London and South East Regional Medicines Information

Evidence behind change in treatment regimen recommendations and monitoring for ranibizumab and data on use in clinical practice for age related macular degeneration

Review prepared for South West London Medicines Commissioning Group
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Summary

The SPC for ranibizumab was updated in Sep 2014 removing the requirement for monthly monitoring and advising that following the initial induction, subsequent monitoring and treatment intervals should be determined by the physician. A new treat and extend regimen (TER) was also been introduced – this involves stepwise extension of monitoring and treatment intervals by 2 weeks at a time, provided that there are no signs of disease activity. Novartis supplied a number of studies in support of the recent licensing change but the specific evidence upon which the removal of the monthly monitoring requirement was based remains unclear, but seems to be extrapolated from data on the use of other ranibizumab regimens, for example the Treat-and-Extend Regimen (TER), where extension of the monitoring frequency may be possible. Interestingly, the main studies supporting the initial marketing authorisation for ranibizumab for AMD evaluated monthly dosing and not PRN. The PRN regimen, with monthly monitoring (which appeared in the original SPC) was approved based on a model submitted to the EMA and not on clinical data. Although it was assumed that PRN dosing, with an average of 8 doses in the first year and six in the second year (as discussed in the NICE TA) would be associated with similar outcomes to monthly dosing (as seen in MARINA and ANCHOR studies), it is unclear if this is the case and NICE raised this uncertainty in its guidance.

Although the TER studies suggest a reduction in average number of visits (to about 8 in the first year versus 12 if the previous SPC was rigidly adhered to), with the same number of injections (assuming that in practice there are an average of 8 in the first year, as assumed in the NICE TA), they were single-arm and non-comparative. It is therefore not known how the visual outcomes and number of injections given compare to those seen with PRN dosing. A press release from Novartis announcing the license change cited the single-arm SUSTAIN study of PRN dosing – although the mean number of injections was 5.6 in the first year, all patients were monitored on a monthly basis.

Real-world data for the use of ranibizumab in treating AMD in the UK suggest that the visual outcomes achieved in the pivotal studies are not translated into clinical practice. A large UK study reported that there is less visual acuity (VA) gain, vision tails off after the peak gain, and there is a lower proportion of patients gaining 15 letters of vision or maintaining vision of 20/40 or better. It is likely that the visual outcomes achieved in this real-world cohort are worse than those achieved in RCTs because of capacity constraints preventing intended monthly review at some centres, reduced treatment frequency, and broader inclusion criteria (i.e., a different case mix) in the real world compared with clinical trials. The researchers suggest that to achieve the best outcomes with ranibizumab, more frequent monitoring and injections are required which is reflected in similar 'real world' studies. No equivalent UK data on usage patterns of aflibercept in UK clinical practice were identified.

In the pivotal studies of aflibercept, ranibizumab (monthly for 1 year then PRN) and aflibercept were found to be equally effective in improving BCVA and preventing BCVA loss at 96 weeks. The licensed dose of aflibercept was similar to ranibizumab in VA outcomes during 96 weeks but with an average of 5 fewer injections. There are no published data directly comparing outcomes with the new treatment and monitoring schedule for ranibizumab and the current aflibercept schedule. Further research is needed on the impact of alternative treatment schedules on the trade-off between treatment burden and visual outcomes.

Background:
The original SPC for ranibizumab advised the following in terms of dose frequency and monitoring when used in the treatment of wet AMD (section 4.2)[1]:

> *The recommended dose for Lucentis is 0.5 mg given **monthly** as a single intravitreal injection. Treatment is given **monthly** and **continued until maximum visual acuity is achieved** i.e. the patient`s visual acuity is stable for three consecutive monthly assessments performed while on ranibizumab treatment.*
> ***Thereafter patients should be monitored monthly for visual acuity.***
> *Treatment is resumed when monitoring indicates loss of visual acuity due to wet AMD. **Monthly** injections should then be administered until stable visual acuity is reached again for three consecutive monthly assessments (implying a minimum of two injections). The interval between two doses should not be shorter than one month"*

This section was recently updated (September 2014). The updated version is less specific in terms of treatment and monitoring frequency (including removal of the specific recommendation to monitor visual acuity monthly). In addition a new treatment schedule referred to as 'treat-and-extend' (TER) has been introduced:[2]:

