Clinical Ophthalmology

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ORIGINAL RESEARCH

Twelve-Month Outcomes of Faricimab for Patients with Sub-Optimally Responsive Diabetic Macular Oedema: A Retrospective Single-Centre Study

Kamal El-Badawi[1,2], Benjamin Scrivens[3], Oluwaniyi Eke[1], Rehab Ismail[4], Lina Kobayter[1], Serena Salvatore[1]

[1]Ophthalmology Department, Bristol Eye Hospital, University Hospitals Bristol and Weston, Bristol, UK; [2]Medical Education department, Queen Elizabeth the Queen Mother Hospital, Margate, UK; [3]Emergency department, Salisbury District Hospital NHS Foundation Trust, Salisbury, UK; [4]Ophthalmology department, Aberdeen Royal Infirmary, NHS Grampian, Aberdeen, UK

Correspondence: Kamal El-Badawi, Medical Education department, Queen Elizabeth the Queen Mother Hospital, 10 Gainsborough Drive, Maidstone, Kent, ME16 0UZ, UK, Tel +447547733153, Email Kamal_el-badawi@live.com

Purpose: To evaluate the visual and anatomical outcomes of switching diabetic macular oedema (DMO) patients with suboptimal response to aflibercept 2mg to faricimab over a 12-month period.

Patients and Methods: This retrospective single centre study enrolled 62 eyes from 50 patients with diabetic macular oedema (DMO) who demonstrated a sub-optimal response to aflibercept 2mg. Sub-optimal response was defined by a central subfield thickness (CST) exceeding 325µm or greater than 20% increase from the best CST despite receiving aflibercept 2mg at intervals of 8 weeks or less. Patients had received at least six 4-weekly doses of aflibercept 2mg. Faricimab was administered as four intravitreal loading injections at 4-weekly intervals, followed by a treat-and-extend approach. Outcome measures, including best-recorded visual acuity (BRVA), CST, and treatment intervals, were assessed at baseline, post-loading (6.5 ± 1.9 weeks) and at the latest clinic review (57.1 ± 19.7 weeks). Statistical analysis included paired t-tests (normal distribution) and Wilcoxon signed-rank tests (non-normal distribution), with $p < 0.05$ considered statistically significant.

Results: Mean age was 63.9 (±11.4) years, 56% participants were male. At baseline, the mean BRVA was 67.6 (±11.8) letters, and CST measured 406.4 (±105.9) µm. The initial mean treatment interval was 6.5 (±1.8) weeks. BRVA increased to 70.4 (±12.7) letters (p=0.008), while CST reduced to 372.8 (±132.0) µm (p=0.002). The mean injection interval extended to 7.4 (±2.6) weeks (p=0.03). At the latest follow-up BRVA was maintained at 68.7 (±14.6) letters (p=0.572), and CST reduced further to 343.1 (±117.5) µm (p=0.020). At the final follow-up 53.2% were on ≥8-weekly intervals. The mean injection interval increased to 9.2 (±3.2) weeks ($p < 0.001$), and a mean of 7.92 (±2.53) faricimab injections was administered.

Conclusion: DMO patients with sub-optimal response to aflibercept 2mg experienced improved anatomical outcomes and extended treatment intervals while maintaining vision on faricimab, with no new safety concerns.

Keywords: anti-VEGF, Ang2, diabetic retinopathy

Introduction

Diabetic retinopathy (DR) is a frequent microvascular complication of diabetes mellitus (DM) that can result in macular thickening due to retinal vascular hyperpermeability, a condition known as diabetic macular oedema (DMO). DMO is the most common cause of moderate visual impairment in patients with DR.[1] The global prevalence of DMO is estimated to be around 6.8%, equating to about 27 million adults worldwide being affected by DMO.[2] The number of adults with DMO worldwide is anticipated to increase by 51.9% in the next 20 years.[3,4]

Received: 30 January 2025
Accepted: 11 April 2025
Published: 16 May 2025

Intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) is currently the mainstay treatment of DMO.[5,6] The landmark trials demonstrated improved anatomical and functional outcomes when followed up for at least two years.[7–10]

However, a subset of patients does not respond satisfactorily to anti-VEGF injections. A post hoc analysis of Diabetic Retinopathy Clinical Research (DRCR) Retina network Protocol T showed that 44% of patients receiving aflibercept 2mg for DMO had persistent macular oedema after two years of treatment.[11,12] Additionally, real-world data often demonstrate nuanced variations between clinical trial outcomes and routine healthcare practice[13] and some patients exhibit an inadequate response even with frequent and regular anti-VEGF therapy.[14,15]

