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NICE National Institute for Health and Care Excellence

Brolucizumab for treating wet age-related macular degeneration

Chair presentation ACM1 (FTA)

ERG: Warwick evidence

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Company: Novartis

November 10 2020

Issues for consideration

1. Dose frequency

What approach should be used to estimate dose frequency?

- **Company:** a weighted calculation of flexible and continuous regimens
- **ERG preferred:** a dual base-case based on TREX and PRN regimens?

How should brolucizumab year 3+ dose frequency be calculated?

- **Company:** assumed equivalent to year 2 dosing frequency
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- **Scenario:** based on % of patients dosed q8w at w92 in HAWK/HARRIER?

How should comparator year 3+ dose frequency be calculated?

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2. Monitoring visits

How many monitoring visits would be expected in clinical practice for comparator PRN / PRNX regimens?

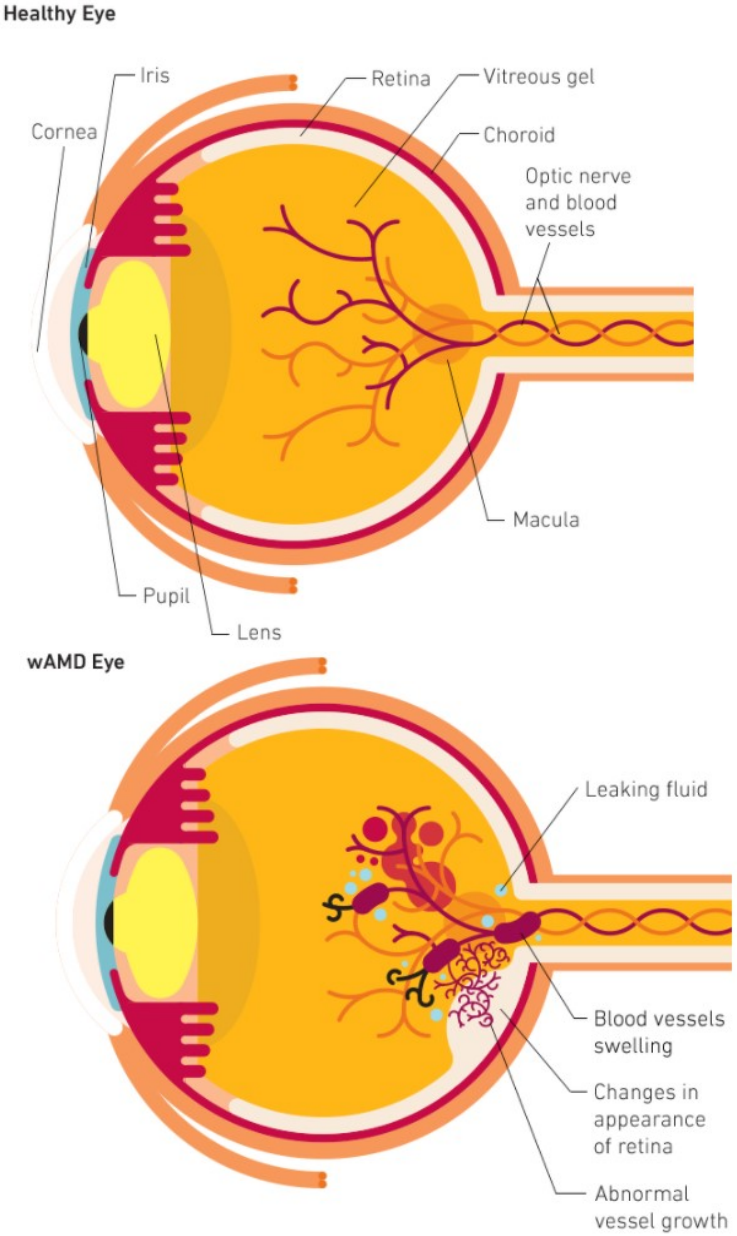
- **Company:** apply total clinic visits from NG82
- **ERG:** apply additional monitoring visits from NG82?

3. Fast Track Appraisal (FTA) decision

- Does brolucizumab provide similar or greater health benefits than the comparators?
- Is brolucizumab likely to result in a similar or lower cost than the comparators?

