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Clinical Trials

Bradykinin 1 Receptor Antagonist BI1026706 Does Not Reduce Central Retinal Thickness in Center-Involved Diabetic Macular Edema

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Received: November 7, 2018
Accepted: December 9, 2019
Published: March 30, 2020

Keywords: bradykinin; diabetic macular edema; BI 1026706

Citation: Lang GE, Tadayoni R, Tang W, Barth C, Weiss-Haljiti C, Chong V, on behalf of the BI 1026706 Study Group. Bradykinin 1 receptor antagonist BI1026706 does not reduce central retinal thickness in center-involved diabetic macular edema. Trans Vis Sci Tech. 2020;9(4):25, https://doi.org/10.1167/tvst.9.4.25

Purpose: The bradykinin 1 receptor may be important in inflammatory retinal vascular leakage in diabetic macular edema. BI 1026706 is an antagonist of bradykinin 1 receptor that has demonstrated efficacy in preclinical studies. Boehringer Ingelheim trial 1320.22 (NCT02732951) was a randomized, double-blind, placebo-controlled study. The pharmacodynamics, safety, and tolerability of oral BI 1026706 for 12 weeks were evaluated in patients with type 1 or type 2 diabetes mellitus and mild visual impairment owing to center-involved diabetic macular edema.

Methods: Patients ($n = 105$) were randomized to receive either oral BI 1026706 100 mg twice daily (morning and evening) or placebo for 12 weeks. The primary end point of the study was week 12 change from baseline in central subfield foveal thickness (CSFT) by spectral domain optical coherence tomography. Additional end points included absolute CSFT values, safety, and pharmacokinetics.

Results: After 12 weeks of treatment, there was no meaningful change from baseline in the adjusted mean CSFT in either treatment group (BI 1026706, 10.3 µm; placebo, –6.2 µm; adjusted mean treatment difference, 16.5 µm [95% confidence interval, –16.2 to 49.1]). There were also no differences in best-corrected visual acuity outcomes between treatment groups. Most reported adverse events were of mild or moderate intensity, and were balanced between treatment groups.

Conclusions: BI 1026706 was not superior to placebo in CSFT week-12 change from baseline. Therefore, BI 1026706 does not reduce CSFT, a morphologic sign of diabetic macular edema.

Translational Relevance: Kinin-kallikrein inhibition effects may not be apparent over 12 weeks for bradykinin 1 receptor inhibition alone.

Introduction

Diabetic macular edema (DME) is a chronic, ocular complication of diabetes in which fluid accumulates in the central area of the retina.[1] DME is closely linked to the development of diabetic retinopathy and disruption of the blood–retinal barrier.[2] DME has become one of the leading causes of vision loss in persons of working age.[3] The prevalence of DME is likely to increase in line with increases in the global incidence of diabetes.[3,4]

Up until 2010, the standard of care in DME was laser photocoagulation.[2] However, 2010 saw the introduction of anti-vascular endothelial growth factor (anti-VEGF) therapy for the treatment of DME,[5] transforming the treatment landscape by establishing

intravitreal anti-VEGF as the preferred option for treating DME, alongside intravitreal steroids for some patients.[6]

Despite the success of anti-VEGF therapy, challenges remain in the treatment of DME. Some patients do not respond readily to anti-VEGF agents. In some cases, there is no improvement despite repeated intravitreal injections, and incomplete or relapsing responses may be observed.[7,8] Regular intravitreal injections are required over a long period of time, and these have been linked to rare, serious ocular adverse events (AEs) including endophthalmitis, vitreous hemorrhage, retinal detachment, traumatic cataract, and increased intraocular pressure.[9–12] Additionally, there is concern over the systemic effects of intravitreal anti-VEGF agents, particularly in elderly patients susceptible to stroke and other vascular complications; however, data on these side effects remain equivocal.[12]

The burden that intravitreal injections place on the patient and healthcare system is considerable. Manufacturers have recognized this burden, and have introduced flexible dosing regimens including treating as needed and treat and extend.[13] Real-world data gathered over 5 years indicate that patients with DME receive a median of six anti-VEGF injections in their first year of therapy—injection counts decrease thereafter.[14] Real-world outcomes for DME seem to be better than those for age-related macular degeneration, but improvements can still be made.[14,15] Certainly, the development of an oral compound would have obvious advantages in reducing injection burden and improving compliance. Therefore, despite the transformational benefits of anti-VEGF therapy, research continues to provide additional treatment options for patients with DME; this research includes the identification and targeting of novel therapeutic pathways.

