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# CANBERRA: A Phase II Randomized Clinical Trial to Test the Therapeutic Potential of Oral Vicasinabin in Diabetic Retinopathy

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***Objective:*** Nonproliferative diabetic retinopathy (NPDR) is a progressive disease that can lead to blindness. Current therapies for NPDR are invasive and not extensively used or accessible until the disease progresses, pointing to the need for an early noninvasive treatment. The objective of CANBERRA was to assess the safety, tolerability, and efficacy of oral administration of vicasinabin (RG7774) on the severity of diabetic retinopathy (DR) in participants with moderately severe to severe NPDR and good vision.

***Design:*** CANBERRA was a global, multicentric randomized, double-masked, parallel-group, placebo-controlled, phase II study. The study duration was 36 months.

***Participants:*** A total of 139 treatment-naïve patients with type 1 or type 2 diabetes mellitus and Diabetic Retinopathy Severity Scale (DRSS) levels of 47 or 53 in $\geq$1 eye were enrolled.

***Intervention:*** Eligible patients were randomized 1:1:1 to 36 weeks of daily oral placebo, vicasinabin 30 mg, or vicasinabin 200 mg. Participants were followed for an additional 12 weeks.

***Main Outcome Measures:*** The primary safety objective was to evaluate the safety and tolerability of vicasinabin by the frequency and severity of adverse events (AEs). The primary efficacy objective was to assess the effect of vicasinabin on the severity of DR, assessing the proportion of participants with $\geq$2-step improvement in DRSS from baseline at week 36 in the study eye.

***Results:*** Results are presented in the following order: placebo, vicasinabin 30 mg, vicasinabin 200 mg; 47, 48, and 44 participants were enrolled. Baseline characteristics were balanced. Adherence to treatment was approximately 90%, and pharmacokinetic analysis showed dose-dependent plasma exposure to vicasinabin. The primary efficacy endpoint was not met: the percentage of participants who improved their DRSS by $\geq$2 steps at week 36 from baseline were 7.9, 9.5, and 5.7, without statistically significant differences. The systemic and ocular safety profiles of vicasinabin were favorable, and AEs distributed evenly across arms. Vicasinabin did not induce changes in glycemic control or any kidney function or cardiovascular parameters. Three patients in the placebo arm discontinued the study due to serious AEs not related to the drug.

***Conclusions:*** At the doses tested, vicasinabin did not improve DRSS in participants with NPDR. The role of the cannabinoid system in DR remains elusive.

***Trial Registration:*** ClinicalTrials.gov identifier: NCT04265261. EUDRACT number: 2019-002067-10.

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*Supplemental material available at www.ophthalmologyscience.org.*

Diabetic retinopathy (DR) and diabetic macular edema (DME) are serious eye conditions that affect people with diabetes. If left untreated, they can progress to vision-threatening stages and ultimately blindness. Treatments include laser photocoagulation, intravitreal injections of anti-VEGF, steroids, and vitrectomy.[1–3] Earlier DR stages (i.e., moderately severe to severe nonproliferative DR [NPDR]) are rarely treated with laser, as photocoagulation is destructive and associated with peripheral visual field defects and possible vision loss. Anti-VEGF injections have shown benefits in slowing down or improving NPDR with or without DME, particularly for Diabetic Retinopathy Severity Scale (DRSS) levels 47/53.[4,5] However, even where approved, they are rarely used. Reasons may include concerns about the potential risks of injecting eyes with normal vision and the significant treatment burden of anti-VEGF therapy, aggravated when bilateral treatment is required.



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Vicasinabin is an oral synthetic small molecule and a potent cannabinoid receptor 2 (CB2R) agonist.[6] The involvement of the endocannabinoid system in the pathology of diabetes mellitus and its complications, including DR, has been extensively discussed.[7,8] Cannabinoid receptor 2 is mainly expressed in immune cells, including microglia in the retina.[6,9] Activation of CB2R by vicasinabin produces effects that are indicative of an immune-modulatory mode of action by inhibiting leukocyte adhesion and microglia activation, decreasing vascular permeability, and consequently preserving endothelial barrier function.[6] The high selectivity of vicasinabin for the CB2R (>10 000-fold over cannabinoid receptor 1) makes psychotropic effects by central cannabinoid receptor 1 activation highly unlikely.[10,11]

Therefore, vicasinabin was considered a potential option to treat patients with NPDR with good vision for whom anti-VEGF intravitreal is usually deferred in clinical practice.