Wet age-related macular degeneration

- Age-related macular degeneration (AMD) is a chronic and progressive eye condition characterised by macula degeneration
  - The macula is the area of the retina responsible for sharp, central vision
- If untreated AMD can lead to severe visual impairment or blindness
- Neovascular (wet) AMD (wAMD) accounts for 10-20% of AMD cases, but is responsible for 80-90% of vision loss associated with AMD
  - It is the leading cause of vision loss in people aged over 65 years
- wAMD occurs when abnormal blood vessels grow under the macula and retina; they leak blood and fluid causing problems with vision
- wAMD incidence in over 50s is estimates to be 1.4 and 2.3 per 1,000 for men and women → incidence increases with age



The technologies

	Brolucizumab	Aflibercept	Ranibizumab
Mechanism of action	Inhibits vascular endothelial growth factor-A [VEGF-A]	Inhibits VEGF-A, VEGF-B and placental growth factor	Inhibits VEGF-A
Marketing authorisation	Indicated in adults for the treatment of neovascular (wet) age-related macular degeneration (wAMD)		
Administration and dose	6 mg (intravitreal injection) once a month for 3 months, then extend depending on absence/presence of disease activity	2 mg (intravitreal injection) once a month for 3 months, then extend	0.5 mg (intravitreal injection) once a month until maximum visual acuity is achieved then extend
Monitoring	Patients should be monitored for elevation in intraocular pressure	No monitoring requirement. Based on physicians' judgement	Based on disease activity, as assessed by visual acuity and/or anatomical parameters

TA294: Aflibercept for wAMD (2013)
Key drivers of cost-effectiveness

Clinical outcomes (VIEW 1 and VIEW 2)	• Proportion of patients losing <15 ETDRS letters from Baseline at Week 52 (and Week 96) • Proportion of patients gaining ≥15 letters from Baseline to Week 52 (and Week 96) • Mean change in BCVA from Baseline at Week 52 (and Week 96)
Key clinical drivers	• Drug acquisition costs • Proportion in one-stop or two-stop models • The relative risk of gaining or losing visual acuity with ranibizumab treatment • Frequency of injections and monitoring
Clinical uncertainties	• Exclusion of bevacizumab as a comparator (accepted as consistent with TA155) • Comparative effectiveness at 24 months
Resource use assumptions	• Both treatment groups need 8 treatment visits in year 1 of the model • 50% need separate monitoring visits
Resource use uncertainties	• Cost of treatment and monitoring visits

TA155; Ranibizumab for wAMD (2008)
Key drivers of cost-effectiveness

Clinical outcomes (MARINA, ACHOR, PIER)	• Proportion of patients losing <15 ETDRS letters from Baseline to 12 months (and 24 months) • Gain of more than 15 ETDRS letters of visual acuity from Baseline to 12 months (and 24 months) • Mean change in visual acuity (mean number of ETDRS letters lost or gained) from Baseline to 12 months (and 24 months)
Key clinical drivers	• The costs of blindness • The costs of administering the injections • The number of injections of ranibizumab • The utility values used in the analysis
Clinical uncertainties	• Whether the clinical benefit achieved in the trials could be achieved with fewer injections
Resource use assumptions	• Ranibizumab treatment stops after year 2, with benefit declining at the same rate as usual care
Resource use uncertainties	• The costs of administering the injections

FTA: cost-comparison overview

- A cost-comparison FTA can be used if the drug provides similar/greater benefits at a similar/lower overall cost than a NICE-recommended comparator
- FTA comparators are aflibercept (TA294) and ranibizumab (TA155):
  - Cost-effectiveness needs only be demonstrated against one of these
  - Both comparators have confidential commercial arrangements
- Any FTA recommendation for brolucizumab can only cover the same population recommended in TA155 and TA294:
  - people with wAMD, and
  - best-corrected visual acuity (BCVA) between 6/12 and 6/96
  - no permanent central fovea damage
  - lesion size ≤ 12 disc areas
  - evidence of recent disease progression.

