# Efficacy and Safety of Intravitreal Aflibercept for Polypoidal Choroidal Vasculopathy: Two-Year Results of the Aflibercept in Polypoidal Choroidal Vasculopathy Study

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• PURPOSE: We sought to evaluate longer-term efficacy and safety of intravitreal aflibercept monotherapy (IAI) vs IAI plus rescue photodynamic therapy (rPDT) in patients with polypoidal choroidal vasculopathy (PCV).

• DESIGN: This was a prospective multicenter, double-masked, sham-controlled randomized clinical study across 62 centers.

• METHODS: In this phase 3b/4 study, patients with PCV with best-corrected visual acuity of 73–24 Early Treatment Diabetic Retinopathy Study letters (20/40–20/320 Snellen equivalent) received IAI 2 mg every 4 weeks until week 12, when they were randomized 1:1 to receive IAI or IAI plus rPDT if rescue criteria were met. Patients not requiring rescue received IAI every 8 weeks; those requiring rescue received IAI every 4 weeks plus sham/active PDT. At week 52 (the primary endpoint), IAI was noninferior to IAI plus rPDT. After week 52, treatment intervals could be extended beyond 8 weeks at the investigators' discretion. Noninferiority of IAI vs IAI plus rPDT for mean best-corrected visual acuity change from baseline to week 96 was evaluated.

• RESULTS: Over 96 weeks, 54 patients (17.0%) met rescue criteria. At week 96, IAI was noninferior to IAI plus rPDT in terms of Early Treatment Diabetic Retinopathy Study letters gained (+10.7 vs +9.1, $P = .48$). Proportions of patients with complete polyp regression (33.1% vs 29.1%) or without active polyps (82.1% vs 85.6%) were similar. In year 2, the mean number of injections was 4.6 in both arms. No new safety signals were observed.

• CONCLUSION: IAI monotherapy was noninferior to IAI with rescue PDT up to 96 weeks, and functional and anatomical improvements achieved at 52 weeks were maintained. Few patients required rescue PDT, which provided no additional visual benefit. (Am J Ophthalmol 2019;204:80–89. © 2019 Published by Elsevier Inc.)

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POLYPOIDAL CHOROIDAL VASCULOPATHY (PCV) IS A subtype of neovascular age-related macular degeneration (nAMD) that is characterized by an abnormal branching vascular network with polypoidal dilations.[1,2] PCV predominantly affects patients ≥50 years of age and is more commonly reported among Asian than non-Asian populations, with evidence suggesting that approximately 25% to 65% of Asian patients with presumed nAMD suffer from PCV.[3–7] As has been shown for nAMD, PCV often follows a natural remitting–relapsing course, and without proactive treatment the chronic nature of the disease results in significant long-term visual morbidity.[8]

The introduction of anti-vascular endothelial growth factor (VEGF) agents has revolutionized treatment for typical nAMD for more than a decade,[9,10] with aflibercept and ranibizumab being approved agents in most countries, including the United States and countries in Europe and Asia.[11,12] Anti-VEGF agents have typically been given as monotherapy in landmark randomized controlled trials[13–17] and in real-world studies[18–25] with improvements in visual outcomes up to 2 years. Furthermore, similar findings have been reported in studies of anti-VEGF agents in Asian patients with nAMD.[26]

The best treatment option for PCV has been less clear.[8] Photodynamic therapy (PDT) with verteporfin was previously recommended as a possible treatment



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but it can lead to recurrent hemorrhage and late atrophy, which results in a loss of visual acuity with prolonged use.[27–29] With regard to anti-VEGF therapy, several case studies and small randomized controlled trials have shown the benefits of anti-VEGF monotherapy or in combination with PDT in patients with PCV.[30–37] Two large pivotal randomized controlled trials were conducted to help physicians determine the optimal treatment algorithm for PCV. The 12-month findings of EVEREST II, evaluating ranibizumab in combination with PDT (administered at baseline and thereafter pro re nata) vs ranibizumab monotherapy, reported higher best-corrected visual acuity (BCVA) gains (8.3 vs 5.1 letters) and higher rates of polyp regression (69.3% vs 34.7%) for the combination group.[38] In the first year of the Aflibercept in Polypoidal Choroidal Vasculopathy (PLANET) study, where PDT was given only if rescue criteria were met at week 12 and beyond, intravitreal aflibercept (IAI) monotherapy resulted in comparable BCVA gains to IAI plus active rescue PDT (IAI plus rPDT; 10.7 vs 10.8 Early Treatment Diabetic Retinopathy Study [ETDRS] letters).[39] In the PLANET study, only a small proportion of patients (42/318, 13.2%) required rescue therapy during the first 52 weeks, and therefore the potential benefit of adding PDT could not be determined. However, the addition of PDT to IAI did not demonstrate additional benefits in terms of visual outcomes in the small group of patients who required rescue treatment (absolute mean [standard deviation] change in BCVA from baseline of 1.9 [8.6] letters for IAI monotherapy [n = 19] and 4.2 [13.8] letters for IAI + rPDT [n = 23]).[39]

There were several questions that could not be answered by the first-year results of the PLANET study, including: What are the longer-term (2-year) results of anti-VEGF monotherapy in patients with PCV? Is a regimen of anti-VEGF IAI monotherapy with rescue PDT given for those who do not respond in the first 3 months of IAI monotherapy efficacious and safe? Among patients who do not respond to IAI monotherapy and require rescue PDT, does the addition of PDT from 3 months onwards provide superior functional and anatomical gain? What are the outcomes when patients receive treatment as a treat-and-extend regimen? Finally, do the relatively low complete polyp regression rates observed at the end of year 1 have a detrimental effect on vision or rebleeding?

