ISPOR EUROPE 2026 · VIENNA, AUSTRIA

EE582

Modeling therapeutic persistence and durability in ocular therapies: a review of HTA appraisals

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1 BACKGROUND & OBJECTIVE

Background

- Therapeutic persistence, defined here more broadly than adherence to include **treatment durability of effect** and **maintenance of treatment delivery over time**, is a key driver of cost-effectiveness uncertainty in ocular disease health technology assessments (HTAs).[1-3]
- Persistence enters cost-effectiveness models through three inputs: treatment-effect duration (quality-adjusted life years [QALYs]), administration and monitoring frequency (costs) and discontinuation (both).[1,2] Because benefits accrue over decades while costs are up front, duration interacts strongly with the discount rate.
- This is particularly relevant for **one-time gene therapies** and **extended-duration anti-vascular endothelial growth factor (VEGF) treatments**, where long-term benefit and/or reduced treatment frequency may extend beyond trial evidence.[3,4] With one-time anti-VEGF gene therapies now in phase 3, this question is also moving from rare disease into mainstream ophthalmology.

Objective

To evaluate how persistence assumptions are modeled and scrutinized across ocular therapeutic classes and HTA jurisdictions, focusing on five persistence-related domains:

Durability/waning · **Injection burden** · **Treat-and-extend (T&E) modeling** · **Visual acuity (VA) extrapolation** · **Discontinuation**

2 METHODS

21 HTA appraisals

7 HTA bodies

2008–2025 assessment period

HTA evidence base: 21 appraisals across 3 classes over 2008-2025

7 appraisals

Inherited retinal & optic nerve diseases

Voretigene neparvovec, idebenone

10 appraisals

Extended-interval anti-VEGFs

Faricimab, brolucizumab, aflibercept 8 mg

4 appraisals

Standard anti-VEGFs

Aflibercept 2 mg, ranibizumab, bevacizumab gamma

HTA jurisdictions

NICE England · **CDA-AMC** Canada (formerly CADTH) · **ICER** United States · **SMC** Scotland · **HAS** France · **G-BA** Germany · **PBAC** Australia

Analytical approach

1 Retrieve
Final guidance, committee papers and evidence review reports from each HTA body

2 Extract
Persistence-related assumptions and the HTA critique of them

3 Rate
Each domain rated as primary driver, contributing factor, minor contribution or not applicable (Table 1), by its weight in committee critique

Limitations

- Domain ratings are qualitative and rely on reviewer judgement; only publicly available HTA documents were reviewed. Ratings reflect the weight of committee critique, not the final recommendation; a domain can be the primary driver without changing the decision.
- The inherited retinal/optic nerve class is small (7 appraisals, 2 products) and idebenone is a small molecule, so durability findings may not generalise to pipeline gene therapies.
- Appraisals span 2008–2025; the earliest predate T&E practice and current HTA methods.

3 RESULTS

Persistence-related uncertainty differed by therapeutic class

Table 1. Persistence domains by therapeutic class (reviewer-rated across 21 appraisals)

Persistence domain	Inherited retinal & optic nerve diseases	Extended-interval anti-VEGFs	Standard anti-VEGFs
Durability/waning	**Primary driver**	Contributing factor	Contributing factor
Injection burden	–	**Primary driver**	Contributing factor
T&E modeling	–	**Primary driver**	–
VA extrapolation	**Primary driver**	Contributing factor	Contributing factor
Discontinuation	Minor contribution	Minor contribution	Minor contribution

Primary driver · Contributing factor · Minor contribution · Not applicable (–)

Inherited retinal & optic nerve diseases

Durability/waning and VA extrapolation were dominant.

- **Voretigene neparvovec:** every HTA body applied more conservative durability than submitted, raising ICERs: NICE shortened effect duration; CDA-AMC broadened conservative assumptions; HAS modeled 10-year stabilization then 10-year waning; SMC varied duration, residual effect and waning period; ICER's single/short-term transformative therapy (SST) framework adds a 10-year waning scenario.[5]
- **Durability is not one parameter:** committees separately questioned functional durability (full-field stimulus threshold [FST] and multi-luminance mobility test [MLMT] gains held to year 4 in phase 3),[6] structural progression (chorioretinal atrophy in ~13% of registry patients),[7] no re-treatment pathway after adeno-associated virus (AAV) exposure, and the natural-history trajectory to which effect reverts, itself criticised for small, retrospective source data.
- **Idebenone (LHON):** a small molecule, so the issue was extrapolating a short trial using observational follow-up, not whether a one-time effect persists.

Durability structures applied to the one-time therapy, by HTA body (schematic: effect over time)



Lifelong effect (company base cases) · **Fixed duration, then loss** (NICE, CDA-AMC) · **Plateau, then linear decline** (HAS: 10 + 10 years) · **Gradual waning** (SMC, ICER scenarios)

Extended-interval anti-VEGFs

T&E maintenance and injection frequency were dominant.

- **CDA-AMC:** re-analysis assuming injection frequency equal to the comparator required price reductions of up to 98% (faricimab vs. bevacizumab-referenced pricing)
- **G-BA:** rejected claims because aflibercept was not dosed per its T&E label
- **VA extrapolation less impactful:** committees accepted non-inferior outcomes and scrutiny fell on dosing frequency

Standard anti-VEGFs

More heterogeneous persistence considerations.

- Greater focus on treatment frequency, long-term VA outcomes and assumptions around treatment continuation.
- **The key domain varied by product:** long-term maintenance of VA gains for ranibizumab and aflibercept 2 mg in diabetic macular edema (DME), but T&E dosing assumptions for bevacizumab gamma (NICE 2024)

4 CONCLUSIONS

- **Ocular HTA scrutiny differed by persistence domain and therapeutic class:** durability and VA extrapolation dominated when there was no strong evidence on extended benefit, while T&E maintenance and injection frequency dominated in interval-extension paradigms.
- **Discontinuation was generally not a key driver:** captured through durability in inherited retinal/optic nerve appraisals and minor in extended-interval anti-VEGF appraisals, where dosing frequency dominated.
- **Sustained-expression anti-VEGF gene therapies and sustained-release implants will merge both scrutiny patterns:** durability of effect and rescue-injection frequency will be interrogated together — and for gene therapies first at EU level under Joint Clinical Assessment (JCA).[8]
- **One-time therapies should pre-specify a standard durability scenario set** (lifelong; fixed duration; plateau-then-decline; gradual waning), **report breakeven durability** and discount-rate sensitivity, and pair modeling with ≥5-year extension data, registries and outcome-linked access agreements. **Interval-maintenance claims** need data on patients sustaining the labelled interval without rescue.

Poster presented at the ISPOR Europe 2026 Conference, 8–11 November 2026, Austria Center Vienna, Vienna, Austria.

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ABBREVIATIONS

AAV: Adeno-associated virus; DME: Diabetic macular edema; FST: Full-field stimulus threshold; HTA: Health technology assessment; JCA: Joint Clinical Assessment; MLMT: Multi-luminance mobility test; QALY: Quality-adjusted life year; SST: Short-term transformative therapy; T&E: Treat-and-extend; VA: Visual acuity; VEGF: Vascular endothelial growth factor.

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DISCLOSURES

All authors are employees of Red Nucleus.