Scrutiny panel agreed to proceed as FTA

The objective of today's appraisal is to decide whether brolucizumab provides similar or greater health benefits at a similar or lower cost than the comparators

Clinical expert & professional group comments

Royal College of Ophthalmologists

- Aim of treatment is to improve visual outcomes usually by preventing disease progression
- The need for long-term repeated injections is well established
  - Treat and extend (TREX), pro re nata (PRN) and fixed dosing provides flexibility But, regime choice is based on capacity issues not outcomes/results (see notes)
- Brolucizumab may require fewer injections – more research is required
- No additional investment required to introduce brolucizumab
- Superior retinal drying achieved with brolucizumab could benefit some patients
- NICE guidelines (TA155, TA294) require vision drops below 6/12 before starting treatment, although there are advantages to starting treatment before vision loss

Clinical expert statements

- Unmet need for a treatment with lower injection frequency, to improve capacity
- Brolucizumab use and resource use is expected to be similar to existing practice
- Improvements in quality of life expected from reducing injection frequency

Notes: continuous dosing regimens used in clinical practice

- **PRN:** Patients monitored frequently, treatment administered as needed
- **PRNX:** PRN, but with potential to extend monitoring interval
- **TREX:** Treatment interval extended in stepwise manner based disease activity

Clinical effectiveness evidence

HAWK and HARRIER trials

- **Design:** compare the safety and efficacy of brolucizumab with aflibercept
- **Population**: anti-VEGF treatment-naive patients aged 50 years or more with active choroidal neovascularisation (CNV) caused by AMD
- **Primary outcome:** BCVA change from baseline to Week 48
- **Trial dosing:** monthly for 3 months (both arms), maintenance phase (brolucizumab [q12w or q8w* if disease activity], aflibercept [q8w*])
- **Clinical practice dosing (aflibercept and ranibizumab)**
  - There is a range of dosing schedules for aflibercept and ranibizumab
  - No standard regimen is used
  - After an initial loading phase (LP) the most common regimens used in clinical practice include
  - A survey of 50 retinal experts suggested TREX is the most commonly used regimen in practice

Aflibercept	Ranibizumab
• q4w*	• q4w*
• q8w*	• q4w*→PRN
• q8w*→PRN	• PRN
• TREX	• TREX

Note: *qXw, one injection every X weeks

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Clinical effectiveness results

Company:

- Brolucizumab non-inferior to aflibercept in mean change in BCVA (baseline to week 48):
  - **HAWK:** BROL 6.6 (95% CI 5.2 to 8.0) vs. AFLI 6.8 (95% CI 5.4 to 8.2)
  - **HARRIER:** BROL 6.9 (95% CI 5.7 to 8.1) vs. AFLI 7.6 (95% CI 6.4 to 8.8)
- Brolucizumab superior to aflibercept in improvement in CSFT, retinal fluid and disease activity
- 30% fewer people receiving brolucizumab had disease activity
- Similar improvements in health-related quality of life
- Safety profile comparable to aflibercept. No new AEs vs. other anti-VEGFs

ERG review:

- No major concerns → HAWK and HARRIER were considered of high quality
- Brolucizumab non-inferiority to aflibercept supported by trial evidence
- Data for rare adverse events is sparse
- Adverse effects are likely to be similar for both treatments

Network meta-analysis (NMA)

Company:

- Brolucizumab treatment leads to comparable changes in BCVA compared with aflibercept and ranibizumab
- Brolucizumab superior in decreasing retinal thickness with lower injection frequency
- Comparable safety profile and probability of discontinuation for all treatments

ERG review:

- Considered the NMA robust → results supports claims of non-inferiority
- No notable differences in age, sex, and race/ethnicity between studies
- Inclusion of additional studies could have strengthened the network, though unlikely to alter direction of results
- Differences in distribution of CNV lesion type and size between studies could modify treatment effect estimates, though unlikely to alter direction of results

A retinal vasculitis and/or retinal vascular occlusion safety issue has been confirmed

- The company has conducted a review of spontaneously reported cases of significant vision loss, retinal artery occlusion and potential vasculitis in patients who have had treatment with brolucizumab in the USA
  - As of 28 February 2020, the company had received reports of 44 cases of interest, from a total estimated vial use of around 56,000
  - The company considers that there is a validated signal of an emerging new safety issue of retinal vasculitis and/or retinal vascular occlusion with or without intraocular inflammation, which may result in severe vision loss
- SmPC update:

  > "Retinal vasculitis and/or retinal vascular occlusion, typically in the presence of intraocular inflammation, have been reported with the use of [brolucizumab] … In patients developing these events, treatment with [brolucizumab] should be discontinued and the events should be promptly managed"