In the present clinical trial, CANBERRA, the safety, tolerability, and efficacy of vicasinabin were tested in patients with NPDR. The present report focuses on the primary, secondary, and key exploratory outcomes of this phase II clinical study.

## Methods

### Study Design

CANBERRA was a randomized, double-masked, parallel-group, placebo-controlled, phase II proof-of-concept study conducted across 47 sites in the United States, Poland, United Kingdom, Spain, Australia, and Slovakia between June 2020 and July 2023. The study was performed in adherence with the principles of the Declaration of Helsinki. All participants provided written informed consent. The study protocol was approved by the institutional review board or ethics committee of each participating site before study commencement.

### Participants

Eligible patients were adults with type I or II diabetes mellitus (as defined by the World Health Organization and/or American Diabetes Association) and treatment-naive DR in ≥1 eye, with an ETDRS DRSS level of either 47 or 53 at screening (confirmed by the central reading center). The lowest threshold for best-corrected visual acuity (BCVA) was 70 ETDRS letters. Mild DME, defined as treatment-naive DME with BCVA of ≥75 letters and a central subfield thickness on spectral-domain OCT of ≥300 μm, was allowed if not expected to require treatment during the duration of the study. Glycosylated hemoglobin threshold was ≤10% but subsequently increased to 12%.

Key exclusion criteria included proliferative DR, prior treatment for DR with any approved therapy (including intravitreal injected steroids, anti-VEGF, and laser), end-stage renal or liver disease, and uncontrolled hypertension. Use of nontopical cannabidiol within 12 weeks prior to screening and during the study was not allowed to avoid potential confounding effects. Full inclusion and exclusion criteria are provided in the eMethods (available at www.ophthalmologyscience.org). Race and ethnicity were self-reported by each participant.

A total of 544 participants were screened for the study, of which 139 were randomized through the interactive voice and web response system (IxRS). A comprehensive list of reasons for screen failure can be found in Table S1 (available at www.ophthalmologyscience.org). Only 1 eye was selected as the study eye.

### Study Treatment and Procedures

Participants were randomized 1:1:1 to receive vicasinabin 30 mg, vicasinabin 200 mg, or placebo through IxRS. Randomization was stratified based on DRSS 47/53 level, uni/bilateral NPDR, and presence/absence of DME at screening. The doses were selected based on a comprehensive evaluation of preclinical and phase I clinical data. Doses were shown safe and well tolerated in phase I and expected to result in half-maximal to maximal CB2R target engagement, allowing the assessment of the exposure-response relationship in clinical outcomes.

Participants self-administered treatment once daily at approximately the same time. Adherence to treatment was determined by the content of the bottles returned at the next visit. At any time during the study, eyes could receive any approved treatment for DR progression as rescue therapy, including laser, anti-VEGF (except brolucizumab), steroids, or surgery, as deemed appropriate by the investigator.

CANBERRA included an active treatment period, from baseline to week 36, and an off-treatment follow-up period, from week 36 to week 48. Participants had a maximum of 8 site visits and phone calls at other times (see Fig S1 for study design, available at www.ophthalmologyscience.org).

Masked readers from the Wisconsin Reading Centre (University of Wisconsin) assessed the stereoscopic fundus photographs, spectral-domain OCT, and fluorescein angiography images. Plasma samples for pharmacokinetic analysis were collected at regular time points during the study. Vicasinabin was analyzed in plasma using a validated liquid chromatography-mass spectrometry method with a lower limit of quantification of 5 ng/mL.

