



Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1623 – Luxturna™ (voretigene neparvovec) for the treatment of biallelic RPE-65-mediated Inherited Retinal Dystrophies

Applicant: Novartis Pharmaceuticals Australia Pty Ltd

Date of MSAC consideration: MSAC 79th Meeting, 28-29 July 2020
MSAC 80th Meeting, 26-27 November 2020

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](#)

1. Purpose of application

November 2020 Application

MSAC re-considered the Novartis Pharmaceuticals Australia (Novartis) application for public funding for voretigene neparvovec (VN) for the treatment of adult and paediatric patients with vision loss due to inherited retinal dystrophy (IRD) caused by confirmed biallelic RPE65 pathogenic variants and who have sufficient viable retinal cells at its November 2020 meeting, following receipt of Novartis' response to the issues raised by MSAC in its July 2020 deferral.

State and Territory Health Departments were provided an opportunity to make submissions to MSAC on the revised Novartis funding proposal.

July 2020 Application

An Applicant Developed Assessment Report (ADAR), requesting public funding for voretigene neparvovec (VN) for the treatment of adult and paediatric patients with vision loss due to inherited retinal dystrophy (IRD) caused by confirmed biallelic RPE65 pathogenic variants and who have sufficient viable retinal cells, was received from Novartis Pharmaceuticals Australia by the Department of Health.

VN was assessed as suitable for assessment by MSAC for joint funding by the Commonwealth and the States/Territories under the National Health Reform Arrangements (NHRA) on the basis that it will be administered to admitted patients in public hospital based Specialist Treatment Centres. As part of the NHRA arrangements, State and Territory Health Departments were provided an opportunity to make submissions to MSAC on the funding proposal.

2. MSAC's advice to the Minister

November 2020

MSAC supported joint Commonwealth and State/Territory funding of VN through the National Health Reform Agreement (NHRA). MSAC agreed VN addresses a high unmet clinical need for patients with biallelic RPE-65-mediated inherited retinal dystrophies for which no treatment is currently available and considered the available evidence indicates VN improves vision in patients with this condition, as long as the patient has sufficient viable retinal cells at the time of treatment.

MSAC considered the reapplication did not satisfactorily address the significant outstanding uncertainties related to the economic modelling, resulting in high and uncertain cost-effectiveness remaining a concern for the Committee. MSAC considered a further reduction of **redacted**% to the proposed price would be required to adequately address the remaining uncertainties associated with the cost-effectiveness of VN, the duration of treatment effect and the absence of a financial or patient number cap in the risk sharing proposal. MSAC considered the following measures should also be implemented in order to contain the risks associated with public funding:

- treatment must be delivered in accordance with the TGA Risk Management Plan (TGA RMP) treatment centre eligibility criteria;
- governance and prescribing rules to ensure treatment is directed to patients most likely to benefit including confirmation of RPE65 biallelic pathogenic variants through genetic testing in a NATA accredited laboratory, and the treating clinician to document the results of all investigations including the basis on which a decision is made that patient has sufficient viable cells. In addition, MSAC requested that data comparing the outcomes of the assessment of retinal cell viability with the outcomes of treatment with VN for Australian patients be provided to MSAC as part of its three-year review of VN (see also below);
- adherence to the TGA RMP requirements relating to the applicant providing treatment centres with appropriate training and support needed for successful product delivery;
- the financial risk associated with unsuccessful delivery of VN to the injection site is shared between the applicant and the payer (noting the applicant's proposed split payment arrangement would achieve this, as would an arrangement involving a single payment on response);
- a limit to one successful VN treatment per eye per lifetime;
- a pay-for-performance arrangement where the price for VN is significantly reduced (or not made if the arrangement was a single payment on response) if the patient fails to demonstrate at least a 0.3 log₁₀ (cd.s/m²) improvement in FST 60 days after VN administration;
- the applicant to provide a biannual report to the Department including information on the number of patients treated with VN in Australia and their individual baseline and post-treatment FST results. This report will be shared with the jurisdictions;
- data on the use of VN in Australia to be recorded in the Novartis international registry and made available to MSAC as part of the three-year review (see below), with the cost of data collection met by the applicant. MSAC considered the registry should track long term efficacy and safety of VN and include data about vision at baseline and post-treatment, how viable retinal cells were determined and genotype; and
- a full review of clinical effectiveness, cost-effectiveness and budget impact to be conducted by the MSAC no later than 3 years post the commencement of public subsidy, with the applicant to use its best endeavours to construct an economic model based on changes in FST for inclusion in the review submission. The price will be

renegotiated as part of this review. (Note: the applicant will provide a submission to initiate this review.)

MSAC advised that a “hub and spoke” approach to service delivery utilising one to two specialist Australian treatment centres would be appropriate for VN given the rarity of the condition, the need for specialist treatment centres and the clinical expert advice that Australian ophthalmologists who manage patients with IRDs are very aware of the availability of VN so will be able to refer appropriate patients to the treatment centres.

MSAC requested the Department work with the applicant to finalise arrangements to achieve a lower average-price and appropriate risk sharing arrangements. MSAC reiterated the importance of a three year review and provided advice regarding the nature of health outcome and resource use data to be collected following the commencement of public funding.

July 2020

After considering the strength of the available evidence in relation to the safety, clinical effectiveness and cost-effectiveness of VN for the treatment of adult and paediatric patients with vision loss due to inherited retinal dystrophy (IRD) caused by confirmed biallelic RPE65 pathogenic variants, MSAC decided to defer its advice on the suitability for joint Commonwealth and State/Territory funding to allow further negotiations with the applicant on the price and risk sharing arrangements.

MSAC accepted there is a high clinical need for effective treatment options for patients with a rare condition that causes progressive loss of vision leading ultimately to near-total blindness. MSAC agreed the available evidence indicates VN improves vision in patients with this condition. However, MSAC considered there were significant uncertainties with the economic modelling resulting in a high and uncertain cost-effectiveness, and with the financial estimates.

Consumer summary

Novartis Pharmaceuticals Australia Pty Limited has applied for public funding of voretigene neparvovec (VN, brand name: Luxturna[®]).

VN is a gene therapy that can be given to adults and children who have vision loss caused by pathogenic variants (mutations) in both copies of the RPE65 gene. This is a rare condition that can eventually lead to near total blindness.

MSAC considered Novartis' application on two occasions in 2020.

MSAC's November 2020 advice to the Commonwealth Minister for Health

MSAC agreed the applicant had addressed many of the matters MSAC had raised in its July 2020 consideration of public funding for VN.

MSAC supported the public funding of VN for the treatment of adults and children who have vision loss caused by pathogenic variants (mutations) in both copies of the RPE65 gene and who are assessed as having enough working cells in the retina of their eye that treatment is likely to be effective, as long as a lower price can be negotiated.

MSAC also noted that a number of other measures need to be put in place to manage the use of public funds for VN and that these measures will need to be agreed between the applicant and Commonwealth and State/Territory Governments.

MSAC's July 2020 advice to the Commonwealth Minister for Health

MSAC acknowledged the impact on the people's lives of a condition that causes progressive loss of vision, and that even in its early stages, can cause nystagmus (rapid involuntary eye movements), night blindness and problems adjusting to rapid changes in light conditions.

MSAC noted that VN is the first potential treatment for this condition. Before a patient can be treated with VN, the patient's treatment team needs to do a series of tests to make sure the patient still has enough working cells in the retina of their eye for treatment to be effective.

MSAC agreed the available evidence indicates VN improves vision in people with this condition, and that the improvement has been shown to last for at least four years.

MSAC advised that VN is a very expensive therapy. MSAC advised that more work needs to be done to ensure that the price paid for VN is value-for-money and that the right measures are in place to manage the use of public funds for VN, including a registry that allows the outcomes of treatment to be monitored into the future.

3. Summary of consideration and rationale for MSAC's advice

November 2020 MSAC

MSAC recalled it had a number of concerns with the previous Novartis public funding proposal for VN, as summarised below.

Summary of key matters of concern

Component	Matter of concern (November 2017)	How the reapplication addresses it
Clinical effectiveness	Durability of response	No new relevant clinical data were identified.
Cost-effectiveness	Mismatch in measures of effectiveness of VN: between primary outcome in RCT (MLMT), outcome measures used to define health states in the economic model (VA and VF) and outcome proposed as basis for risk sharing (FST).	Not addressed
	Use of healthcare, not societal perspective	Addressed
	Selective use of utilities that favour VN	Proposed using adjusted HUI-3 utilities for incident population and unadjusted utilities for prevalent population to arrive at a range of ICER/QALY. Reapplication also proposed MSAC take into account consequences of treatment for well-being of family members or carers, which are not captured by economic analysis.
	Time horizon	Asserts base case assumption that efficacy will be maintained over 40 years is reasonable. Applicant also asserts use of a shorter time horizon and a 5% discount rate arguably leads to double counting of longer term uncertainty.
	Uncertainty regarding costs of ancillary services in Australia	Not addressed, will require data collection by IHPA
	High ICER per QALY	Acquisition price reduced to \$redacted (from \$redacted), with claim that final average price will be \$redacted (assumes 93% response rate and only 50% of price paid for non-responders)
Financial	Likely overestimated patient numbers	Three year Deed of Agreement with no caps on patient numbers, as small numbers overall, and low risk of leakage to patients with other conditions.
Risk management	Requirement for clinician to document results of all investigations, including basis on which decision is made that patient has sufficient viable cells.	Addressed, as included in the TGA Risk Management Plan
	Measures be implemented to ensure applicant's commitment to deliver the training and support needed for successful service delivery.	Addressed, as included in TGA Risk Management Plan.
	Financial risk associated with unsuccessful delivery to be shared between applicant and payer	Addressed by proposal for split payments: 50% at order and 50% on demonstration of response.
	Financial risk associated with non-responders (assuming successful delivery) to be shared between applicant and payer	Addressed through proposal for split payments: at order and on demonstration of response.
	Proposed threshold for response of 0.3 log units on FST may not represent clinically meaningful change.	Argues this is an appropriate measure of response, particularly for incident patients whose disease has not yet progressed.
	Pay for performance arrangements administratively burdensome and could be replaced with single payment on response	Not agreed
	MSAC review within 3 years of funding commencing, with potential for price to be re-negotiated as a result of review	Agreed
	Registry and collection of cost data	Registry agreed. Cost data will be collected through IHPA processes.

