MATERIALS AND METHODS

Study methodology

All eligible patients were assigned to treatment groups in accordance with a computer-generated randomization schedule prepared by the Alcon SAS Programming Group. Patients were randomized 1:1 by an interactive voice response system to receive nepafenac 0.1% or vehicle stratified by severity of the disease (mild, moderate, or severe NPDR). The use of a randomization code to assign the study drug protected against selection bias. Additionally, the study was double-masked, and neither the patient nor the study personnel (the investigators, the staff at each investigational center, the sponsor, the clinical monitors) had knowledge of the assigned treatment; designated staff at each investigational center (ie, individuals other than the investigator or subinvestigator) dispensed and collected the study drugs as appropriate. Patients instilled 1 drop of study treatment into the study eye 3 times daily (upon waking in the morning, midafternoon, and bedtime), with treatment beginning on the day before surgery (Day -1) and continuing through the last study visit (Day 90 [or Early Exit]). Designated study personnel instilled 1 additional dose into the study eye on the day of surgery (Day 0), 30 to 120 minutes before the scheduled start of the procedure. Patients self-administered the study drug at all other times. All patients instilled 1 drop of TOBRADEX® (tobramycin 0.3% and dexamethasone 0.1%, Alcon Research Ltd., Fort Worth, TX) into the study eye 4 times daily for 2 weeks after surgery, starting at the first postsurgical dosing time point, and may have been extended beyond 2 weeks at the investigator's discretion.

Patients

The study population included male and female diabetic (type 1 or type 2) patients aged 18 years or older of any race or ethnicity who required cataract extraction with planned implantation of a posterior chamber intraocular lens. Key inclusion criteria included history of diabetes (Type I or II), NPDR as defined by the International Clinical Diabetic Retinopathy Disease Severity Scale and verified by the reading center (Vienna Reading Center, Department of Ophthalmology, University of Vienna, Vienna, Austria), and CSMT ≤320 µm in the study eye determined using a Heidelberg SD-OCT or ≤300 µm using a Zeiss Cirrus SD-OCT before cataract surgery. Key exclusions were signs of vitreomacular traction, epiretinal membrane, or current or previous ocular diseases other than DR in the study eye that could have confounded assessment of the macula, retina, or central vision. Concomitant use of daily doses of systemic NSAIDs or corticosteroids or use of topical NSAIDs or steroids in the study eye (apart from assigned study treatments) was not permitted during the course of study.

