Clinical Outcomes Using Treat and Extend Ranibizumab Regimen for Neovascular Age-Related Macular Degeneration: Real-World Data from the TERRA Study

S. Abugreen,[1] R. Asaria,[2] S. Banerjee,[3] R. Chhabra,[4] H. Mehta,[2] B. Mushtaq,[5] N. Narendran,[6] P. Prakash,[7] A. Vardarinos,[8] Y. Yang,[6] S. Younis[9]

[1]Royal Blackburn Hospital, East Lancashire Hospitals NHS Trust, Blackburn, UK; [2]Royal Free NHS Foundation Trust, London, UK; [3]University Hospital of Wales, Cardiff, UK; [4]Manchester NHS Foundation Trust, Manchester, UK; [5]City Hospital, Eye Hospital – BMEC, Birmingham, UK; [6]Wolverhampton and Midland Counties Eye Infirmary, New Cross Hospital, Wolverhampton, UK; [7]The Princess Alexandra Hospital NHS Trust, Harlow, Essex, UK; [8]West Suffolk NHS Foundation Trust, Bury St Edmunds, UK; [9]Western Eye Hospital, London, UK

OBJECTIVE

- To provide a two-year prospective evaluation of the clinical effectiveness, treatment patterns and safety of ranibizumab in two cohorts of patients with neovascular age-related macular degeneration (nAMD) in UK routine clinical practice.

BACKGROUND

- nAMD progression is associated with a loss of visual acuity (VA) which can significantly impact patients' quality of life and lead to blindness.[1]
- Ranibizumab is a vascular endothelial growth factor-A inhibitor (anti-VEGF) approved for the treatment of nAMD.[2]
- In 2014, the approval of ranibizumab was extended to include a novel treat and extend (T&E) regimen:[2]
  - T&E refers to the individual adjustment of injection intervals based on the response to the preceding injection.

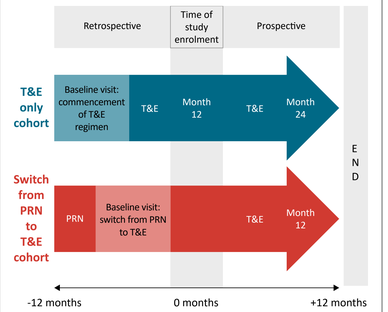
METHODS

- TERRA was an observational, non-comparative, real world study conducted in outpatient ophthalmology practices in the UK.
- Eligible patients were aged ≥50 years with active choroidal neovascularisation secondary to AMD at the time of diagnosis and scheduled for treatment with ranibizumab in accordance with T&E.
- Patients were also required to have ≥1 year of retrospective medical records documenting ranibizumab pro re nata (PRN) or T&E treatment prior to enrolment.
- Two distinct nAMD patient cohorts were enrolled **(Figure 1)**:
  1. **T&E only cohort**: Patients newly initiating ranibizumab on the T&E regimen as their first anti-VEGF therapy.
  2. **Switch from PRN to T&E cohort**: Patients switching from PRN to T&E regimen (anti-VEGF non-naive).
- Retrospective clinical assessments were collected from medical records (31 August 2016 – 28 June 2018).
- Co-primary objectives reported for the full analysis set (FAS) included:
  - **T&E only cohort**: Change in VA (number of Early Treatment Diabetic Retinopathy Study [ETDRS] letters) from baseline (defined as the commencement of T&E) to Month 12 and Month 24.
  - **Switch from PRN to T&E cohort**: Change in VA from baseline to Month 12.
- Key secondary objectives included:
  - Number of injections received per patient over 12 months (T&E only cohort and switch from PRN to T&E cohort) and 24 months (T&E only cohort) of the T&E regimen for the FAS.
  - Number of clinic visits over 12 months (T&E only cohort and switch from PRN to T&E cohort) and 24 months (T&E only cohort) of the T&E regimen for the FAS.
  - Adverse events (AEs) for the safety set.
    - All AEs suspected to be related to the eye were reported by system organ class (SOC) and preferred term (PT).
    - The most commonly reported serious AEs (SAEs) by SOC (>2% of patients) and by PT (>1% of patients) were reported.

