Aflibercept for treating visual impairment caused by macular oedema secondary to branch retinal vein occlusion

Background and clinical effectiveness

1st Committee meeting
11th May 2016

Kathryn Abel

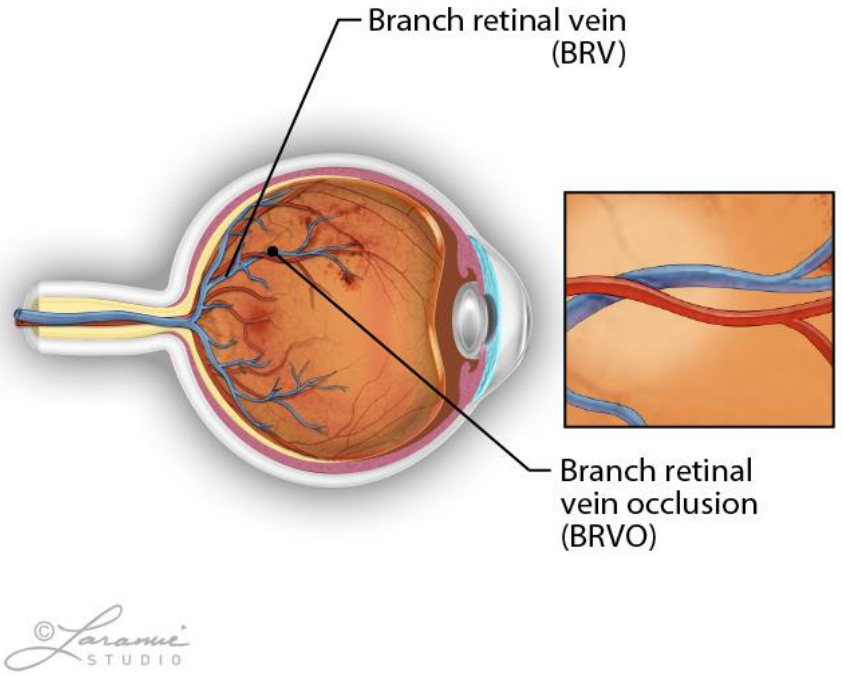
David Chandler

Preview of key issues and uncertainties

- What is the appropriate position in the treatment pathway for aflibercept given current practice (RCO guidelines) and existing NICE pathway?
- Is bevacizumab a relevant comparator in the treatment of macular oedema secondary to BVRO?
- Does the different dosing of aflibercept in the two trial arms reduce the clinical effectiveness of laser-AF below that seen in clinical practice?
- Has the use of Last Observation Carried Forward to handle drop outs overestimated clinical effectiveness of aflibercept-laser arm?
- Is the 6 month trial period sufficient to capture benefits in clinical effectiveness?
- What is the committee's view on the exclusion of the 5 studies from the network meta analysis because of clinical heterogeneity?

Clinical Background

- Retinal vein occlusion (RVO) is the second most common cause of retinal disease visual impairment
- Obstruction of retinal venous system by thrombus formation; may involve the central or branch retinal veins
- Macular oedema is the most frequent cause of vision loss in people with RVO
- In England around 12,900 people with BRVO and macular oedema have visual impairment
- Women and men equally affected
- Greatest risk is in over 50’s



Presentation and prognosis

- Patients with BRVO typically present with sudden painless loss of vision or ‘blind spots’ (caused by macular oedema)
- The majority of RVO cases are unilateral, however 5 – 6% present with evidence of bilateral BRVO*
- BRVO can resolve spontaneously, however many patients may not present immediately. In these people, visual acuity does not improve above 73 ETDRS letters*
- The degree of vision loss depends on the extent of retinal involvement and on macular perfusion status

*Source: RC Ophthalmologists RVO Guidelines July 2015

NICE Existing Guidance

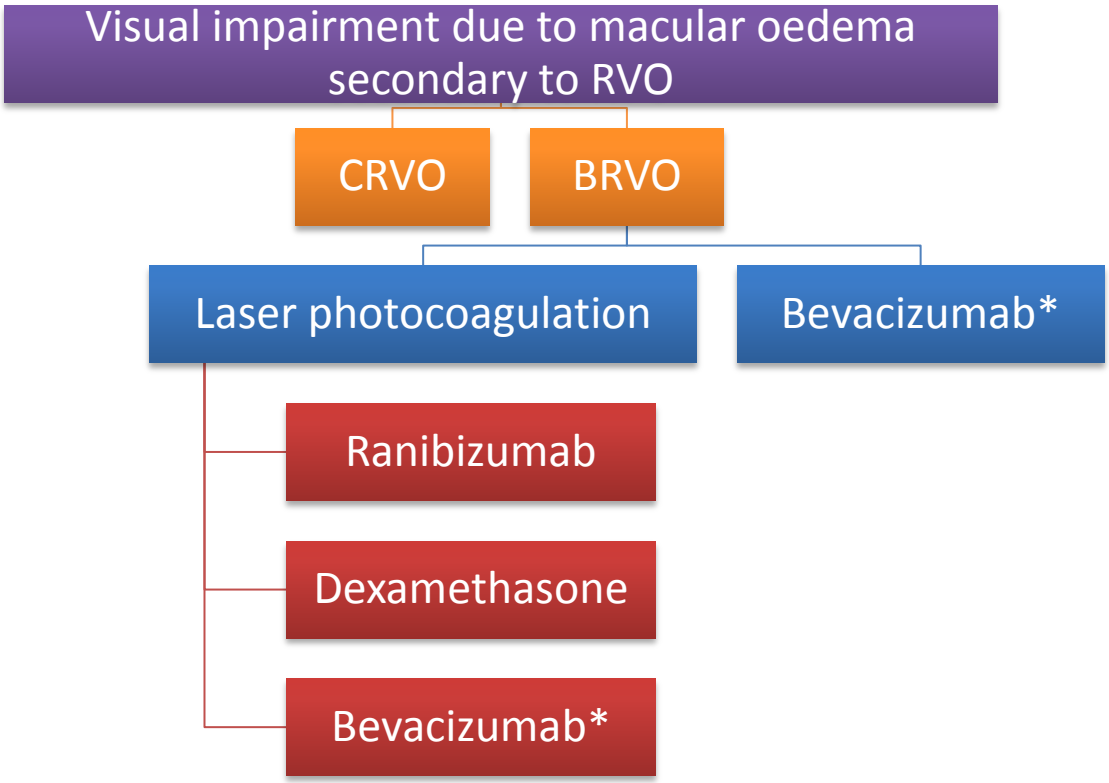
- Existing NICE guidance:
  - TA229 (Jul 2011)

    Recommends dexamethasone intravitreal implant for the treatment of macular oedema secondary to CRVO. Recommends dexamethasone in BRVO only where laser treatment has failed or cannot be used
  - TA283 (May 2013)

    Recommends ranibizumab for treating visual impairment caused by macular oedema secondary to CRVO. Recommends ranibizumab in BRVO only where laser treatment has failed or cannot be used
  - TA305 (Feb 2014)