This resistance phenomenon is believed to stem from a complex interplay of genetics, tachyphylaxis, and alternative angiogenic pathways beyond VEGF. Thus, various pathogenic mechanisms are implicated in DMO progression.[16] Persistent DMO results in the propagation of oedematous changes driven by multiple inflammatory mediators earlier in the cascade, including angiopoietin-2 (Ang-2), which contributes to vascular destabilisation, vascular permeability, and neovascularization.[17–19] The accumulation of reactive oxygen species (ROS) further exacerbates this process.

Faricimab (VabysmoTM, Roche/Genentech, Basel, Switzerland) is the first and currently the only bispecific molecule that targets both Ang-2 and VEGF. Blocking the Ang-2 pathway improves vascular stability, culminating in DMO reduction.[20] We aim to assess the real-world outcomes of intravitreal faricimab in DMO with sub-optimal response to previous treatment with aflibercept 2mg.

Materials and Methods

Study Design and Population

This retrospective study was conducted in a single tertiary centre: Bristol Eye Hospital, University Hospitals Bristol and Weston, Bristol, United Kingdom (UK). The study included 62 eyes of 50 patients with sub-optimally responsive DMO that were switched to faricimab. A sub-optimal response was defined after at least six 4-weekly aflibercept 2mg doses, as:

- A central subfield thickness (CST) greater than 325 μm after the loading dose.
- An increase of more than 20% from their best CST was recorded despite treatment intervals of 8-weekly or less.

Exclusion criteria for the study included: 1) less than 6 doses of aflibercept at 4-weekly intervals, 2) less than four doses of 4-weekly faricimab injection, 3) intravitreal dexamethasone implant in the previous six months, 4) fluocinolone acetonide intravitreal implant in the previous three years, 5) macular laser within the previous 3 months to commencing faricimab. If an eye received an intravitreal steroid implant or macular laser, they were excluded from the study at that point. Data collected from our Electronic Medical Records (EMR) included demographics, diabetes type, diabetic retinopathy (DR) grading, HbA1c, and treatment intervals.

Outcome measures were best recorded visual acuity (BRVA) in early treatment diabetic retinopathy study (ETDRS) letters, central subfield thickness (CST) measured using optical coherence tomography (OCT) (Topcon DRI OCT Triton plus; Tokyo, Japan) and treatment intervals in weeks. These were recorded at baseline (day of first faricimab injection) after four loading doses of faricimab and at the latest clinic appointment.

Treatment Protocol

Four doses of faricimab at 4-weekly intervals were given, with a review after the fourth loading dose. From this point, they moved on to a treat and extend (T&E) regime, with intervals being maintained, extended, or reduced guided by anatomical outcomes compared to a reference CST value. The reference CST was the lowest CST recorded after loading (aflibercept 2mg or faricimab). Treatment intervals were reduced by 4 weeks if CST increased by >20% of the reference CST, maintained if CST increased by 10–20% of the reference CST, or extended by 4 weeks if CST increased by <10% of this reference value. This local treatment protocol was adapted and modified from the Personalised Treatment Interval (PTI) arm of the landmark trials in YOSEMITE and RHINE.[21]

Statistical Analysis

The study's data were analysed using JASP statistical software. Descriptive statistics were presented as mean averages with standard deviation. A paired *t*-test was utilized for normally distributed data, while the Wilcoxon signed-rank test was applied to non-normally distributed datasets. Statistical significance was established at a p-value less than 0.05. Effect sizes were calculated using Cohen's d. The effect size interpretation followed established parameters: negligible ($d < 0.2$), small ($0.2 \leq d < 0.50$), moderate ($0.5 \leq d < 0.80$), and large ($d \geq 0.8$).

Results

The mean age of participants was 63.9 (±11.4) years, with the majority being male (56%) and predominantly of white ethnicity (80%). Table 1 summarises patient's demographics. The mean HbA1c within 6 months of baseline was 64.5 (±18.2) mmol/mol. At the latest follow-up, the mean HbA1C remained stable at 65.5 (±18.7) mmol/mol, CI[3.9, −1.8](p=0.283).