We evaluated the results of the second year of the PLANET study to determine the longer-term efficacy and safety of IAI monotherapy with sham rescue PDT vs a regimen of IAI plus active rescue PDT in patients with PCV. We also assessed the longer-term outcomes in the subgroup of patients who required and received rescue PDT and evaluated if outcomes were similar in those who did not receive rescue PDT.

# METHODS

• **STUDY DESIGN:** The PLANET Study was a 96-week, randomized, double-masked, sham-controlled phase 3b/4 study conducted in Asia (57 sites) and Europe (1 site in Germany; 4 sites in Hungary). The study protocol was approved by the institutional review board or ethics committee at each participating clinical center before the start of the study. This trial was registered with ClinicalTrials.gov (NCT02120950). All patients signed a written consent form before initiation of the study-specific procedures. This study was conducted in compliance with regulations of the Declaration of Helsinki. The methodology has previously been described in full.[39]

• **INTERVENTIONS:** After screening and eligibility confirmation, all patients initially received 3 monthly injections of IAI 2 mg. At week 12, patients were randomized 1:1 to receive either IAI 2 mg plus sham PDT as needed, if rescue criteria were met (IAI monotherapy), or IAI plus active rescue PDT as needed, if rescue criteria were met (IAI plus rPDT) until week 96. The criteria for rescue treatment are described previously.[39] In detail they are:

- BCVA of ≤73 letters at visit AND
- BCVA gain from baseline of <5-letters OR BCVA gain ≥5 but <10 letters, if the investigator considered that PDT could be beneficial AND
- New or persistent fluid on optical coherence tomography (OCT) AND
- Evidence of active polyps on indocyanine green angiography (ICGA)

Importantly, the investigator judgment regarding the potential benefits of PDT was applied only in those cases in which patients gained ≥5 but <10 letters and met the other criteria. Patients who did not require rescue treatment were treated with IAI 2 mg every 8 weeks; patients who required rescue treatment received a combination of IAI 2 mg every 4 weeks plus sham PDT (IAI monotherapy) or active rPDT (IAI plus rPDT) according to the locally approved label. From weeks 52 to 96, patients not meeting the rescue criteria could have their treatment intervals extended (recommendation of either 1- or 2-week increments at a time) at the sole discretion of the investigator and not mandated as part of the study protocol. Patients who did not have their treatment intervals extended continued the same treatment regimen as in year 1 (IAI 2 mg every 8 weeks).

• **PRIMARY AND SECONDARY OUTCOMES:** The primary objectives of the PLANET study were to evaluate the efficacy and safety of IAI monotherapy vs IAI plus rPDT in patients with PCV and to determine whether IAI

monotherapy was noninferior (based on BCVA) to IAI plus rPDT. The primary efficacy endpoint of the study, mean change from baseline in BCVA (ETDRS letter score) at week 52, has been published.[39]

The current paper focused on the secondary endpoints of: 1) mean change from baseline in BCVA (ETDRS letter score) at week 96; 2) the proportion of patients who avoided a loss of ≥15 ETDRS letters from baseline, 3) change in OCT-measured central subfield thickness over time, 4) the proportion of patients with complete polyp regression, and 5) the proportion of patients with no active polyps (defined as eyes without polyps on ICGA [complete polyp regression] or with polyps on ICGA but no new/persistent fluid on OCT). All endpoints were assessed at week 96 for all patients regardless of the timepoint of their last treatment and are reported here.

• **STATISTICAL ANALYSIS:** Statistical analyses were performed using SAS software (version 9.2; SAS Institute, Cary, NC, USA). Descriptive statistics are provided for all variables. For statistical testing, analysis of covariance models was used for continuous variables and Cochran-Mantel-Haenszel models for categorical values. For the primary analysis, statistical testing was conducted at a significance level of .05 (2-sided). No adjustment was made for multiple comparisons.

Statistical testing was conducted to prove the noninferiority of IAI monotherapy to IAI plus rPDT at week 52; IAI monotherapy was considered noninferior to IAI plus rPDT if the lower bound of the 95% confidence interval (CI) for the difference between groups was $> -5$ ETDRS letters. If IAI monotherapy was noninferior to IAI plus rPDT, confirmatory noninferiority testing was continued for the proportion of patients who avoided a moderate loss of vision of ≥15 ETDRS letters from baseline to weeks 52. Two-sided 95% Cochran-Mantel-Haenszel intervals adjusted for race/ethnicity and qualification for rescue therapy at week 12 were used. IAI monotherapy was considered noninferior to IAI plus rPDT if the difference was $> -7\%$.