The bradykinin 1 receptor (B1R) is a G-protein–coupled receptor that is a component of the kinin–kallikrein system and may be important in retinal vascular leakage and the inflammatory component of DME. The kinin–kallikrein system has been proposed for some time as a potential therapeutic target for retinal vascular disorders.[16] B1R is only weakly detectable under normal physiologic conditions; however, it is strongly expressed in pathologic and inflammatory states.[17–19] Expression of B1R messenger RNA is up-regulated in the retina and choroid of patients with diabetes versus controls.[19] Primary inflammatory processes regulated by bradykinin occur upstream of angiogenesis;[19] therefore, agents that inhibit B1R have the potential for activity in patients with DME whose disease is refractory to anti-VEGF therapies. Additionally, there are obvious advantages of an oral agent over an intravitreal injection.

BI 1026706 is a potent antagonist of B1R that was in development for the treatment of patients with DME. For preclinical assessment, it is not possible to use BI 1026706 as a B1R blocker owing to its low affinity in rat and mouse models. Therefore, in preclinical proof-of-concept studies, a rat cross-reactive B1R antagonist (BI 113823) was used, and was found to almost completely prevent the increase of retinal vascular permeability induced by an intravitreal B1R agonist injection (Thomas L and Bakker RA, unpublished observations, 2014).

Subsequent phase 1 single-dose and dose-escalating pharmacokinetic studies in healthy volunteers and patients with osteoarthritis of the knee found dose-proportional exposure at oral doses of BI 1026706 up to 100 mg.[20] Food had a minimal impact on exposure (Liu D, unpublished observations, 2013). Based on the geometric mean ratios, the maximum concentration was similar in fed and fasted conditions. The area under the concentration-time curve from time zero to infinity was somewhat lower in fed conditions than in fasted conditions. No major differences in median time to maximum concentration were observed between fed and fasted conditions (1.74 hours and 1.26 hours in fasted and fed conditions, respectively).

Boehringer Ingelheim trial 1320.22 (ClinicalTrials.gov: NCT02732951; EudraCT: 2015-003529-33) was a randomized, double-blind, placebo-controlled exploratory study to evaluate the pharmacodynamics, safety, and tolerability of orally administered BI 1026706 over 12 weeks in patients with mild visual impairment owing to center-involved DME. The objective of the trial was to investigate the mechanism and pharmacodynamics of orally administered BI 1026706 100 mg twice daily (bid) in these patients. The study also assessed the safety and tolerability of BI 1026706 treatment over 12 weeks.

Methods

Patients

The study aimed to enroll approximately 100 patients with type 1 or type 2 diabetes mellitus with center-involved DME. Patients with early stage, mild vision loss were selected. These patients are less likely to undergo clinical deterioration than patients with more severe vision loss. In such early stage cases, anti-VEGF agents are not the standard of care in many countries, and patients would therefore be likely to accept enrolment into a placebo-controlled trial. In addition, rescue treatment is available if the patient deteriorates. It is therefore considered ethical to withhold anti-VEGF, as

the patients eligible for this trial would not normally receive anti-VEGF agents.

The sample size was calculated to achieve 80% power at the 5% level for a two-sided test. It was assumed that the mean difference in central subfield foveal thickness (CSFT) between the two treatment groups would be 20 µm and that the common standard deviation would be 40 µm. Therefore, a total sample size of 102 patients was determined for this trial. One hundred and five patients were enrolled. For each enrolled patient, only one eye could be selected for study, and center involvement was confirmed by the central reading center.

Male patients or female patients of nonchildbearing potential who were age 18 years of age or older were enrolled if they met the following inclusion criteria: diagnosis of type 1 or type 2 diabetes mellitus; retinal thickening (CSFT ≥300 µm) owing to DME with center involvement; study eye best-corrected visual acuity (BCVA) measured by an Early Treatment Diabetic Retinopathy Study letter score of 70 to 84 letters (Snellen equivalent, 20/40–20/20); clarity, pupillary dilation, and individual cooperation sufficient for adequate spectral domain optical coherence tomography and fundus photographs.

Patients were excluded if they met any of the following exclusion criteria (ocular criteria related to the study eye): macular edema owing to causes other than DME; additional vision-impairing eye disease or abnormalities; yttrium aluminum garnet laser capsulotomy within 2 months before randomization; proliferative diabetic retinopathy or iris neovascularization; and aphakia. Patients were also excluded if they required immediate study eye treatment; laser photocoagulation, surgical, intravitreal, or peribulbar treatment within 4 months before randomization; fluocinolone acetonide intravitreal implant; intraocular corticosteroids within 2 years (9 months in pseudophakia) before randomization; topical steroid or nonsteroidal anti-inflammatory drugs within 30 days before randomization; systemic anti- or pro-VEGF treatment within 4 months before randomization; systemic steroids (>10 mg prednisone equivalent per day) within 4 weeks before randomization; or disease requiring intrastudy steroid intervention (rescue medication). Further exclusion criteria included current or planned intrastudy medication that is toxic to the retina, lens, or optic nerve; intensive insulin treatment within 3 months before randomization or planned in the next 4 months; change in oral antidiabetic medication within 3 months before randomization; clinically relevant abnormal laboratory values at screening; current or likely renal impairment (Cockcroft–Gault creatinine clearance <30 mL/min at screening); myocardial infarction or unstable angina within 3 months before randomization; uncontrolled hypertension (a single measurement of systolic >180 mm Hg, two consecutive measurements of systolic >160 mm Hg, or diastolic >100 mm Hg on optimal medical regimen); other conditions that could put the patient or participation at risk; significant alcohol or drug abuse; and allergy to any component of the trial drug.