MSAC again acknowledged the clinical need for effective treatment options for this rare and significantly disabling condition and agreed the available clinical data supports the claim VN provides a relevant patient benefit in improving vision and preventing vision deterioration and that this benefit can be expected to continue for up to 4 years, and, based on the limited data from Study 101/2 potentially for up to 7.5 years. MSAC also recalled the clinical expert advice that photoreceptor cells do not replicate or regenerate, so there is biological plausibility for VN having a longer-term treatment effect, but whether this is true in practice remains to be established.

MSAC noted the revised subsidy proposal used the same economic model as the July 2020 subsidy proposal, with variations to some of the inputs. MSAC considered this approach to the economic modelling does not address the fundamental mismatch between the primary outcome in the clinical trial (MLMT), the outcomes used to define health states in the model (VA and VF) and the outcome proposed for use in the pay-for-performance arrangement (FST). MSAC noted the applicant had attempted to address this issue in the reapplication by suggesting the utility adjustment that was applied to the HUI3 utility Health State 1(HS1) in the July 2020 base case (see Table 17) be applied to incident patients, and unadjusted HUI3 utilities be applied for prevalent patients (“who have experienced emotional and psychological challenges from the prospect of having irreversible vision loss until they are blind” (reapplication, page 21)). MSAC noted that this approach resulted in ICERs of **\$redacted** and **\$redacted** per QALY, respectively (see Table 11), or **\$redacted** using the MSAC preferred EQ5D(L) utilities in place of the unadjusted HUI3 utilities.

However, MSAC noted these ICER values continue to assume a duration of treatment effect of 40 years. If the duration of effect is reduced to 20 or 15 years, the ICER increases to **\$redacted** and **\$redacted**, respectively (using EQ5D(L) utilities).

MSAC agreed with the applicant that incident and prevalent patients will experience benefit in different ways, and considered it may be better to express response as an ‘absence of deterioration’ and for this to be captured in the economic modelling with a baseline distribution of FST values rather than ad hoc (differential) adjustments to the utility values applied to HS1.

MSAC also agreed with the applicant that it is appropriate to give consideration to the benefits of treatment with VN to family members and carers but that those benefits are not captured in the economic model. MSAC did not agree it is appropriate to vary the discount rate from the standard 5%, noting MSAC already has flexibility to support subsidy at higher ICER/QALY levels if it considers that appropriate (eg in the context of a severe disease with limited or no treatment options).

However, overall, MSAC remained concerned that the structural issues with the model had not been addressed in the reapplication thus making interpretation and application of the economic modelling difficult.

Against this background and in the context of a high clinical need for effective treatments for this rare condition, the MSAC considered a further reduction in price would be appropriate to manage the remaining uncertainties associated with the subsidy proposal. Thus MSAC advised that the cost-effectiveness of VN, although high and uncertain, would likely be acceptable if the final average price was **redacted**% lower than proposed in the reapplication, and if the measures described in Section 2 above were implemented to contain the risks associated with public funding.

In this context, MSAC noted the cost-effectiveness of VN would be re-evaluated 3 years after subsidy commenced (see below) and the price would be renegotiated (upwards or downwards) as the result of that review.

MSAC noted the applicant proposed a simplified payment arrangement where 50% of the acquisition price is paid on order and 50% upon demonstration of an agreed response 60 days post VN administration. As previously, MSAC noted a single payment would be administratively simpler and considered that if this payment was made on demonstration of response at 60 days post VN administration, this would also manage the risk of non-response due to unsuccessful delivery, and non-response due to a lack of viable retinal cells. MSAC requested the Department explore this alternative payment arrangement with the applicant.

MSAC noted the applicant continued to assert that the threshold for response of $-0.3 \log_{10}[\text{cd.s/m}^2]$ units on FST is the appropriate measure to use both for patients who maintain vision and those who gain vision. The applicant noted VN will be increasingly given to patients whose disease has not yet progressed (incident patients), thus many would maintain healthy vision. A log change in FST which is equivalent to a 2 lux change in MLMT as suggested by MSAC as a measure of response would diminish the value that VN offers incident patients whose disease has not yet progressed.

The applicant contended a $0.3 \log_{10}[\text{cd.s/m}^2]$ in FST improvement represents a doubling in white light sensitivity in RPE65 mutation-associated inherited retinal disease, a progressive disorder for which FST scores would be expected to worsen over time without treatment with VN, and reiterated the results of a post-hoc analysis of the Phase 3 clinical trial showed that the FST improvement threshold of $\geq 0.3 \log_{10}[\text{cd.s/m}^2]$, averaged over both eyes, accurately classified a patient's response to VN one hundred percent of the time

The applicant also noted data from Australian patients treated with VN will be captured in a registry as part of the TGA required Risk Management Plan. Baseline characteristics, safety and efficacy outcomes will be captured as well as surgical outcome. FST will be one of the clinical measures captured. The FST test will be performed only by a technician, based on an FST protocol, who has successfully completed the Novartis-specific FST training, as evidenced by written training records.

On balance, MSAC considered a $0.3 \log_{10}[\text{cd.s/m}^2]$ in FST an appropriate measure of response for the first 3-years of public funding, and requested that the FST data captured by the registry be included in the 3-year review submission.

Contingent on agreement on a lower average price, MSAC supported the applicant's proposal that no financial or patient number caps be included in a funding agreement. MSAC considered this approach reasonable given the expected small patient numbers (up to 57 over 3 years which MSAC considers a likely overestimate), the low risk of leakage outside the target patient population with biallelic RPE-65-mediated inherited retinal dystrophies and a 3-year funding agreement. As noted in Section 2 of this PSD, MSAC requested the applicant provide the Department 6-monthly status reports, including, among other things, the number of patients treated with VN in Australia.

MSAC noted the applicant has confirmed data from Australian patients treated with VN will be captured in a registry as part of the TGA required RMP. Baseline characteristics, safety and efficacy outcomes will be captured as well as surgical outcomes (reapplication page 24). MSAC requested the requirement for data collection also be captured in any funding agreement, and that the collected data be included in the 3-year MSAC review submission.

MSAC indicated it wished to undertake a full review of the clinical effectiveness, cost-effectiveness and budget impact of funding VN no later than 3 years post the commencement of public subsidy, with the applicant to use its best endeavours to construct an economic model based on changes in FST for inclusion in the review submission (Note: the applicant will provide a submission to initiate this review).

MSAC noted there is no Australian experience with VN, resulting in uncertainty in the ancillary costs associated with treatment delivery. MSAC noted the Independent Hospital Pricing Authority (IHPA) will work with the jurisdictions to collect high level data on the costs of treating patients with VN for reconciliation of National Health Reform funding. MSAC noted the jurisdictions and treatment centres collect further data on the cost breakdown and the ancillary costs associated with treatment. MSAC recommended the applicant work with the treatment centres to verify the ancillary costs associated with treatment delivery in Australia for inclusion in the review submission.

MSAC noted the applicant's claim the **\$redacted** price offered in the reapplication "is lower than in any other country in which this treatment is available" (reapplication page 27). However, this claim cannot be verified based on publicly available information (as overseas prices are subject to confidentiality arrangements) and the applicant provides no other basis on which it can be verified.

Finally, the MSAC noted the very high acquisition prices reported publicly for gene therapies. The MSAC advised the Minister may wish to consider alternative approaches to pricing gene therapies going forward in order to best ensure these therapies are affordable for taxpayers as well as being cost-effective.

July 2020 MSAC

MSAC noted the ADAR requested public funding for VN for the treatment of adult and paediatric patients with vision loss due to inherited retinal dystrophy (IRD) caused by confirmed biallelic RPE65 pathogenic variants. MSAC noted this is a rare condition with no current treatment options other than best supportive care. MSAC noted VN is a gene therapy that is designed to deliver a normal copy of the gene encoding the human retinal pigment epithelial 65 kDa protein (*RPE65*) to cells of the retina in persons with reduced or absent levels of biologically active *RPE65* caused by pathogenic variants in the *RPE65* gene.

MSAC noted VN meets the NHRA definition of a highly specialised therapy in terms of average treatment cost (greater than \$200,000) and delivery setting (public hospital admitted patient) and that VN is not otherwise funded through a Commonwealth program or the costs of the therapy would be appropriately funded through a component of an existing pricing classification.

MSAC provided the following advice on the applicant's proposal for public funding.

Access and eligibility

MSAC noted patients with IRDs are usually diagnosed on the basis of medical history and clinical symptoms with genetic testing offered subsequently to identify the causative gene. MSAC noted over 100 genetic pathogenic variants, including the one involving the RPE65 gene, result in IRDs. MSAC noted that access to genetic testing is not the same in all Australian jurisdictions, but was satisfied that a "hub and spoke" approach to service delivery involving 1 – 2 Specialised Australian Treatment Centres would adequately address this. In forming this view, MSAC also noted the clinical expert advice that the Australian

ophthalmologists who manage patients with IRDs are very aware of the availability of VN, and have been actively searching for patients with this condition for many years.