The primary analysis was conducted on the full analysis set. All exploratory analyses, including analysis of patients who did and did not qualify for rescue treatment, were prespecified and conducted on the full analysis set and not the subgroup of patients who completed 96 weeks of the study. Additional prespecified analyses were conducted on populations that did or did not require rescue therapy. The safety analysis set included all patients who received any study drug (including those not randomized). A last observation carried forward approach was used for imputation of the missing values. A 3-way analysis of covariance models with baseline measure as a covariate, and treatment group, ethnicity, and qualification for rescue therapy at week 12 as fixed factors.

# RESULTS

OF THE 428 PATIENTS SCREENED, 333 INITIATED TREATMENT (up to week 8). At week 12, 318 patients were randomized as follows: 157 to IAI monotherapy and 161 to IAI plus rPDT. Patient disposition was previously reported for the 52-week study.[39] A total of 284/333 (85.3%) patients completed 96 weeks of the study, the main focus of this article; of those, 137 (87.3%) were in the IAI monotherapy group and 147 (91.3%) in the IAI plus rPDT group. As previously reported, baseline demographics and characteristics of patients were similar across treatment groups.[39]

• **TREATMENT:** During the 96-week treatment period, patients received a mean of 12.7 and 12.6 total IAI injections in the IAI monotherapy and IAI plus rPDT arms, respectively (mean 8.1 across both groups in the 0- to 52-week period and mean 4.6 in the 52- to 96-week period). The mean number of PDT administrations (including sham) was only 0.3 overall (0.2 in the 0- to 52-week period and 0.1 in the 52- to 96-week period). Overall by week 96, 54 (17.0%) patients required and received rescue therapy (25/157 [15.9%] in the IAI monotherapy group and 29/161 [18.0%] in the IAI plus rPDT group), representing an additional 6 patients per group requiring rescue treatment in the second year of the study compared with year 1. Among the subgroup of patients who required rescue treatment, the mean number of IAI injections and PDT treatments from baseline to week 96 was 16.5 and 2.3, respectively, in the IAI monotherapy group, and 13.8 and 1.3 in the IAI plus rPDT group.

• **VISUAL ACUITY OUTCOMES:** At week 96, the mean change from baseline in BCVA score for IAI monotherapy was noninferior to IAI plus rPDT (+10.7 vs +9.1 letters; least-squares mean [LSM] difference 0.9 [95% CI –1.7 to 3.6]; $P = .48$; Figure 1, A). In the larger subgroup of patients (n = 264) who did not qualify for PDT rescue therapy (treated with IAI regardless of randomization group), improvements in BCVA score from baseline at week 96 were similar: +12.3 letters for the IAI monotherapy arm and +11.1 letters for the IAI plus rPDT arm (LSM difference 0.4 [95% CI –2.3 to 3.2]; $P = .75$; Figure 1, B). In contrast, in the smaller subgroup of patients who met the criteria for rescue therapy (n = 54), the prespecified exploratory analysis also indicated noninferiority for IAI monotherapy (sham PDT) vs IAI plus rPDT; the mean change from baseline in BCVA was +2.6 letters for IAI monotherapy and 0.0 letters for IAI plus rPDT (LSM difference 2.9 [95% CI –3.9 to 9.7]; $P = .40$; Figure 1, C).

The proportion of patients avoiding vision loss of ≥15 letters from baseline to week 96 was similarly high in both groups: 96.8% (n = 152) for IAI monotherapy and 94.4% (n = 152) for IAI plus rPDT therapy (difference 2.1% [95% CI –2.5 to 6.7]; $P = .37$). In patients not requiring