Patients could withdraw consent for trial treatment and participation any time without the need to justify the decision, and were removed from the trial if the investigator deemed it necessary. Rescue medication could be given if patients underwent significant worsening of disease. Specifically, in the event of vision loss of five or more letters, or in the event of CSFT increase of 10% or more as compared with the previous visit, administration of local standard of care treatment such as intravitreal therapy, peribulbar injections, laser, or other surgical treatment of DME was allowed. After the end of study (visit 5), standard of care therapy was at the discretion of the investigator.

Ethics

The trial was conducted in compliance with the clinical trial protocol, in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use Good Clinical Practice Guidelines, and applicable regulatory requirements and Boehringer Ingelheim standard operating procedures. Before the initiation of any trial-related procedure, all patients were informed about the trial verbally and in writing by the investigator. Each patient was allowed sufficient time to consider participation in the trial and to ask questions concerning the details of the trial. Each patient also signed and dated an informed consent form according to the local regulatory and legal requirements.

Design and Interventions

Patients attended six clinic visits: one at screening (between 28 days and 2 days before first administration of study drug at day 1); four on treatment at days 1, 29, 57, and 85 (end of treatment); and one follow-up visit 28 days later (end of study). An additional consultation was conducted by telephone on day 8. Blood samples were taken during each scheduled clinic visit, and this was generally done before drug administration. At day 29 only, three blood samples were taken after drug administration.

On day 1, patients were randomized to receive either oral BI 1026706 100 mg bid (morning and evening) or placebo. Randomization was stratified by patients' previous DME treatment and conducted using a validated Boehringer Ingelheim system that was verified by a trial-independent statistician. BI 1026706 or placebo was administered at the study site for the first dose, at the clinic visit for each morning dose, and by the patients for all other time points. Patients were supplied with instructions for storage, maintaining dose intervals, and explaining how to deal with missed or duplicate doses. BI 1026706 tablets were allowed to be taken with or without food or water. Dosing was conducted over a 12-week period for the two parallel groups. After 12 weeks, all treated patients underwent 4 weeks of follow-up, during which standard of care therapy was applied at the discretion of the investigator.

The dose of BI 1026706 100 mg bid was selected on the basis of the drug levels observed in animal pharmacology studies and the pharmacokinetic characteristics observed in humans. At this dose, the unpublished animal and pharmacokinetic data indicated that efficacy was expected (Sauer A and Bakker RA, unpublished observations, 2014).

Rescue medication, according to local standard of care, was permitted if deemed necessary by the investigator (e.g., if the patient had undergone clinically significant worsening of DME). Data obtained after the start of rescue medication were excluded from the primary analysis of the primary end point. Investigational drugs, drugs that may affect the retina or optic nerve, drugs that may affect macular edema, and systemic VEGF treatments were not permitted during the trial. The use of oral corticosteroids was restricted to a daily dose equivalent to 10 mg or less of prednisone. Use of inhibitors of cytochrome P450 3A4 were to be assessed by the investigators in accordance with the summary of product characteristics for BI 1026706.

Primary End Point

The primary end point of the study was the change from baseline in CSFT in micrometers at week 12 as measured by spectral domain optical coherence tomography. The baseline value was the CSFT recorded at the visit on day 1.

Further End Points

All further efficacy end points were exploratory and intended to investigate the extent, onset, and duration of potential BI 1026706 activity over time and to describe changes from baseline. Additional end points included central subfield thickness (measured by spectral domain optical coherence tomography), CSFT response at week 12 (defined as $\geq$10% CSFT reduction from baseline), BCVA (measured by Early Treatment Diabetic Retinopathy Study letter charts), the proportion of patients requiring ocular rescue medication (and time to first rescue), vascular leakage, hard exudates and new vessel formation (determined by fluorescein angiography), nonperfused area (also determined by fluorescein angiography), and trough plasma concentrations of BI 1026706.

Secondary Safety End Points

Frequencies of AEs (including drug-related AEs, and AEs of special interest) were recorded. Serious AEs were defined as life threatening or fatal, resulting in persistent or significant disability, requiring or prolonging hospitalization, congenital anomaly, or those deemed serious for any other reason by the investigator. AE intensity was captured as mild, moderate, or severe.