MSAC noted successful treatment with VN requires the presence of sufficient viable retinal cells and both the commentary and the ESC report recommended consideration be given to defining an assessment method and thresholds for retinal cell viability. MSAC accepted the clinical expert advice that the results of a range of both functional and structural assessments are used to determine if a patient has sufficient viable retinal cells and considered it would be appropriate for this to be a clinical judgement made by the specialist treatment team, rather than specify the tests and thresholds used to define this requirement for use. MSAC noted that in patients who respond to treatment, the effect on light sensitivity is measurable (using FST) by 30 days post injection. MSAC advised that, in the event public funding for VN proceeds, prescribing clinicians should be required to document the results of all investigations and their reasoning for concluding a patient has sufficient retinal cells to be eligible for VN, and that the financial risk associated with using VN in a patient who does not respond be shared between the applicant and the payer. In addition, MSAC requested that data comparing the outcomes of the assessment of retinal cell viability with the outcomes of treatment with VN for Australia patients be provided to MSAC as part of its three-year review of VN (see below for further information on MSAC's proposed review).

MSAC agreed the lower age limit for treatment with VN should be aligned with the TGA approved PI. MSAC did not consider it was necessary to define an upper age limit for therapy, noting that a specialist will undertake formal assessment of retinal cell viability for all patients who have a diagnosis of IRD caused by confirmed biallelic RPE65 pathogenic variants.

MSAC noted treatment with VN requires successful delivery to the subretinal site of action in a highly specialised procedure. MSAC also noted the specialised requirements for handling and storing VN. MSAC advised that, in the event public funding for VN proceeds, measures be implemented to ensure the applicant's commitment to delivering the training and support needed to assure these aspects of service delivery are maintained into the future. MSAC also considered it appropriate to require the treating surgeon to document successful delivery and for the financial risks associated with unsuccessful delivery to be shared between the applicant and the payer, except when the unsuccessful delivery is attributable to a product fault, in which case the cost should be borne by the applicant.

MSAC considered treatment should be limited to one successful delivery per eye per patient lifetime.

Effectiveness and Safety

MSAC noted the primary data on the effectiveness of treatment with VN comes from a single trial, study 301. Study 301 was a randomised controlled trial comparing VN given in both eyes (n = 21) to best supportive care (BSC, n = 10). After 1 year, patients in the BSC group (n = 9) could have VN. Follow up data up to 4 years are available for 29 patients (20 who commenced in the VN arm and 9 who commenced in the BSC arm). MSAC noted the limited evidence available (small patient numbers, no Australian clinical trial sites, a single effectiveness trial with crossover allowed, and short follow-up in the context of a lifelong condition) created some uncertainty that the observed effect would be replicated in clinical practice, but overall considered the evidence base suitable for decision making in the context of a very rare condition.

MSAC noted the primary measure of effectiveness for study 301 was the multiluminance mobility test (MLMT) which measured the effect of functional vision in a standardised way at specified light levels. Secondary outcome measures included visual field (VF), visual acuity (VA) and light sensitivity (FST). MSAC noted only VF and VA were used to define health states in the economic model but only FST was proposed as an outcome measure in the risk sharing arrangement. This mismatch in outcomes was a key issue for MSAC (see also Value for Money and Cost to Governments section below).

MSAC noted that at year 1, the mean bilateral MLMT change score was 1.8 in the intervention group compared to 0.2 in the control group, which resulted in a statistically significant difference of 1.6 (0.72, 2.41, $p=0.001$). MSAC agreed the clinical evidence shows that VN treatment was associated with statistically significant and, based on expert opinion, clinically relevant differences in the change in the MLMT score. However, MSAC noted this measure was developed for use in VN clinical trials only and cannot be replicated as a performance measure in routine clinical practice.

MSAC noted the change in VF, although statistically significant, showed important inter-test variability, was not a pre-specified outcome and no clinically meaningful threshold was proposed. Finally, the change in VA did not show a statistically significant difference at 1 year on the pre-specified Holladay scale, however a statistically significant difference was seen in a post hoc analysis using the Lange scale (7.4 letter gain, treatment difference -0.16 (95% CI: -0.31, -0.01; $p = 0.035$). No changes reached the applicant's proposed clinically meaningful thresholds.

MSAC noted the clinical expert's advice on the difficulties inherent in measuring VA and VF in patients with IRD and accepted that overall, change in light sensitivity (FST), may have the most utility for use in routine clinical practice. However, the MSAC also noted that the applicant did not propose a clinically meaningful threshold for this measure, rather relying on the fact that the 27/29 MLMT responders (MLMT change ≥ 1) in the clinical trial had a change of >0.3 log units in FST and 2/29 MLMT non-responders had a change of <0.3 log units, thereby nominating a 0.3 log change in FST as a measure of response. However, the CSR for Study 301 suggests a clinical significance threshold of 1 log unit change in FST (Spark CSR for study 301, 1 year, pp 117), and the UK NICE also cites this degree of change as the company's defined threshold for clinical significance (NICE, Final Evaluation Report, August 2019, paragraph 4.17).

Overall, MSAC agreed that, although limited, the available evidence supports the claim VN provides a relevant patient benefit in improving vision and preventing vision deterioration and that this benefit can be expected to continue for up to 4 years, and, based on the limited data from Study 101/2 potentially for up to 7.5 years. MSAC also noted the clinical expert advice that photoreceptor cells do not replicate or regenerate, so there is biological plausibility for VN having a longer-term treatment effect. Nonetheless, MSAC considered that duration of effect remains an area of uncertainty (see also Value for Money and Cost to Governments section below).

MSAC agreed that, based on the available evidence, VN appears to have an acceptable safety profile with most of the adverse events reported to date being related to the administration procedure.

Value for Money and Cost to Governments

MSAC noted the applicant presented an economic model to estimate the value, in terms of incremental cost per quality adjusted life year (QALY) gained of treatment with VN compared with BSC.

MSAC noted the model did not use the primary clinical trial outcome, MLMT, because there are no data linking this outcome to costs, utilities or mortalities. MSAC noted the same issue appears to exist for FST, however it considered this alone did not adequately justify why FST was not used. The modelled health states were instead based on the worst of either VA or VF and were intended to capture progressively severe levels of visual impairment (Table 14). However as noted above, VA and VF may not be very useful as single measures of response to treatment with VN. Moreover clinically relevant changes in VA and VF were not observed in trial 301. Although MSAC acknowledged the available data may have necessitated this approach, MSAC considered it made interpretation and application of the economic modelling difficult.

MSAC agreed it was appropriate to use a health care perspective to inform the base case as opposed to the societal perspective initially used in the application, noting this increased the applicant's proposed base case incremental cost-effectiveness ratio from **\$redacted/QALY** gained to **\$redacted/QALY** gained.

MSAC noted the model outcome was highly sensitive to the duration of VN efficacy and to changes in utilities and that the assumptions used to populate the model base case for these parameters are highly uncertain. MSAC further noted the moderate sensitivity of the model to health care costs, the use of cross over data to inform transition probabilities and the age of entry into the model (see Table 16).

In terms of the duration of benefit, the model assumes VN treatment effect at 1 year is maintained for up to 40 years in the model, when the majority of follow-up data extends only to 4 years, with limited additional data available to 7.5 years. The MSAC noted that reducing the assumed duration of effect to 15 years, increases the ICER to **\$redacted/QALY** and reducing it further to 7.5 years increases the ICER to **\$redacted/QALY** gained. The applicant noted in its pre-MSAC response that reverting to natural history decline "immediately after 7.5 years" would not be realistic.

The MSAC considered the selection of the base case utility values were not adequately supported, noting they were a major driver of the economic model. The MSAC considered the utility values included by the applicant were selective and favoured the intervention, given they created the widest spread of utility values across all health states, thereby enhancing the apparent effectiveness of VN in the model ($-0.04 - 0.75 = \Delta 0.79$). MSAC noted the base case takes the HUI-3 utility values from Lloyd, 2019 for all five health states, with the exception that the utility for health state one (moderate vision impairment) is increased from the 0.52 value reported by Lloyd to 0.75 derived from the study by Brown, 1999 because of the applicant's concerns whether health state one is sensitive enough to capture meaningful differences for patients. In addition, the utility value for health state five is negative 0.04, being worse than death. A sensitivity analysis was carried out with all utility weights taken from Brown, 1999 with the ICER increasing to **\$redacted/QALY**. If the alternative EQ-5D (5L) utilities from Lloyd, 2019 are used in the model, the ICER increases to **\$redacted**. On balance, MSAC considered the EQ-5D (5L) most appropriate for informing the base case noting, the 0.71 utility value for health state one is close to the 0.75 value used by the applicant in the base case, the utility for health state 5 is a more plausible 0.15, and the

overall range in utilities across all five health states is a more plausible 0.56, compared to 0.79 (see Table 17).

Thus MSAC considered that the current economic evaluation base case delivers an overly optimistic estimate of the VN cost per QALY. Although acknowledging the promising clinical trial results and the difficulties in modelling long term outcomes in the context of a rare condition, MSAC considered a revised base case that take into account the issues detailed above would provide a more informative basis for determining a cost effective treatment price.

MSAC noted the applicant estimates up to **redacted** patients will receive treatment with VN over the first 6 years of listing (Table 19), with around two-thirds of this number being prevalent patients (**redacted** patients) and around one-third being incident (up to **redacted** per year). The clinical expert considered these numbers to be greatly overestimated, noting that despite ophthalmologists who work with patients with IRDs having actively looked for patients with biallelic RPE65 pathogenic variants for some years, only 7 Australian patients have been identified. The clinical expert also did not expect the number of incident patients to be as high as the **redacted** per year estimated by the applicant. However, MSAC also noted that based on prevalence data presented to the USA FDA the prevalent patient pool could be between 78 – 228 patients. Although MSAC considered the risk of leakage outside the population with biallelic RPE65 pathogenic variants to be low, MSAC noted the uncertainty in patient numbers to have large financial implications for payers. MSAC advised that a risk sharing arrangement may be appropriate to manage this financial uncertainty.