### Outcome Measures

The primary efficacy endpoint was the proportion of participants with ≥2-step improvement in DRSS from baseline at week 36 measured in the study eye (responders). The primary safety endpoint was the frequency and severity of adverse events (AEs). Secondary endpoints were the change from baseline in BCVA at week 36 in the study eye and the incidence of vision-threatening DR (VTDR), defined as anterior segment neovascularization, new proliferative DR, new DME, and preexisting DME requiring intervention. Exploratory endpoints included other measurements of DRSS such as worsening of 2, 3, or more steps and assessments in both eyes of the same participant for a bilateral (participant level) DRSS result. Vicasinabin plasma concentrations over time were summarized by treatment arm. Additional systemic exploratory measures included glycemic status, kidney markers, and inflammation markers.

### Statistical Analysis

A total of 135 participants randomized at a 1:1:1 ratio provided a 74% to 88% power to detect a 20% to 25% difference for the

primary endpoint comparing vicasinabin versus placebo, assuming (1) a percentage of responders in vicasinabin of ~40% to 45%, (2) a percentage of responders in placebo of ~15%, with a 2-sided 0.1 false positive probability, and (3) a 10% drop-out rate.

Efficacy analyses were performed in the modified intent-to-treat (ITT) population, defined as the set of participants randomized and having taken ≥1 dose of study treatment. Safety analyses were performed in a safety population, i.e., like modified ITT but with actual treatment rather than planned. The ITT population, defined as all participants who were randomized, was used to summarize demographics, protocol deviations, vision-threatening events, and sensitivity analyses when appropriate.

The primary endpoint was analyzed cross-sectionally at week 36 using the stratified Cochran-Mantel-Haenszel test.

Continuous records were summarized with number observed, minimum, maximum, mean, median, and standard deviation (SD). Categorical variables were summarized with number of observations per category and proportions.

The main analyses did not impute missing data. A sensitivity analysis imputed under the missing at random assumption.[12]

The following general considerations applied: records below the lower limit of quantification were set to missing; stratification errors after randomization were not corrected; subgroup analyses were obtained for each stratification level and for participants whose study eye DRSS was reconfirmed at baseline; and confidence intervals were given at 90% coverage.

## Results

### Study Disposition and Baseline Characteristics

A total of 544 patients with diabetes mellitus type 1 or type 2 were screened for the study, and 139 patients were enrolled (ITT population). The main reasons for screen failure were DRSS levels other than 47 or 53, glycosylated hemoglobin higher than inclusion criterion level, or BCVA below inclusion criterion level (see Table S1 for screen failure reasons, available at www.ophthalmologyscience.org). One patient withdrew before receiving any dose; thus, the modified ITT population consisted of 138 participants. Overall, the study was completed by 116 participants (83.5%). The main reasons for discontinuation were loss to follow-up (8 participants) or withdrawal by subject (7 participants) (Fig 2).

Baseline participant demographics and study eye ocular characteristics were generally balanced across treatment arms (Table 1). Eighty-seven participants (63.0%) were male. The majority of participants had a DRSS value of 47 in the study eye. There were 53 participants (38%) who had DRSS values of either 47 or 53 in both eyes at screening. Mean (SD) BCVA score was 83.5 (6.2), 82.9 (6.1), and 83.7 (5.1) ETDRS letters in the placebo, 30 and 200 mg vicasinabin groups, respectively. Overall, 54 (39.1%) participants had DME in the study eye at screening.

**Study Drug Exposure.** The median treatment duration and number of doses were comparable between the active treatment and placebo arms. Adherence to the treatment was calculated indirectly by counting the number of tablets remaining in each bottle when the participants returned them at each site visit. Based on this metric, the mean (SD) treatment adherence was high and similar across arms: placebo, 91.0% (13.4); vicasinabin 30 mg, 90.4% (12.0); vicasinabin 200 mg, 92.5% (15.0).

As expected, no vicasinabin could be detected in plasma samples that were analyzed from participants that received placebo. High interpatient variability in vicasinabin plasma exposure was observed. Mean trough concentrations in the vicasinabin 200 mg group were five to seven fold higher than in the 30 mg group, which is consistent with dose-proportional pharmacokinetics of vicasinabin (Fig 3).