Baseline (n=62)

The mean number of injections received before the switch to faricimab was 17.3 (±10.7). All patients had received aflibercept 2mg before the switch to faricimab and six patients (9.7%) had initially been treated with ranibizumab followed by aflibercept 2mg before being switched to faricimab. Treatment received prior to faricimab initiation can be found in Table 2. At baseline, the BRVA was 67.6 (±11.8) letters, and CST was 406.4 (±105.9) µm (Table 3).

Table 1 Demographic Data from the Electronic Medical Records (EMR), 50 Patients, 62 Eyes

Sex, n(%)	Male	28 (56%)
	Female	22 (44%)
Age	Mean (±SD)	63.9 (±11.4)
Ethnicity, n(%)	White	40 (80%)
	Unknown/Not listed	9 (18%)
	White and black Caribbean	1 (2%)
Type of diabetes, n(%)	Type 1	7 (14%)
	Type 2	43 (86%)
Grade of diabetic retinopathy (DR), n eyes (%)	Mild non-proliferative (NP) DR	15 (24%)
	Moderate to severe NPDR	25 (40%)
	Proliferative DR	22 (36%)

Abbreviations: n, the actual number; %, the percentage of the total sample.

Table 2 A Summary of Treatment Received for All Eyes Prior to Switching to Faricimab. All Previous Treatments Were Given in Line with the Study's Inclusion Criteria

Total number of previous injections		1069
Mean duration of previous DMO management (months) (±SD)		62.9 (±36.4)
Mean number of previous injections (±SD)		17.3 (±10.7)
	Mean of previous Eylea (Aflibercept 2mg) (n=62) (±SD)	16.5 (±9.5)
Mean injection interval (weeks) (±SD)		7.5 (±2.8)

(*Continued*)

https://doi.org/10.2147/OPTH.S513009

Table 2 (Continued).

Treatment intervals (n=62 eyes) (%)	4 weeks		15 (24.2%)
	>4≤6 weeks		12 (19.4%)
	>6≤8 weeks		35 (56.5%)
Previous DMO management (n=62 eyes), (%)	Anti-VEGF intravitreal injections	Eylea® (Aflibercept 2mg)	62 (100.0%)
		Lucentis® (Ranibizumab 0.5mg)	6 (9.7%)
	Intravitreal dexamethasone implant (Ozurdex®)		4 (6.5%)
	Intravitreal fluocinolone acetonide implant (Iluvien®)		2 (3.2%)
	Macular Laser		16 (25.8%)
	Vitrectomy		6 (9.7%)

Table 3 Summary of the Functional and Anatomical Outcomes for Faricimab T&E at Baseline, Post-Loading, and Latest Follow-up

	Baseline (n=62)	**After Loading (n=54)**	**Latest Clinic Visit (n=42)**
BRVA (letters) (±SD)	67.6 (±11.8)	70.4 (±12.7)	68.7 (±14.6)
>10 letter gain (%)	0	17.7	12.9
CST (μm) (±SD)	406.4 (±105.9)	372.8 (±132.0)	343.1 (±117.5)
Mean CST reduction (μm)	0	45.4 (p=0.002)	56.5 (p=0.020)
CST <325μm (%)	14.5	50.0	45.2
Absence of IRF (%)	0	6.5	3.2

Visit After Loading

After the fourth injection in the loading phase, the mean review time was 6.5 (±1.9) weeks. Fifty-four eyes continued in the T&E pathway as per the local protocol; 5 eyes were switched to an intravitreal dexamethasone implant due to poor response, and three were switched to a pro re nata (PRN) treatment regime and therefore excluded from further analysis (Table 4).

Table 4 Summary of Treatment Intervals at Baseline, Post-Loading, and Follow-up

	Baseline (n=62)	**After Loading (n=62)**	**Latest Follow-Up (n=62)**
Treatment interval (weeks) (±SD)	6.5 (±1.8)	7.4 (±2.6)	9.2 (±3.2)
4-weekly (%)	24.2	21.0	3.2
6-weekly (%)	19.4	9.7	9.7
8-weekly (%)	56.5	41.9	30.6
10-weekly (%)	0.0	1.6	3.2
12-weekly (%)	0.0	12.9	11.3

(*Continued*)

Table 4 (Continued).