    Recommends aflibercept for treating visual impairment caused by macular oedema secondary to CVRO

Treatment pathway



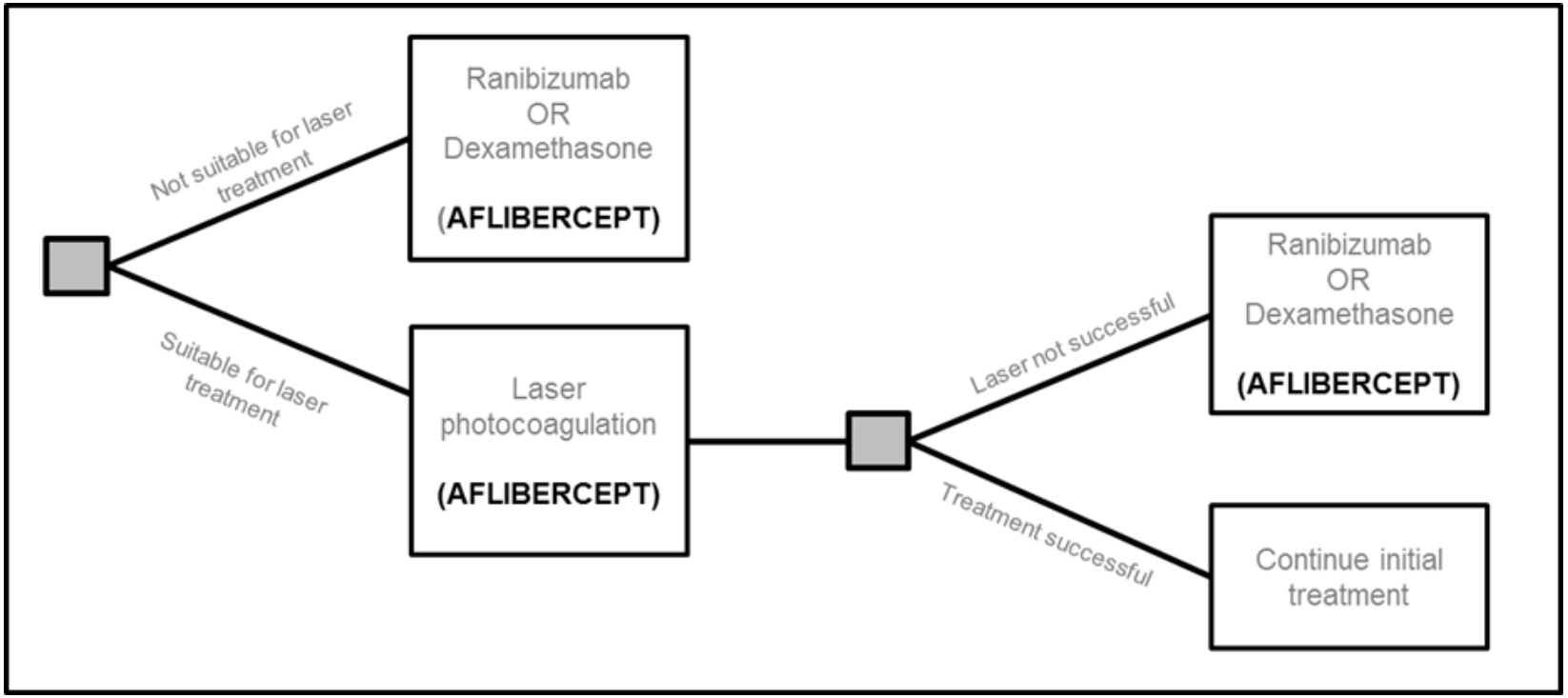
Royal College of Ophthalmologists guidelines for treatment of BRVO (July 2015) suggest anti-VEGF-therapy or dexamethasone as 1st line

* Not licensed for this indication

Treatment being appraised: aflibercept

- Aflibercept has a marketing authorisation in adults for the treatment of visual impairment due to macular oedema secondary to BRVO or CRVO (February 2015)
- Aflibercept is a soluble vascular endothelial growth factor (VEGF) receptor fusion protein which binds to all forms of VEGF-A, VEGF-B, and the placental growth factor, to inhibit VEGF
- Administered by intravitreal injection – the usual dose is 2mg
- Each vial contains 40mg/ml so 2mg = 50 microlitres and rest must be discarded
- The company have agreed an aflibercept PAS with Department of Health. The size of the discount is commercial in confidence

Company's proposed positions in the treatment pathway



Source : Company submission, figure 3

Patient perspective - 1

Living with the impact of sight loss

- Negative impact on everyday living
- Anxiety of going blind
- Profound emotional and psychological impact
- Loss of independence and mobility
- Personal care
  - Grooming, dressing
  - Preparing food
  - Managing basic activities
  - Fear of falls, creating a loss of confidence
  - Managing medicines where co-morbidities exist such as diabetes, hypertension,
- Feel a loss of personal safety, dependent on others
- Income, employment and ability to work in the future
- Looking after family members, particularly children

Patient perspective - 2
Treatment

- Stop vision loss and the potential of irreversible damage
- Improve existing poor vision
- Allow for independent living
  - Less dependent on others
- Lower risk of complications and side-effects
  - advantages over laser - which can cause retinal scarring

Key messages

- Safety of treatment is important – low AEs
- Provides further choice where existing therapies are unsuitable or unresponsive
- Addresses a current unmet need

Decision Problem

PICO table from NICE scope (with indication of adherence/deviations in company submission)

		✓ / ✗
Intervention(s)	Aflibercept solution for injection	✓
Population(s)	Adults with visual impairment caused by macular oedema secondary to branch retinal vein occlusion	✓
Comparators	• Laser photocoagulation • Bevacizumab (not licensed in the UK for this indication) For people for whom laser photocoagulation has not been beneficial or is not suitable: • Ranibizumab • Dexamethasone intravitreal implant • Bevacizumab (not licensed in the UK for this indication)	✓ ✗ ✓ ✓ ✗
Outcomes	• visual acuity (the affected eye) • visual acuity (the whole person) • adverse effects of treatment • health-related quality of life • mortality	✓ ✓ ✓ ✓ ✓

Source : NICE final scope

Clinical evidence

- The company presented evidence from one clinical trial VIBRANT assessing aflibercept compared with grid laser photocoagulation

Characteristic	Details
Population	Macular oedema secondary to BRVO (n=183)
Location	United States and Japan
Design	Phase III multicentre randomised double-masked, sham-controlled study
Intervention arm (Aflibercept)	• Received aflibercept every 4 weeks until week 24 and every 8 weeks from week 24 to 48; received sham laser treatment on day 1. • Could also receive grid laser photocoagulation (GLP) (from week 36)