### Safety

In general, vicasinabin was well tolerated and had a favorable safety profile (Table 2). One hundred (72.5%) participants experienced ≥1 AE: 11.6% were serious AEs, none of which were related to the drug. The most frequently reported AEs by system organ class included infections and infestations (placebo 23.4%, vicasinabin 30 mg 22.9%, vicasinabin 200 mg 27.9%), gastrointestinal disorders (placebo 14.9%, vicasinabin 30 mg 12.5%, vicasinabin 200 mg 14.0%), and musculoskeletal and connective tissue disorders (placebo 8.5%, vicasinabin 30 mg 14.6%, vicasinabin 200 mg 11.6%). Most AEs were mild or moderate in intensity and were evenly distributed across arms. Three participants (all on placebo) discontinued the study due to serious AEs (atrioventricular block second degree, worsening DR, and sepsis). Systemic AEs of special interest (prespecified in the protocol) were related to diabetic complications (diabetic foot, 2 events). No clinically meaningful change from baseline to any postbaseline visits was observed in vital sign and electrocardiogram parameters in any arm.

Vicasinabin did not show any ocular safety signal of concern in the study or the fellow eyes: 34 patients experienced ≥1 ocular AE; 4 of these AEs were considered serious (1 retinal tear, 3 DR progression events), none related to the study drug. The most common ocular AEs in the study eye were diabetic retinal edema (placebo 4.3%, vicasinabin 30 mg 8.3%, and vicasinabin 200 mg 7.0%) and worsening of DR (placebo 6.4%, vicasinabin 30 mg 6.3%, and vicasinabin 200 mg 2.3%). Ocular AEs of special interest included DR worsening (4 events), retinal tear (2 events), and vitreous hemorrhage (1 event).

In total, 19 participants (13.8%) required rescue treatment in the study eye at any time point during the study (5 in placebo, 9 in vicasinabin 30 mg, and 5 in vicasinabin 200 mg).

Vicasinabin did not induce any clinically meaningful changes in vital signs, glycemic control, kidney function, or cardiovascular parameters (data not shown).

### Primary and Secondary Prespecified Efficacy Outcomes

CANBERRA did not meet its primary efficacy endpoint: the proportion of participants who had at least a 2-step improvement in ETDRS DRSS from baseline to week 36 in the active treatment arms and in the placebo arm showed no statistically significant difference (placebo 7.9%, vicasinabin 30 mg 9.5%, and vicasinabin 200 mg 5.7%) (Table 3).

The secondary endpoints were the incidence of VTDR and BCVA change at week 36.