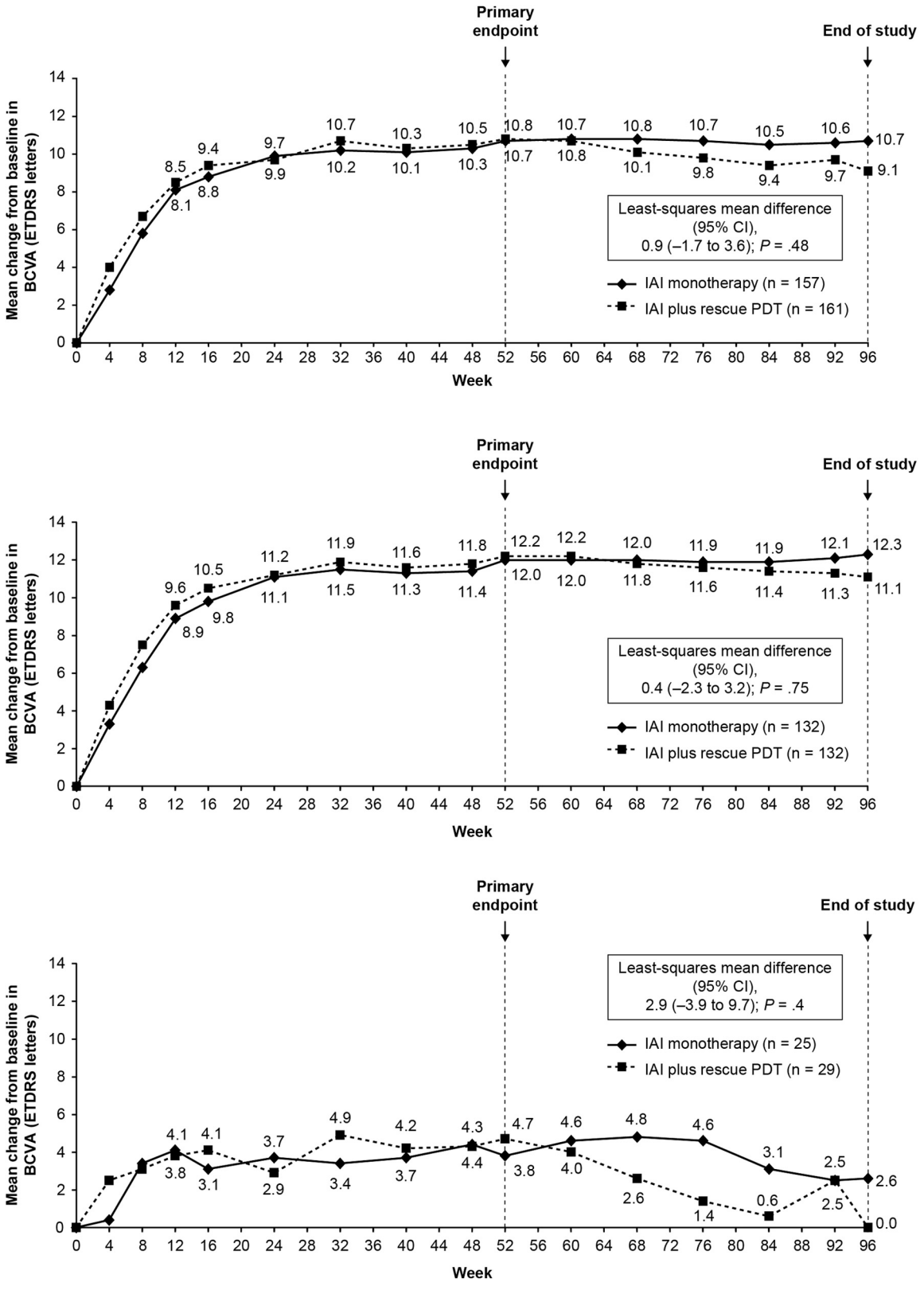


**FIGURE 1. Change in best-corrected visual acuity (BCVA) (Early Treatment Diabetic Retinopathy Study letters) from baseline to week 96 (full analysis set) in (A) overall population, (B) population not requiring rescue therapy, and (C) population requiring rescue therapy. BCVA = best-corrected visual acuity; CI = confidence interval; ETDRS = Early Treatment Diabetic Retinopathy Study; IAI = intravitreal aflibercept; PDT = photodynamic therapy.**

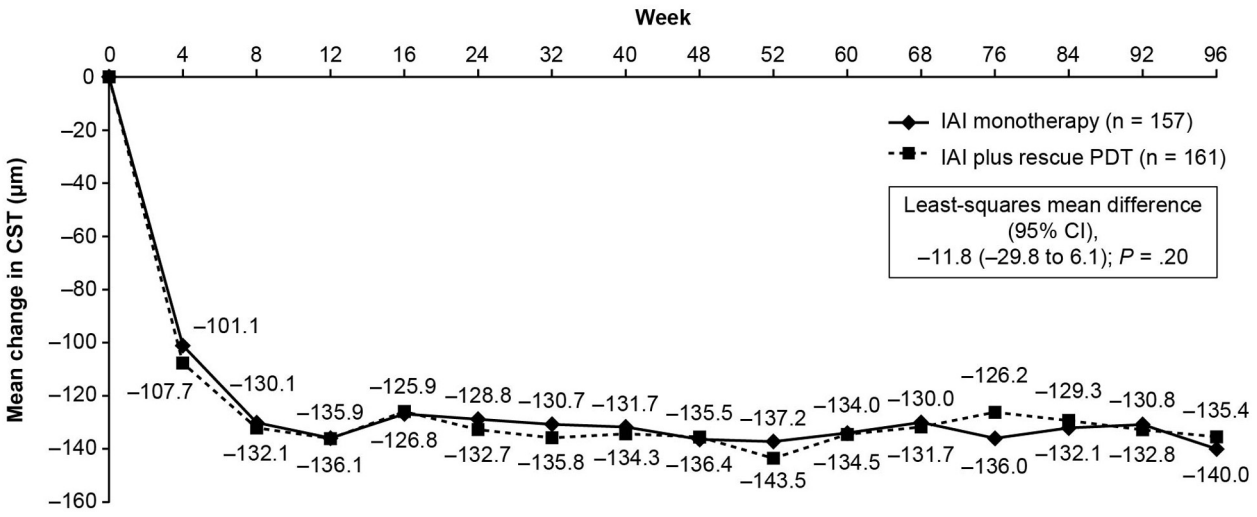


**FIGURE 2. Change in central subfield thickness from baseline to week 96 (full analysis set). CI = confidence interval; IAI = intravitreal aflibercept; PDT = photodynamic therapy.**