Source : Company submission

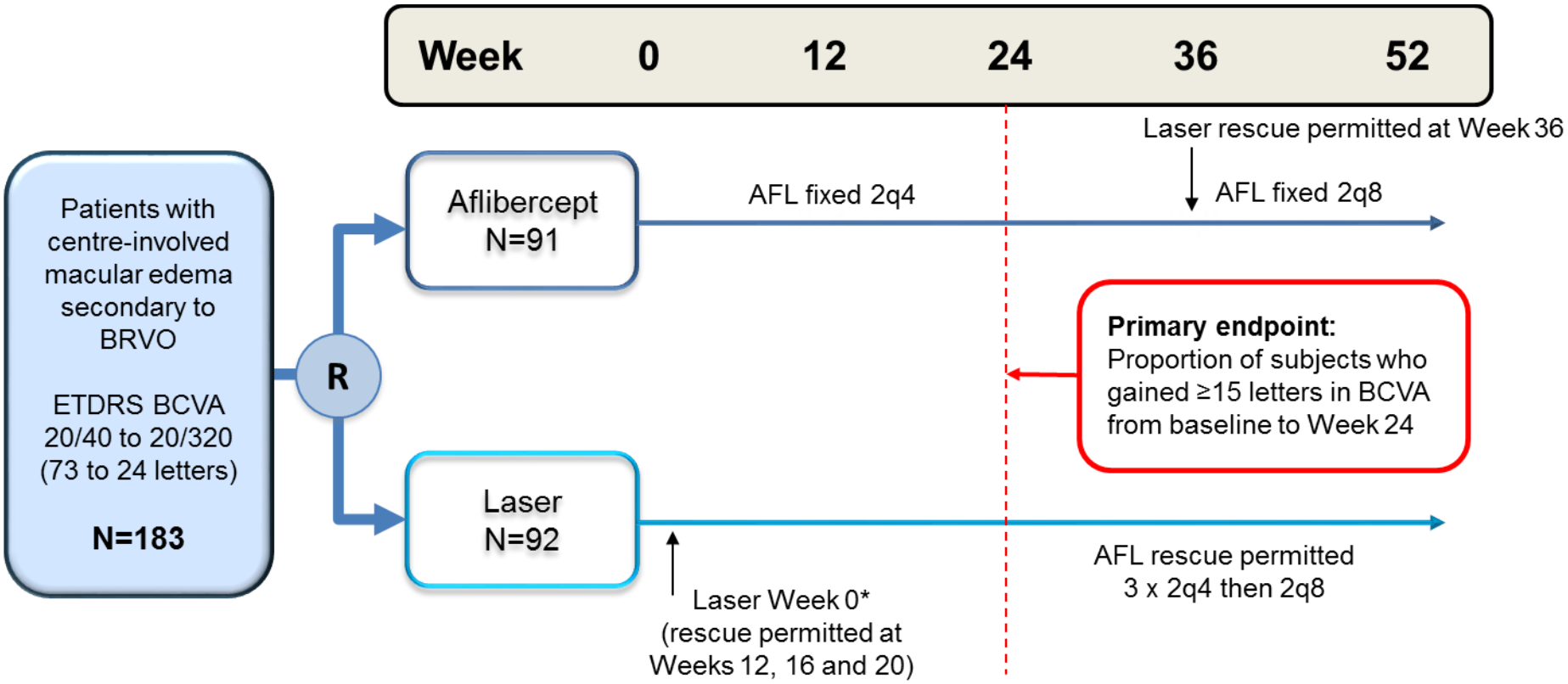
Clinical evidence (II)

Characteristic	Details
Comparator arm (grid laser photocoagulation)	• Received laser treatment on day 1; sham injections every 4 weeks • Could receive GLP at weeks 12, 16 and 20 • Sham injections were then given from weeks 24 to 52 • could receive rescue aflibercept from 6-months
Outcomes	• Gaining at least 15 letters ETDRS in BCVA • Change in BCVA (ETDRS letter score) • Change in central retinal thickness • Health related quality of life

Source : Company submission

BCVA: Best Corrected Visual Acuity
ETDRS: Early Treatment Diabetic Retinopathy Study

VIBRANT trial design



Source : Company submission, figure 5

Clinical results

	Week 24		Week 52	
	Aflib (n=91)	Laser (n=90)	Aflib (n=91)	Laser (n=90)
Gaining ≥15 letters in BVCA				
Event, n (%)	48 (52.7)	24 (26.7)	52 (57.1)	37 (41.1)
Difference	26.1%		16.0	
Adjusted difference (95% CI)	26.6 (13.0, 40.1)		16.2 (2.0, 30.5)	
p-value	0.0003		0.0296 (nominal)	
Change in BCVA (ETDRS letter score)				
Mean change from baseline (± SD)	17.0 (± 11.88)	6.9 (± 12.91)	17.1 (±13.07)	12.2 (±11.94)
LS mean change in BCVA	13.7	3.2	12.4	7.1
Difference in LS mean vs. Laser [+aflibercept] (95% CI) c	10.5 (7.1, 14.0)		5.2 (1.7 to 8.7)	
p-value c	<0.0001		<0.005	
Received rescue treatment				
N(%) 24 weeks and 36 weeks			9 (10)	67 (74)

Abbreviations: BCVA, best corrected visual acuity; N, number; CI, confidence intervals; SD, standard deviation; ETDRS, Early Treatment Diabetic Retinopathy Study ; LS, least squared

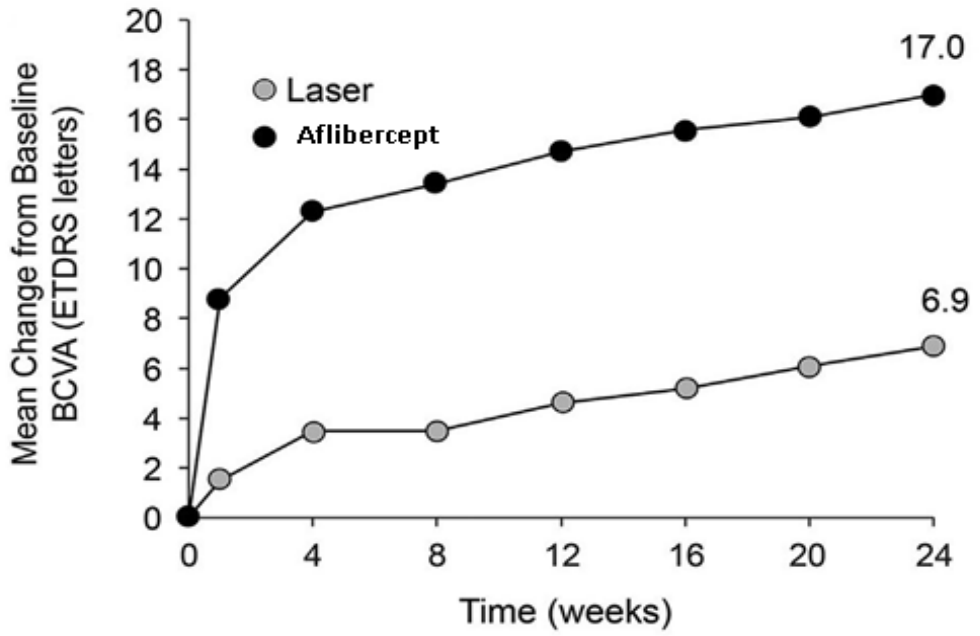
Source : Company submission, tables 20, 22 and 25