MSAC also noted there is uncertainty that all the costs of the ancillary services associated with the delivery of this therapy have been captured, particularly as no Australian centres have delivered treatment with VN to date. MSAC advised that work be undertaken to measure the actual costs of delivering treatment with VN in practice and requested the outcomes of that be provided to MSAC as part of its three-year review of VN should VN be recommended for public funding (see below for further information on MSAC's proposed review).

Risk Management and Review

MSAC noted the applicant outlined a proposed Pay for Performance (PfP) arrangement in its pre-MSAC response. MSAC considered the PfP as currently proposed may go some way to sharing the financial risk associated with patients without sufficient viable retinal cells being treated with VN, as it proposes splitting the payment for VN into two parts with the second part only being payable if the patient achieves a pre-specified response by 30 – 60 days after VN administration. However, the MSAC noted the proposed threshold for response of 0.3 log units on FST may not represent a clinically meaningful change, given test-retest variability for FST is +/- 0.3 log units (Maguire 2019). Therefore the MSAC questioned whether a ≥ 1 log change in FST should be used as defining a clinically meaningful response for the terms of the PfP, or conversely the log change in FST which is equivalent to a 2 lux change in MLMT.

MSAC was not convinced of the need for the PfP to include a durability of response measure at 1 year, noting the available clinical trial evidence suggests that the benefit of treatment with VN is sustained for at least four years in responders.

MSAC also noted the PfP arrangements proposed by the applicant are administratively burdensome and suggested a simpler arrangement involving a single payment on

achievement of an agreed response following a successful injection procedure may be appropriate for managing the risks identified by MSAC.

MSAC advised it may be appropriate for the risk management plan to manage the financial uncertainty for payers.

MSAC advised that, in the event public funding for VN proceeds, with a full review of clinical effectiveness, cost effectiveness and budget impact to be conducted by the MSAC no later than 3 years post the commencement of public subsidy (note: Novartis will provide a submission to initiate this review). MSAC noted the applicant will keep a registry of patients treated with VN which tracks long term efficacy and safety. MSAC agreed this registry should include data about vision at baseline, how viable retinal cells were determined, and genotype. MSAC requested information from the registry be included in the applicant’s review submission. MSAC noted the price for VN may need to be renegotiated as a result of this review.

4. Background

Application 1623- voretigene neparvovec for the treatment of biallelic RPE65-mediated inherited retinal dystrophies, has not been previously considered by MSAC.

This application followed a fit-for-purpose pathway, therefore a PICO Confirmation outlining the proposed use of VN in the Australian clinical practice was not presented to the PICO Confirmation Advisory Sub-Committee (PASC). The ADAR proposed a PICO which is largely based on the indication submitted to the Therapeutics Goods Administration (TGA) and is summarised in Table 1.

Table 1 PICO basis for voretigene neparvovec MSAC submission

Patients	Adult and paediatric patients with vision loss due to IRDs caused by confirmed biallelic RPE65 pathogenic variants and who have sufficient viable retinal cells.
Intervention	Voretigene neparvovec
Comparator	BSC
Outcomes	<p><u>Primary and patients relevant outcome</u></p> <ul style="list-style-type: none"> • Mobility testing (MLMT, measure of functional vision); • FST (measure of retina sensitivity to light, probes potential differential effects on rod versus cone photoreceptors); • Visual Acuity (measure of central vision, foveal/cone mediated function); • Visual Field (measure of visual field, rod mediated function); • Macula sensitivity; • Foveal sensitivity; • Visual function questionnaire; • Safety and tolerability. <p><u>Economic/Financial outcome</u></p> <ul style="list-style-type: none"> • Total and disaggregated costs for the intervention; • Predicted long term outcomes of treatment; • Cost per (quality adjusted) life year gained; • Cost per blindness free years; • Number of patients eligible and likely to be treated; • Financial implications for the Australian Government.

Abbreviations: FST = Full-field light sensitivity threshold; BSC = best supportive care; MLMT = Multi-luminance mobility test; MSAC = Medical Services Advisory Committee.

Source: Developed during the evaluation process.

The Commentary noted the MSAC may wish to consider the following two aspects in regard to the proposed population:

- Paediatric population would consider patients aged two and above, however, the trial inclusion criteria defined patients > three years of age.
- There is uncertainty on the criteria that will be applied in Australia to assess patients for sufficient viable retinal cells and how this will be ensured in the current clinical setting. In the event VN is recommended for public funding, the criteria used in the pivotal trial (Study 301) to assess sufficiency of viable retinal cells should be considered for implementation in the Australian clinical setting.

The Pre-ESC response suggests this assessment is best left to the treating ophthalmologist but indicates the applicant is willing to work collaborative on developing criteria for sufficiency of viable retinal cells if considered appropriate.

5. Prerequisites to implementation of any funding advice

The applicant submitted a product registration application for VN to the TGA on 27 June 2019 and an orphan drug designation was approved on 15 March 2019. A TGA registration decision is expected by 31 August, 2020. As VN is a gene therapy, a parallel submission to the office of gene therapy regulation (OGTR) was also submitted (outcome expected in July 2020).

All patients require RPE65 confirmed biallelic pathogenic variants through genetic testing. All genetic diagnoses are required to be performed by a certified laboratory (NATA accredited in Australia) with results made available to the patients or legal guardian with appropriate genetic counselling. There are two broad approaches to sequencing that are commonly used in Australia: (1) Sanger sequencing (useful in the diagnosis of a disease predominantly caused by mutations in a single causative gene) and; (2) Next Generation Sequencing (NGS) (allows parallel sequencing of numerous DNA fragments at the same time). The most commonly used NGS approaches are: (a) targeted gene panels (TGP), (b) whole exome sequencing (WES) and (c) whole genome sequencing (WGS). The MSAC noted the second of these approaches is more likely to be used in usual practice.

In order to ensure the effective delivery of VN, implementation of one or possibly two Specialised Treatment Centres (STC) nationally, with a multi-disciplinary team (MDT) including a specialist ophthalmologist with expertise in the care and treatment of patients with IRDs, genetic testing and counselling services, and presence of/affiliation with a retinal surgeon experienced in subretinal surgery and capable of administering VN (a highly specialised procedure) was proposed. Proper pharmacy equipment for the storage and preparation of VN (e.g. class II Laminar Flow Cabinet) would also be required, for which a capital investment may be necessary.

The Risk Management Plan (RMP), as part of the TGA application, includes intensive hands-on training of eye surgeons and product handling training of pharmacists to ensure quality of service. The applicant stated the vitreoretinal surgeon responsible for the vitrectomy and subretinal injection will be required to attend overseas training while the pharmacists involved in the preparation of VN will require onsite training as per the proposed RMP. This costs of training will be met by the applicant.

The applicant will also conduct a product registry study in the EU (final report expected June 2030) and other countries to follow newly treated patients for five years and collect long-term data on the real-world use of VN. The TGA RMP round 1 evaluation report stated that the applicant did not propose this registry for Australia and recommended including data from

Australian patients in an Australian or the international registry (p. 3 of the RMP evaluation report, Attachment 1 of the submission). In its application for subsidy, the applicant noted an Australian product registry is likely to be necessary to support a Managed Access Program (see also Section 4). It is expected that the cost associated with data collection will be met by the applicant.

6. Proposal for public funding

VN for the treatment of adult and paediatric patients with vision loss due to IRD caused by confirmed biallelic RPE65 pathogenic variants and who have sufficient viable retinal cells, is proposed for shared public funding between the Commonwealth and State/Territory governments through the National Health Reform Agreement (NHRA). Accordingly, no MBS item descriptor was proposed in the submission.

The submission stated that VN would require a managed access funding arrangement in order to secure reimbursement due to the high uncertainty surrounding its utilisation and ongoing treatment effect. To support a managed access programme in Australia, the applicant noted that an Australian product registry is likely to be necessary. In addition, the applicant noted that elements of the VN funding proposal such as the high cost per patient and the once-only treatment with expected lifetime benefits, mean it expects that the funding arrangements for VN will be complex.

The Commentary notes funding structures in the form of Risk Sharing Arrangements (RSA) could include payments by instalment, PBS-style expenditure caps, rebates for partial/non-responders and outcome-based payments. The identification of robust and reproducible criteria for establishing eligibility for treatment and for measuring patient response will be critical to ensuring the cost-effectiveness of VN in clinical practice, particularly as the primary outcome measure used in the pivotal clinical trial is not an outcome measure that can be adopted for use in routine clinical practice.

Currently, in Australia, the funding of and access to genetic testing for this disease is via public hospitals. There is no MBS listed genetic test to confirm an IRD. The costs of genetic testing are included in the application.

7. Summary of state and territory submissions

The state submissions to MSAC made the following comments in relation to the safety, effectiveness, cost effectiveness and overall cost of treatment with VN:

- There has been no Australian experience with this treatment to date,
- A number of potentially eligible patients have been identified, but there is continuing uncertainty about the total number of eligible patients,
- There is uncertainty about whether the availability of a funded treatment option will increase the demand for testing,
- The actual costs associated with delivering this therapy in practice need to be collected and reviewed, and
- Although supporting the applicant's proposal that one to two specialised treatment centres be established nationally, the states noted this creates potential governance and co-ordination issues (Note: the Department and States will work to progress these matters outside of the MSAC process).

These comments were taken into account by MSAC during its considerations of the VN subsidy proposal (see also Section 3). MSAC noted the Department and States will work

together to progress issues relating to the governance and co-ordination of treatment delivery.

8. Summary of public consultation feedback/consumer Issues

One consumer comment was received for this application. This comment detailed the impacts of living with a condition that limits vision, particularly at night or when light conditions change quickly. It noted the potential for VN to improve and/or stabilise vision and to prevent blindness and expressed the hope that this treatment could be made available to Australians with IRDs caused by biallelic RPE65 pathogenic variants.

