Background: The purpose of this study was to evaluate the safety and tolerability of pegaptanib in patients with diabetic macular edema.

Methods: An open-label, multicenter, noncomparative, one-year study of approximately 500 patients was planned. Recruitment was terminated after enrollment of 46 patients. Enrolled patients were fully informed and reconsented; 12 patients elected to complete the study. Patients received intravitreal injections of pegaptanib 0.3 mg once every 6 weeks or less frequently, as determined by the investigator. Clinical benefit was evaluated after the patient received two or more injections. Ocular and nonocular adverse events were closely monitored throughout the study.

Results: Compared with baseline, mean best-corrected visual acuity increased by week 6. Ten patients reported ocular-related adverse events, none of which were severe, and eight patients reported nonocular adverse events, two of which were severe but unrelated to study treatment. Three serious adverse events, unrelated to study treatment, were reported.

Conclusion: In this limited set of patients with diabetic macular edema, pegaptanib appeared to be well tolerated with evidence of efficacy.

Keywords: pegaptanib, diabetic macular edema, safety, tolerability

Introduction
Diabetic macular edema (DME) is a complication of diabetic retinopathy occurring in patients with type 1 or type 2 diabetes.\(^1\)\(^-\)\(^3\) It is characterized by diffuse or cystic macular thickening with or without lipid exudation caused by breakdown of the inner and outer blood retinal barriers. If untreated, DME can lead to vision loss, and the condition is responsible for 4.8% of cases of blindness worldwide.\(^4\) Patient quality of life is affected at all stages of the disease, but may improve with treatment.\(^1\)\(^-\)\(^3,5\)\(^-\)\(^7\) As the incidence of diabetes increases worldwide,\(^8\)\(^-\)\(^10\) so does the prevalence of DME.\(^11,12\) Approximately 10% of all adults with diabetes experience vision-threatening diabetic retinopathy, and half of these progress to developing DME.\(^13\) Until recently, the standard treatment for DME has been laser photocoagulation, with no approved therapeutic options available for those who fail to respond to laser therapy. Therefore, clinical research has been performed to identify safe and effective treatments that improve both visual function and quality of life for patients with DME.

In the past few years, several studies have demonstrated that treatment with vascular endothelial growth factor (VEGF) inhibitors can result in statistically
significant improvement of visual acuity in patients with DME.\textsuperscript{14–19} Pegaptanib sodium (Macugen\textsuperscript{®}; Pfizer Inc, New York, NY, USA) is an aptamer that binds with high specificity and affinity to VEGF\textsubscript{165}, a protein implicated in the pathogenesis of age-related macular degeneration\textsuperscript{20} and DME.\textsuperscript{21–23} Thus, pegaptanib acts as a VEGF antagonist and is currently approved for the treatment of age-related macular degeneration but not for DME. A Phase II/III trial demonstrated that compared with sham treatment, administration of intravitreal pegaptanib every 6 weeks for one year resulted in statistically significant improvement in visual acuity as measured by ≥10-letter gains ($P=0.0047$) and patient quality of life as measured by a greater than five-point difference in the National Eye Institute Visual Functioning Questionnaire 25.\textsuperscript{3}

This Phase IIIb study was designed to extend and further evaluate the safety and tolerability of pegaptanib in patients with DME. However, soon after study initiation, the sponsor decided to withdraw the regulatory application for DME. Further recruitment of patients was immediately stopped. Patients already enrolled in the study were informed and given the opportunity to either withdraw or continue treatment until the end of the study upon providing written informed consent.