	Baseline (n=62)	After Loading (n=62)	Latest Follow-Up (n=62)
14-weekly (%)	0.0	0.0	1.6
16-weekly (%)	0.0	0.0	6.5
8-weekly (%)	0.0	56.5	53.2
Intravitreal dexamethasone injection	0	5 eyes (8.1%)	14 eyes (22.6%)
PRN (%)	0	4.8	3.2
Macular laser (%)	0	0	3.2
Death (%)	0	0	4.8

BRVA was 70.4 (±12.7) letters, with a gain of 2.8 letters, 95% CI [0.8, 4.7] letters from baseline (p=0.008, d=0.23). 11 eyes (17.7%) gained ≥10 letters. CST improved to 372.8 (±132.0) µm (95% CI [9.7, 81.0], p=0.002, d=0.28). At this point, 31 eyes (50%) had CST <325 µm, 4 eyes (6.5%) had no IRF at this visit compared to 0% at baseline. The treatment intervals prescribed from this visit were as follows: 13 eyes (21%) 4-weekly, 6 eyes (9.7%) 6-weekly, 26 (41.9%) 8-weekly, 1 eye (1.6%) 10-weekly, and 8 eyes (12.9%) 12-weekly. This equates to 56.5% being on treatment intervals of 8 weeks or more. The mean treatment interval was now 7.4 (±2.6) weeks, a gain from baseline of 0.8 weeks (p=0.030).

Latest Follow-up Outcomes

The mean follow-up was 57.1 (±19.7) weeks, receiving a mean of 7.92 (±2.53) faricimab injections from baseline. Forty-one eyes remained on the T&E pathway with faricimab; 14 switched to intravitreal dexamethasone implants; 2 patients (3 eyes) died, and one discontinued treatment (Table 4).

Outcome metrics were available for 42 eyes; at their latest follow-up, the BRVA was stable at 68.7 (±14.6) letters (p=0.572, d=0.08). Eight (12.9%) gained ≥10 letters. CST was 343.1 (±117.5) µm with a reduction from baseline of 56.5µm (95% CI [4.6, 108.3], p = 0.020, d=0.57). Two eyes (3.2%) had resolution of diabetic macular oedema. Thirty-nine eyes (62.9%) had a reduction in CST compared to baseline.

The treatment intervals recommended at the latest follow-up were based on CST reference values. These are as follows: 2 eyes (3.2%) 4-weekly, 6 eyes (9.7%) 6-weekly, 19 eyes (30.6%) 8-weekly, 2 eyes (3.2%) 10-weekly, 7 eyes (11.3%) 12-weekly, 1 eye (1.6%) 14-weekly, 4 eyes (6.5%) 16-weekly. The mean injection interval was 9.2 (±3.2) weeks, a gain of 2.4 weeks (95% CI[1.3,3.6], p < 0.001, d = 0.96). 53.2% of those on the T&E regime at the latest clinic visit were on a treatment interval of 8 weeks or more.

A total of 14 eyes (22.6%) had poor response to treatment, demonstrated by either no improvement or a significant increase in CST, and these were switched to intravitreal dexamethasone implant. Two eyes (3.2%) received adjunctive treatment with macular laser and were subsequently excluded from the analysis at this point.

Safety

A total of 491 faricimab injections were analysed. Two patients (3 eyes) died from pre-existing health conditions unrelated to their intravitreal treatment. Two eyes, accounting for 0.42% of our total injections, had a flare-up of pre-existing anterior uveitis and responded well to topical steroid treatment only. This is in line with landmark trials, and no other safety concerns were reported.[21]

Discussion

This study evaluated faricimab's effectiveness in treating DMO in patients who showed sub-optimal response to prior aflibercept 2mg therapy. Switching this cohort to faricimab allowed us to extend treatment intervals, enhance macular anatomy, and maintain stable vision outcomes.

The cohort's demographic profile and significant retinal disease aligns with DMO epidemiology. These challenging cases had a high treatment burden, averaging 17.3 aflibercept 2mg injections prior to the switch. A small subset remained poorly responsive and required intraocular steroid implants post-switch.

Real-world studies corroborate faricimab's benefits in similar challenging cohorts, summarised in Table 5.[22–29] Like ours, these studies demonstrate stable vision, anatomical improvements, and no new safety concerns following the switch. Visual acuity in our cohort was maintained throughout, with modest, non-significant improvements after the loading phase. Anatomical outcomes showed a statistically significant CST reduction, with 67.7% achieving CST reduction after loading, increasing to 84.8% at the latest visit.