Prespecified AEs of special interest were alterations in hepatic parameters defined as an aspartate transaminase (AST) and/or alanine transaminase (ALT) elevation of three-fold the upper limit of normal or greater, combined with a total bilirubin elevation of two-fold the upper limit of normal or greater measured in the same blood-draw sample, or as a marked peak AST and/or ALT elevation of 10-fold the upper limit of normal or greater. Patients who showed abnormalities in these laboratory parameters were followed-up according to the drug-induced liver injury process. There was one potential drug-induced liver injury case during the course of this trial.

Physical examinations, recording of vital signs, electrocardiograms, and methods for capturing ocular AEs were also conducted at selected visits. Each AE was recorded, and the clinical relevance was judged by the investigator.

Statistics

The primary end point comparing the two treatment groups was based on a mixed effect model repeated measures analysis. The model included treatment, previous DME treatment, week, and treatment by week interaction as fixed categorical effects. Baseline CSFT and baseline CSFT by week interactions were included as continuous fixed effects in the model. Adjusted mean values, as well as treatment differences, were presented together with 95% confidence intervals

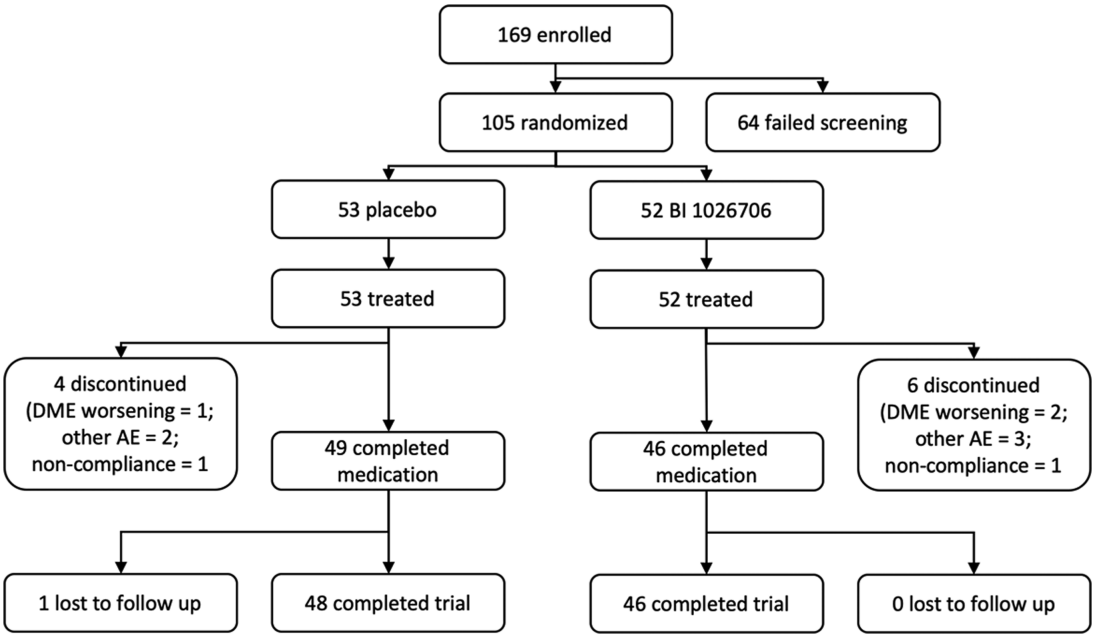

Figure 1. Disposition.

and *P* values. Descriptive statistics were used for all further end points.

Subgroup analyses were performed for the change from baseline in CSFT at week 12 by the following subgroups: previous DME treatment status (treatment naïve and treated for DME), BCVA at baseline (≤79 letters vs. >79 letters in the Early Treatment Diabetic Retinopathy Study letter chart), and CSFT at baseline (≤368 µm vs. >368 µm).

Safety analyses were descriptive in nature and included all treated patients in the trial.

Results

Efficacy

A total of 169 patients were enrolled at 35 trial sites in Germany, France, the United Kingdom, Spain, Portugal, Hungary, Greece, and Belgium. Of the 169 enrolled patients, 105 were randomized in a 1:1 ratio to the two treatment groups (BI 1026706, 52 patients; placebo, 53 patients). All 105 randomized patients were treated. Ten patients (9.5%) discontinued trial medication prematurely (six in the BI 1026706 group and four in the placebo group). Eight patients (7.6%) discontinued owing to AEs, including three patients (2.9%) who discontinued owing to worsening of DME (BI 1026706, two patients; placebo, one patient). Disposition is shown in Figure 1. Demographics were balanced between treatment groups and are shown in Table 1.