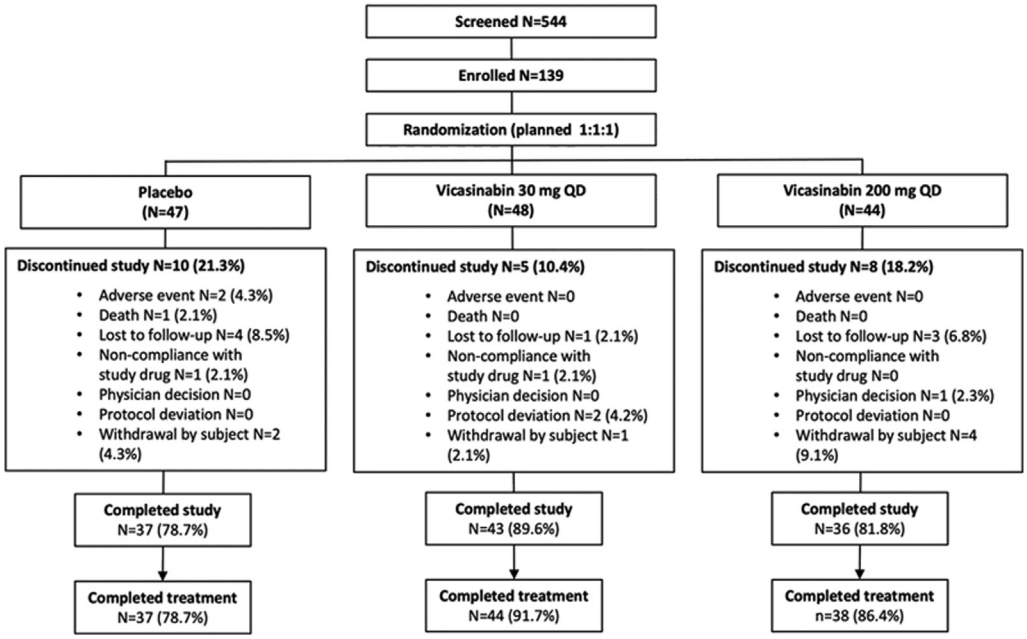


**Figure 2.** Study disposition. QD = every day.

The median time to first occurrence of VTDR (defined as the time where 50% of the population develops a VTDR event) in the study eye was not reached in any arm. The stratified hazard ratio of VTDR in the study eye was 1.35 (95% confidence interval: 0.38, 4.87; $P = 0.6407$) in the vicasinabin 30 mg arm and 1.27 (95% confidence interval: 0.4, 4.77; $P = 0.7255$) in the vicasinabin 200 mg arm with placebo as reference. (Fig S2, available at www.ophthalmologyscience.org). The percentage of participants developing VTDR in the study eye at any time point during the study was 10.6% in placebo, 18.8% in vicasinabin 30 mg, and 11.4% in vicasinabin 200 mg (Table S5, available at www.ophthalmologyscience.org).

The mean BCVA (SD) at week 36 was 84.7 (7.0), 83.3 (5.8), and 83.7 (6.7) ETDRS letters in placebo, vicasinabin 30 mg, and vicasinabin 200 mg. There were no changes from baseline in BCVA in any arm (Fig S3, available at www.ophthalmologyscience.org).

### Key Prespecified Exploratory Endpoints

Due to the systemic exposure of vicasinabin, a prespecified analysis of DRSS changes considering both eyes of the participant was performed. This bilateral assessment considers 3 steps as the threshold for a meaningful change at a participant-level and has been used in previous studies for systemic treatment of DR.[13–15] To calculate bilateral effects in DRSS, the DRSS change from baseline in the study eye was added to the DRSS change from baseline in the fellow eye. There were no significant differences between the active treatment arms and placebo in DRSS worsening or improvement rates (Table S6, available at www.ophthalmologyscience.org).

The DRSS level at study start did not impact the outcomes in DRSS at week 36 (Table S7, available at www.ophthalmologyscience.org). Similarly, the presence or absence of DME in the study eye did not have any impact on DRSS changes, with a similar percentage of participants improving or worsening by $\geq$2 steps in DRSS in all arms at week 36. The stratified Cochran-Mantel-Haenszel analysis of active arms vs. placebo showed no statistically significant differences except for the 200 mg arm in participants with DME (Table S8, available at www.ophthalmologyscience.org). Vicasinabin treatment did not affect DME, as shown by the lack of changes in central subfield thickness (Table S9, available at www.ophthalmologyscience.org).

The glycemic status of the participants, measured by glycosylated hemoglobin percentage, did not change significantly during the study (mean change from baseline to week 36 [SD]: placebo, 0.14 [1.09], vicasinabin 30 mg, 0.6 [1.3], and vicasinabin 200 mg, 0.18 [1.41]). There were no statistically or clinically significant differences between placebo and the active arms, and no dose-dependent changes were observed.

## Discussion

Vicasinabin, as a noninvasive and potentially accessible oral drug, was tested as a therapeutic option for patients with NPDR levels 47/53 who are at high risk of progressing to vision loss. However, none of the multiple efficacy and sensitivity analyses performed in CANBERRA showed any treatment benefit with vicasinabin as measured by changes