**Patients and methods**

**Patients**

This open-label, multicenter, noncomparative Phase IIIb trial (ClinicalTrials.gov identifier NCT01189461) was conducted in patients aged ≥18 years with type 1 or type 2 diabetes and a documented clinical diagnosis of DME with proliferative or nonproliferative diabetic retinopathy and who, according to the investigator, could have benefited from anti-VEGF therapy. Over 500 patients were to be enrolled in the study. For enrollment, patients were required to have a best-corrected visual acuity (BCVA) letter score between 78 and 24 inclusive (20/32 to 20/320 Snellen equivalents), intraocular pressure ≤21 mmHg, clear ocular media, and adequate pupillary dilatation. Furthermore, the treating investigator needed to certify that focal laser treatment could be deferred for ≥18 weeks in the study eye. Key exclusion criteria were: prior scatter photoagulation treatment within 4 months of study initiation or anticipated within the following 6 months; other reasons for macular edema, atrophy, scarring, or fibrosis involving the center of the macula; significant media opacities, including cataracts; any intraocular surgery within 4 months of study entry; previous vitrectomy; and previously documented glycated hemoglobin >10% or recent evidence of uncontrolled diabetes. All patients provided written informed consent.

**Treatment**

Patients were administered intravitreal pegaptanib 0.3 mg in the study eye under aseptic conditions by ophthalmologists experienced in the procedure. Patients were treated at baseline and at subsequent visits once every 6 weeks after BCVA evaluation, biomicroscopy, dilated fundus examinations in both eyes, and tonometry measurements. After the first two injections, additional injections could be administered less frequently than once every 6 weeks, as determined by the investigator. Clinical benefit was evaluated after two or more injections. Retreatment was left to the discretion of the investigator, and patients who demonstrated a clinical benefit could continue to receive intravitreal pegaptanib injections for up to 48 weeks.

**Endpoints**

The primary endpoint was the incidence of ocular and nonocular adverse events (AEs), defined as any untoward medical occurrence not necessarily having a causal relationship with the treatment. One secondary endpoint was the incidence of ocular and nonocular serious AEs, defined as any AE resulting in, but not limited to, death, is life-threatening, hospitalization, persistent disability, or congenital anomaly. All observed and reported AEs were recorded using Medical Dictionary for Regulatory Activities (MedDRA) version 15.0 throughout the study. Other secondary endpoints included the mean number of injections per patient and efficacy of treatment as evaluated by change in BCVA from baseline to end of treatment. BCVA was measured using retroilluminated modified Ferris-Bailey Early Treatment Diabetic Retinopathy Study charts starting at 4 m. Complete ophthalmological examinations (including slit-lamp biomicroscopy, ophthalmoscopy, tonometry, BCVA measurements, and fundus examinations) were performed at screening, baseline, each treatment visit, and at follow-up. Applanation tonometry was performed for all patients at screening and to verify postinjection intraocular pressures ≥30 mmHg lasting for >30 minutes post injection or for a reading of ≥30 mmHg at any other time.

**Statistical analyses**

In total, 500 patients were to be enrolled based on a requirement of 459 patients, which would provide a >99% chance of detecting at least one occurrence of any AE with a true
underlying rate of one or more in 100. Descriptive statistics were used for reporting efficacy (BCVA scores and change from baseline in BCVA scores to each visit and end of study) and safety endpoints. Statistics are presented using observed data with no imputation for missing values.

### Table 1 Baseline demographics of patients enrolled in the study

| Parameter | Patients (n=46) |
|-----------|----------------|
| Patients, n (%) | 46 (100.0) |
| Sex, n (%) | |
| Male | 30 (65.2) |
| Female | 16 (34.8) |
| Mean (SD) age (years) | 65.0 (10.6) |
| Race, n (%) | |
| White | 42 (91.3) |
| Black | 1 (2.2) |
| Asian | 2 (4.3) |
| Other | 1 (2.2) |
| Median (range) duration since diagnosis of DME (years) | 2.4 (0.0–14.7) |
| Mean (SD) baseline BCVA score (letters) | 58.9 (16.5) |
| Mean (SD) IOP (mmHg) | 15.9 (2.6) |
| Secondary diagnoses | |
| Diabetes, n (%) | 1 (2.2) |
| Mean duration since first diagnosis (years) | 22.3 |
| Type 1 diabetes, n (%) | 5 (10.9) |
| Mean duration since first diagnosis (years) | 23.0 |
| Type 2 diabetes, n (%) | 39 (84.8) |
| Mean duration since first diagnosis (years) | 14.9 |
| Glaucoma, n (%) | 1 (2.2) |
| Mean duration since first diagnosis (years) | 11.3 |

Note: One patient was not classified.
Abbreviations: SD, standard deviation; DME, diabetic macular edema; BCVA, best-corrected visual acuity; IOP, intraocular pressure.