Compared to YOSEMITE and RHINE trials, where 78–86% achieved <325 µm CST by 52 weeks in the PTI group, 50% of our cohort achieved this after the loading phase, and 45.2% maintained it at the most recent visit. Similarly, our findings align with real-world data from Rush et al, where 37.5% achieved a CST of <300 µm after four months. Given the complexity of our treatment-experienced cohort, these outcomes are highly encouraging.

A key finding in our study was the statistically significant extension of the injection interval to an average of 9.2 weeks at 12 months. This is particularly noteworthy and has significant real-world benefits given the significant psychological and economic burden that frequent injections impose on patients, their caregivers, and healthcare systems. These burdens, well-documented in the literature, can adversely impact adherence and overall quality of life.[30,31] In our study, the average injection interval increased by 2.4 weeks, with the proportion of patients needing injections every 8 weeks dropping from 56.5% to 30.6%. Notably, 53.2% of our cohort achieved intervals of 8 weeks or longer by 12 months, surpassing the 39.2% reported by Rush et al.[23] Comparable results were seen for 12-week intervals, and fewer patients required 4-week injections.

While Durrani et al demonstrated interval extension, their study lacked long-term follow-up and a defined loading protocol.[28] Reducing the injection burden significantly benefits patients and caregivers by easing logistical and financial pressures. For example, this approach could free up 2040 appointments and save £230,520 annually per 1000 patients in appointment costs alone, not accounting for additional savings from transportation or lost work hours.

The psychological relief of extended intervals and fewer treatments is invaluable. As these data reflect only the first year with mandatory loading doses, further improvements in the second year could enhance long-term outcomes and healthcare efficiency.

No new safety signals were identified across the 491 injections administered. Two unrelated deaths and two cases of anterior uveitis flare in a patient with a known history of the condition were reported. Importantly, no endophthalmitis, retinal vasculitis, or new intraocular inflammation were reported.

The variability in BRVA and CST outcomes highlights the need for predictive biomarkers to better determine which patients are likely to respond favourably to faricimab. Given the real-world nature of our study, there were certain limitations, including our cohort's predominantly white demographic, which limits the generalisability of these findings to other ethnic groups. CST recordings were not completed at a fixed, pre-determined time, which, with the diurnal variation on fluid accumulation in DMO, may contribute to variation in the recorded CST.[32] Additionally, the retrospective nature of this study imposes inherent limitations.

Our cohort size was relatively small due to our deliberate inclusion of only patients with complete datasets, ensuring data integrity despite reducing overall numbers. Notably, this is the first study to clearly delineate and implement a defined T&E pathway for faricimab administration. Despite these constraints, we maintained methodological rigor by implementing strict control measures for confounding factors through comprehensive inclusion and exclusion criteria. We further enhanced study validity by excluding patients who deviated from protocol requirements. HbA1c levels remained consistently elevated at both baseline and final visits, which may contribute to the challenges in managing diabetic macular oedema in this cohort. Future prospective, longitudinal real-world studies will provide more comprehensive insights into effective management strategies for this challenging patient population.