> *Treatment is initiated with **one injection per month** until maximum visual acuity is achieved and/or there are no signs of disease activity i.e. no change in visual acuity and in other signs and symptoms of the disease under continued treatment. **In patients with wet AMD, DME and RVO, initially, three or more consecutive, monthly injections may be needed.***
> *Thereafter, **monitoring and treatment intervals should be determined by the physician** and should be based on disease activity, as assessed by visual acuity and/or anatomical parameters……..*
> *…….If patients are being treated according to **a treat-and-extend regimen**, once maximum visual acuity is achieved and/or there are no signs of disease activity, the **treatment intervals can be extended stepwise** until signs of disease activity or visual impairment recur. **The treatment interval should be extended by no more than two weeks at a time for wet AMD**"*

In comparison, aflibercept (Eylea) is initiated with one 2mg injection per month for three consecutive doses, followed by one injection every two months. There is no requirement for monitoring between injections. After the first 12 months of treatment with Eylea, the treatment interval may be extended based on visual and anatomic outcomes. In this case the schedule for monitoring should be determined by the treating physician and may be more frequent than the schedule of injections[3].

What was the evidence to support the INITIAL dosing/monitoring frequency?

The main studies supporting the licensing of ranibizumab for the treatment of wet AMD (MARINA and ANCHOR) evaluated the safety and efficacy of monthly treatment with ranibizumab, rather than an initial monthly loading period followed by monthly monitoring and retreatment when required (as advised in the initial SPC). The NICE guidance on ranibizumab for wAMD acknowledges this difference between the (original) licensed dosing regimen and that used in the main RCTs, and states that the rationale for this was based on evidence from a drug and disease model submitted by the manufacturer indicating that its beneficial effects peak after three

injections at 3 months, after which a plateau of effect is reached, and that continued monthly injections may not be necessary in all patients to maintain this benefit. This drug dosing model was accepted by the EMA as a basis for the initial regimen in the marketing authorisation; this model assumed that the individualised dosing would result in stable visual acuity for the majority of patients, with a mean of 8 injections required in the first year and a mean of 6 injections in the second year. Clinical specialists and consultees (including the Royal College of Ophthalmologists) noted that this would likely be frequently borne out in practice. The Appraisal Committee however remained concerned about the assumption that the benefit achieved in the pivotal trials could be matched if injections were less frequent (a small study suggesting similar outcomes with fewer injections had been submitted but it was of a low quality)[4].

On what basis was the change in licensing granted?

There is a large amount of published literature discussing the use of various dosing/monitoring schedules of ranibizumab in an attempt to reduce treatment burden and cost. There appears however to be a lack of good quality comparative evidence to allow determination of the most effective regimen in terms of maintaining the improvements in visual acuity seen in the ANCHOR and MARINA trials (monthly dosing) whilst optimising the frequency of follow-up +/- reducing the number of injections.

Data supplied by Novartis in support of licensing change are summarised in Appendix 1. This includes evidence for TER and also studies that have reported on a variety of other dosing and monitoring regimens:

Quarterly maintenance dosing regimen

The PIER 1[5] study, which was one of the studies used to support the original marketing authorisation, compared quarterly maintenance injections of 0.3mg and 0.5mg ranibizumab (following 3 initial monthly loading doses) to a sham. Both ranibizumab groups had >10 letter gain in BCVA vs. the sham group after the three initial monthly doses, but this gain was lost during maintenance dosing. Although it prevented significant vision loss, the results were inferior to the results obtained from MARINA[6] and ANCHOR[7] (the trials used for the original marketing authorisation) in which patients had monthly injections. The EXCITE[8] trial directly compared monthly vs. quarterly maintenance dosing, following an initial loading of 3 monthly injections, and this failed to demonstrate non-inferiority of quarterly vs. monthly dosing. Although this regimen did decrease the injection load, it did little to lower the outpatient visit burden (as monthly assessment was performed in all patients, regardless of treatment assignment)**.** Neither of these studies supports use of a quarterly maintenance dosing regimen and therefore data on associated frequency of monitoring visits are not relevant (both included monthly monitoring anyway and so would not support any move away from this).