rescue, the proportion of patients avoiding vision loss of ≥15 letters was 97.0% (n = 128) for both treatment groups (difference 0.0% [95% CI –4.2 to 4.2]; $P = .99$). In the smaller subgroup that required rescue therapy, the proportions of patients avoiding vision loss of ≥15 letters were 24/25 (96.0%) for IAI monotherapy and 24/29 (82.8%) for IAI plus rPDT (difference 12.5% [95% CI –4.5 to 29.6]; $P = .15$). These findings are like those previously reported at week 52.[39]

• **OCT CHANGES:** The rapid and marked reduction in central subfield thickness achieved during the initial 8-week treatment period in both treatment groups was maintained until week 96. The reduction in central subfield thickness from baseline to week 96 was –140.0 µm in the IAI monotherapy group and –135.4 µm in the IAI plus rPDT group (LSM difference –11.8 µm [95% CI –29.8 to 6.1]; $P = .20$; Figure 2).

• **POLYP REGRESSION ON ICGA:** The proportions of patients with complete polypoidal lesion regression on ICGA were not different between treatment groups at weeks 52 (difference –6.0% [95% CI –17.8 to 5.9]; $P = .32$) and 96 (difference 3.5% [95% CI –7.9 to 14.9]; $P = .55$; Figure 3, A). However, the proportions of patients with complete polypoidal lesion regression decreased in the IAI monotherapy group from 38.9% (49/126) at week 52 to 33.1% (39/118) at week 96, and in the IAI plus rPDT group from 44.8% (60/134) at week 52 to 29.1% (37/127) at week 96. In the subgroup of patients requiring rescue therapy who had week 96 assessments available, the proportion of patients with complete polypoidal lesion regression was not significantly different between groups (25.0% [5/20] for IAI monotherapy vs 26.1% [6/23] for IAI plus rPDT) at week 96 (compared with 6.7% and 44.4%, respectively, at week 52).

• **POLYPOIDAL LESION ACTIVITY:** The absence of active polypoidal lesions includes complete polypoidal lesion regression as described above and was high in both treatment groups at week 96; 110 patients (82.1%) in the IAI monotherapy group and 125 patients (85.6%) in the IAI plus rPDT group had no evidence of active polypoidal lesions (Figure 3, B). These findings are like those previously reported at week 52 (116 and 136 patients [81.7% and 88.9%], respectively). In the subgroup of patients requiring rescue therapy, the proportion of patients with no evidence of active polypoidal lesions was 90.0% in the IAI monotherapy group and 80.0% in the IAI plus rPDT group at week 96 (compared with 31.3% and 60.0%, respectively, at week 52). Whether the presence of active polypoidal lesions at week 52 predicted visual outcome at week 96 weeks was evaluated. Among the subgroup of patients with evidence of active polypoidal lesions at week 52, mean change in BCVA was similar in both treatment arms from baseline to week 96 (+11.2 letters for IAI monotherapy and +11.7 letters for IAI plus rPDT) and from weeks 52 to 96 (+0.2 letters for IAI monotherapy and −0.8 letters for IAI plus rPDT). In comparison, among patients with no evidence of active polypoidal lesions at week 52, mean changes in BCVA were greater in the IAI monotherapy group compared with the IAI plus rPDT group from baseline to week 96 (+12.1 vs +8.4 letters) and from week 52 to week 96 (−0.2 vs −3.0 letters), respectively.

At week 96, a similar number of patients (16.9% [n = 23] for IAI monotherapy and 18.4% [n = 27] for IAI plus rPDT group) in each arm had new or persistent fluid on OCT (Figure 3, C). These findings were like those reported at week 52, with 20% of patients in each arm having new or persistent fluid on OCT. In the subgroup of patients