- ERG considers that events are sufficiently rare that they are unlikely to affect the its view that brolucizumab has a similar AE profile to the comparators

Company base-case cost-comparison
Costs, dosing and monitoring assumptions

	Brolucizumab	Aflibercept	Ranibizumab
Acquisition cost*	[redacted]	[redacted]	[redacted]
Dose	6 mg	2 mg	0.5 mg
Dosing regimen	Loading phase [LP] → quarterly [q12w] or bi-monthly[q8w] dosing	Weighted average of continuous and flexible dosing regimens**	Weighted average of continuous and flexible dosing regimens***
No. of injections	Year 1: 6.66 Year 2: 4.76 Year 3+: 4.76	Year 1: 8.82 Year 2: 6.85 Year 3+: 6.85	Year 1: 9.16 Year 2: 7.91 Year 3+: 7.91
Total no. of visits (incl. monitoring)	Year 1: 6.66 Year 2: 4.76 Year 3+: 4.76	Year 1: 8.82 Year 2: 8.17 Year 3+: 8.17	Year 1: 10.97 Year 2: 10.12 Year 3+: 10.12

*Includes PAS discounts; ** includes PRN and TREX; ***includes PRN, PRNX and TREX

PRN: Frequent monitoring, treatment administered as needed

TREX: Treatment interval extended in stepwise manner based on disease activity

PRNX: PRN, but with potential to extend treatment interval

Summary company and ERG base-case assumptions

Assumption	Company	ERG
Brolucizumab dosing frequency	Years 1 and 2 frequency taken from NMA using pooled HAWK and HARRIER data	
Comparator dosing regimen	Weighted average of continuous and flexible dosing regimens (weights determined from survey of retinal experts)	Individual comparison vs PRN* and TREX regimens
Year 3+ dose frequency	**Same as year 2** Brolucizumab: 4.76 Aflibercept: 6.85 Ranibizumab: 7.91	**Based on TA294** Brolucizumab: 4.0 Aflibercept: 4.0 Ranibizumab: 4.0
Monitoring visits for PRN/PRNX regimens	**Applying the <u>total</u> clinic visits from NG82** PRN: 12.7 total visits in each of years 1-3+ PRNX: 10.1 visits in each of years 1-3+ 0.2 year 1 loading phase visits No additional monitoring for continuous regimens	**Applying the <u>additional</u> clinic visits from NG82** Year 1: 6.1 additional visits in for ranibizumab Year 2+: 4.5 additional visits for aflibercept and ranibizumab The above additional visits are applied 2 years later for brolucizumab

* Aflibercept: LP → q8w → PRN; Ranibizumab: LP → PRN

Dosing and monitoring frequencies

	Company (weighted approach)			ERG base case 1 (TREX)			ERG base case 2 (PRN)		
	BROL	AFLI	RANI	BROL	AFLI	RANI	BROL	AFLI	RANI
Dosing frequencies									
Year 1	6.7	8.8	9.2	6.7	9.7	9.5	6.7	7.1	7.1
Year 2	4.8	6.9	7.9	4.8	7.3	8.2	4.8	5.0	5.6
Year 3	4.8	6.9	7.9	4.0	4.0	4.0	4.0	4.0	4.0
Monitoring frequencies (total visits)									
Year 1	6.7	8.8	11.0	6.7	9.7	9.5	6.7	7.1	13.2
Year 2	4.8	8.2	10.1	4.8	7.3	8.2	4.8	9.5	10.1
Year 3	4.8	8.2	10.1	4.0	4.0	4.0	10.1*	8.5	8.5
Year 4+	4.8	8.2	10.1	4.0	4.0	4.0	8.5	8.5	8.5

* Brolucizumab is assumed to transition from fixed dosing to PRN dosing in year 3, the additional monitoring visits outlined above are applied from year 3+