ERG comments

- Benefits of 2nd line aflibercept may not have been realised in the laser-aflibercept arm
  - Aflibercept dosing in 0-6 months was more frequent and for a longer duration compared to rescue aflibercept (2nd line)
  - May have biased the estimated benefits in favour of 1st line aflibercept
- Drop-out rates were quite high in both arms:
  - AF: 6 (7%) at 6 months and 14 (13%) at 1 year: total (20%)
  - GLP: 9 (10%) at 6 months and 6 (7%) at 1 year: total (16%)
- Last observation carried forward (LOCF) was used to impute missing data except baseline values
  - Many patients will not have resolved when they drop out
  - Rebound may be bigger in aflibercept arm, particularly among patients discontinuing before 6 months

Last Observation Carried Forward

Mean change from baseline in BCVA (ETDRS letter score) to week 24 (FAS; LOCF) (24)

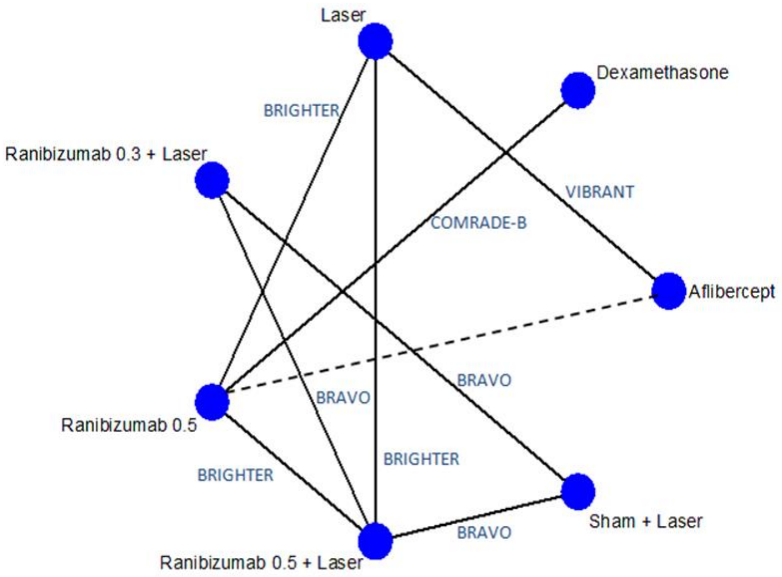


Source: company submission, figure 9

While any rebound among drop-outs is unobservable, drop-out rates may be a cause for concern when measuring relative treatment effects

Network meta-analysis

- No direct trial evidence for the comparison of dexamethasone and ranibizumab, NMA to assess the relative efficacy
- 9 eligible studies
- 5 studies excluded because of ‘clinical heterogeneity’
- Assessed the gaining ≥15 letters at 6 months for aflibercept compared with dexamethasone and ranibizumab for 1st line treatment
- ORs are applied to the week 24-52 VIBRANT data for 2nd line rescue treatment with aflibercept



Source : Company submission, figure 18

Network meta-analysis (II)

Network meta-analysis results from a fixed effect model

	Mean OR (CrI)	Median OR (CrI)
Gaining ≥15 letters in BVCA		
Ranibizumab vs. Aflibercept	1.04 (0.38, 2.31)	0.93 (0.38, 2.31)
Dexamethasone vs. Aflibercept	0.39 (0.12, 0.96)	0.34 (0.12, 0.96)
Change in BCVA (ETDRS letter score)	Mean PAIRDIFF	Median PAIRDIFF
Ranibizumab vs. Aflibercept	-2.68 (-7.43, 2.05)	-2.68 (-7.43, 2.05)
Dexamethasone vs. Aflibercept	-10.59 (-16.08, -5.10)	-10.59 (-16.08, -5.10)
Abbreviations: BCVA, best corrected visual acuity; ETDRS, Early treatment diabetic retinopathy study; CrI, credible interval; OR, odds ratio		

Source: Company submission, figure 25, 26, 29, 30

ERG comments

- 5 studies excluded from the NMA met the inclusion criteria specified in NICE's final scope and could have been included in the base case
- The company preferred the results of the median and random effect model. If different assumptions are used an alternative point estimate favouring ranibizumab could be obtained

Health Related Quality of Life

- VIBRANT trial collected EQ-5D data
- Relationship between BCVA and EQ-5D was significant BUT explained a very small proportion of total variance (3.2% or 3.1%)
- The insensitivity of EQ-5D to changes in BCVA has been highlighted by Fenwick et al. 2012, Finger et al. 2013, Gonder 2014, Loftus 2011 and Brown 2012
- Given this evidence, utility estimates based on direct valuation techniques were preferred for the base case analysis and results of the EQ-5D utility analysis are used as a sensitivity analysis
- Utilities were drawn from the Czoski-Murray study, and it was assumed that any change in the BCVA of the worst seeing eye (WSE) has 30% of the quality of life impact of the same change in the best seeing eye (BSE)

Equality and Innovation

- No equality concerns were identified at the scoping stage, or by the company, ERG, patient groups, clinical specialists or professional groups

- Aflibercept solution for injection is purported to be innovative because of
  - higher binding affinity for VEGF-A compared to ranibizumab, which may result in a longer duration of disease control
  - Inhibiting a wider range of growth factors

Key issues and uncertainties

- What is the appropriate position in the treatment pathway for aflibercept given current practice (RCO guidelines) and existing NICE pathway?
- Is bevacizumab a relevant comparator in the treatment of macular oedema secondary to BVRO?
- Does the different dosing of aflibercept in the two trial arms reduce the clinical effectiveness of laser-AF below that seen in clinical practice?
- Has the use of Last Observation Carried Forward to handle drop outs overestimated clinical effectiveness of aflibercept-laser arm?
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- What is the committee's view on the exclusion of the 5 studies from the network meta analysis because of clinical heterogeneity?

FOR PUBLIC

Aflibercept for treating visual impairment caused by macular oedema (MO) secondary to branch retinal vein occlusion (BRVO)

1st Appraisal committee meeting

Cost Effectiveness

Andrea Manca

11th May 2016

Preview of key issues for consideration

- Current NICE guidance for macular oedema secondary to BRVO is laser coagulation, with anti-VEGF treatment as 2nd line. Does the clinical and economic evidence support aflibercept in the 1st line?
- Model uncertainties:
  - Method for estimating transition probabilities
  - Dosing requirements for aflibercept, ranibizumab and dexamethasone
  - Management of dropout data
  - Preferred sources for quality of life data
  - Quality of life estimation for WSE (relative to BSE)
- Innovation
- Equality

Decision Problem

PICO table from NICE scope (with indication of adherence/deviations in company submission)

		✓ / ✕
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Outcomes	• visual acuity (the affected eye) • visual acuity (the whole person) • adverse effects of treatment • health-related quality of life • mortality	✓ ✓ ✓ ✓ ✓