Statistical Analyses

- Mean VA at baseline is reported.
- Mean changes in VA from baseline (95% confidence intervals) are reported.
- Mean (SD) number of injections and clinic visits per patient are reported.

Figure 1. Study design



In the T&E only cohort, the baseline visit was defined as the initiation date (and first ranibizumab injection) on the T&E regimen; at least 12 months of treatment on the T&E regimen was required for the T&E only cohort prior to study enrolment. In the Switch from PRN to T&E cohort, the baseline visit was defined as the date of switch from the PRN to the T&E regimen (i.e., the date of the first ranibizumab injection under the T&E regimen) after at least 12 months of treatment on the PRN regimen. PRN: pro re nata; T&E: treat and extend.

RESULTS

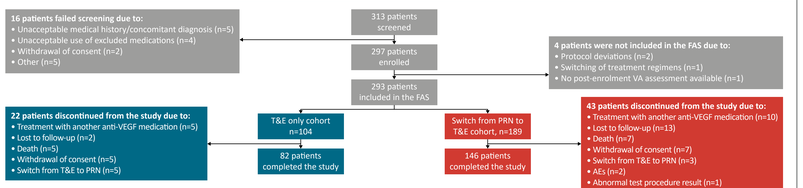
Patient Disposition

- 293 patients were included in the FAS: 104 patients in the T&E only cohort and 189 patients in the Switch from PRN to T&E cohort **(Figure 2)**.

Patient Demographics

- The mean age of patients in the study was 80.9 years **(Table 1)**.
- At baseline, 257/293 patients (87.7%) had active nAMD in their study eye.

Figure 2. Patient disposition



AE: adverse event; FAS: Full Analysis Set; PRN: pro re nata; T&E: treat and extend; VA: visual acuity; VEGF: vascular endothelial growth factor.

Table 1. Patient demographics

Variable	T&E only cohort (n=104)	Switch from PRN to T&E cohort (n=189)	All patients (N=293)
Age (years), mean (SD)	79.4 (7.5)	81.7 (7.6)	80.9 (7.7)
Female, n (%)	64 (61.5)	122 (64.6)	186 (63.5)
Race, n (%)			
Caucasian	102 (98.1)	184 (97.4)	286 (97.6)
Black	0 (0.0)	1 (0.5)	1 (0.3)
Asian	1 (1.0)	4 (2.1)	5 (1.7)
Other	1 (1.0)	0 (0.0)	1 (0.3)
Baseline VA (number of letters), mean (SD)	55.8 (15.4) *n=97*	58.0 (18.1) *n=153*	N/A
Baseline CSRT (µm), mean (SD)	338.0 (84.7) *n=83*	249.4 (66.7) *n=122*	N/A
Baseline nAMD in study eye, n (%)	104 (100)	189 (100)	293 (100)

CSRT: central subfield retinal thickness; N/A: not applicable; nAMD: neovascular age-related macular degeneration; PRN: pro re nata; SD: standard deviation; T&E: treat and extend; VA: visual acuity.

Change in Mean Visual Acuity

- Patients in the T&E only cohort demonstrated substantial increases from baseline in mean VA **(Figure 3)**.
- No changes in mean VA from baseline were observed at Month 12 in patients in the Switch from PRN to T&E cohort.

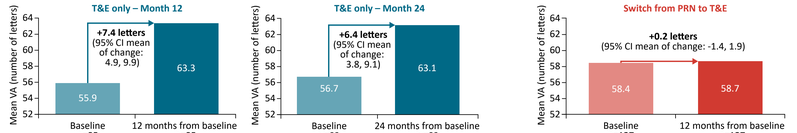
Mean Number of Injections

- Patients in the T&E only cohort received a mean (SD) of 8.3 (1.8) and 14.2 (3.6) injections over 12 and 24 months, respectively **(Figure 4)**.
- Patients in the Switch from PRN to T&E cohort received 6.3 (2.9) injections over 12 months.