9. Proposed intervention's place in clinical management

Description of Proposed Intervention

VN is a recombinant adeno-associated viral serotype 2 (AAV₂) gene therapy which must be delivered in close proximity to the retinal pigment epithelium (RPE) target cells. To access the retina, the vitreous gel that fills the eye is completely removed through a vitrectomy. VN is then injected into the space between the retina and the RPE, as a “subretinal” injection.

The application proposes VN should be delivered through one or possibly two specialised treatment centres (STCs) nationally (likely to be a tertiary public hospital), with a multi-disciplinary team including a specialist ophthalmologist with expertise in the care and treatment of patients with IRDs, genetic testing and counselling services, and presence of/affiliation with a retinal surgeon experienced in subretinal surgery and capable of administering VN (a highly specialised procedure).

The pharmacy in the STC will need access to proper equipment for the storage and preparation of VN (e.g. class II Laminar Flow Cabinet), and pharmacy personnel will need to be trained on its handling.

Description of Medical Condition(s)

Biallelic RPE65 pathogenic variants, the most severe form of IRD, are a major cause of early-onset blindness. They occur when there are pathogenic variants in both alleles of the RPE65 gene in RPE cells. Depending on the type of RPE65 pathogenic variant, the gene produces proteins which lack varying degrees of function, hence leading to different diagnoses which include, among others, Leber congenital amaurosis (LCA), severe early childhood onset retinal dystrophy (SECORD) and retinitis pigmentosa (RP).

The current and proposed clinical algorithms were convened by the applicant and included an expert advisory panel consisting of three retinal surgeons, six adult paediatric ophthalmologists and two geneticists (refer to Figure 1 and Figure 2 below).

The ADAR stated that the “Clinical practice guidelines for the assessment and management of patients with IRD’ for use in Australia” are currently under development. A draft of the guidelines was accessed during the evaluation. The Commentary noted that the draft version of the guidelines did not provide specific guidance on the management of gene therapy for this patient population. The assessment and management for patients with suspected IRDs, based on the draft Australian IRD guidelines, falls into four areas:

1. Establishing the clinical diagnosis of an IRD;
2. Determining the visual function level;
3. Establishing the genetic diagnosis and genetic management; and

4. Monitoring of disease progression (natural History) and preparation for therapeutic interventions.

The Commentary noted the introduction of VN to current practice in Australia would position this treatment as a first line therapy in the defined target population. Because this is a novel therapy likely to positively impact the natural history of IRD patients with a biallelic RPE65 pathogenic variant, there is a potential incentive to more actively identify these patients which in turn may increase the use of the diagnostic tools confirm diagnosis.

The main co-administered and substituted interventions are summarised in the Table 2. In addition, because vitrectomy surgery is associated with a higher risk of developing/progression of cataracts, the Commentary noted the use of cataract surgery may increase among this patient population.

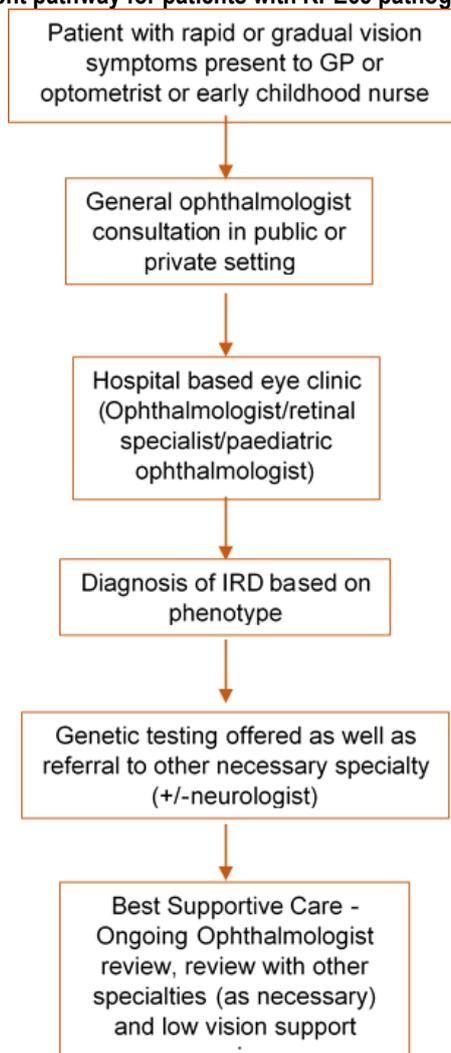
Table 2 Co-administered and substituted interventions required as part of the course of treatment.

Co-administered interventions	Substituted interventions
Vitrectomy	Low vision support services (this is unlikely to occur for all patients).
Other diagnostics to assess the phenotype of the disease (these services are currently provided as routine practice in the diagnose of IRD).	
Genetic test to confirm biallelic RPE65 pathogenic variant	
OCT to confirm retinal cell viability	
Immunomodulatory regimen with prednisone (or equivalent) 3 days prior treatment for up to 18-30 days.	
Additional follow-up with consultant ophthalmologist.	

Abbreviations: IRD = inherited retina dystrophies; OCT = optical coherence tomography.

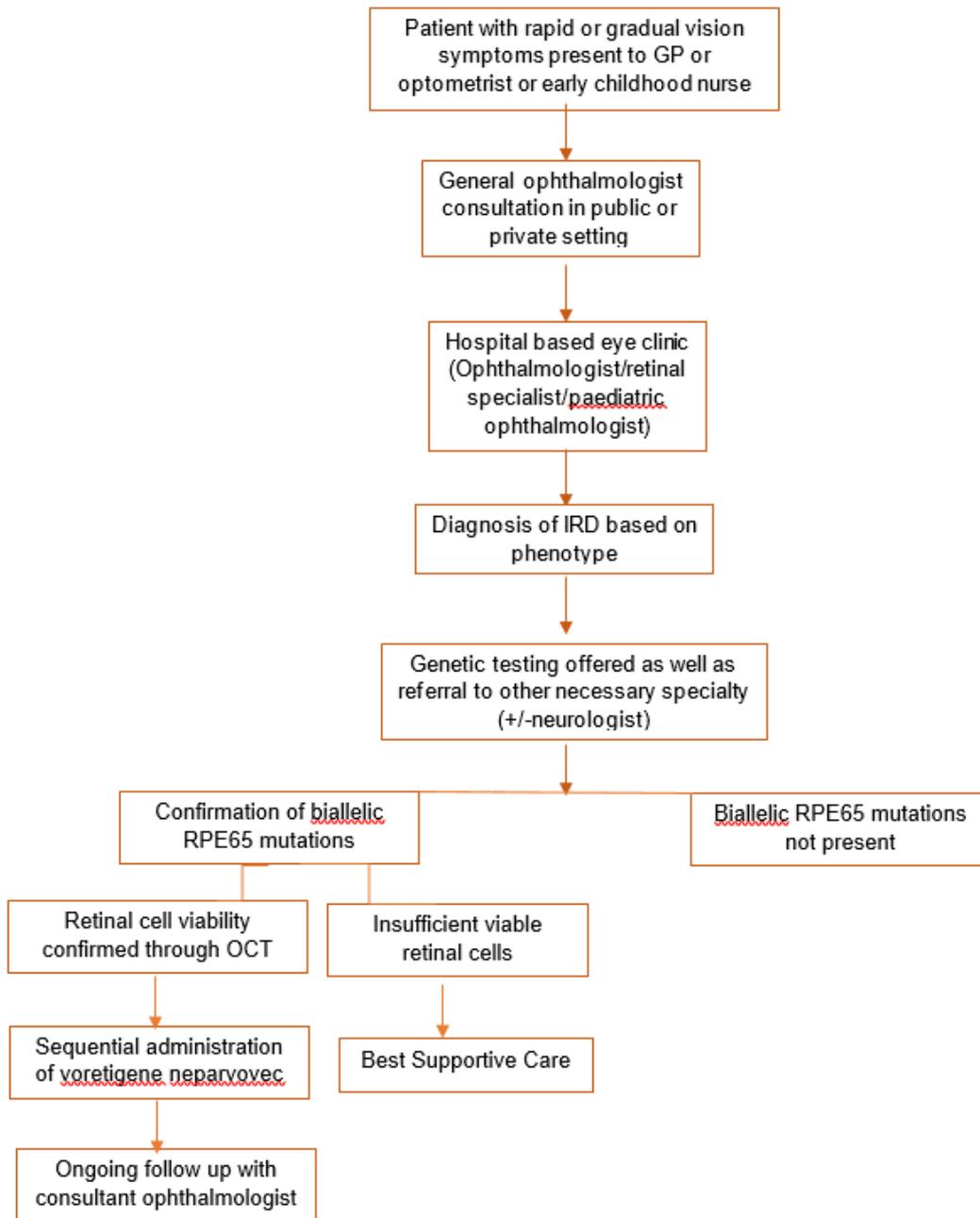
Source: Compiled during the evaluation.

Figure 1 Current clinical management pathway for patients with RPE65 pathogenic variant associated IRD.



Abbreviations: GP = general practitioner; IRD = inherited retinal disorder.
Source: Figure 11, p. 30 of the Submission.

Figure 2 Current clinical management pathway for patients with RPE65 pathogenic variant associated IRD.



Abbreviations: GP = general practitioner; IRD = inherited retinal disorder; OCT = Optical coherence tomography; RPE = Retinal pigment epithelium.

Source: Figure 12, p. 36 of the Submission.

The Commentary stated that overall, the clinical management algorithms were considered reasonable, however three aspects merited further attention:

1. The current algorithm assumes that all patients are subject to genetic testing to confirm diagnoses. However, the genetic test is not MBS listed and the current funding structure and access is through the States via public hospitals. The ADAR noted that the access to this service varied across regions. The ADAR does not identify how equitable access will be achieved for all Australians in the event VN is publicly subsidised and only delivered in one or two specialised treatment centres (STCs) nationally.