The mean CSFT at baseline was similar in both treatment groups. After 12 weeks of treatment, there was no meaningful change from baseline in the adjusted mean CSFT in either treatment group (BI 1026706, 10.3 µm; placebo, –6.2 µm). The adjusted mean treatment difference in CSFT between BI 1026706 and placebo was 16.5 µm (95% confidence interval, –16.2 to 49.1). This finding means that the primary hypothesis that BI 1026706 would be superior to placebo for CSFT change from baseline at week 12 was not supported. The data from the primary analysis are shown in Figure 2.

An additional sensitivity analysis using missing data imputation and data collected after rescue medication did not alter the outcome of the primary end point. There were no meaningful differences between treatment groups for any of the baseline subgroups analyzed. CSFT changes remained similar in both treatment groups at all time points measured. There were also no differences between groups for excess fluid or CSFT (data not shown).

In common with the lack of difference in CSFT measures between treatment groups, there were also no differences apparent in BCVA outcomes for the same analysis sets and subgroup analyses described for CSFT. Mean BCVA values remained similar over time in the BI 1026706 treatment group and in the placebo group. Comparing both treatment groups using a mixed effect model repeated measures analysis, there was no clinically meaningful difference in the adjusted

Table 1. Demographics and Baseline Disease Characteristics

	Placebo	BI 1026706	Total
Patients, *n* (%)	53 (100.0)	52 (100.0)	105 (100.0)
Sex, *n* (%)			
Male	39 (73.6)	38 (73.1)	77 (73.3)
Female	14 (26.4)	14 (26.9)	28 (26.7)
Race, *n* (%)			
White	38 (71.7)	47 (90.4)	85 (81.0)
Asian	1 (1.9)	0	1 (1.0)
Missing	14 (26.4)	5 (9.6)	19 (18.1)
Ethnicity, *n* (%)			
Non-Hispanic/-Latino	35 (66.0)	43 (82.7)	78 (74.3)
Hispanic/Latino	4 (7.5)	4 (7.7)	8 (7.6)
Missing	14 (26.4)	5 (9.6)	19 (18.1)
Age, years, mean (SD)	62.2 (9.7)	63.9 (8.7)	63.0 (9.2)
Age category, years, *n* (%)			
<65	30 (56.6)	26 (50.0)	56 (53.3)
65 to <75	18 (34.0)	20 (38.5)	38 (36.2)
≥75	5 (9.4)	6 (11.5)	11 (10.5)
Smoking status, *n* (%)			
Never smoked	34 (64.2)	34 (65.4)	68 (64.8)
Ex-smoker	14 (26.4)	14 (26.9)	28 (26.7)
Previous DME treatment, *n* (%)			
Naïve	27 (50.9)	26 (50.0)	53 (50.5)
Treated	26 (49.1)	26 (50.0)	52 (49.5)
CSFT, µm, mean (SD)	388 (80)	394 (88)	391 (84)
CSFT, µm, *n* (%)			
≤400	37 (69.8)	31 (59.6)	68 (64.8)
>400	16 (30.2)	21 (40.4)	37 (35.2)
BCVA ETDRS letter score, mean (SD)	79 (6)	78 (6)	78 (6)
BCVA ETDRS letter score, *n* (%)			
≤80	29 (54.7)	35 (67.3)	64 (61.0)
>80	24 (45.3)	17 (32.7)	41 (39.0)

ETDRS, Early Treatment Diabetic Retinopathy Study; SD, standard deviation.

mean change in BCVA from baseline at week 12 (Fig. 3).

The proportion of patients requiring rescue medication, and those with vascular leakage, evidence of hard exudates, new vessel formation, and an area of nonperfusion, all showed no differences between treatment groups. In each treatment group, nine patients received standard of care or rescue medication to treat their DME. Except for one patient in each treatment group, they were treated at least once with an anti-VEGF antibody.

Pharmacokinetics

Pharmacokinetic evaluation of BI 1026706 plasma trough concentrations indicated that steady state was achieved and maintained during treatment (from days 29 to 85) with twice-daily dosing. Peak geometric mean concentration of BI 1026706 was achieved at around 2.5 hours after administration (268, 945, and 711 nmol/L at 0.75, 2.50, and 3.50 hours after the dose, respectively).

In addition to the primary analysis on the overall population, prespecified subgroup analyses were conducted on the primary end point according to baseline CSFT and BCVA categories (data not shown). These analyses validate that the treatment effect between the two arms was not considerably different across these subgroups and demonstrate that any numerical differences apparent at baseline did not have a bearing on the sensitivity of the primary end point analysis.