### Table 2 Drug treatments prior to start of study treatment in ≥25% of patients

| WHO drug dictionary class (v02Q2) | Patients (n=46), n (%) |
|----------------------------------|------------------------|
| Any prior drug treatment excluding diabetes and DME medications | 42 (91.3) |
| Agents acting on the renin–angiotensin system | 29 (63.0) |
| Serum lipid-reducing agents | 22 (47.8) |
| Antithrombotic agents | 18 (39.1) |
| Analgesics | 14 (30.4) |
| Stomatological preparations | 14 (30.4) |
| Drugs for acid-related disorders | 12 (26.1) |

Notes: Excluding treatments given for diabetes or DME. All acetylsalicylic acid use (14 patients) has been reported in this table as a stomatological preparation.
Abbreviations: WHO, World Health Organization; DME, diabetic macular edema.

### Results

#### Patient disposition

Fifty-five patients were screened prior to termination of recruitment. Of these, 46 patients were enrolled and 12 completed the study (Figure 1). The baseline characteristics of the 46 patients enrolled prior to termination of enrollment are given in Table 1. When enrollment was stopped, patients already entered into the study were informed and given the option of withdrawing or continuing in the study.

Of the 46 patients enrolled, 42 (91.3%) had received prior drug treatment for conditions other than diabetes or DME (Table 2) and an equal number were receiving concomitant treatments for conditions other than diabetes or DME during the study (Table 3). The median duration of study treatment for the 46 patients was 13.6 weeks.
Efficacy and safety

Compared with baseline, mean BCVA increased noticeably by week 6 and remained steady, with further small increases thereafter (Table 4). Owing to withdrawals, the results at later visits are based on a small number of patients. Overall, the mean total number of injections in all patients was 3.2, with a median of 3.0 and a range of 1.0–6.0. The mean interval between injections was 7.7 weeks, with a median of 6.5 weeks.

The individual data for the 12 patients who completed the study are given in Table 5. The BCVA change between baseline and the follow-up visit was ≥10 letters in four of 12 patients, and >5 letters in seven of 12 patients.

Sixteen (34.8%) of the 46 patients enrolled in the study reported AEs, of which four (8.7%) reported treatment-related AEs (Table 6). Seventeen ocular-related AEs (none severe) were reported by ten (21.7%) patients. Nineteen nonocular, all-causality AEs (two severe but not related to treatment) were reported by eight (17.4%) patients (Table 7). One moderate hypersensitivity skin reaction was observed, but was reported to be unrelated to study treatment. Three patients had serious AEs (cerebrovascular accident, myocardial infarction, and lung malignancy) that were reported as unrelated to study treatment by the investigator.

Discussion

Several clinical and preclinical studies have demonstrated the role of VEGF in the pathogenesis of DME, and ranibizumab is currently the only anti-VEGF agent approved in the European Union for the treatment of visual impairment due to DME. 3,19,24–28

Two clinical studies were performed to study the efficacy and safety of pegaptanib in patients with DME. 19,24 The primary objective of the study reported here was to further assess the safety and tolerability of pegaptanib in patients with documented DME which, in the opinion of the treating physician, would benefit from anti-VEGF therapy. As such, neither assessment of central macular thickness nor specific standardized retreatment criteria were included in the study design so as to better reflect real-world clinical practice. However, recruitment for this study was stopped following the sponsor’s decision to withdraw the marketing application for this indication. Thus, the primary limitation of this study is the very small number of patients enrolled (46 of the planned 500). The study is further limited by only 12 patients deciding to complete the study after being informed of the sponsor’s decision. Therefore, the sample size for this study was too small for any statistical analyses of the data. Consequently, the data reported here must be interpreted with great caution. Nevertheless, the results of this study are consistent