Mean Number of Clinic Visits

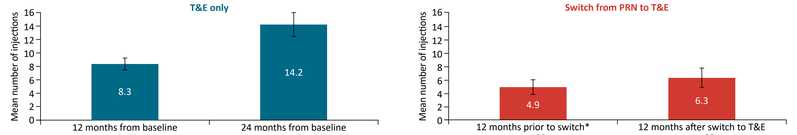
- Mean (SD) clinic visits for patients in the T&E only cohort were 8.5 (1.8) at 12 months from baseline and 14.4 (3.6) at 24 months from baseline **(Figure 5)**.
- Mean (SD) clinic visits for patients in the Switch from PRN to T&E cohort were 7.3 (3.3) prior to switching and 6.3 (2.9) 12 months after switching.

Figure 3. Mean change in VA in patients in the T&E only and Switch from PRN to T&E cohorts



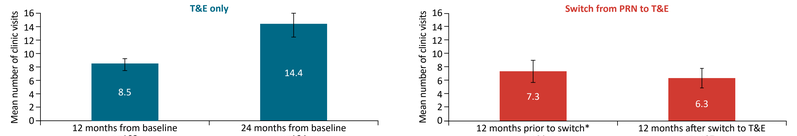
For post-baseline visit, i.e 12/24 months from baseline for T&E only cohort and 12 months after switch for Switch from PRN to T&E cohort, only patients with a valid baseline and post-baseline measurement were included. Numbers may not sum owing to rounding. VA was not recorded in the PRN cohort at 24 months after switch as this cohort was only assessed for 12 months following the switch to T&E. Arrows indicate the mean change in VA. CI: confidence interval; PRN: pro re nata; T&E: treat and extend; VA: visual acuity.

Figure 4. Mean number of injections per patient in the T&E only and Switch from PRN to T&E cohorts



*Injection status for PRN cohort for 12 months before switching to T&E regimen. Number of injections was not recorded in the Switch from PRN to T&E cohort over 24 months as this cohort was only assessed for 12 months following the switch to T&E. Error bars represent SD. PRN: pro re nata; SD: standard deviation; T&E: treat and extend.

Figure 5. Mean number of clinic visits per patient in the T&E only and Switch from PRN to T&E cohorts



*Clinic visit status for PRN cohort for 12 months before switching to T&E regimen. Number of clinic visits was not recorded in the Switch from PRN to T&E cohort over 24 months as this cohort was only assessed for 12 months following the switch to T&E. Error bars represent SD. PRN: pro re nata; SD: standard deviation; T&E: treat and extend.

Safety

- Duration of follow-up was 731 days for the T&E only cohort and 365 days for the Switch from PRN to T&E cohort.
- 129 patients reported ≥1 AE. AEs suspected to be related to the eye (n=10) are shown in **Table 2**.
  - Conjunctival haemorrhage and endophthalmitis were each reported by two patients.
- The most commonly reported SAEs by PT (>1% of patients) were fall (n=8), death (n=7) and pneumonia (n=4).
- Overall, 12 deaths were reported during the study.
  - These deaths were not considered related to the study treatment.

Table 2. Overall safety

n	Ranibizumab (N=293)
Patients with ≥1 AE	129
Mild AEs	52
Moderate AEs	42
Severe AEs	35
Patients with ≥1 AE suspected to be related to the eye	10
SOC	
PT	
Eye disorders	6
Blepharitis	1
Blepharospasm	1
Conjunctival haemorrhage	2
Dry eye	1
Episcleritis	1
Eye pain	1
Meibomian gland dysfunction	1
Infections and infestations	2
Endophthalmitis	2
Injury, poisoning and procedural complications	1
Corneal abrasion	1
Investigations	1
Intraocular pressure increased	1
Skin and subcutaneous tissue disorders	1
Skin irritation	1
Patients with ≥1 SAE[a]	43
Discontinuations due to AE(s)	10
Discontinuations due to SAE(s)	10
Discontinuations due to non-SAE(s)	0
Deaths[b]	12