PRN dosing regimen

This regimen (initial loading phase then PRN) was assessed in the SUSTAIN[9] and HARBOUR studies. HARBOUR[10], the largest and most robust trial, did not meet its primary endpoint of demonstrating non-inferiority of PRN dosing to monthly dosing. However, the gains in VA were similar and the number of injections needed by the PRN group was almost half that of the monthly group over the 2 years. The PRN regimen did not decrease the number of monitoring visits (as this was completed

monthly in all patients), and it relies on disease recurrence as an indicator for treatment. Novartis has referred to the SUSTAIN study in a press release announcing the license change, citing that 20% of patients require only three ranibizumab injections in first year of treatment.[11]

Two monthly regimen

This study was useful in that it replicated the current licensed regimen for aflibercept[12] - after the initial 3-month loading period, the monitoring and dosing interval was extended to every 2 months. This showed favourable results for less frequent treatment but the study design was weak (small; retrospective, non-comparative case series) and it allowed for monthly dosing where necessary. For this reason it also required monthly monitoring but as patients received treatment every 8 weeks, disease recurrence was not criteria for retreatment.

Observe-and-plan treatment regimen

This regimen involved initial 3-monthly doses, with monitoring frequency and subsequent re-treatment depending on response[13]. This showed favourable outcomes for BCVA, number of injections required and number of monitoring visits. The mean number of visits required in the first 12 months was 7, and the authors note that a mean of just below 4 visits required detailed ophthalmological examinations, which should help to reduce the treatment burden. However this was a single arm, single centre trial, providing only limited evidence to support this particular treatment regimen.

Treat-and-Extend Regimens (TERs)

Two studies evaluating these regimens [(14-15)] showed favourable BCVA results at months 12 and 24 that were comparable to those seen in ANCHOR and MARINA. The regimen is designed so that each patient receives an injection at each monitoring visit, which eliminates disease recurrence as criteria for retreatment, and the period between visits can be gradually extended by 2 weeks at a time, if visual acuity outcomes are stable/improved. The studies by Toalster[12] *et al* and Abedi[13] *et al* showed that TERs may be associated with significant BCVA improvements with a similar number of injections as with PRN treatment (according to the NICE TA), but with only around 8 visits in the first year. This is in comparison to 24 injections and visits over 2 years for ANCHOR and MARINA. The studies were however non-comparative.

**Please note the SPC does not stipulate a maximum extend interval but the trials mentioned above used 12 weeks as there are no safety data beyond this.*

Flexible dosing and treatment regimen

Patients were treated with 3-monthly doses initially, and subsequent follow-up visits were progressively spread out to a maximum of every 8 weeks in the absence of disease activity and visual acuity loss[16]. This differs from TER as treatment was not given at each visit if not indicated. Although the BCVA results were positive and were comparable to other studies where monthly monitoring has been carried out (whereas this study had an average of 8 visits in 12 months), the authors note the gradual deterioration of visual acuity after the loading dose, as seen in other PRN studies.

How is ranibizumab used in practice (number of injections and frequency of monitoring) and are there outcome data for use of regimen with reduced dosing

frequency?

The findings of three studies which look at the use of ranibizumab in practice are summarised in appendix 2.

Tufail *et al* [17]
The largest dataset on treatment burden and outcomes of ranibizumab therapy was recently published. The study aimed to define benchmark standards of care for treatment-naïve eyes treated with ranibizumab for nAMD at a large number of UK centres using a loading phase of 3 monthly injections followed by a PRN re-treatment regimen. This found that:

- VA outcomes achieved in the pivotal trials, (ANCHOR and MARINA) are not translated into clinical practice in the UK. This may be explained by the much lower treatment frequency than in the pivotal studies, in the CATT PRN arm, or in the NICE drug and disease model estimate.

- Dichotomous VA outcomes showed a lower proportion of patients gaining 15 letters of vision compared with baseline (17.4% at year 1 and 18% at year 2) than in the ANCHOR, MARINA, and CATT continuous arms by approximately 10% at week 52. Of note, the CATT PRN arm had a 25% rate of 15-letter gainers at 1 year, which increased to 30.7% at the 2-year time point. The difference may be explained by either a lower frequency of follow-up, fewer treatments, prolonged duration of symptoms, or inclusion of eyes with very good baseline VA.