2. The proposed algorithm relies on subjects being assessed for sufficient viable retinal cells. However, because the Australian guidelines for the management of patients with IRDs are currently under development, it is uncertain whether it will address specific aspects related to the treatment guidance on the use of VN to ensure a proper assessment is in place. This is both an implementation and an applicability issue. The MSAC may wish to consider guiding the assessment of viability of sufficient retinal cells in the event VN is recommended for public funding.
3. The proposed clinical algorithm disregards the use of vision support services when a patient is treated with VN. This may not be appropriate as some patients may still require some level of vision support even if their vision improved from baseline. These healthcare resources were accounted for in the economic model in Section D, but not in Section E.

10. Comparator

The submission proposed best supportive care (BSC) as the comparator as there are currently no TGA approved treatments or MBS listed medical procedures available in Australia for the treatment of IRDs caused by biallelic RPE65 pathogenic variants. The Commentary considered this was appropriate.

The algorithm stated that BSC was defined as including follow-up with ophthalmologist and other specialist and low vision support services. The Commentary noted the types of services included as vision support were not specified, so it was not possible to assess their appropriateness relative to current practice in Australia

11. Comparative safety

Three key studies formed the evidence base of the submission (Table 3). Studies 101 and 102 were dose-escalation studies, with patients involved in these studies having the longest clinical follow-up of up to 7.5 years to date.

Table 3 Key features of the included evidence assessing VN

Trial ID; author.	N of patients	Design/ duration	Risk of bias	Patient population	Key outcomes	Result used in economic model
Study 101	12	Phase I, SA, NR, OL, SC/ 2 year	Low	Patients with LCAa > 8 years of age with a confirmed biallelic RPE65 mutation.	Safety and tolerability.	Not used
Study 102	11	Phase I, SA, NR, OL, SC/ 15-year follow-up	Low	Patients with LCAb > 8 years of age with a confirmed biallelic RPE65 mutation.	Safety and tolerability.	Not used
Study 301 Russel et al. 2017	31	Phase III, R, OL, MC ^a . 1 year	Low	Patients with LCAb > 3 years of age with a confirmed biallelic RPE65 mutation and sufficient viable retinal cells.	Primary: Change in bilateral MLMT after 1 year.	Not used
					Secondary: FST; BCVA.	Used (<i>only BCVA and VF</i>)
					Exploratory: VF	

Abbreviations: BCVA = best-corrected visual acuity; BSC = best supportive care; FST = Full-field light sensitivity threshold; LCA = Leber congenital amaurosis; MC=multi-centre; NR=non-randomised; OL=open label (unblinded); PRO = patient reported outcome; QoL=quality of life; R=randomised; SA = single arm; SC = single centre; VF = visual field.

Notes:

^a two sites in the USA (Children's Hospital of Philadelphia and University of Iowa);

^balthough not stated explicitly in the CSR from Study 301 or the inclusion/exclusion criteria, patients in study 301 were all LCA patients;

^cseparate questionnaire to assess activities of daily living relevant to visual deficits.

Source: Compiled as part of the evaluation process.

The Commentary noted Study 301 had a different design and purpose to Studies 101/102, and all had small numbers of subjects. No integrated safety analysis was included in the submission.

The available comparative evidence relied on a total of 29 patients (20 receiving the intervention and 9 allocated to the control arm), which is a small population. The rarity of the disease and the lack of other available treatment options explains the lack of more robust data (e.g. larger sample size) but does not eliminate the risk for potential bias. The risk of bias was due mainly to the underlying open-label study design.

Very few drug related AEs were reported all of which were categorised as mild. The administration of VN (not VN itself) was found to be associated with a high risk of adverse events (AEs) some of which may be serious. There were 29 (71%) subjects across the clinical programme (Study 101/102 and 301, N=41) with treatment emergent adverse events (TEAEs) considered related to the administration procedure (vitrectomy and subretinal injection), including conjunctival hyperaemia (n = 9 [22%]), cataracts (n = 8 [20%]), intraocular pressure (IOP) increased (n = 6 [15%]) and retinal tear (n = 4 [10%]). The majority of events resolved without sequelae. Three serious adverse events (SAEs) considered related to the administration procedure of VN were of clinical significance; one subject with loss of foveal function, one subject with increased IOP resulting in optic atrophy secondary to the use of depo-steroid to treat endophthalmitis related to the procedure and one subject who suffered a retinal detachment (the latter was resolving at the data cut-off date).

Study 101/102

In Study 101 (cut-off point 14th October 2014), no treatment-emergent adverse events (TEAEs) were considered related to VN; 10 (83%) subjects experienced TEAEs considered related to the administration procedure. By data cut off no subjects had discontinued the study due to TEAEs and there were no deaths reported. The most frequent reported TEAEs by System Organ Class (SOC) were infections and infestations (n=11[92%]), and eye disorders (n=10[83%]). By Preferred Term (PT), the most frequently reported TEAEs were conjunctival hyperaemia (n=8[67%]), pyrexia (n=7[58%]), leukocytosis (n=6[50%]), and abdominal discomfort and headache (both n=5[42%]). Two reported SAEs were classified as unrelated to study drug. A summary of TEAEs is provided in Table 4.

Table 4 Results of Treatment-Emergent Adverse Events (mITT / Safety) Study 101 at year 1

Study 101- first single eye	Low Dose (N=3), (1.5x10 ¹⁰ vg) n (%)	Middle Dose (N=6),(4.8x10 ¹⁰ vg) n (%)	-	High Dose (N=3), (1.5x10 ¹¹ vg) n (%)
Subject with at least one TEAE	3 (100%)	6 (100%)		3 (100%)
Subjects with any Study Drug Related TEAE	0	0		0
Subjects with any Administration Procedure Related TEAE	3 (100%)	5 (83%)		2 (67%)
Subjects with any Serious TEAE	1 (33%)	0		0
Subjects Discontinued Study Due to TEAE	0	0		0
Deaths	0	0		0

Abbreviations: TEAEs = treatment-emergent adverse events.
Source: Table 44, Section B.6.6 of the submission.

In Study 102, a total of 157 TEAEs were reported by all subjects (cut-off point 8th October 2015). None of the subjects were reported with study drug related TEAEs, however, eight (73%) subjects were reported with administration procedure related TEAEs; all of these TEAEs were considered mild or moderate in severity. No deaths were reported in the study and no subjects were discontinued early from the study due to TEAEs. The most frequently reported TEAEs following administration of VN were gastrointestinal disorders (n = 9 [82%]) followed by eye disorders, infections and infestations; and renal and urinary disorders (n = 7 [64%] for each). Among these, the most frequently reported TEAEs were pyrexia, influenza, blood creatinine increased, headache, haematuria and proteinuria (n = 4 [36%] for each) followed by cataract, dellen (i.e. uneven surface of the cornea), abdominal discomfort, nausea, vomiting and oropharyngeal pain (n = 3 [27%] for each).

Table 5 Results of TEAE (mITT / Safety) Study 102

Study 102 second single eye	Total (N=11), n(%)
Subject with at least one TEAE	11 (100%)
Subjects with any study drug related TEAE	0
Subjects with any administration procedure related TEAE	8 (73%)
Subjects with any serious TEAE	4 (36%); 1 of these was considered related to the administration procedure.
Subjects discontinued study due to TEAE	0
Deaths	0

Abbreviations: mITT = modified intention to treat; TEAEs = treatment-emergent adverse events.
Source: Table 45, Section B.6.6 of the submission.

Study 301

Safety data for Study 301 (first year) for TEAEs suffered by more than 5% of the safety population is summarised in Table 6. The Commentary noted that given the cross-over study design after Year 1, and because 11 out of 12 control patients were later treated with VN, the comparative safety can only be established for this period. No statistical differences in safety between study groups were observed.

Table 6 Study 301 – Summary of TEAEs reported in more than 5% of the population (safety population)

Adverse event	VN (N = 20)	Control (N = 9)	OR [95% CI]; p-value
	n (%)	n (%)	
Eye disorders			
Cataract	3 (15)	0 (0)	NE
Retinal tears	2 (10)	0 (0)	NE
Eye inflammation	2 (10)	0 (0)	NE
Investigations			
IOP increased	4 (20)	0 (0)	NE
Gastrointestinal disorders			
Vomiting	8 (40)	2 (22)	2.33 (0.38, 14.23)
Nausea	6 (30)	1 (11)	3.43 (0.35, 33.80)
Infections			
Nasopharyngitis	7 (35)	2 (22)	1.88 (0.31, 11.64)
Upper respiratory tract infections	2 (10)	3 (33)	0.22 (0.03, 1.66)
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain	6 (30)	4 (44)	0.54 (0.11, 2.72)
Cough	6 (30)	1 (11)	3.43 (0.35, 33.80)
Nervous system disorders			
Headache	7 (35)	2 (22)	1.88 (0.31, 11.64)
General disorders and administrations site conditions			
Pyrexia	7 (35)	1 (11)	4.31 (0.44, 41.82)
Blood and Lymphatic disorders			
Leukocytosis	9 (45)	0 (0)	NE

Abbreviations: NE = not estimable; OR = odds ratio; TEAEs = treatment emergent adverse events; VN = voretigene neparvovec. Source: Table 55, p. 168-179 of the TGA clinical evaluation report.

Additional safety data is available for Study 301 and its extension, Study 302, which captures follow-up of patients up to 4 years (data cut off point 02 Jul 2018). This data is reported in Table 7. The Commentary noted that overall, AEs did not occur due to VN, however, the administration of VN is associated with a high risk of AEs some of which may be serious.