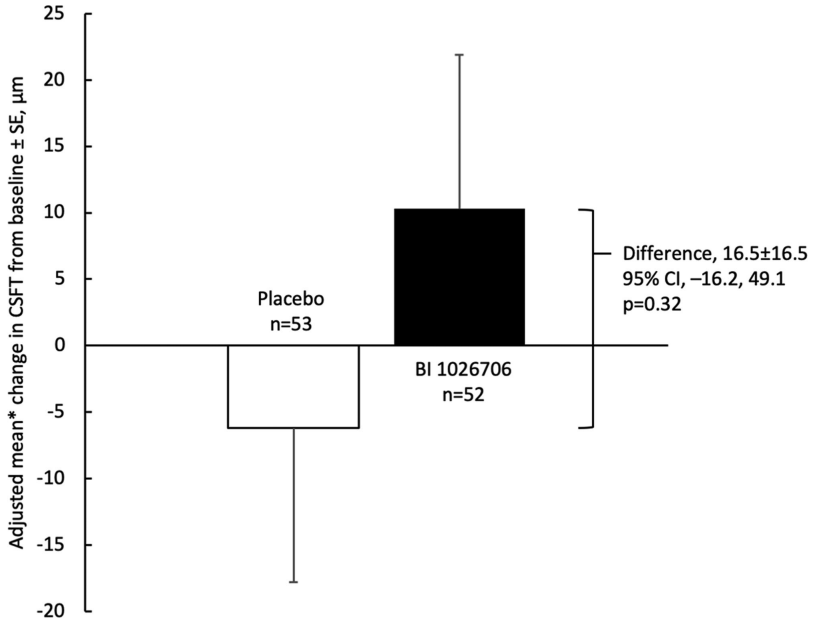

Figure 2. CSFT change from baseline at week 12. Mixed effects model repeated measures analysis on the full analysis set. *Adjusted for baseline covariates. CI, confidence interval; SE, standard error.

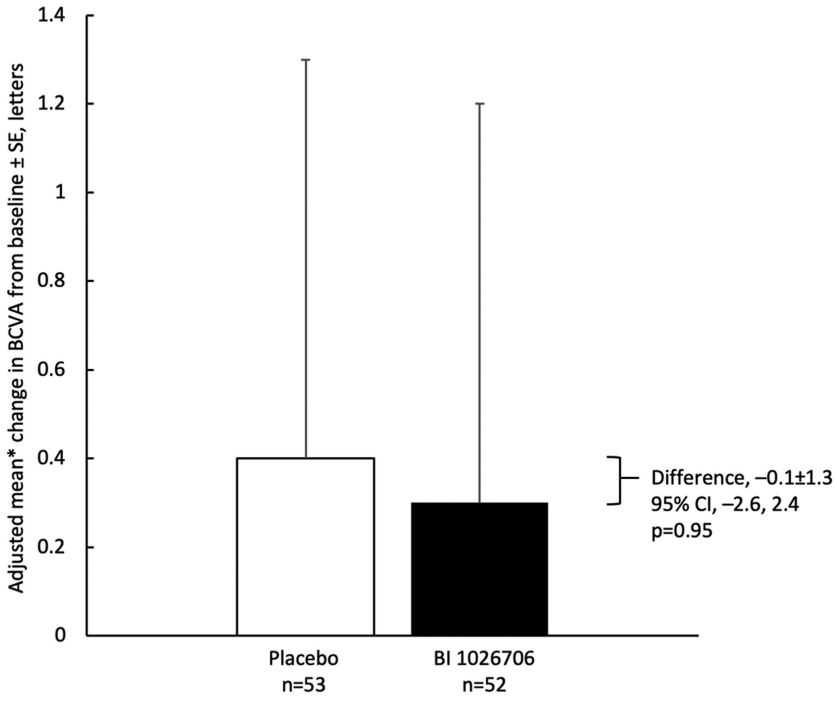

Figure 3. BCVA change from baseline at week 12. Mixed effects model repeated measures analysis on the full analysis set. *Adjusted for baseline covariates. CI, confidence interval; SE, standard error of the mean.

Safety

The frequency of patients with any AE was similar in the BI 1026706 treatment group (65.4%) and in the placebo group (69.8%). Most reported AEs were of mild or moderate intensity. The frequencies of patients reporting AEs judged as drug related by the investigator, as well as frequencies of AEs leading to discontinuation, were low and similar in both treatment groups. An AE of special interest was reported for one patient

Table 2. Frequencies of AEs

Preferred Term	Placebo, *n* (%)	BI 1026706, *n* (%)
No. of patients	53 (100.0)	52 (100.0)
Any AE	37 (69.8)	34 (65.4)
Infections and infestations	9 (17.0)	15 (28.8)
Nasopharyngitis	4 (7.5)	6 (11.5)
Urinary tract infection	2 (3.8)	1 (1.9)
Respiratory tract infection	0	2 (3.8)
Investigations	13 (24.5)	8 (15.4)
Gamma−glutamyltransferase increased	3 (5.7)	0
Blood glucose increased	2 (3.8)	1 (1.9)
Blood lactate dehydrogenase increased	0	2 (3.8)
Blood uric acid increased	0	2 (3.8)
Creatinine renal clearance increased	2 (3.8)	1 (1.9)
Eye disorders	10 (18.9)	11 (21.2)
Visual acuity reduced	2 (3.8)	3 (5.8)
Gastrointestinal disorders	5 (9.4)	8 (15.4)
Abdominal pain upper	0	2 (3.8)
Diarrhea	0	2 (3.8)
Vomiting	2 (3.8)	1 (1.9)
Nervous system disorders	7 (13.2)	6 (11.5)
Headache	1 (1.9)	4 (7.7)
Somnolence	3 (5.7)	1 (1.9)
Amnesia	2 (3.8)	0
Metabolism and nutrition disorders	6 (11.3)	4 (7.7)
Hyperglycemia	2 (3.8)	2 (3.8)
General disorders and administration-site conditions	1 (1.9)	5 (9.6)
Fatigue	0	2 (3.8)
Renal and urinary disorders	5 (9.4)	3 (5.8)
Proteinuria	2 (3.8)	0