Table 1. Demographics and Main Systemic and Ocular Characteristics at Baseline

| | Placebo (N = 47) | Vicasinabin 30 mg (N = 48) | Vicasinabin 200 mg (N = 43) | All Participants (N = 138) |
|---|---|---|---|---|
| Demographics | | | | |
| Age (yrs), mean (SD) | 58.9 (9.3) | 57.3 (10.0) | 56.3 (10.6) | 57.4 (10.0) |
| Sex, n (%) | | | | |
| Female | 17 (36.2%) | 18 (37.5%) | 16 (37.2%) | 51 (37.0%) |
| Male | 30 (63.8%) | 30 (62.5%) | 27 (62.8%) | 87 (63.0%) |
| Ethnicity, n (%) | | | | |
| Hispanic or Latino | 14 (29.8%) | 18 (37.5%) | 14 (32.6%) | 46 (33.3%) |
| Not Hispanic or Latino | 32 (68.1%) | 30 (62.5%) | 29 (67.4%) | 91 (65.9%) |
| Unknown | 1 (2.1%) | 0 | 0 | 1 (0.7%) |
| Race, n (%) | | | | |
| Asian | 2 (4.3%) | 2 (4.2%) | 3 (7%) | 7 (5.1%) |
| Black or African American | 5 (10.6%) | 0 | 4 (9.3%) | 9 (6.5%) |
| White | 40 (85.1%) | 46 (95.8%) | 35 (81.4%) | 121 (87.7%) |
| Unknown | 0 | 0 | 1 (2.3%) | 1 (0.7%) |
| Baseline characteristics | | | | |
| Diabetes mellitus, n (%) | | | | |
| Type 1 | 1 (2.1%) | 6 (12.5%) | 4 (9.3%) | 11 (8.0%) |
| Type 2 | 46 (97.9%) | 42 (87.5%) | 39 (90.7%) | 127 (92.0%) |
| Time since diagnosis of diabetes mellitus, yrs | | | | |
| Mean (SD) | 14.3 (8.7) | 16.6 (7.5) | 16.2 (8.7) | 15.7 (8.3) |
| HbA1c (%) | | | | |
| Mean (SD) | 8.27 (1.53) | 8.08 (1.34) | 8.38 (1.55) | 8.24 (1.47) |
| DRSS distribution of the study eyes, n (%)* | | | | |
| 47 | 38 (80.9%) | 37 (77.1%) | 34 (79.1%) | 109 (79.0%) |
| 53 | 9 (19.1%) | 11 (22.9%) | 9 (20.9%) | 29 (21.0%) |
| DRSS distribution of the fellow eyes, n (%)* | | | | |
| 35 | 1 (2.1%) | 4 (8.3%) | 1 (2.3%) | 6 (4.3%) |
| 43 | 18 (38.3%) | 14 (29.2%) | 19 (44.2%) | 51 (37.0%) |
| 47 | 16 (34.0%) | 16 (33.3%) | 9 (20.9%) | 41 (29.7%) |
| 53 | 2 (4.3%) | 4 (8.3%) | 6 (14.0%) | 12 (8.7%) |
| 61 | 2 (4.3%) | 6 (12.5%) | 1 (2.3%) | 9 (6.5%) |
| 65 | 3 (6.4%) | 0 (0%) | 3 (7.0%) | 6 (4.3%) |
| 71 | 1 (2.1%) | 2 (4.2%) | 1 (2.3%) | 4 (2.9%) |
| 75 | 0 | 0 | 1 (2.3%) | 1 (0.7%) |
| Unknown | 4 (8.5%) | 2 (4.2%) | 2 (4.7%) | 8 (5.8%) |
| Time since DR diagnosis in the study eye, mos | | | | |
| Mean (SD) | 21.72 (42.77) | 12.54 (19.46) | 14.96 (27.20) | 16.60 (31.83) |
| DME in the study eye, n (%) | | | | |
| Present | 17 (36.2%) | 20 (41.7%) | 17 (39.5%) | 54 (39.1%) |
| Absent | 30 (63.8%) | 28 (58.3%) | 26 (60.5%) | 84 (60.9%) |
| BCVA of the study eye, ETDRS letters | | | | |
| Mean (SD) | 83.5 (6.2) | 82.9 (6.1) | 83.7 (5.1) | 83.3 (5.8) |

BCVA = best-corrected visual acuity; DME = diabetic macular edema; DR = diabetic retinopathy; DRSS = Diabetic Retinopathy Severity Scale; HbA1c = glycosylated hemoglobin; SD = standard deviation.
Percentages are calculated per study treatment arm.
Unknown includes either not done or not evaluated due to image quality issues.
*Distribution of DRSS at screening.

in DRSS or incidence of VTDR at either the study eye or the participant levels.