Source : NICE final scope and company submission

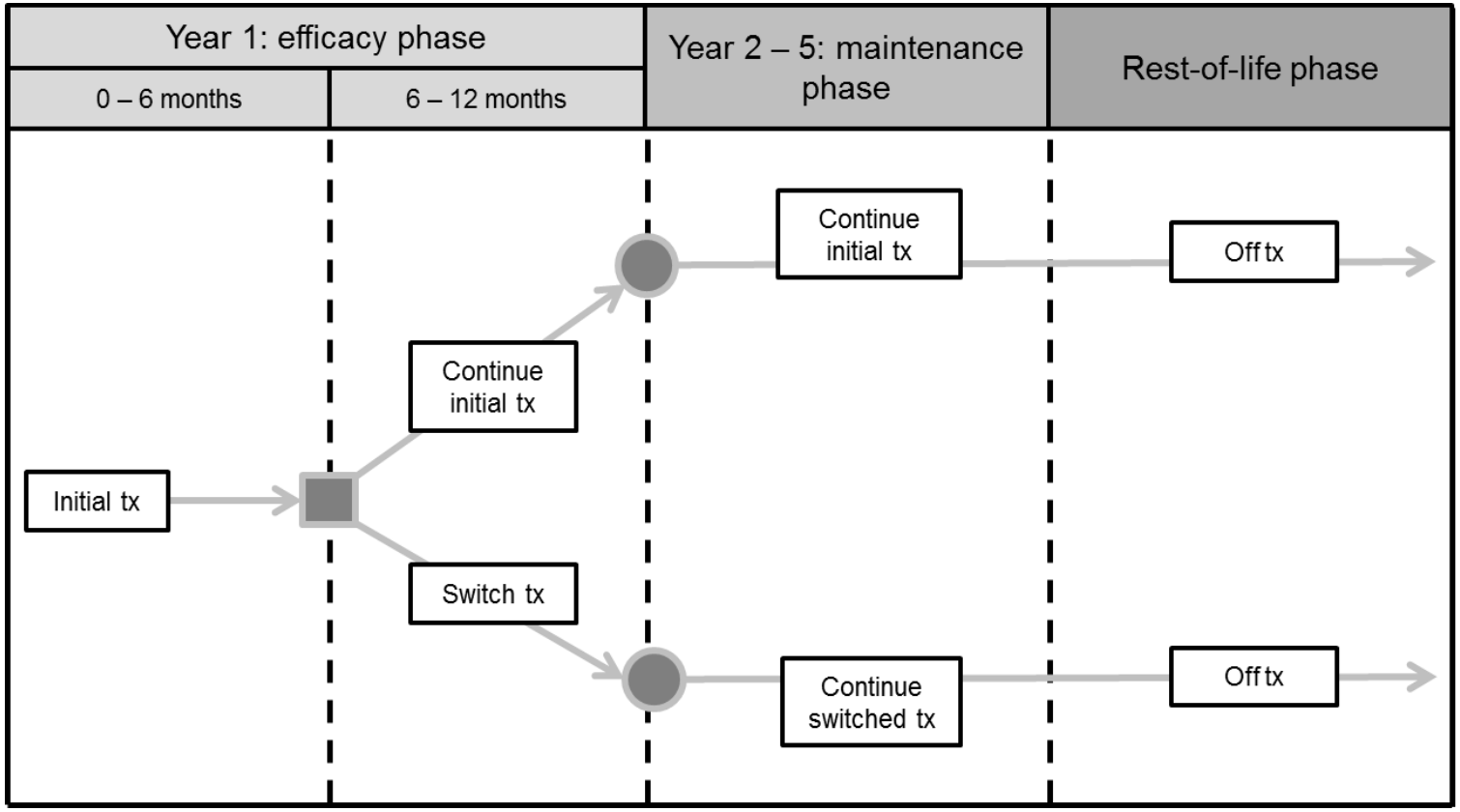
Company's comparisons

Submission addresses two questions:

- Aflibercept after laser
  - When laser has failed, is aflibercept after laser cost effective compared to ranibizumab after laser and dexamethasone after laser?
- Aflibercept for untreated patients
  - Is it more cost effective to try aflibercept before trying laser?
    - i.e. aflibercept followed by rescue laser *vs* laser followed by rescue aflibercept