in the BI 1026706 group. This was an elevation of AST and ALT levels that was associated with high BI 1026706 plasma concentrations, and the drug was discontinued. The incidence of serious AEs was greater for BI 1026706 than for placebo (13.5% vs. 3.8%). However, no single AE occurred in more than one patient, and the increase in serious AE incidence for BI 1026706 was not driven by any particular pattern of serious AEs.

The most common AEs were infections and infestations, which were reported more frequently in the BI 1026706 group compared with the placebo group. Overall, the incidences of AEs were similar between treatment groups. The frequencies of AEs by treatment group are shown in Table 2.

The balance of drug-related AEs was also similar between treatment groups. There were more gastrointestinal AEs in patients receiving BI 1026706 than placebo (5.8% vs. 1.9%; Table 3).

Discussion

The primary end point of the study was change from baseline in CSFT at week 12. This study failed to support the hypothesis that BI 1026706 would have superior efficacy over placebo for reducing CSFT in patients with DME. These data are supported by protocol-specified subgroup analyses and by an analysis of BCVA outcomes between treatment groups, all of which showed no activity for BI 1026706.

Safety results indicated that BI 1026706 was well-tolerated and did not result in any clinically meaningful safety signals compared with placebo, thereby indicating that further pursuit of kinin–kallikrein system inhibitors may not be hindered by the off-target effects of kinin blockade. Only one patient in the BI 1026706 treatment group showed an elevation of AST and ALT

Table 3. Frequencies of Drug-Related AEs

Preferred Term	Placebo, *n* (%)	BI 1026706, *n* (%)
No. of patients	53 (100.0)	52 (100.0)
Total with investigator-defined drug-related AEs	7 (13.2)	7 (13.5)
Gastrointestinal disorders	1 (1.9)	3 (5.8)
Abdominal pain upper	0	1 (1.9)
Constipation	0	1 (1.9)
Diarrhea	0	1 (1.9)
Flatulence	1 (1.9)	0
Investigations	02 (3.8)	2 (3.8)
Alanine aminotransferase increased	1 (1.9)	1 (1.9)
Aspartate aminotransferase increased	1 (1.9)	1 (1.9)
Blood lactate dehydrogenase increased	0	1 (1.9)
Gamma-glutamyltransferase increased	1 (1.9)	0

Terms reported by at least two patients per treatment group.

levels, and this finding was correlated with high plasma concentrations of BI 1026706.

The kinin–kallikrein system remains a promising target for therapeutic intervention in that it seems to be mechanistically distinct from VEGF, and includes multiple potential targets. As such, kinin–kallikrein inhibition is a potentially useful therapeutic mode of action for patients who may require a simple, oral treatment in early stage disease. Therefore, research continues in this area.

A number of agents with kinin-kallikrein activity have been developed to treat hereditary angioedema (HAE).[21] In HAE, a mutation in the C1 inhibitor gene leads to derangement of bradykinin production, which can lead to fatal edema.[22] The similarities between disrupted pathways in HAE and those in DME have led the pharmaceutical industry to explore agents with activity in HAE for the treatment of DME.[21]

Lanadelumab (DX-2930) is a human monoclonal antibody (class immunoglobulin G1 kappa) that targets plasma kallikrein[23,24] and has been designated by the US Food and Drug Administration as a breakthrough therapy. The primary development indication for lanadelumab is for the prevention of HAE attacks;[25] however, the drug is also in development with Shire for DME.

An intravitreal small-molecule inhibitor of plasma kallikrein, KDV001, is also undergoing phase 2 assessment for activity in center-involved DME (NCT03466099). BCX7353 is a potent kallikrein antagonist that has been assessed in a phase 1 trial in healthy subjects in which strong kallikrein inhibition was observed with oral dosing.[26] BCX7353 is in early stage evaluation for DME. A sister agent, BCX4161, is also under investigation for HAE, with potential for study in DME. However, indirect bradykinin inhibition of this type may not result in full inhibition of bradykinin activity.