Diabetic Retinopathy Severity Scale is an approvable endpoint for demonstrating efficacy in DR and was, for example, used to approve the treatment of DR with Eylea and Lucentis.[16,17] However, it has several limitations, such as being focused on vasculopathy and not assessing the coinciding neuropathy. Even the vasculopathy assessment is limited to a small central area of the retina. Further, DRSS was developed to measure progression of DR and has never been validated for the assessment of treatment-induced improvement.[18] Diabetic Retinopathy Severity Scale may not have been specific enough to capture the mechanism of action of vicasinabin, which targets inflammation and leukostasis. The rate of VTDR in the study eye of vicasinabin-treated participants was 18.8 (30 mg arm) and 11.4 (200 mg arm). Interestingly, the rate of participants developing VTDR in the study eye in the placebo arm of CANBERRA (10.6% at week 36) was lower than in the placebo arm of Panorama (40.6% at week 52).[5] A potential explanation is that there was a larger percentage of participants with level 47 in CANBERRA (81% vs. 75% in Panorama) who would progress slower than 53. In addition, CANBERRA duration was shorter than Panorama, and the patient population is slightly different with mild DME included in CANBERRA but excluded in Panorama.

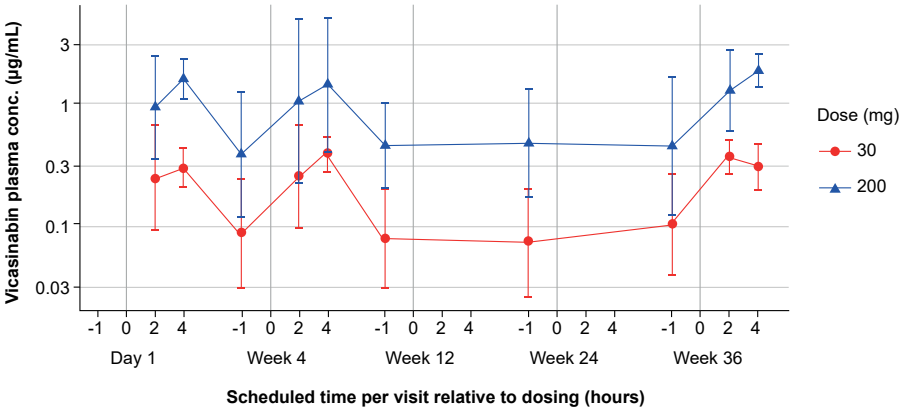


**Figure 3.** Mean (± standard deviation) vicasinabin plasma concentration-time profiles by treatment arm.

The 36-week study duration was chosen based on results of Panorama, which showed clear benefits already after 24 weeks of treatment.[5]

The observed effects of vicasinabin in mouse models of DME, where it reduced permeability-related pathology,[6] were the basis for testing its effect on DME. Diabetic macular edema was present in 39.1% of the CANBERRA population. Collectively, vicasinabin had no beneficial effect on DME, and the worsening in DRSS observed with 200 mg (eTable S7, available at www.ophthalmologyscience.org) may be a consequence of a (too) small number of participants and events and multiple testing.

The lack of efficacy of vicasinabin in DR despite promising preclinical evidence[6] could have several potential explanations:

1) Design of the molecule and pharmacokinetic properties: Despite showing adequate systemic exposure (Fig 3), it is possible that the target cells of a CB2R agonist do not play a role in the human disease. In addition, despite sufficient plasma exposure, it is unsure whether this is leading to sufficient ocular exposure to induce ocular effects.