Table 7 Summary of TEAC related to study drug and administration procedure.

Study 301 both eyes (bilateral)	Original intervention (VN) (N=21), n (%)			Control/DI (N=9), n(%)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Any TEAE	4 (20%)	12 (60%)	4 (20%)	6 (67%)	3 (33%)	0
Drug related AE						
Retinal deposits	0	0	0	3 (33%)	0	0
Administration related AE						
Cataract	3 (15%)	1 (5%)	0	1 (11%)	0	0
Retinal tears ^a	1 (5%)	1 (5%)	0	1 (11%)	0	0
IOP increased	4 (20%)	0	0	1 (11%)	0	0
Nausea	4 (20%)	0	2 (10%)	3 (33%)	1 (11%)	0

Abbreviations: AEs = adverse events; DI = delayed intervention; IOP = intraocular pressure; TEAEs = treatment emergent adverse events; VN = voretigene neparvovec.

Notes: ^a Retinal tears were repaired with laser pexy during the vector administration procedure and all resolved without sequelae.

Source: Table 47, Section B.6.6 of the submission.

A summary of the most common adverse events (incidence $\geq 5\%$) from the entire VN clinical program (Study 101, 102 and 301) is provided in Table 8.

Table 8 Ocular adverse reactions following treatment with VN (n=41)

Adverse reactions, n(%)	Subjects (n=41)	Treated eyes (n=81)
Any ocular adverse reaction	27 (66)	46(57)
Conjunctival hyperemia	9(22)	9 (11)
Cataract	8(20)	15 (19)
Increased ocular pressure	6(15)	8 (10)
Retinal tear	4(10)	4 (5)
Dellen (thinning of the corneal stroma)	3(7)	3 (4)
Macular hole	3(7)	3 (4)
Subretinal deposits*	3(7)	3 (4)
Eye inflammation	2(5)	4 (5)
Eye irritation	2(5)	2 (2)
Eye pain	2(5)	2 (2)
Maculopathy (wrinkling on the surface of the macula)	2(5)	3 (4)
Foveal thinning and reduction of foveal function	1(2)	2 (2)
Endophthalmitis	1(2)	1 (1)
Fovea dehiscence (separation of the retinal layers in the centre of the macula)**	1(2)	1 (1)
Retinal haemorrhage	1(2)	1 (1)

Abbreviations: VN= voretigene neparvovec.

Source: Table 49, Section B.6.6 of the submission.

The Commentary considered that overall, the long-term data and available post-marketing data do not give rise to any additional safety concerns, however the safety data are limited by the small subject numbers; rare AEs are unlikely to be detected in small study populations. A patient registry in Europe was proposed by the applicant, which the TGA suggested should include Australian patients. The aim of the registry is to follow newly treated patients for five years and collect long-term data on the real-world use of VN.

12. Comparative effectiveness

The evidence of efficacy of VN using the primary outcome is based on Study 301, in which all patients were treated with the dose of VN (1.5x10¹¹ vector genomes) proposed for registration. The efficacy outcomes reflect vision function (FST, VA, VF) and functional vision measured via a novel outcome, the Multi-luminance Mobility Test (MLMT), a mobility course to test for visual function under varying light conditions developed in conjunction with the FDA and validated for the phase 3 trial.

Primary outcomes

The primary outcome in Study 301 was the change from baseline in MLMT performance score at 1 year. This instrument was designed to integrate aspects of light sensitivity, VF and VA, and measure functional vision in a quantitative and standardised manner at different light levels (1 to 400 lux). It was hypothesized that by improving functional vision, the ability to perform activities of daily living also improves, hence translates into an improvement in QoL. Ultimately the aim was to determine whether VN improved the ability to navigate a marked path. In practice, patients navigate a marked path, while avoiding obstacles, and relying on vision rather than kinaesthetic input.

This test is not available in Australia and given the technical aspects which include mimicking laboratory situations at different light intensities, it is a performance measure that cannot be easily adopted/implemented in routine clinical practice in Australia.

Patients were assigned scores based on the minimum light level at which they were able to pass the test. Tests were videotaped and success or failure on the course was determined by independent graders masked to treatment allocation. The Commentary considered this an appropriate measure to address potential risk of bias given the open label study design. Patients passed the test if they completed the course in < 180 seconds and with an accuracy score of ≤ 0.25 . Assessments were performed at baseline and one-year post-administration to the second eye. This test does not assess the ability to navigate at light levels lower than 1 lux. The latter means that the change in performance score is restricted to the pre-specified lowest light setting (1 lux) which may underestimate the mean change.

Clinical experts have noted that change in MLMT was a better outcome to assess visual impairments in this patient group compared to other measures of visual performance. However, as discussed above, it is unlikely it will be used/implemented in the Australian clinical setting.

A change in MLMT score of ≥ 1 on a scale 0-6 (Figure 3) was considered a clinically meaningful change from baseline by the applicant. The ADAR illustrated this improvement by providing a descriptive example of what this may look like: “An improvement of one MLMT light level (125 lux to 50 lux) would allow the individual to independently use the train at night for their commute”.

Figure 3 Light (lux) levels alignment with MLMT scores

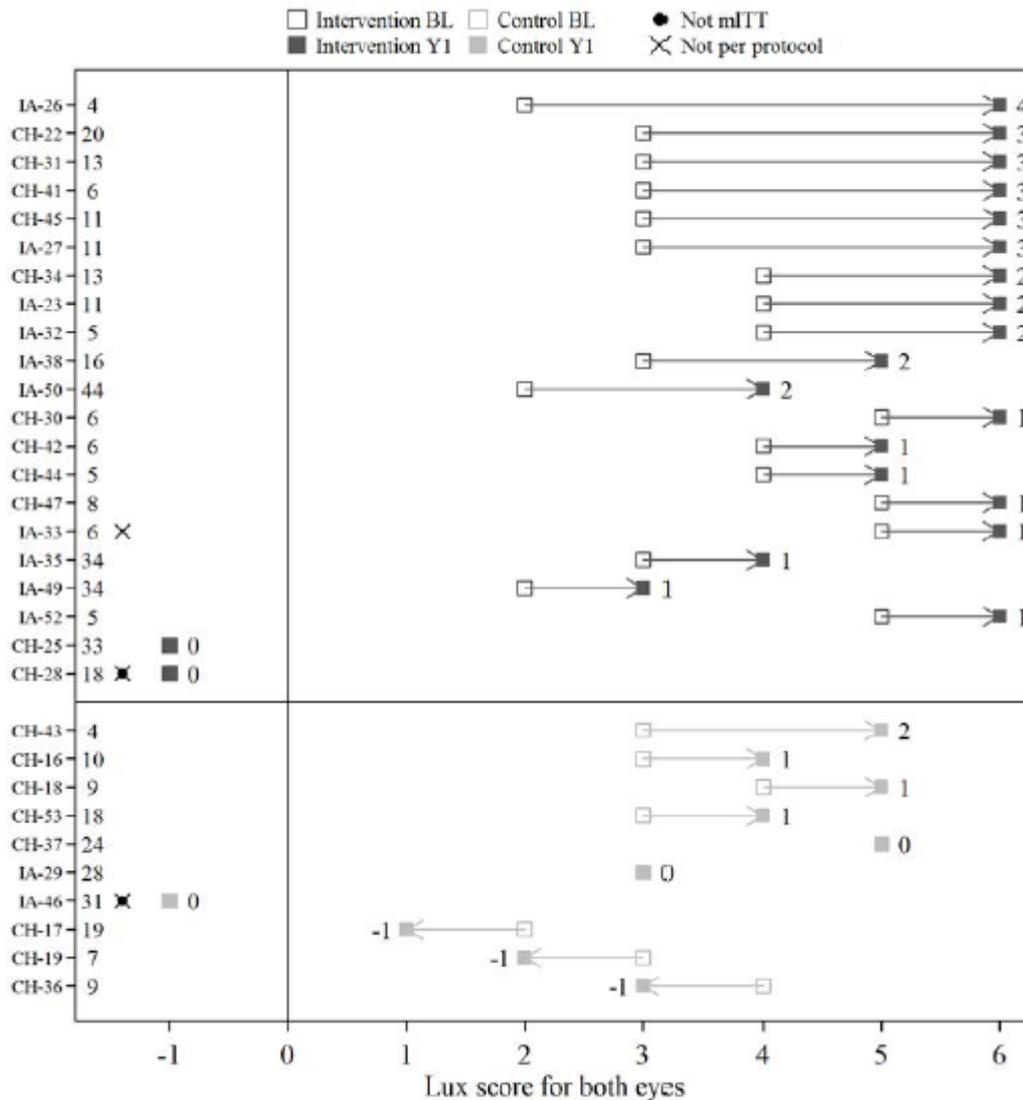
1 lux	4 lux	10 lux	50 lux	125 lux	250 lux	400 lux
Moonless summer night or indoor night-light	Cloudless summer night with half moon or outdoor parking lot at night	An hour after sunset in a city setting or a bus stop at night	Outdoor train station at night or the inside of a stairwell	A half hour before sunrise or the interior of a shopping mall or train or bus at night	Interior of an elevator or office hallway	Office setting
MLMT score	MLMT score	MLMT score	MLMT score	MLMT score	MLMT score	MLMT score
6	5	4	3	2	1	0

Abbreviations: MLMT = multi luminance mobility test.
Source: Figure 19, Section B.5.3 of the submission.

The FDA “Summary Basis for Regulatory Action – LUXTURNA” document suggests an MLMT score change of two or greater as the clinically meaningful benefit for functional vision¹. The Commentary noted that the improvement in MLMT scores may not necessarily be linear in terms of clinical significance. The change of 1 in the MLMT score in a patient with very poor baseline vision may not necessarily represent the same clinical benefit in a patient with moderate vision impairment. In addition, the submission did not provide a clear and robust justification for the selection of a 1 point change in MLMT score as the clinical meaningful change from baseline. Moreover, it was noted from the results presented in the CSR of Study 301 (Figure 4) that there was variability of change from baseline from +1 MLMT score (improvement) to - 1 MLMT score (deterioration) in patients in the control arm.