Table 4 Mean ± SD BCVA scores by study visit

| Study visit | Patients (n=46), n (%) | Mean ± SD BCVA score |
|-------------|------------------------|----------------------|
| Baseline    | 42 (91.3)              | 58.9±16.5            |
| Week 6      | 36 (78.3)              | 63.1±14.1            |
| Week 12     | 34 (73.9)              | 63.4±13.2            |
| Week 18     | 32 (69.6)              | 60.6±16.5            |
| Week 24     | 22 (47.8)              | 65.6±12.7            |
| Week 30     | 20 (43.5)              | 65.1±10.7            |
| Week 36     | 12 (26.1)              | 62.3±11.7            |
| Week 40     | 11 (23.9)              | 66.6±10.8            |
| Week 48     | 14 (30.4)              | 65.0±12.2            |
| Week 54     | 5 (10.9)               | 68.6±11.8            |
| > Week 54   | 1 (2.2)                | 78.0                 |
| Final visit | 42 (91.3)              | 63.4±13.1            |

Abbreviations: SD, standard deviation; BCVA, best-corrected visual acuity.

Table 5 Relevant data for individual patients completing study

| Patient | Age | Duration (years) DME | Diabetes | Type of diabetes | Receiving statins? | Laser treatment in study eye | VA in study eye | IVT |
|---------|-----|----------------------|----------|------------------|--------------------|-----------------------------|----------------|-----|
|         |     |                      |          |                  |                    | Past history During study   | Baseline Follow-up |     |
| 1       | 57  | 0.5                  | 15.4     | 2                | No                 | No                          | No             | 28  |
| 2       | 43  | 0                    | 22.3     | NC               | No                 | Yes                         | No             | 73  |
| 3       | 61  | 5.0                  | 5.0      | 2                | Yes                | Yes                         | No             | 47  |
| 4       | 64  | 0.9                  | 2.2      | 2                | No                 | Yes                         | No             | 43  |
| 5       | 52  | 1.3                  | 16.8     | 2                | No                 | Yes                         | No             | 59  |
| 6       | 57  | 2.2                  | 28.4     | 2                | Yes                | Yes                         | Yes            | 62  |
| 7       | 81  | 0.2                  | 22.1     | 2                | No                 | No                          | No             | 75  |
| 8       | 68  | 0.1                  | 13.4     | 2                | Yes                | No                          | No             | 70  |
| 9       | 77  | 0.7                  | 14.1     | 2                | Yes                | Yes                         | No             | 72  |
| 10      | 62  | 10.4                 | 26.3     | 1                | No                 | Yes                         | No             | 52  |
| 11      | 66  | 3.6                  | 23.0     | 2                | No                 | Yes                         | No             | 69  |
| 12      | 64  | 2.0                  | 23.0     | 2                | No                 | Yes                         | No             | 71  |

Abbreviations: DME, diabetic macular edema; VA, visual acuity; IVT, intravitreal treatment; NC, not classified.
with those reported for another small study of 20 patients in whom pegaptanib was demonstrated to be efficacious and safe over a 12-month period.29

Treatment-related AEs were mild or moderate in severity in 46 patients receiving at least one dose of pegaptanib. There were no severe drug-related AEs observed or deaths reported, suggesting that pegaptanib was well tolerated in this cohort of patients with DME. These data are consistent with those reported for the Phase II/III trials comparing intravitreal pegaptanib injections with sham treatment.3,18,24,25

Table 6 Summary of treatment-emergent AEs

| Parameter | All causality, n (%) | Treatment-related, n (%) |
|-----------|----------------------|--------------------------|
| AEs (n)   | 37                   | 5                        |
| Patients with AEs | 16 (34.8) | 4 (8.7) |
| Patients with SAEs | 3 (6.5)   | 0                        |
| Patients with severe AEs | 2 (4.3)   | 0                        |
| Patients discontinued owing to AEs | 2 (4.3)   | 1 (2.2) |
| Patients with dose reduced or temporary discontinuation owing to AEs | 1 (2.2)   | 1 (2.2) |

Abbreviations: AE, adverse event; SAE, serious adverse event.