2) Mechanism of action: Vicasinabin showed strong evidence in features known to have an impact on DR[6] in rodent animal models, but no animal models exist that recapitulate the disease complexity, and translatability to the human condition may be limited. In fact, while preclinical studies have been promising in several indications, the translation of these findings into successful clinical outcomes has been challenging. Many CB2R agonists have not progressed beyond early-phase clinical trials due to issues with efficacy, pharmacokinetics, or safety profiles.[19]

3) The primary endpoint, DRSS, which at the time of designing this study was the only approvable endpoint for NPDR, is an imaging-based variable focusing on vascular alterations and may not

Table 2. Overview of AEs (Safety-Evaluable Population)

| | Placebo (N = 47) | Vicasinabin 30 mg (N = 48) | Vicasinabin 200 mg (N = 43) | All Participants (N = 139) |
|---|---|---|---|---|
| Total number of AEs | 102 | 110 | 97 | 309 |
| Total number of participants with at ≥1: | | | | |
| AE | 34 (72.3%) | 31 (64.6%) | 35 (81.4%) | 100 (72.5%) |
| AE with fatal outcome | 1 (2.1%) | 0 | 0 | 1 (0.7%) |
| Serious AE | 8 (17.0%) | 3 (6.3%) | 5 (11.6%) | 16 (11.6%) |
| Related serious AE | 0 | 0 | 0 | 0 |
| Serious ocular AE | 1 (2.1%) | 2 (4.2%) | 1 (2.3%) | 4 (2.9%) |
| Serious systemic AE | 7 (14.9%) | 1 (2.1%) | 4 (9.3%) | 12 (8.7%) |
| Serious AE leading to withdrawal from treatment | 3 (6.4%) | 0 | 0 | 3 (2.2%) |

AE = adverse event.

Table 3. Primary Endpoint: Proportion of Participants with ≥2-Step Improvement in ETDRS DRSS from Baseline at Week 36 Measured in the Study Eye

| Parameter | Placebo (n = 47) | Vicasinabin 30 mg (n = 48) | Vicasinabin 200 mg (n = 43) |
|---|---|---|---|
| Number of participants (n) | 38 | 42 | 35 |
| Proportion of participants, n (%) | 3 (7.9) | 4 (9.5) | 2 (5.7) |
| (95% CI) | (2.7, 20.8) | (3.8, 22.1) | (1.6, 18.6) |
| Stratified analysis (CMH) (vs. placebo) | | | |
| Percentage difference[a] (95% CI)[b] | NA | 1.2 (−11.9, 14.2) | −2.9 (−15.2, 9.1) |
| *P* value | | 0.8586 | 0.6388 |
| Stratified analysis (CMH) (30 vs. 200 mg) | | | |
| Percentage difference[a] (95% CI)[b] | NA | NA | 4.4 (−7.2, 15.9) |
| *P* value | | | 0.4608 |

CI = confidence interval; CMH = Cochran-Mantel-Haenszel test; DRSS = Diabetic Retinopathy Severity Scale.
[a]Based on the CMH estimate of the common risk difference using Mantel-Haenszelstratum weights and the Sato variance estimator.
[b]Wilson's method.

adequately capture other aspects of the disease as discussed earlier.

4) Duration of treatment with vicasinabin in CANBERRA may have been too short (36 weeks) to have a measurable benefit.[20]

## Limitations

The main limitations of CANBERRA were the focus on vasculopathy (DRSS endpoint) and the limited duration of treatment (36 weeks). A large majority of White participants recruited could make these results not generalizable.

This well-controlled, well-conducted clinical trial provided a clear answer to the 2 main research questions posed: vicasinabin did not impact DR severity but did show an acceptable safety profile. Based on the lack of efficacy of vicasinabin as applied in this phase II study, the sponsor decided not to pursue further clinical development activities for DR.

Further research is needed to offer noninvasive treatment options to patients with NPDR.

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Author Contributions:

Conception and design: Armendariz, Luhman, Wenzel, Fauser

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Abbreviations and Acronyms:
**AE** = adverse event; **BCVA** = best-corrected visual acuity; **CB2R** = cannabinoid receptor 2; **DME** = diabetic macular edema; **DR** = diabetic retinopathy; **DRSS** = Diabetic Retinopathy Severity Scale;

**ITT** = intent-to-treat; **NPDR** = nonproliferative diabetic retinopathy; **SD** = standard deviation; **VTDR** = vision-threatening diabetic retinopathy.

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