[a]The most commonly reported SAEs by SOC (>2% of patients) were infections and infestations (n=44), injury, poisoning and procedural complications (n=10), general disorders and administration site conditions (n=8). The most commonly reported SAEs by PT (>1% of patients) were fall (n=8), death (n=7) and pneumonia (n=4). [b]Death refers to the number of patients who died between the first treatment and within 30 days of the last treatment. As the total number of injections was not reported in the study, the percentage as the incidence of endophthalmitis/number of injections is not reported. AEs were reported for the safety set, which included all enrolled patients who received ≥1 dose of ranibizumab and had ≥1 post-treatment safety assessment. A patient with multiple AEs was counted only once in the "≥1 AE" row. A patient with multiple AEs within a SOC was counted only once in that SOC total row. A patient with multiple AEs with the same PT was counted only once for that preferred term total row. All AEs starting on or after the time of first administration of study drug, but not later than 7 days (30 days in case of an SAE) after the last administration, were included. AE: adverse event; PT: preferred term; SAE: serious adverse event; SOC: system organ class.

CONCLUSIONS

- Clinically meaningful increases in VA were observed in the T&E only cohort.
- Patients in the Switch from PRN to T&E cohort maintained the VA gains that they achieved prior to switching to T&E.
- The safety profile of ranibizumab was consistent with previous studies.[3-6]
- Ranibizumab T&E may be a practical, effective and tolerable treatment regimen for nAMD patients in the real-world NHS setting.

References

1. Yang Y, *et al.* Ophthalmol Ther 2017;6:175–186; **2**. EMA. Lucentis 10 mg/ml solution for injection SmPC. https://www.ema.europa.eu/en/documents/product-information/lucentis-epar-product-information_en.pdf. Accessed April 2021; **3**. Massin P, *et al.* Diabetes Care 2010;33:2399–405; **4**. Mitchell P, *et al.* Ophthalmology 2011;118:615–25; **5**. Silva R, *et al.* Ophthalmology 2013;120:130–9; **6**. Silva R, *et al.* Ophthalmology 2018;125:57–65.

Author Contributions

Substantial contributions to study conception/design, or acquisition/analysis/interpretation of data: SA, RA, SB, RC, HM, BM, NN, PP, AV, YY, SY; Drafting of the publication, or revising it critically for important intellectual content: SA, RA, SB, RC, HM, BM, NN, PP, AV, YY, SY; Final approval of the publication: SA, RA, SB, RC, HM, BM, NN, PP, AV, YY, SY.

Disclosures

SA: None; RA: None; SB: Honoraria from Allergan; RC: Honoraria for advisory boards, travel grants, consultancy and speaker engagements with Novartis, AbbVie and Bayer; HM: Honoraria from Novartis, Bayer, Roche and Allergan; BM: Consultant on Advisory board and travel grants from Novartis, Bayer and Alimera; NN: Honoraria, speaker fees and travel grants for Bayer and Novartis; PP: Presenting in the Novartis DMO Webinar in the College Congress, previously attended conferences with Bayer and Novartis; AV: Speaker fees, consultancy fees, research support, hospitality and support to attend congresses from Novartis UK. Consultancy fees, hospitality and support to attend congresses from Bayer UK; YY: Speaker fees and honoraria from Novartis, Bayer, Roche and Allergan; SY: None.

Acknowledgements

This study was funded by Novartis Pharmaceuticals UK Ltd. We thank the patients and their caregivers in addition to the investigators and their teams who contributed to this study. The authors acknowledge Ahmad Mahmoud, Novartis Pharmaceuticals UK, for publication coordination, Sophie Engler, MSc and Sarah Jayne Clements, PhD for medical writing and editorial assistance, and Mark Tassell, BA for graphic design assistance, Costello Medical, Cambridge, UK. All costs associated with development of this poster were funded by Novartis Pharmaceuticals UK.

NOVARTIS

Presented at the Royal College of Ophthalmologists Congress 2021 | 24–27 May 2021