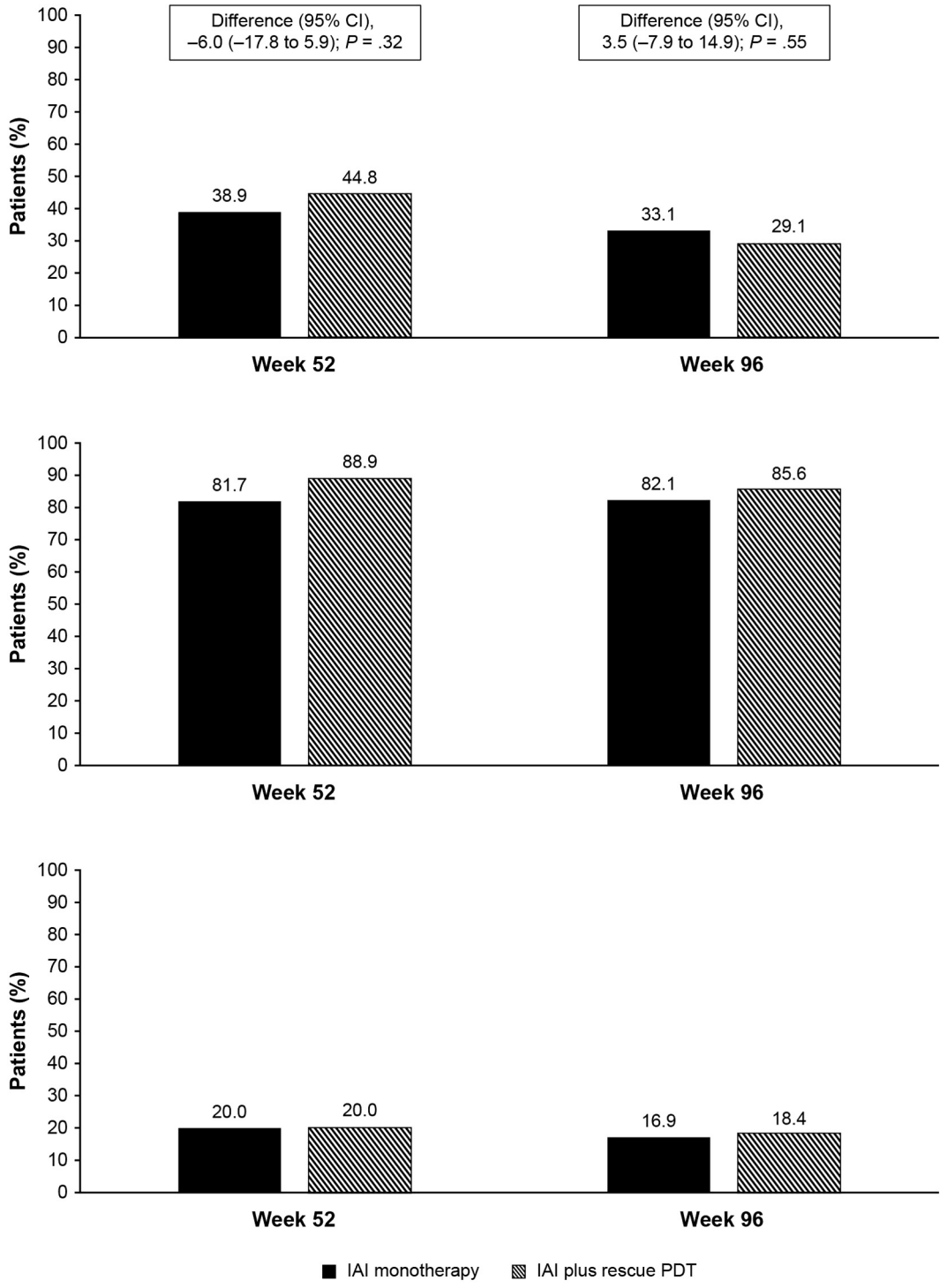


**FIGURE 3. Proportion of patients at week 96 (full analysis set) with (A) complete polyp regression, (B) no active polypoidal lesions on ICGA/OCT, and (C) new or persistent fluid on OCT. Cochran–Mantel–Haenszel test. CI = confidence interval; IAI = intravitreal aflibercept; ICGA = indocyanine green angiography; OCT = optical coherence tomography; PDT = photodynamic therapy.**

requiring rescue therapy who had week 96 assessments available, 7 of 22 patients (31.8%) in the IAI monotherapy group and 4 of 26 patients (15.4%) in the IAI plus rPDT group had new or persistent fluid on OCT at week 96 (data not shown).

• **TREAT-AND-EXTEND REGIMEN:** The proportion of patients who, at the discretion of the investigator, had at ≥1 treatment interval extended to ≥10 weeks was 84 of 145 (57.9%) and 80 of 154 (51.9%) in the IAI

**TABLE.** Adverse Events from Baseline to 96 Weeks (Safety Analysis Set)

| Patients with AEs, n (%) | IAI + Sham PDT n = 157 | IAI + rPDT n = 161 | Treated but not randomized[a] n = 15 | Total N = 333 |
|---|---|---|---|---|
| Any AE | 114 (72.6) | 110 (68.3) | 6 (40.0) | 230 (69.1) |
| Any TEAE | 111 (70.7) | 105 (65.2) | 6 (40.0) | 222 (66.7) |
| Ocular TEAE | 64 (40.8) | 65 (40.4) | 3 (20.0) | 132 (39.6) |
| Conjunctival hemorrhage | 10 (6.4) | 5 (3.1) | 0 (0.0) | 15 (4.5) |
| Dry eye | 6 (3.8) | 11 (6.8) | 0 (0.0) | 17 (5.1) |
| Retinal hemorrhage | 6 (3.8) | 6 (3.7) | 0 (0.0) | 12 (3.6) |
| Vitreous hemorrhage | 1 (0.6) | 1 (0.6) | 0 (0.0) | 2 (0.6) |
| Any SAEs | 30 (19.1) | 27 (16.8) | 4 (26.7) | 61 (18.3) |
| Any ocular SAEs | 3 (1.9) | 7 (4.3) | 1 (6.7) | 11 (3.3) |
| Any death | 3 (1.9) | 0 (0) | 1 (6.7) | 4 (1.2) |
| Any APTC-classified events | 2 (1.3) | 0 (0) | 1 (6.7) | 3 (0.9) |

AE = adverse event; APTC = Antiplatelet Trialists' Collaboration; IAI = intravitreal aflibercept; PDT = photodynamic therapy; SAE = serious AE; TEAE = treatment-emergent AE.