Table 7 All-causality and treatment-related incidence and severity of treatment-emergent ocular AEs

| MedDRA preferred term                      | All causality (treatment-related), n |
|--------------------------------------------|--------------------------------------|
|                                            | Mild | Moderate | Severe |
| Ocular AEs                                 |      |          |        |
| Macular edema                              | 13 (2) | 4 (2) | 0 |
| Visual acuity reduced                      | 2 (0) | 1 (0) | 0 |
| Vitreous floaters                          | 1 (1) | 0 | 0 |
| Cataract                                   | 1 (1) | 0 | 0 |
| iOP increased                              | 0 | 1 (1) | 0 |
| Uveitis                                    | 0 | 1 (1) | 0 |
| Conjunctival hemorrhage                     | 1 (0) | 0 | 0 |
| Conjunctival hyperemia                      | 1 (0) | 0 | 0 |
| Conjunctivitis                              | 1 (0) | 0 | 0 |
| Eye discharge                              | 1 (0) | 0 | 0 |
| Eye pain                                   | 1 (0) | 0 | 0 |
| Eye pain                                   | 1 (0) | 0 | 0 |
| Eyelid pruritus                            | 1 (0) | 0 | 0 |
| Conjunctivitis                              | 1 (0) | 0 | 0 |
| Maculopathy                                | 1 (0) | 2 (0) | 2 (0) |
| Nonocular AEs                              | 11 (1) | 6 (0) | 2 (0) |
| Wheezing                                   | 1 (1) | 0 | 0 |
| Anemia                                     | 1 (0) | 0 | 0 |
| Gastric polyps                             | 1 (0) | 0 | 0 |
| Gastrointestinal hypermotility             | 1 (0) | 0 | 0 |
| Hiatus hernia                              | 1 (0) | 0 | 0 |
| Upper respiratory tract infection           | 1 (0) | 0 | 0 |
| Carcinoembryonic antigen increased         | 1 (0) | 0 | 0 |
| Lung neoplasm malignant                    | 1 (0) | 0 | 0 |
| Headache                                   | 1 (0) | 0 | 0 |
| Renal colic                                | 1 (0) | 0 | 0 |
| Hypertension                               | 1 (0) | 0 | 0 |
| Biopsy vocal cord                          | 0 | 1 (0) | 0 |
| Anxiety                                    | 0 | 1 (0) | 0 |
| Cough                                      | 0 | 1 (0) | 0 |
| Asthenia                                   | 0 | 1 (0) | 0 |
| Gastroenteritis                            | 0 | 1 (0) | 0 |
| Diarrhea                                   | 0 | 1 (0) | 0 |
| Cerebrovascular accident                    | 0 | 0 | 1 (0) |
| Myocardial infarction                       | 0 | 0 | 1 (0) |

Note: *Not likely to be drug related.

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; iOP, intraocular pressure.
Evidence of a modest initial clinical benefit, measured as improvement in BCVA, was observed in the patients by week 6. Although data are limited, this benefit appears to be sustained throughout the study; of the 12 patients completing the study, about 30% gained >10 letters of BCVA, while approximately 60% gained >5 letters of BCVA. These data appear to be consistent with those reported in the Phase II/III trials. However, the number of patients in this study is too small to derive any definitive conclusions. The magnitude and duration of the benefit suggested in this study for patients with DME will need to be confirmed in a larger study powered to address these questions.

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Author contributions
SS recruited patients for the study, and participated in interpretation of the analysis and data, development of the manuscript, and final approval of the manuscript. RCB was involved in the design of the study, monitoring of safety, analysis and interpretation of the data, development of the manuscript, and final approval of the manuscript. CS was involved in the design of the study, analysis and interpretation of the data, development of the manuscript, and final approval of the manuscript.

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