years.[1] Most of the genetic polymorphisms associated with AMD reside in genes encoding the complement pathway, and the mutations studied so far are thought to lead to complement overactivation, resulting in inflammation and cell death.[2]

Geographic atrophy (GA), a late stage of nonexudative AMD, results in the loss of central vision and legal blindness after the fovea becomes involved. Even before central vision is lost, patients report difficulties seeing in dim light, reading, recognizing faces, and driving. More than 50% of patients with GA have bilateral disease.[3,4] Currently, there are no treatments for GA and a number of mechanisms, many related to complement, are under investigation. Recent evidence that complement activation plays a role in AMD comes from genetic association studies and the results from a phase 2 study using the complement C3 inhibitor, APL-2 (clinicaltrials.gov identifier, NCT02503332).[5] Although the phase 2 study using complement factor D inhibitor, lampalizumab (clinicaltrials.gov identifier, NCT01229215),[6] reported positive results, 2 large phase 3 studies failed to replicate these findings.[7,8]

https://doi.org/10.1016/j.oret.2018.03.001
ISSN 2468-6530/18

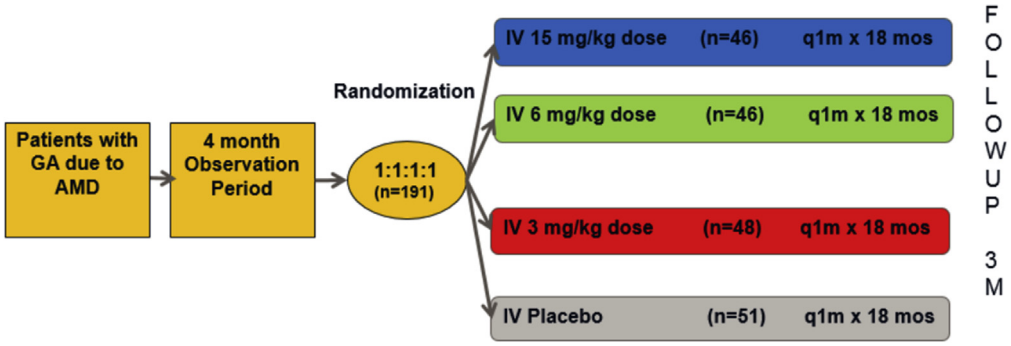

Figure 1. Schematic design for study BAM114341 (clinicaltrials.gov identifier, NCT01342926). Participants with geographic atrophy (GA) secondary to age-related macular degeneration (AMD) were enrolled in an observation period of approximately 4 months (M) to monitor GA enlargement rate in the study eye. Participants then were randomized to 1 of 4 arms (once monthly [q1m] GSK933776 at 3, 6, or 15 mg/kg or placebo) for 18 months. A follow-up visit occurred approximately 3 months after the last intravenous (IV) administration.

In an AMD genome-wide genetic analysis,[2] complement factor I (*CFI*) was one of 34 loci associated with AMD. In the MAHALO study of lampalizumab, a variation in the *CFI* gene was reported to be associated with an increased rate of GA enlargement. The MAHALO study reported on 2 correlated genetic variants in *CFI*: rs4698775 and rs17440077.[6] Additionally, the study reported on an association between genotype and mRNA levels of *CFI* in normal liver tissue.[6,9] These 2 *CFI* variants, rs4698775 and rs17440077, were shown to be highly correlated ($r^2 = 0.82$).[9]

Complement activation seems to be modulated by amyloid β in AMD and in experimental models of AMD. In postmortem retinal samples, activated complement components are present in drusen, the early hallmarks of AMD, and are colocalized with amyloid β, which is thought to trigger activation of the alternative complement cascade.[10] Amyloid precursor protein and amyloid β 1−40 are increased in the plasma of GA patients, but not in age- and gender-matched controls.[11] Furthermore, amyloid β directly inhibits *CFI*, and this inhibition can be reversed with an anti−amyloid β monoclonal antibody (mAb).[12] In addition, amyloid β has been reported to increase complement factor B indirectly.[13] Both activities of amyloid β lead to activation of the alternative complement cascade.

Multiple lines of evidence suggest that amyloid β inhibition with an anti−amyloid β mAb may be a useful strategy to decrease complement activation. Systemically administered murine anti−amyloid β mAb (GSK1532968) reduced deposits containing amyloid β and activated complement found in the retina of aged complement factor H−deficient mice, which served as an animal model for AMD.[14] Also, a separate anti−amyloid β mAb reduced both amyloid β and complement from the brain and retina of a human apolipoprotein E transgenic mouse on a high-fat diet.[15,16] Furthermore, amyloid β was shown to activate the alternative complement cascade.[13] These associations between amyloid β and complement together with the elevated levels of amyloid precursor protein and amyloid β 1−40 in the plasma of patients with GA suggested that a clinical investigation of amyloid β inhibition may slow the enlargement of GA.

GSK933776 is a humanized immunoglobulin G subclass 1 mAb directed against the N-terminal amino acid residues 1 through 7 of amyloid β. The mAb was designed to decrease complement fixation and interactions with Fc receptors, limiting the potential for immune cell−mediated toxicity. In addition, the humanization process was used to minimize the potential for immunogenicity.[17] The purpose of this phase 2 trial was to investigate the efficacy and safety of GSK933776 in slowing the enlargement of GA in patients with AMD.

Methods

Study Design

This trial was a randomized, parallel-group, double-masked, placebo-controlled phase 2 study (Fig 1) conducted between June 2011 and April 2016 (ClinicalTrials.gov identifier, NCT01342926; GlaxoSmithKline protocol, BAM114341). This multicenter study was conducted in the United States (40 centers) and Canada (1 center) according to the ethical principles of good clinical practice and the tenets of the Declaration of Helsinki after obtaining written informed consent from each participant. The protocols and their amendment were approved by the central Western Institutional Review Board (Olympia, WA) as well as local clinical site academic institutional review boards where necessary. Written informed consent with a Health Insurance Portability and Accountability Act−compliant statement (United States only) was obtained from each study participant before conducting any protocol-related procedures.

After qualifying for entry into the study, each participant was monitored monthly for approximately 4 months during an observation period to establish the enlargement rate of GA in the study eye. There was a baseline visit at the end of the observation period of the study, and this baseline visit was within 2 weeks of randomization and the first dose of the treatment period.

Participants were randomized centrally to 1 of 4 treatment arms in the study (3 dose levels of GSK933776 and placebo) at a 1:1:1:1 ratio. The highest dose of GSK933776 was added as the fourth treatment arm in a protocol amendment to the original 3-arm study after the first participant had received the first dose. A randomization schedule included all arms to maintain masking in the study. Participants returned for outpatient visits to receive monthly intravenous infusions of study medication over an 18-month treatment period.