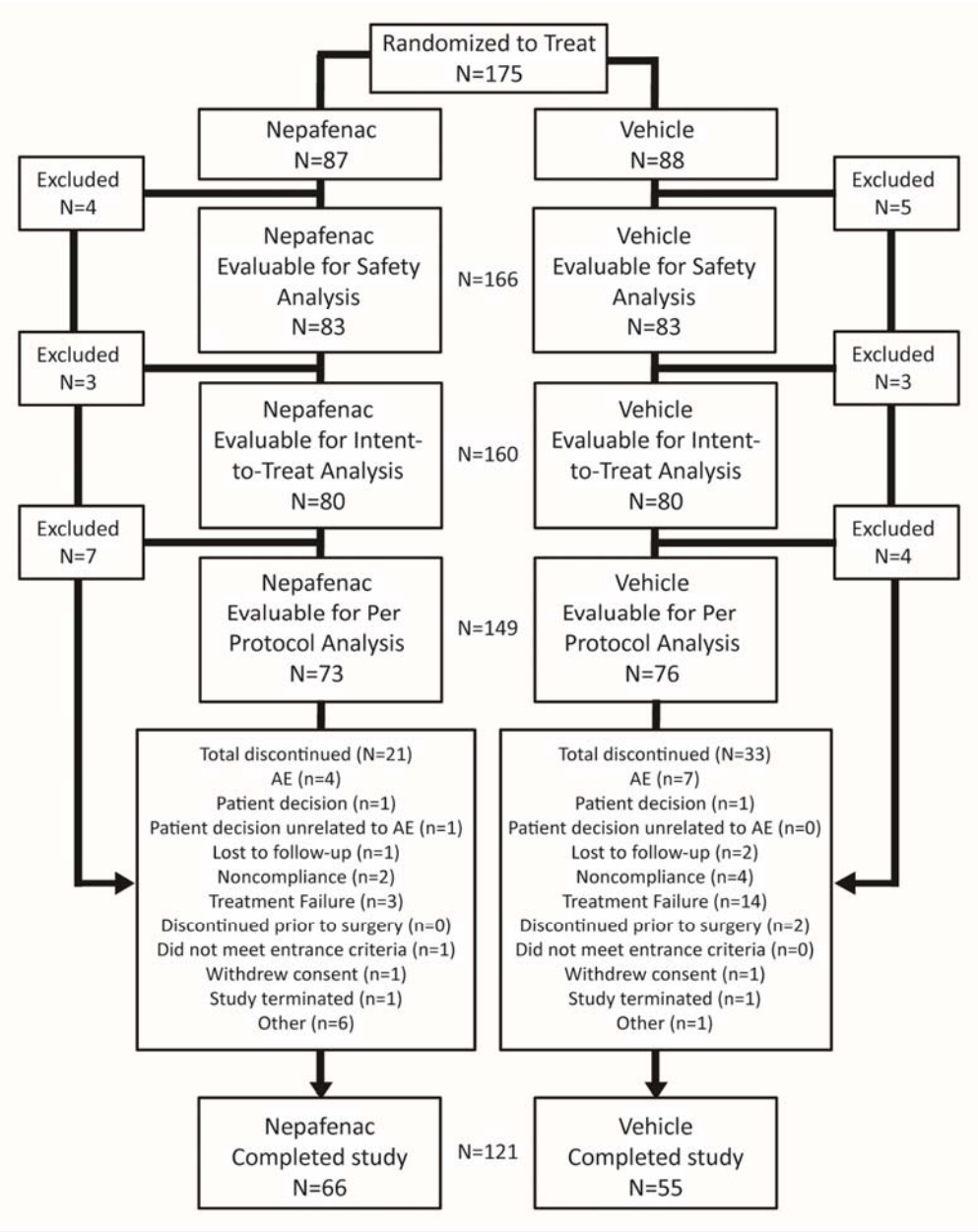
Safety assessment

All adverse events were assessed for seriousness, severity (mild, moderate, or severe), onset, duration, outcome, and relationship to study drug. Safety assessments also included evaluations of intraocular pressure, ocular signs (inflammatory cells, aqueous flare, bulbar conjunctival injection, corneal edema), dilated fundus examinations (optic nerve, retina/macula/choroid), and corneal fluorescein staining.

Statistical analysis

All statistical analyses were performed using SAS® software version 9.2 (SAS Institute, Cary, NC). The ITT analysis population comprised of all patients who were exposed to the study drug,

completed cataract surgery including implantation of the posterior intraocular lens, and had at least one postbaseline study visit at which SD-OCT was performed. All efficacy analyses were conducted using ITT population with last observation carried forward method to impute missing values. The safety analysis population included all patients who were exposed to study drug or had potential exposure to study drug. All obtained data were used in the safety analysis without imputation for missing values.

Comparison of percentage of patients who developed ME within 90 days following cataract surgery between the treatment groups was conducted using a chi-square test, with 95% Clopper-Pearson confidence intervals provided for each treatment arm, and BCVA change from baseline between the treatment groups was compared using a Mixed Model Analysis of Variance. A P value of <0.05 was considered statistically significant.

Supplemental Figure 1. Patient Disposition for the Nepafenac Clinical Trial. Of the 175 enrolled patients, 166 (94.9%) were evaluable for the safety set, 160 (91.4%) were evaluable for the intent-to-treat analysis set, and 149 (85.1%) were evaluable for the Per Protocol analysis set. A total of 121 patients (N=66 nepafenac, N=55 vehicle) completed the study.