Dosing and monitoring frequency *ERG scenarios*

1. **Brolucizumab year 3+ dose frequency**
   - Company assumed year 3+ brolucizumab dose frequency to be equivalent to injections observed in year 2 (4.76)
   - HAWK/HARRIER permitted an increase in brolucizumab dosing frequency when insufficient treatment response: [redacted] increased frequency q12w→q8w
   - ERG scenario: assumes [redacted] q8w, [redacted] q12w (average 5.7 doses/year)
     - *But in HAWK/HARRIER, once people moved to q8w dosing, not permitted to move back to q12w but expected this would be tried in practice → scenario likely biases against brolucizumab*
2. **Aflibercept and ranibizumab year 3+ dose frequency (NG82 approach)**
   - NG82 used an alternative approach to estimate year 3+ dosing frequencies
   1. Calculate a ratio of year 2 dose frequencies for AFLI and RANI continuous regimen (TREX/PRN) from year 2 frequencies observed in the clinical trials
   2. Find a report of year 3 dose frequency for any continuous regimen
   3. Apply the ratio (step 1) to reported year 3 dose frequency (step 2) to estimate year 3+ dose frequency for other continuous regimens
   - *ERG applies this approach in a scenario analysis, but notes this approach resulted in lower than expected estimates of comparator dose frequency*

Other resource use assumptions	
Treatment discontinuation	• Company assumed treatment discontinuation to be constant over time, with different annual discontinuation rates for each treatment → brolucizumab (7.86%) aflibercept (8.95%) and ranibizumab (7.89%) • ERG noted that if brolucizumab dosing intervals cannot be lengthened beyond 12 weeks, discontinuation rates become more important. A higher dose frequency than comparators may produce greater long-term costs
Bilateral (both eyes) treatment multipliers	• The company assumed bilateral treatment assumed takes place in a one-stop appointment. Cost multipliers: drug costs (x2); administration costs (x1.5) • The ERG agreed that these assumptions align with NG82, and are unlikely to alter conclusions
Adverse event costs	• No significant differences in adverse events were observed versus aflibercept in HAWK/HARRIER. Adverse event costs were not included in company base case, and the ERG agreed that including them has little impact on results • Vasculitis safety reports were made after the company submission and ERG report, and related costs were not included in the model. The ERG considers that these AEs are sufficiently rare and unlikely to affect the CEA outcomes

Company base-case cost comparison outputs (comparator PAS prices)

Costs	Brolucizumab	Aflibercept	Ranibizumab
Drug	[redacted]	[redacted]	[redacted]
Admin	[redacted]	[redacted]	[redacted]
OCT	[redacted]	[redacted]	[redacted]
FFA	[redacted]	[redacted]	[redacted]
AE	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]
Incremental	-	[redacted]	[redacted]

Source: tech team calculated, ERG checked
Abbreviations: AE, adverse events; FFA, fluorescein angiography; OCT, optical coherence tomography; PAS, patient access scheme

Brolucizumab has [redacted] compared with aflibercept and ranibizumab

- Analysis incorporates the following confidential commercial arrangements:
  - Brolucizumab PAS discounts
  - Aflibercept and ranibizumab PAS discounts

ERG base-case cost comparison outputs

- ERG base case amendments:
  1. Dual base-case vs TREX and PRN comparator regimens
  2. 4.0 injections in year 3+ for brolucizumab, aflibercept and ranibizumab
  3. Applying the additional clinic visits from NG82

Costs	TREX			PRN		
	BROL	AFLI	RANI	BROL	AFLI	RANI
Drug	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Admin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FFA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental		[redacted]	[redacted]		[redacted]	[redacted]

Source: calculated by tech team, ERG checked
Abbreviations: see s18

Brolucizumab has [redacted] compared with aflibercept and ranibizumab (TREX and PRN regimen)