In addition to modulators of the kinin–kallikrein system, additional agents are under study that affect non-VEGF pathways in exudative macular diseases, including DME. These agents include inhibitors of the renin–angiotensin system, angiotensin-converting enzyme inhibitors, angiopoietin, and even nonsteroidal anti-inflammatory drugs.[21] This mixture of modes of action, including inhibitors of dedicated angiogenic pathways and inhibitors of inflammation, could yield a very useful range of drugs for individualized treatment of DME.

Owing to the range of factors that can affect response to anti-VEGF agents,[27–30] true resistance to anti-VEGF agents remains a controversial topic. One of the possibilities raised by the development of B1R antagonists is potential activity in patients with so-called resistance to anti-VEGF inhibitors by virtue of activity upstream of VEGF-mediated permeability, which is distinct to the angiogenic activity that characterizes wet age-related macular degeneration. In the present study, there was no evidence of the anti-inflammatory activity of BI 1026706 over placebo. The reasons for this may lie in the adaptive nature of the inflammatory cascade, or in the speed at which B1 inhibition can exert an effect on ongoing edema. Inflammation comprises a huge number of pleiotropic mediators and cytokines, and a large number of cell types that can undergo differentiation and adaptation during the inflammatory process.[31] Therefore, it is possible that, for DME,

inhibition of the inflammatory cascade at the level of bradykinin may not be sufficient to prevent dynamic modulation of inflammatory processes to bypass the inhibition.

Alternatively, the speed of action may be insufficient to have an effect on ongoing edema, and may be better applied as a preventative treatment in at-risk patients. Certainly, it has been proposed that the inflammatory cascade features a number of stop and go signals, some of which need to be active in groups or sets rather than as single points of control.[31] Therefore, if B1 inhibition is to be effective, it may need to be combined with another activity to enable an effective inflammatory block. The outcomes of studies of the HAE agents in DME may provide some answers to this puzzle, with the caveat that plasma kallikrein antagonists differ from B1R antagonists by virtue of activity slightly further up the kinin–kallikrein cascade.[32]

The study we have described had some limitations. First, the 12 weeks of treatment was much less than the 52-week studies that enabled the regulatory approval of the currently available anti-VEGF agents. However, in these trials, efficacy was evident at months 3 and 4, which would indicate that a drug capable of delaying macular permeation ought to show efficacy compared with placebo within the 12-week time frame. However, it is also possible that processes driven by the VEGF system follow a different time course to those driven by the kinin–kallikrein system. There is also no certainty that there was sufficient time for the B1R antagonist to arrive at the retina to exert a full effect, and certainly intravitreal injection is a much quicker method of delivering drugs to the retina than oral administration. Retinal BI 1026706 was not measured, but the pharmacokinetic data indicate that a steady state was achieved in the plasma from days 29 to 89, which indicates that plasma levels were maximal at the time of the week 12 efficacy determination (84 days).

Importantly, we have not had an opportunity to examine the efficacy of BI 1026706 as an adjunct to anti-VEGF inhibitors, nor has there been an opportunity to determine if BI 1026706 is effective in patients who have failed to response to anti-VEGF therapy. The original intention for the development of BI 1026706 was to produce an oral therapy that could extend the time before patients with mild vision loss might require an anti-VEGF inhibitor; therefore, the patient selection for the present study was logical.

In this study, the B1R antagonist BI 1026706 was not effective in reducing the clinical or morphologic signs of DME; however, this finding may be related to the time course of B1R inhibition. Certainly, the future of DME therapies is exciting, and the range of agents under study indicate that patients have a real prospect of new therapies that will enable individualized, noninvasive care.

Acknowledgments

The authors thank Eastmond Medicomm Ltd and OPEN Health Medical Communications (Choice) for editorial support funded by Boehringer Ingelheim International GmbH.

The trial was sponsored by Boehringer Ingelheim International GmbH & Co. KG, Biberach an der Riss, Germany.

Disclosure: **G.E. Lang,** Novartis Pharma GmbH (F, C, S), Allergan (C, S), Alcon Pharma GmbH (C, S), Bayer AG (F, S), Boehringer Ingelheim (C, S), Carl Zeiss Meditec (F, S), Alimera Sciences (S); **R. Tadayoni,** Alcon Laboratories Inc. (C), Alimera Sciences, Inc. (C), Allergan (C), Bausch & Lomb (C), Bayer HealthCare Pharmaceuticals (C), Carl Zeiss Meditec (C), Chibret International (C), FCI Ophthalmics (C), Genentech (C), Moria (C), Novartis (C), Roche (C), ThromboGenics, Inc. (C); **W. Tang,** Boehringer Ingelheim (E); **C. Barth,** Boehringer Ingelheim (E); **C. Weiss-Haljiti,** Boehringer Ingelheim (E); **V. Chong,** Boehringer Ingelheim (E)

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