Table 5 Summary Table of Current Literature on the Use of Faricimab in DMO

	Eyes	Patients	Follow-Up (Months)	Number of Injections	VA Change (ETDRS letters)	CST Change (μm)	Treatment Interval Post-Loading (weeks)	Were Eyes Reloaded after Switching to Faricimab?	Criteria for Switching to Faricimab
Rush 2022.[24]	24	24	4	3	5.0	−59.6	Not reported	Yes. Treatment was given monthly until DMO resolved then extended by 1–2 week.	- ≥6 aflibercept injections in the past 12 months, ≥4 in the past 6 months, - central macular thickness ≥300 μm
Rush 2023.[23]	52	51	12	>6	6.5	−59.6	39.2% reached >8 weeks after loading	Yes	- ≥8 aflibercept injections in the past 12 months, ≥4 in the past 6 months - CMT ≥320 μm - macular oedema on OCT
Bailey 2023.[22]	225	Not reported	4	3.5	1.1	Not reported	Last mean treatment interval 7.2 weeks	Unknown	- ≥ 1 faricimab injection after June 2022. The study included both treatment naive and treatment experienced eyes.
Pichi 2024.[25]	100	100	6	2.9	5.0	−67.9	N/A	No	- Clinically significant, centre-involving DMO (per ETDRS guidelines) - Best-corrected visual acuity (BCVA) between 20/200 and 20/20 - Central subfield thickness (CST) ≥300 μm - At least 3 prior intravitreal aflibercept injections. Included treatment experienced eyes only
Quah 2024.[26]	72 DMO eyes	58	2.5	4.7	2.5	−104	N/A	Yes	At least one dose of faricimab 6mg for DMO or nAMD with at least 4 weeks follow up.
Tatsumi 2024.[27]	29	21	N/A	4	−3.3	−53	N/A	No	Patients with DMO previously treated with intravitreal aflibercept with persistent or recurrent macular oedema and the following: - CRT ≥370 μm after ≥4 IVA injections - CRT initially <350 μm after ≥8 IVA injections, but rebounded to >400 μm or worsened by >100 μm within 12 weeks
Durrani 2024.[28]	69	53	N/A	3	−1.0	−57	25 eyes were able to be extended by 2 or more weeks	No	Inadequate response to at least three prior injections of bevacizumab, ranibizumab, or aflibercept before switching to faricimab, with persistent DMO observed on clinical examination and/or SD-OCT
Borchet 2024.[29]	44 DMO eyes	28	6	5	1.0	−38	Last treatment interval 6.6 weeks (1.4-week difference from baseline)	78% of DMO eyes were reloaded, at clinician's discretion	Partial response to prior anti-VEGF therapy, defined as some improvement on OCT but with persistent fluid in DMO despite 4–6 weekly anti-VEGF injections
Present study, El-Badawi 2024	62	50	13	7.9	1.1	−56.5	The last treatment interval 9.2 weeks, a gain of 2.4 weeks from baseline	Yes	Previously treated with > 6 Aflibercept injections at 4 weekly intervals with CST ≥ 325 μm after loading, Or an increase of >20% from best CST despite ≤ 8 weekly injections.

Abbreviations: Ang-2, angiopoietin-2; Anti-VEGF, anti-vascular endothelial growth factor; BRVA, best recorded visual acuity; BCVA- Best Corrected Visual Acuity; CST, central subfield thickness; CMT, Central Macular Thickness; CRT Central Retinal Thickness; DM, diabetes mellitus; DMO, diabetic macular oedema; nAMD, neovascular Age-Related Macular Degeneration: DR, diabetic retinopathy; ETDRS, early treatment diabetic retinopathy study; SD-OCT, Spectral Domain Optical Coherence Tomography; OCT, optical coherence tomography.a; VA, visual acuity; CST, central subfield thickness; IVA, intravitreal injections of aflibercept.

Conclusion

This study demonstrated that in DMO cases with sub-optimal response to aflibercept 2mg, switching to faricimab can maintain visual acuity, whilst improving anatomical outcomes, and extend injection intervals. These benefits, combined with absence of new safety concerns in our cohort, not only enhance patient outcomes but also reduce the treatment burden. This approach allows for better alignment with patient needs while improving efficiency and lowering healthcare costs.

Ethical Statement

This study was completed in accordance with the ethical standards of the Helsinki Declaration of 1964 (as revised in 2024) and was approved by a local audit committee at University Hospitals Bristol and Weston (reference MEDRET/CA/2023-24/03). As this was a retrospective review of anonymised medical records, the requirement for individual patient consent was waived per institutional and national guidelines for anonymised observational studies.

Acknowledgments

We extend our heartfelt gratitude to the patients and their families for their participation and trust and to the clinical and administrative staff at the Bristol Eye Hospital for their invaluable support in patient care and data collection.

Special thanks go to Miss Salvatore and Dr. Kobayter for their efforts in developing and implementing the treatment protocol, which was instrumental in achieving this study's outcomes. We are also grateful to Mr Eke for his valuable assistance with the writing and preparation of this manuscript.

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Funding

Roche Products Ltd. supported with funding for the article submission charges by a hands-off grant. Roche Products Ltd did not have any involvement in the preparation, drafting, or editing of this manuscript or in the choice of authors.

Disclosure

Benjamin Scrivens reports educational grant from Roche, outside the submitted work. Oluwaniyi Eke reports travel bursary from and advisory board for Bayer; speaker fees from Roche and Alimera Sciences. Serena Salvatore reports advisory board for Bayer, Roche; speaker fees and travel bursary from Alimera Sciences, Roche Products Limited, and Bayer. Lina Kobayter reports advisory board for and travel bursary from Roche Products Limited; speaker fees from Bayer, Alimera Sciences and Roche Products Limited. The authors report no other conflicts of interest in this work.

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