Company submission: model structure

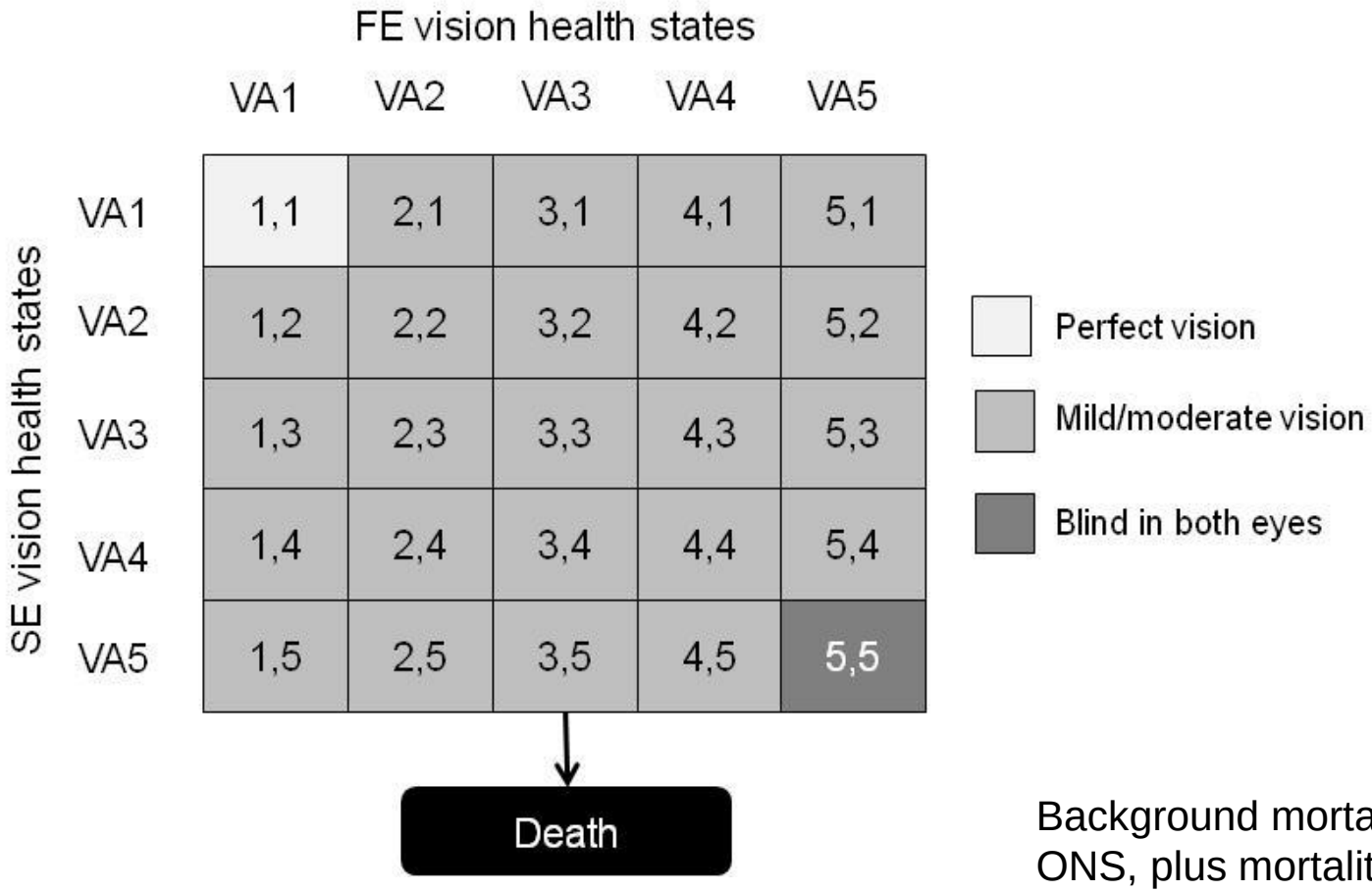
Model phases



Source: Company submission, figure 42

Company submission: model structure

Model health states defined by vision in both study eye (SE) and fellow eye (FE)

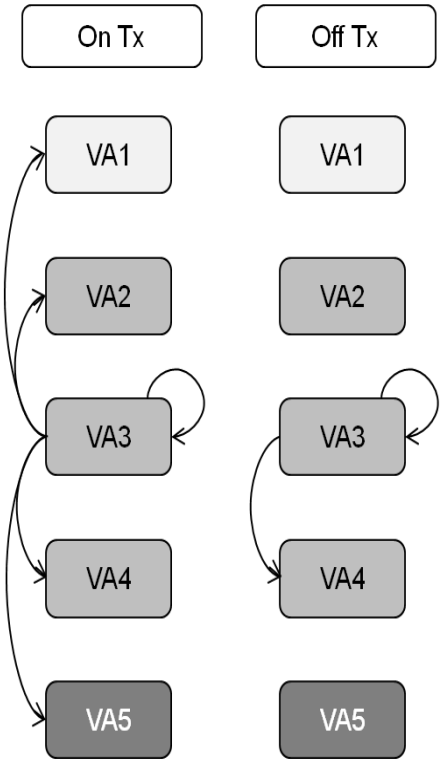


Source: Company submission, figure 37

Background mortality from ONS, plus mortality risk associated with loss of vision (mortality multiplier of 1.23 for those in health state 5)

Model Assumptions – Efficacy phase

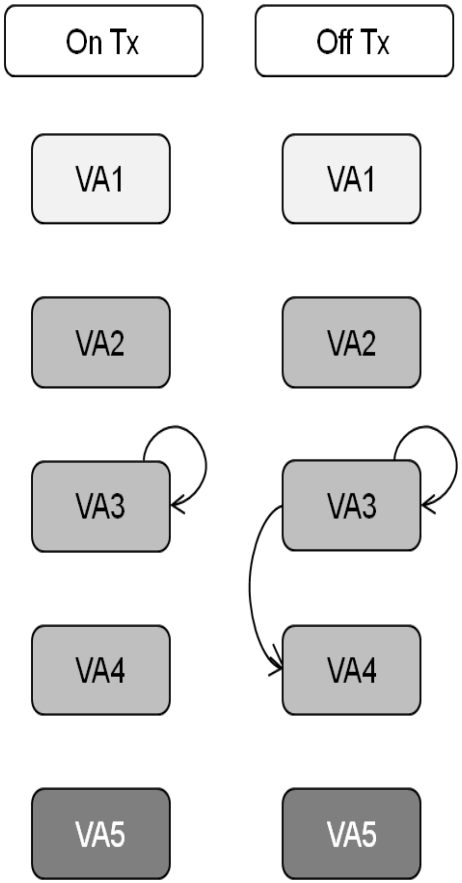
Transition between health states: efficacy phase using health state VA3 as an example



- Health states (HS) **defined by the visual acuity (VA) in both the SE and the FE**
- HS can improve, remain stable, or worsen (by 15 letter BCVA change) for those on treatment This is the only phase where VA improves.
- TPMs for afilbercept-laser and laser-aflibercept from pooled 4-weekly data in VIBRANT
- TPMs for laser-dexamethasone, laser-ranibizumab derived by applying the NMA odds ratios of gaining 15 letters
- Failing 1st line treatment can switch to rescue treatment after 6 months
- Only 50% of fellow eyes affected by BRVO will receive treatment
- Dosing and administrations based on mean number of treatments in the VIBRANT study during the 1st year
- Dosing for rescue ranibizumab is assumed to be the same as for rescue aflibercept , and dosing for rescue dexamethasone based on Summary of product characteristics

Model Assumptions – Maintenance phase

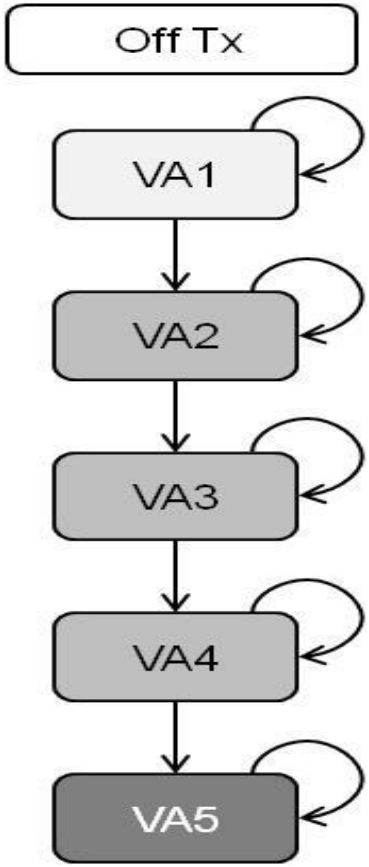
Transition between health states: maintenance phase using health state VA3 as an example



- Assumed that this phase lasts 4 years
- Patients on treatment:
  - visual stability is assumed through this period
  - benefit accrued at the end of the efficacy phase is maintained throughout the phase
  - patients remain on treatment throughout the phase but can discontinue (rates from year 1 apply)
  - Decreasing mean number of injections required to maintain vision
- Patients off treatment,
  - Patients can remain visually stable or move to a worse health states
- Dosing based upon expert opinion

Model Assumptions – Rest-of-life phase

Transition between health states: rest-of-life phase



- All patients continue off treatment
- Patients vision declines steadily throughout the remainder to their life
- Assumed slow visual decline of 2% of eyes losing 15 letters annually

Drug Unit Costs (list prices)

- Aflibercept - £816.00 list price (£XXXX with the PAS)
- Ranibizumab - £742.17 list price (£XXXX with the PAS)
- The level of discounts are commercial-in-confidence.