- Other reasons for poor translation of clinical trial outcomes into clinical practice may be differences in patient population, which would affect the capacity for visual gain.

Unlike the pivotal trials and CATT PRN arm, there is less VA gain, vision tails off after the peak gain, and there is a lower proportion of patients gaining 15 letters of vision or maintaining vision of 20/40 or better. This represents what is currently being achieved in real life and acts as a real-life outcomes benchmark with which to compare local outcomes. These benefits, however, are obtained with fewer injections and fewer visits than the pivotal studies or in the CATT trial. It is noted that these results are similar to those in outcome studies with most of the published treat-and-extend re-treatment approaches. It is likely that the visual outcomes achieved in this real-world cohort are worse than those achieved in RCTs because of capacity constraints preventing intended monthly review at some centres, reduced treatment frequency, and broader inclusion criteria (i.e., a different case mix) in the real world compared with clinical trials. The researchers note that real-life delivery of therapy is problematic, with patients having intercurrent illness limiting follow-up, becoming lost to follow-up (death or moving to another area), or having difficulty achieving regular follow-up because of transportation or hospital capacity issues. They suggest that to achieve the best outcomes with ranibizumab, more frequent monitoring and injections are required which is reflected in similar 'real world' studies that show increased visits and injections maximise the visual gains from ranibizumab treatment though lower frequency regimens reduced the patient/ clinician burden, the outcome was only visual stability as oppose to visual gain[15]

Chvan et al[18]

A representative cohort of British patients 3 years after commencing ranibizumab therapy, for AMD under the current European licensing and according to NICE was assessed, taking into account the impact of incomplete follow-up on estimates of VA outcomes It noted that over the course of 3 years, this cohort made a total of 3,188 visits and received 1,365 injections. From data on service provision, the researchers deduced that for a population of 1 million, approximately 2,446 injections would be required in a 3-year period. However, if fixed monthly injections were given, 7,282 injections would be required over a 3-year period for the new cases arising each year from a population of 1 million. The treatment benefit for this cohort of patients after 3 years was visual stability. The visual outcomes after 3 years were broadly considered comparable to those described in other "real-world" outcomes studies from the UK and other countries.[16]

Holz et al[19]

AURA[iv], an international, retrospective study, assessed management of patients with wAMD receiving anti-VEGF treatment in clinical practice between 2009 and 2011. It found that the number of visits, injections and visual acuity outcomes differed substantially between countries. In clinical practice, fewer injections are administered than in clinical trials and anti-VEGF treatment resulted in an initial improvement in visual acuity; however, this was not maintained over time. In all countries, the mean number of visits was lower in the second year than the first year. Patients in the UK had the highest number of visits (18.4 in the full 2 years). The number of anti-VEGF injections received differed between countries. Of the countries enrolling more than 400 patients, patients in the UK and the Netherlands had the highest number of injections. More visits and injections appeared to be correlated with more successful maintenance of visual acuity gains. The researchers call for further research into treatment schedules and alternative therapies to asses the trade-off between treatment burden and visual outcomes.[17]

Ongoing study

Long-term observational data on ranibizumab are continuing to be collected as part of the five-year LUMINOUS trial, in which currently more than 26,000 patients with AMD have been enrolled, with over 10,000 patients recruited in the UK.[11o]

How does this compare to aflibercept usage.

No published data on the use of aflibercept in practice in the UK were identified. Two studies from the US have analysed treatment patterns of use with ranibizumab and aflibercept for AMD and expenditure. Ferreria[20] *et al* found that the mean number of anti-VEGF injections for patients starting treatment were similar: 5.6 ranibizumab (n= 2799) and 5.4 aflibercept (n= 117). For patients on treatment for over 12 months the mean number of injections was again similar: 4.9 ranibizumab (n= 1,898) and 5.2 aflibercept (n= 87). This study did not evaluate visual outcomes. These limited data suggest that in routine US clinical practice, patients receive a comparable number of injections of ranibizumab to aflibercept.