ERG scenario analyses: dosing regimens

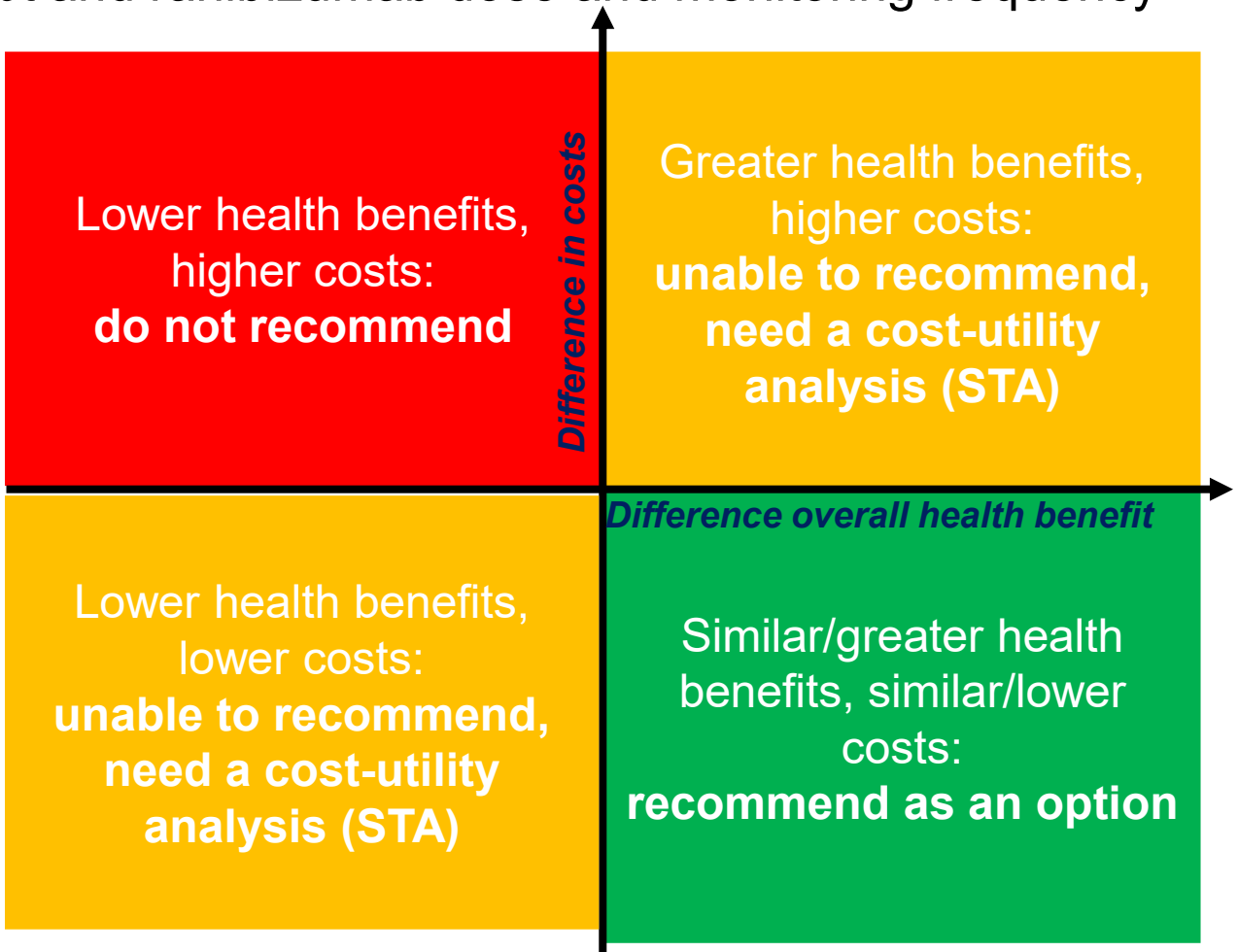
Scenario analyses (SA)				
SA	Dosing and monitoring frequencies *Assumptions or regimen applied in the model*		Brolucizumab incremental cost	
	Brolucizumab	Comparator	AFLI	RANI
1a:	• Company estimates in years 1 and 2 • **ERG scenario:** *5.7 doses for brolucizumab in year 3+.*	q4w	[redacted]	[redacted]
1b:		q4w > PRN	[redacted]	[redacted]
1c:		LP > q8w	[redacted]	N/A
1d:		PRN	N/A	[redacted]
1e:		PRNX	N/A	[redacted]
2a:		• TREX in years 1 and 2 • NG82 derived in year 3	[redacted]	[redacted]
2b:		• PRN in years 1 and 2 • NG82 derived in year 3	[redacted]	[redacted]
3a:	• Company estimates in years 1, 2 and 3+ *4.76 doses for brolucizumab in year 3+.*	• TREX in years 1 and 2 • NG82 derived in year 3	[redacted]	[redacted]
3b:		• PRN in years 1 and 2 • NG82 derived in year 3	[redacted]	[redacted]

Source: Tech team calculated, ERG checked

Potential recommendations: cost comparison

Key issues

- Brolucizumab dose and monitoring frequency
- Aflibercept and ranibizumab dose and monitoring frequency



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