	Frequency of use		Cost in 1st year (list prices)	Source
	0-6 months	6-12 months		
Aflibercept followed by laser in treatment failures				
AFL only		9 AFL	£7,344.00	VIBRANT
AFL followed by LSR	3.0 AFL	1.0 LSR	£2,559.00	VIBRANT
Laser followed by ranibizumab in treatment failures: Comparison				
LSR only		1.7 LSR	£188.70	VIBRANT
LSR followed by RAN	1.0 LSR	4.4 RAN	£3,376.55	VIBRANT and assumed equal to aflibercept
Laser followed by dexamethasone in treatment failures: Comparison				
LSR only		1.7 LSR	£188.70	VIBRANT
LSR followed by DEX	1.0 LSR	1.0 DEX	£981.00	VIBRANT and from SmPC
Laser followed by aflibercept in treatment failures: Comparison				
LSR only		1.7 LAR	£188.70	VIBRANT
LSR followed by AFL	1.0 LSR	4.4 AFL	£3,701.40	VIBRANT
Abbreviations: AFL, aflibercept; DEX, dexamethasone; LSR, laser photocoagulation; RAN, ranibizumab				

Drug Unit Costs in the Model

- Dosing is based on the mean number of treatments in the VIBRANT study in the efficacy phase, and on clinical expert opinion during the maintenance phase

- Dosing for rescue ranibizumab is assumed to be the same as for rescue aflibercept, and dosing for 2nd line rescue dexamethasone is based upon the summary of product characteristics and expert opinion. From year 6 patients are in the ‘rest of life’ phase, it is assumed that patients will no longer be receiving treatment

Health States and Utility Values

- VIBRANT collected EQ5D data; regression analysis of these data against BCVA showed a significant relationship between the two
- However, the model used utilities drawn from Czoski-Murray et al, as used in previous appraisals (TA305)
- It was assumed that any change in the BCVA of the worst seeing eye (WSE) has a 30% of the quality of life impact of the same change in the best seeing eye (BSE)

Health States and Utility Values

BSE quality of life values in WSE BCVA VA5

BSE	Czoski-Murray	VIBRANT EQ-5D OLS linear model)	VIBRANT EQ-5D Random effects linear model
VA1	0.71	XXXX	XXXX
VA2	0.61	XXXX	XXXX
VA3	0.52	XXXX	XXXX
VA4	0.44	XXXX	XXXX
VA5	0.29	XXXX	XXXX

Source: ERG report table 23, 25, 27

Company's deterministic base case results

Incremental cost-effectiveness results from the base case (inc PAS for aflibercept only)

	Cost	QALYs	Inc. cost	Inc. QALYs	ICER
Laser-dexamethasone	XXXX	XXXX			
Laser-aflibercept	XXXX	XXXX	XXXX	XXXX	£11,792
Laser-ranibizumab	XXXX	XXXX	XXXX	XXXX	Dominated
Aflibercept-laser	XXXX	XXXX	XXXX	XXXX	£15,365

Source: Manufacturer's submission, table 4

ERG validation of the company's base case deterministic results

Includes PAS for aflibercept only

		AFLI-LASE	LASE-AFLI	LASE-RANI	LASE-DEXA
Costs	1st line	XXXX	XXXX	XXXX	XXXX
	2nd line	XXXX	XXXX	XXXX	XXXX
	Monit.	XXXX	XXXX	XXXX	XXXX
	FA	XXXX	XXXX	XXXX	XXXX
	Cat.	XXXX	XXXX	XXXX	XXXX
	IOP	XXXX	XXXX	XXXX	XXXX
	Blind	XXXX	XXXX	XXXX	XXXX
	Total	XXXX	XXXX	XXXX	XXXX
QALYs	VA	XXXX	XXXX	XXXX	XXXX
	Cat.	XXXX	XXXX	XXXX	XXXX
	IOP	XXXX	XXXX	XXXX	XXXX
	Total	XXXX	XXXX	XXXX	XXXX
ICER AFLI-LASE versus			£15,365	£8,939	£14,303
ICER LASE-AFLI versus				DOM	£11,792

Source: ERG report, table 34

ERG validation of the company's base case probabilistic results

Central probabilistic cost effectiveness estimates (Includes PAS for aflibercept only)

	Cost	QALYs	Inc. cost	Inc. QALYs	ICER	
					All compared	Laser 1st
Laser-dexamethasone	XXXX	XXXX				
Laser-aflibercept	XXXX	XXXX	XXXX	XXXX	£11,198	£11,198
Laser-ranibizumab	XXXX	XXXX	XXXX	XXXX	Ext. DOM	£10mn
Aflibercept-laser	XXXX	XXXX	XXXX	XXXX	£13,902	n.a.

Source: ERG report table 38

Company's sensitivity and scenario analyses

Overall there were 94 sensitivity and scenario analyses conducted for the base-case.

Among the sensitivity analyses undertaken by the company, results were sensitive to:

- The odds ratios of gaining letters
- The time horizon
- The cohort starting age
- The number of injections
- The cost per monitoring visit
- The proportion of treatment visits that double as monitoring visits
- The application of VIBRANT EQ-5D data
- To some extent the proportion of fellow eyes that are treated

Company's sensitivity and scenario analyses (II)

Four scenario analyses were conducted:

1. Equivalent efficacy between aflibercept and ranibizumab
   - The results were stable

2. All trials included in the NMA and results used to derive ORs to apply to TPMs (for comparisons against ranibizumab)
   - The results were all stable, except for the comparison of laser followed by aflibercept versus laser followed by ranibizumab, which resulted in an ICER of £158,853

Company's sensitivity and scenario analyses (III)

3. EQ5D estimated from VIBRANT used for the health state utilities
   - The results were all below the £20,000/QALYs, except for comparison (aflibercept 1st line versus laser followed by dexamethasone, ICER £23,971) and (aflibercept first-line versus laser followed by aflibercept, ICER £25,471)

4. Use of 'shift tables' as source of efficacy data for the TPMs (only done for comparison - Aflibercept first-line versus laser followed by aflibercept - using data from the VIBRANT trial)
   - The results were stable

Main ERG comments on cost effectiveness

- MSM derived TPMs *versus* shift-tables approach. The MSM approach results in the application of the TPMs multiple times which exaggerate the effect and overestimate differences between the treatments
- The six-month ORs of the NMA applies to 1st line treatments, but the model also uses them for 2nd line rescue treatments
- The six-month ORs have been applied to four-weekly TPMs. These are then compounded seven times, which appears to exaggerate the differences between the treatments and may largely invalidate the comparisons with laser-ranibizumab and laser-dexamethasone
- The company has not reported the results of its expert survey for dosing and monitoring for years 6+ of the model. The RETAIN trial suggests that there is a requirement for ongoing anti-VEGF dosing, among perhaps as many as half the patient population
- Handing of dropout data (assumed LOCF)

Note: RETAIN was non inferiority trial of ranibizumab with/without laser for best-corrected visual acuity (BCVA) in patients with diabetic macular oedema (DMO)

ERG's corrected base case

Based upon clinical expert opinion, the ERG has revised the company's economic model to:

- Assume quarterly monitoring for 1st year laser based upon expert opinion
- Assume 80% of administration visits can double as monitoring visits
- Assume 100% of fellow eye involvement will be treated