Johnson[21] *et al* report a retrospective anaylsis of first line anti-VEGF treatment patterns in the US in patients with wAMD, but with a focus only on expenditure of ranibizumab and aflibercept. Neither the 6 month (n= 319 aflibercept, n= 1,054 ranibizumab) nor the 12 month analyses (n= 57 aflibercept, n= 374 ranibizumab) showed significant differences between the number of injections used (at 6 months: aflibercept mean = 3.8, ranibizumab = 3.9). There was no evaluation of visual

outcomes.

Visual acuity data from pivotal studies of aflibercept (View 1 and View 2)

The pivotal phase 3 studies of aflibercept in wet-AMD (VIEW 1; n=1217 and VIEW 2; n=1240) were large multi-centre non-inferiority studies of similar design conducted over 96 weeks. Both studies compared aflibercept with monthly ranibizumab in patients with wet AMD over 1 year. Further follow-up was conducted up to 96 weeks in patients receiving PRN dosing from week 52. In both studies patients were randomised to one of four groups: intravitreal aflibercept 0.5mg monthly (0.5q4); 2mg monthly (2q4); the licensed treatment regimen of 2mg every 2 months after three initial monthly doses (2q8)**;** or ranibizumab 0.5mg monthly (Rq4). The primary endpoint was non-inferiority (margin of 10%) of aflibercept regimens to ranibizumab in proportion of patients maintaining vision at week 52 (losing <15 letters on ETDRS chart; per protocol analysis). Non-inferiority was shown for all aflibercept groups compared with monthly ranibizumab. Additional key comparisons of secondary endpoints were conducted to test for superiority. Mean changes in best corrected visual acuity (BCVA) from baseline to 52-week were found to be similar with all treatments, although only aflibercept 2q4 group in VIEW 1 study was statistically superior to ranibizumab. After week 52, all treatment groups were dosed PRN which was at least quarterly with more frequent dosing allowed based on predetermined re-treatment criteria. Visual improvements achieved at week 52 were maintained through week 96; overall 92% of patients maintained visual acuity (loss of <15 ETDRS letters) with BCVA gain of 7.9 and 7.6 letters, with aflibercept and ranibizumab respectively. The breakdown of data for licensed dose of aflibercept are presented below:[22]

Data for 2mg aflibercept every 8 weeks vs. ranibizumab 0.5mg every 4 weeks:[23]

	Aflibercept 2mg every 8 weeks	**Ranibizumab 0.5mg every 4 weeks**
BCVA at 52 weeks	+8.4	+8.7
BCVA at 96 weeks	+7.6	+7.9
Mean no. injections over 96 weeks	11.2	16.5
Mean no. injections 2nd year (PRN dosing)	4.2	4.7

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Search strategy:

EMC/ EMA/ FDA / Novartis Pharmaceuticals UK Ltd Medical Information (supplied the supporting studies upon which the write up is based)

Appendix 1: Summary of trials submitted by Novartis to support amendment of ranibizumab dosing and monitoring frequency in AMD