[a]All study patients who were enrolled in the study and received treatment but were not randomized at week 12 due to protocol deviation, adverse event, withdrawal, death, or loss to follow-up.

monotherapy and IAI plus rPDT groups, respectively, at week 96. Furthermore, 60 of 145 (41.2%) and 57 of 154 (37.0%), respectively, had intervals extended to ≥12 weeks. Mean BCVA change from baseline to week 96 was +11.1 and +11.0 ETDRS letters in the IAI monotherapy and IAI plus rPDT groups, respectively, among patients with treatment intervals ≥10 weeks; and +10.5 and +11.5 ETDRS letters, respectively, among patients with treatment intervals ≥12 weeks. From weeks 52 to 96, the mean number of IAI injections was 4.1 and 4.4 in the IAI monotherapy and IAI plus rPDT groups, respectively, among patients with treatment intervals ≥10 weeks; and 3.9 and 4.2, respectively, among patients with treatment intervals ≥12 weeks. Among patients with a treatment interval extension and for whom data were available, 44 patients had an extension of 1 week, 92 patients had an extension of 2 weeks, and 7 patients had an extension of >2 weeks.

• **SAFETY:** At week 96, the incidence of treatment-emergent ocular adverse events (AEs) was similar in the IAI monotherapy group (64 patients, 40.8%) and the IAI plus rPDT group (65 patients, 40.4%) (Table). The most commonly reported ocular AEs were conjunctival hemorrhage (10 patients, 6.4%) in the IAI monotherapy group and dry eye (11 patients, 6.8%) in the IAI plus rPDT group. The rates of retinal hemorrhage were similar in the IAI monotherapy (6 patients, 3.8%) and IAI plus rPDT (6 patients, 3.7%) groups, while only 1 patient (0.6%) in each group experienced a vitreous hemorrhage. At week 96, 6 (3.8%) and 9 (5.6%) patients in the IAI monotherapy and IAI plus rPDT groups, respectively, had an increase in intraocular pressure, and 3 (1.9%) and 6 (3.7%) patients, respectively, had a cataract. Ocular serious AEs were reported in 3 patients (1.9%) in the IAI monotherapy group and 7 (4.3%) in the IAI plus rPDT group. The incidence of nonocular AEs was also similar between treatment groups (89 and 82 patients [56.7% vs 50.9%], respectively). There were no meaningful differences in the incidence of Antiplatelet Trialists' Collaboration-defined arterial thromboembolic events between treatment groups (2 vs 0 patients [1.3% vs 0.0%], respectively).

## DISCUSSION

THE 2-YEAR FINDINGS OF THE PLANET STUDY SHOW THAT the favorable results of IAI monotherapy observed at 1 year are maintained over the longer term, with IAI monotherapy still demonstrating noninferiority to a regimen of IAI with active rescue PDT among patients who met the criteria for rescue PDT at 3 months onwards. Our overall findings are summarized here. First, in patients treated with IAI monotherapy (the vast majority in this trial), there was a sustained improvement in visual outcomes with the BCVA gain achieved at week 52 (+10.7 letters) being maintained at week 96 (+10.7 letters). Second, <20% of patients required and met the criteria for rescue PDT. In fact, there was no notable increase in the number of patients requiring rescue PDT therapy at week 96 (54 patients [17.0%], which was slightly higher than at week 52 [42 patients; 13.2%]). Third, among this small subgroup who did not respond to 3 months of IAI monotherapy and met the criteria for rescue PDT, continuing on an IAI monotherapy regimen (with sham PDT) was noninferior to active rescue PDT given from 3 months up to week 96 (+2.6 vs 0 letters, $P = .40$). Overall, most patients (304 [96%]) avoided a loss of ≥15 letters, although the IAI plus rPDT subgroup experienced a loss of approximately 5 ETDRS

letters from weeks 52 to 96, regardless of whether they received sham or active rescue PDT. The patients who required and received rescue therapy had significantly lower visual acuity gains than those not requiring rescue therapy, so they might be expected to have poorer outcomes regardless of treatment. Unfortunately, there were no specific clinical or imaging characteristics to define this group of poor responders before treatment who were only defined as needing rescue therapy after 3 initial IAI loading doses. Therefore, it was not known if these patients would have had better outcomes if they had received PDT at the start of the study. However, we speculate that active rescue PDT may have a greater beneficial effect only when the presence of polyps (on ICGA) is accompanied by fluid activity (on OCT).