The ERG has also revised the model to:

- Applied shift-tables to estimate TMP
- Correct indexing for fellow eye costing
- Correct 1st year indexing of rescue costs
- Correct referencing for laser costs in aflibercept-laser
- Assume the same administration costs for laser as for anti-VEGF
- Correct the mortality averaging during the first 7 cycles of the model
- Apply ongoing mortality for cycles 396+, as previously outlined
- Revise dosing inputs to take into account discontinuations and cross-over, as previously outlined. Note that the ERG has not revised the dosing for dexamethasone due to time constraints.
- Anti-VEGF dosing for years 6+ of 3.2 annual administrations for 30% of patients for 5 years, implemented as previously outlined
- Not apply the cataract QALY decrement to IOP, by simply setting this to zero in the summary of results.
- Include fellow eye SAE disutilities

ERG's exploratory sensitivity analyses

SA01: Applying the R MSM derived TPMs for the comparison of aflibercept-laser with laser-aflibercept

SA02: Applying the 8 studies median ORs of gaining at least 15 letters of 1.08 for ranibizumab and 0.40 for dexamethasone

SA03: Revising the quality of life percentage for the WSE to be 15%

SA04: Revising the quality of life percentage for the WSE to be 43%

SA05: Revising the quality of life function to have a coefficient of -0.292

SA06: Revising the quality of life to be the VIBRANT EQ-5D OLS linear model

SA07: Revising the quality of life to be the VIBRANT EQ-5D REs linear model

SA08: Altering anti-VEGF dosing for years 6+ lasting 0, 5 and 10 years

SA09: Altering anti-VEGF dosing for years 6+ of an annual 2.0 doses

SA10: Altering ranibizumab to have one less administration than aflibercept during year 1

ERG's exploratory analyses – treatment after laser

ERG's corrected base case cost effectiveness estimates laser-aflibercept compared with laser-ranibizumab and laser-dexamethasone(inc PAS for aflibercept only)

		Laser-aflibercept	Laser-ranibizumab	Laser-dexamethasone
Costs	1st line	XXXX	XXXX	XXXX
	2nd line	XXXX	XXXX	XXXX
	Other	XXXX	XXXX	XXXX
	Total	XXXX	XXXX	XXXX
	Net		XXXX	XXXX
QALYs	QALYs BCVA	XXXX	XXXX	XXXX
	QALYs cataract	XXXX	XXXX	XXXX
	Total QALYs	XXXX	XXXX	XXXX
	Net QALYs		XXXX	XXXX
ICER			DOM	£18,542

Source. ERG report, table 61

ERG's exploratory analyses – treatment after laser (II)

ERG sensitivity analyses: laser-aflibercept vs 2nd line treatment (inc PAS for aflibercept only)

	vs laser-ranibizumab			vs laser-dexamethasone		
	Inc. cost	Inc. QALYs	ICER	Inc. cost	Inc. QALYs	ICER
Corrected base case	XXXX	XXXX	DOM	XXXX	XXXX	£18,542
SA01: R MSM TPMs (company's method	XXXX	XXXX	n.a.	XXXX	XXXX	n.a.
SA02: 8 study NMA	XXXX	XXXX	£204k	XXXX	XXXX	£20,969
SA03: 15% WSE QoL	XXXX	XXXX	DOM	XXXX	XXXX	£21,468
SA04: 43% WSE QoL	XXXX	XXXX	DOM	XXXX	XXXX	£17,162
SA05: Crude -0.292 Brown QoL	XXXX	XXXX	DOM	XXXX	XXXX	£23,518
SA06: VIBRANT EQ-5D OLS	XXXX	XXXX	DOM	XXXX	XXXX	£32,846
SA07: VIBRANT EQ-5D Rand. Eff.	XXXX	XXXX	DOM	XXXX	XXXX	£48,815
SA08a: No anti-VEGF yrs 6+ (company's method)	XXXX	XXXX	n.a.	XXXX	XXXX	n.a.
SA08b: 5 yrs anti-VEGF yrs 6+	XXXX	XXXX	DOM	XXXX	XXXX	n.a.
SA08c: 10 yrs anti-VEGF yrs 6+	XXXX	XXXX	DOM	XXXX	XXXX	n.a.
SA09: 2.0 per yr anti-VEGF yrs 6+	XXXX	XXXX	DOM	XXXX	XXXX	n.a.
SA10: Ranibizumab admin 1 less	XXXX	XXXX	DOM	XXXX	XXXX	n.a.

Source: ERG report, table 62

ERG's exploratory analyses – before laser

ERG's corrected base case cost effectiveness estimates aflibercept-laser compared with laser-aflibercept (inc PAS for aflibercept only)

		Aflibercept-laser	Laser-aflibercept
Costs	1st line	XXXX	XXXX
	2nd line	XXXX	XXXX
	Other	XXXX	XXXX
	Total	XXXX	XXXX
	Net	XXXX	XXXX
QALYs	QALYs BCVA	XXXX	XXXX
	QALYs cataract	XXXX	XXXX
	Total QALYs	XXXX	XXXX
	Net QALYs		XXXX
ICER			£27,259

Source: adapted from ERG report, table 59

ERG's exploratory analyses – before laser (II)

ERG sensitivity analyses: aflibercept-laser v laser-aflibercept (inc. aflibercept PAS only)

	Inc. cost	Inc. QALYs	ICER
Corrected base case	XXXX	XXXX	£28,813
SA01: R MSM TPMs (company's method	XXXX	XXXX	£25,549
SA02: 8 study NMA	XXXX	XXXX	n.a.
SA03: 15% WSE QoL	XXXX	XXXX	£33,380
SA04: 43% WSE QoL	XXXX	XXXX	£26,309
SA05: Crude -0.292 Brown QoL	XXXX	XXXX	£36,631
SA06: VIBRANT EQ-5D OLS	XXXX	XXXX	£50,578
SA07: VIBRANT EQ-5D Rand. Eff.	XXXX	XXXX	£74,405
SA08a: No anti-VEGF yrs 6+ (company's method)	XXXX	XXXX	£18,355
SA08b: 5 yrs anti-VEGF yrs 6+	XXXX	XXXX	n.a.
SA08c: 10 yrs anti-VEGF yrs 6+	XXXX	XXXX	£33,178
SA09: 2.0 per yr anti-VEGF yrs 6+	XXXX	XXXX	£24,709
SA10: Ranibizumab admin 1 less	XXXX	XXXX	n.a.

Source: ERG report, table 60

Key issues for consideration

- Current NICE guidance for macular oedema secondary to BRVO is laser coagulation, with anti-VEGF treatment as 2nd line. Does the clinical and economic evidence support aflibercept in the 1st line?
- Model uncertainties:
  - Method for estimating transition probabilities
  - Dosing requirements for aflibercept, ranibizumab and dexamethasone
  - Management of dropout data
  - Preferred sources for quality of life data
  - Quality of life estimation for WSE (relative to BSE)
- Innovation
- Equality