Study	Population	Trial Description	Outcome measure	Ranibizumab Dose/regimen	Outcome of Visual Acuity (BCVA)	# Injections	# monitoring visits	Other Issues
Schmidt-Erfurth *et al (2011)* (**EXCITE)** **Monthly vs quarterly maintenance dosing**	Patients with AMD. N=353 >50 years	Multicentre double-blind RCT (Phase IIIb) 3 Arm (1:1:1) Active controlled	Mean change in BCVA from baseline to 12 months (designed to test non-inferiority of quarterly vs. monthly) CRT Adverse effects	3 initial monthly injections followed by: 0.3mg quarterly 0.5mg quarterly 0.3mg monthly (active control) Total 12 months	From baseline to 12 months: +4.9 letters +3.8 letters +8.3 letters In all 3 arms, BCVA increased >5.0 letters from baseline in loading phase. Thereafter the quarterly arms lost 1.8 (0.3mg) and 2.8 (0.5mg) letters and the monthly arm gained 0.8 letters	6 in 12 months (quarterly) 12 in 12 months (monthly)	12 in 12 months for all groups	The licensed 0.5mg dose was only evaluated as a quarterly treatment in this study. Non-inferiority of the 0.5mg quarterly regimen to the 0.3mg monthly regimen was not demonstrated
Ho *et al. (2014)* (**HARBOUR)** **Monthly vs PRN**	Patients with AMD N= 1098 >50 years	24 month Multicentre double-blind RCT (Phase III 4 arm Active Controlled	Main outcome: mean change in BCVA from baseline to month 12 Others: BCVA 24 months BCVA gain >15 letters # injections CRT	3 initial monthly injections followed by: 0.5mg monthly 0.5mg PRN	12 mth: +10.1 letters / +8.2 letters 24 mth: +9.1 letters / +7.9 letters Although PRN dosing was associated with similar gains in visual acuity, superiority or non-inferiority vs. monthly dosing was not demonstrated	Monthly dosing: 11.3 in yr 1 and 10.1 in yr 2 PRN: 7.7 in yr 1 and 5.6 in yr 2	24 in 24 mths (even PRN dosing patients were evaluated monthly)	The average treatment interval for the 0.5mg PRN group was 9.9 weeks 2mg dose groups were also evaluated but the results are not reported here
Holz *et al.* **(SUSTAIN) PRN dosing**	Patients with AMD N =513	12 month Multicentre Single-arm Open-label	BCVA 12 months CRT Adverse effects Time to re-treatment # of treatments	0.3mg loading for 3 months and PRN dosing thereafter for 9 months	+5.8 letters months 1-3 Letter loss months 3-6 Letters stable months 6-12 +3.6 letters months 6-12	5.6 in 12 mths (incl loading at mth 12)	12 in 12 mths	Note: Pts were switched from 0.3mg to 0.5mg during the study after EMEA approved higher dose.
Cohen *et al. (2014)* **Maintenance every two months**	Patients with AMD N= 27 Mean 81.2 years	12 month Retrospective analysis Single-arm Uncontrolled Non-randomised	BCVA % losing <15 # injections CRT Pt gaining > 15	0.5mg loading for 3 months followed by maintenance every two months*	+8.4 letters over 12 months	8.77 in 12 mths	12 in 12 mths	*unscheduled rescue doses were permitted. 8 pts required these with a mean gain of 0.7 letters as a result.
Mantel *et al. (2014)* **Algorithm to predict monitoring freq and tx needs**	Patients with AMD N= 104 >50 years	12 months Prospective case series Single centre 'Observe & Plan'	BCVA SD-OCT Disease recurrence	0.5mg monthly loading for 3 months then monthly monitoring, with extension to every 1.5 months and 2 months after 3 and 6 months since last injection,respectively I(see algorithm attached)	+8.7 letters at 3mths +9.8 letters at 12mths Mean treatment interval of 1.97 months after the loading doses	7.8 in 12 mths	7 in 12 mths	Tx interval remained stable (ie, within ±2 wks) in 80% of pts. The interval was progressively lengthened in 15% of pts, while 5% of pts needed a shortening of the interval by more than 2 weeks as compared to the first measured interval.

Study	Population	Trial Description	Outcome measure	Ranibizumab Dose/regimen	Outcome of Visual Acuity (BCVA)	# Injections	# monitoring visits	Other Issues
Toalster *et al. (2013)* **Treat and Extend**	Patients with AMD N= 45 Mean 81.7 years	12 months Prospective Multicentre Nonrandomised Open label	BCVA CRT # injections # visits	0.5mg loading for 3 months… If retreatment criteria met shorten interval by 2 wks If retreatment criteria not met extend interval by 2 wks	+9 letters at 3mths +7 letters at 12mths	8 in 12 mths	7 in 12 mths	Mean treatment interval extended to 9.1 weeks Pt receives inj at each visit- do not wait for recurrence as with PRN.
Abedi *et al. (2014)* **Treat and Extend**	Patients with AMD N= 120 > 50 years	24 months Prospective Single Arm	BCVA at 12 mths BCVA at 24 mths % losing <15 letters	0.5mg loading for 3 months, continue monthly until no disease activity then extend interval by 2 weeks (max interval 12wks), if signs of disease activity reduce interval by 2 weeks.	+9.5 letters in 12 mths +8.0 letters in 24 mths	8.6 in year 1 5.6 in year 2	8.6 in 12 mths 5.6 in 24 mths	Comparable results to MARINA and ANCHOR. Pt receives inj at each visit. Do not wait for recurrence as with PRN.
Arias *et al. (2011)* **Flexible regimen**	Patients with AMD N= 90 > 50 years	12 month Prospective non-comparative Single-centre Single-arm	BCVA % losing <15 # inj CRT Pt gaining > 15	0.5mg loading for 3 months, then PRN, with follow-up visits progressively spread out to max 8 weeks in the absence of VA loss	+10 letters in 12 mths	4.4 in 12 mths (unclear if this included the initial 3 monthly doses)	8 in 12mths	PRN treatment but with follow-up visits also extended (up to maximum of every 8 weeks) in the absence of visual acuity loss There was a gradual deterioration of BCVA after the loading dose, as shown in other PRN studies