The discrepancies in treatment approaches with respect to PDT administration between the PLANET (rescue PDT from month 3 onwards among patients who met criteria for rescue) and EVEREST II (baseline adjunct PDT to all patients) studies at 1 year have been discussed previously.[39,40] While the 2 trials are clearly not similar, with caution, results of the 2-year EVEREST II study can be descriptively compared with the 2-year results of the PLANET study. Such an indirect comparison suggests that over 2 years IAI monotherapy provided higher numerical visual acuity gains than ranibizumab with baseline active PDT (+10.7 vs +8.3 ETDRS letters), despite having comparable total interventions (total anti-VEGF plus PDT was 12.7 for IAI in PLANET and 10.3 for ranibizumab combination in EVEREST II). These findings suggest that baseline adjunct PDT provided no demonstrated advantage in terms of visual acuity, although it is not known if the higher baseline BCVA score in EVEREST II than in the PLANET study had an impact.

A traditional important parameter of anatomical success in PCV management is ICGA-defined polyp regression. In our study, the proportion of patients with complete polyp regression at week 96 was similar in both groups. However, some patients who had no polyps at the end of year 1 developed polyps during year 2 (21/48 patients in the IAI monotherapy group and 29/60 patients in the IAI plus rPDT group). In the rescue subgroup, polyp regression rates were similar in both treatment arms at 2 years (25.0% and 26.1%, respectively), representing an increase from 6.7% in the IAI monotherapy arm at week 52 but a reduction from 44.4% in the IAI plus rPDT arm. The reappearance of polyps did not influence the overall visual acuity outcomes, suggesting that a more important measure of anatomical success is the presence or absence of active polyps, which are defined based on both ICGA and OCT. In our study, 234 patients (84%) in both treatment groups had no evidence of active polyps at week 96, which was consistent with findings at week 52. These results show that substantially more patients had no evidence of active polypoidal lesions than complete regression of polyps, suggesting that not all polyps behave similarly, and not all lead to fluid accumulation.

The goal of treatment of PCV in a real-world setting is to achieve optimal visual improvements with a minimum number of office visits and interventions (injections and/or PDT), and it has been suggested that this can be achieved by using combination approaches. During the second year of the PLANET study, where patients received IAI treatment as an optional investigator-determined treat-and-extend regimen, there was a meaningful reduction in the number of visits and total treatments, with no loss of the improvements in visual acuity attained in year 1. Such a treat-and-extend regimen is now commonly performed as routine clinical practice for typical nAMD.

In the clinical setting, the population of patients with nAMD who do not respond to anti-VEGF monotherapy represents an important challenge for physicians. In patients with PCV, the option of adding on rescue PDT was suggested for those who do not respond. The results of the PLANET study suggest that first, only a relatively small proportion of patients (<20% over 2 years) required rescue therapy and secondly, among those who did, there were no differences in visual acuity, complete polyp regression, or evidence of active polypoidal lesions regardless of whether PDT was administered. Therefore, the addition of rescue PDT to patients who did not respond initially to IAI monotherapy did not provide any benefit. However, it may be that the favorable BCVA outcomes reported in patients requiring rescue therapy may be related to continuation of IAI every 4 weeks compared with the extended treatment intervals (≥8 weeks) in patients who did not require rescue therapy.

Finally, there were no new or additional AEs beyond those previously observed in trials of IAI or other anti-VEGF agents, supporting use of IAI over 2 years of treatment of patients with PCV.

There are several limitations to our study. The PLANET study did not compare a regimen of IAI monotherapy with IAI in combination with active PDT at the start of the study (a typical combination regimen) but evaluated active rescue PDT given after 3 months' IAI monotherapy. The criteria for rescue therapy was evidence of disease activity (based on OCT, ICGA, and BCVA gain <5 or ≥5 but <10 ETDRS letters, with investigator judgment of a potential benefit for PDT), which most patients did not meet. Therefore, PLANET only evaluated the efficacy of rescue PDT amongst the group of nonresponders to IAI monotherapy. As a consequence, it is not possible to ascertain whether a regimen of IAI plus active PDT at baseline or IAI plus active PDT to all patients at 3 months is noninferior to IAI monotherapy in terms of mean change in BCVA. In addition, the requirement for rescue therapy was lower (<20%) than the predicted need for rescue PDT (32%). Although this limits the statistical conclusions that can be drawn, the fact that rescue PDT was not required in >80% of patients also speaks to the robustness of the treatment benefits of IAI. Furthermore, the possible extension of

IAI treatment interval (beyond the initial 4 weeks, at the investigator's discretion based on visual and anatomic outcomes) in those requiring rescue PDT may have had an effect on BCVA outcomes.

In conclusion, the improvements in visual, functional, and anatomical outcomes achieved with IAI monotherapy in the first year of the PLANET study were maintained with longer-term follow-up to 2 years. Less than 20% of patients met the criteria for the addition of PDT given in the rescue setting from 3 months onwards. In this subgroup of patients requiring rescue therapy, there were no differences in outcomes between those treated with IAI monotherapy compared with those who received IAI and active rescue PDT. These findings suggest that most patients with PCV can be treated with a simple anti-VEGF monotherapy regimen, as for patients with typical nAMD, and that treatment intervals can be extended in the second year.

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