Key: BCVA= Best Corrected Visual Activity; CRT= Central Retinal Thickness; ETDRS= Early treatment Diabetic Retinopathy Study-like charts; SD-OCT: Spectral Domain Optical Coherence Tomography; TER= Treat-and-Extend Regimen

Appendix 2: Summary of data on use of ranibizumab in clinical practice

Title	Population Description inc. (n)	Study Description	Outcome measure	Ranibizumab Dose/regimen	Outcome of Mean Visual Acuity (BVCA)			# Injections			# monitoring visits		
Tufail *et al* The Neovascular Age-Related Macular Degeneration Database: Multicenter Study of 92 976 Ranibizumab Injections	92.976 treatment episodes, 12,951 eyes of 11,135 patients with AMD	Retrospective, observational multicentre, data collection, electronic medical record systems were used to collect data from 14 NHS hospitals that deliver ranibizumab AMD treatment	Number of visits Number of injections Visual acuity	3 monthly loading doses of 0.5mg ranibizumab followed by PRN therapy	Year 1 +2 letters	Year 2 +1 letters	Year 3 -2 letters	Year 1 9.2	Year 2 8.2	Year 3 8.2	Year 1 5.7	Year 2 3.7	Year 3 3.7
The visual outcomes achieved in this real- world cohort are worse than those achieved in the RCTs, likely due to capacity constraints preventing intended monthly review at some centres, reduced treatment frequency, and broader inclusion criteria in the real world compared with clinical trials.													
Chavan *et al* Bilateral visual outcomes and service utilization of patients treated for 3 years with ranibizumab for neovascular age-related macular degeneration	3,188 hospital visits (1823 non-injection, 1365 injection visits) of 120 patients with AMD	Retrospective, observational data collection at a single NHS center over 36 months for patients being treated with ranibizumab for AMD according to NICE criteria	Number of visits Number of injections Visual acuity	3 monthly loading doses of 0.5mg ranibizumab followed by PRN therapy	Year 1 +2 letters	Year 2 +1 letters	Year 3 -2 letters	Year 1 5.87 (1–11) Range	Year 2 4.06 (0–10) Range	Year 3 4.21 (0-11) Range	Year 1 12.3 (7-18)	Year 2 10.6 (3-18)	Year 3 11.47 (1-17)
The treatment benefit demonstrated here was vision stability. These results as well as usage statistics are broadly comparable to other UK based 'real world' studies. Over the course of 3 years, this cohort of patients made a total of 3,188 visits and received 1,365 injections													
Holz *et al* Multi-country real-life experience of anti-vascular endothelial growth factor therapy for wet age-related macular degeneration	2227 patients with AMD (UK n= 410)	Retrospective, observational, multicenter data collection from 8 countries for patients being treated with ranibizumab for AMD	Number of visits Number of injections Visual acuity	3 monthly loading doses of 0.5mg ranibizumab followed by PRN therapy	Year 1 +2.4 letters	Year 2 +0.6 letters		Year 1 5.0	Year 2 2.2		Year 1 8.6	Year 2 4.9	
					UK Data: +4.1 letters at 2 years			UK Data: 9 in 2 years			UK Data: 18.4 in 2 years		
There was a good initial response to treatment but this declined over time. To achieve the best outcomes with ranibizumab, the researchers suggest more frequent monitoring and injections are required which is reflected in similar 'real world' studies showing that increased visits and injections maximise the visual gains from ranibizumab treatment.													

Key: BCVA= Best Corrected Visual Activity , CRT= Central Retinal Thickness , ETDRS= Early treatment Diabetic Retinopathy Study-like charts , SD-OCT: Spectral Domain Optical Coherence Tomography , TER= Treat-and-Extend Regimen