¹ FDA, 2018. Summary Basis for Regulatory Action. Accessed 30/04/2020 from <https://www.fda.gov/media/110141/download>

Figure 4 MLMT scores at baseline and Year 1 by individual, bilateral ITT population (N=31)



Abbreviations: BL = baseline; ITT = intention to treat; MLMT = multi luminance mobility test.
Source: Figure 21, Section B.6.1 of the submission.

Results of Primary Outcome(s)

Mean MLMT score improved by the day 30 visit and remained stable for the duration of available data, up to 4 years in Study 301 (Table 9). At year 1, the mean bilateral MLMT change score was 1.8 (SD 1.1) in the OI group compared to 0.2 (SD 1.0) in the control group which results in a statistically significant difference of 1.6 (0.72, 2.41, p=0.001). Similarly, for the mITT and for the PP population the treatment difference was 1.6 (95%CI, 0.76, 2.50, p = 0.004) and 1.7 (95%CI, 0.79, 2.56; p = 0.004) respectively. The ADAR also noted that for the ITT population, 13 of 21 (62%) subjects in the OI group passed the MLMT at 1 lux (score = 6) at Year 1, representing the maximal improvement measurable while no Control subjects passed at this low light level (p.96, Figure 32, CSR Study 301).

These improvements were sustained to Year 4 for OI subjects (N=20) with an MLMT change score of 1.7 (SD 1.1) and to Year 3 for Control / DI subjects (N=8) with a MLMT change score 2.4(SD1.5). The Commentary noted that the difference between the groups after year 1 was not reported in the submission given the cross-over nature of the trial. By Year 3, 69% of all patients and 89% of Control/ DI patients were able to pass the MLMT at the lowest light level. The results for the longer-term follow-up for the OI and DI arms are presented in Figure 5.

Table 9 Results of MLMT change lux score study 301, year 1 compared with baseline (ITT)

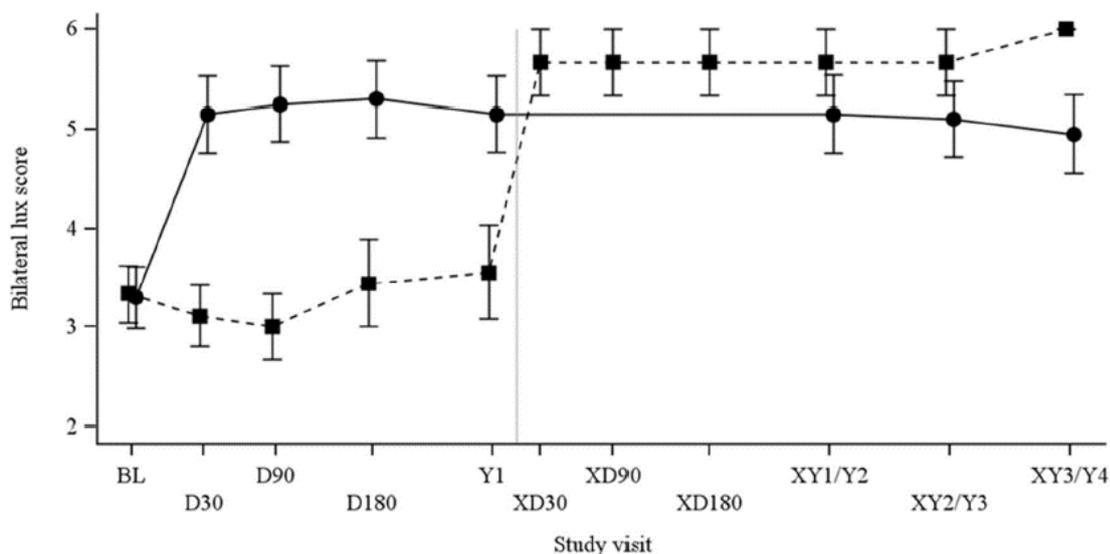
Trial ID	Original intervention (VN) (N=21)	Control/Delayed Intervention(N=10)	Difference (95%CI)
Both eyes (bilateral) change to year 1			
	N= 20	N=9	
Mean (SD)[range]	1.8 (1.1) [0,4]	0.2 (1.0) [-1,2]	1.6 (0.72, 2.41), p-value =0.001
First eye change to year 1			
	N= 20	N=9	
Mean (SD)[range]	1.9 (1.2) [0,4]	0.2 (0.6) [-1, 1]	1.7 (0.89, 2.52) p-value=0.001
Second eye change to year 1			
	N= 20	N=9	
Mean (SD)[range]	2.1 (1.2) [0,5]	0.1 (0.7) [-1, 1]	2.0 (1.14, 2.85) p-value=0.001
Source	CSR Study 301 Table 11.11 and Table 11.17; Russell 2017		
Both eyes (bilateral) change to year 3			
	N= 20	N=8	
Mean (SD)[range]	1.8 (1.0)[0, 3]	2.4(1.5)[2,5]	NR
Both eyes (bilateral) change to year 4			
	N= 20	N=2	
Mean (SD)[range]	1.7 (1.1)[0, 3]	3.5 (2.1)[2,5]	NR
Source	CSR Study 301 Addendum 2018 Table 11.1		

Abbreviations: CI = confidence intervals; SD = standard deviation; VN = voretigene neparovec.

Note: bold text represents statistically significant differences.

Source: Table 37, Section B.6.1 of the submission.

Figure 5 Year 4 Bilateral MLMT scores, means over time (mITT/Safety) (Study 301)



Abbreviations: mITT = Modified intention-to-treat; MLMT = multi luminance mobility test.

Note: Circles represent the intervention arm while the squares (dotted line) represents the control group.

Source: Figure 22, Section B.6.1 of the submission.

Figure 4 above, presents the individual results for change in MLMT. The submission noted that 1/20 patients in the mITT population had an MLMT change score of zero. The ADAR argued that this patient had severely reduced baseline VA and was one of only two patients with off-chart BCVA measurements after the immediate postoperative period. The Commentary considered this argument suggests there could be some level of relationship between baseline severity (as per VA) and treatment response. It was also noted that 11/21

subjects in the treatment group had an improvement in ≥ 2 lux scores compared to 1/10 patients in the control group. The only patient in the control arm with a positive change of 2 was a 4-year-old child at randomisation which the submission suggested could have an increased ability to ambulate due to maturation (which could be related to a less severe stage of the disease).

If the clinically meaningful threshold is increased to 2 points (as recommended by the FDA), the relative improvement falls from 0.51 (95% CI, 0.18-0.83) (change in MLMT = 1) to 0.42 (95% CI, 0.14- 0.71) (change in MLMT = 2). In addition, 3/9 subjects in the control arm in the mITT population had a positive MLMT bilateral change score of one. The submission argued this could be due to test variability around the binary pass/fail cut-off or learning effect. Two patients in the mITT population in the control arm had a change score of zero. An additional post-hoc supportive analysis showed a substantial drop in the average time to complete the course in the OI compared to the control group (mean treatment difference of -49.5 seconds; 95% CI -77.9, -21.2; p=0.001).

The Commentary noted that the treatment effect of VN was associated with a statistically significant and clinically meaningful improvement in MLMT score which means that patients were now able to navigate at lower light levels. The Commentary considered the change in 1 on the MLMT scale suggested as clinically meaningful may be inappropriate because patients in the control arm had a variability of change from baseline from +1 MLMT (improvement) to - 1 (deterioration).

Secondary outcomes

A summary of the secondary outcomes and analyses in the direct randomised trials (Study 10/102, 103) is presented in Table 10.

In Study 301, secondary efficacy endpoints were: (1) FST testing averaged over both eyes, (2) MLMT testing of the assigned first eye and, (3) BCVA averaged over both eyes². The outcomes FST and VA were evaluated for each individual eye and the results were then averaged over both eyes.

FST testing assesses light sensitivity of the entire retina by measuring the subject's perception of different luminance levels (i.e., differing levels of light brightness). FST threshold testing is a subjective physiological test of retinal function relevant to the visual deficit experienced by patients with IRDs. Significant improvement in light sensitivity demonstrates that the visual pathway of associated photoreceptors is favourably impacted. The Commentary noted the submission did not address or suggest a clinical meaningful threshold for FST.

VA is a traditional measure of central visual function that captures the ability of the eye to perceive details. Primarily cone-mediated, VA is the most common measure of visual function both in clinical practice as well as in clinical trials. In patients with IRD due to biallelic RPE65 pathogenic variants (primarily a rod-cone disease), VA is often impaired and gets progressively worse over the course of the disease depending on the severity of the patient (Chung et al. 2019). The Commentary noted the draft Australian guideline for IRDs developed by the RANZCO considers the use of BCVA for diagnosis purposes. On the other hand, the German Society of Ophthalmology recommends that at the very least, BCVA, FST

² Russell S, Bennett J, Wellman JA, Chung DC, Yu ZF, Tillman A, et al. Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65-mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial. *Lancet*. 2017;390(10097):849-60.

testing as well as OCT and fundus autofluorescence (FAF) imaging should be performed pre and post operatively to assess VN treatment response.

The Early Treatment Diabetic Retinopathy Study (ETDRS) chart used to measure VA includes letter sizes on each line following a geometric progression, such that VA can be converted to a visual angle score (LogMAR, or Logarithm of the Minimum Angle of Resolution) allowing for comparison analyses, where smaller LogMAR values indicate better acuity. A pre-specified statistical analysis was conducted for VA using the Holladay scale while a post-hoc analysis was presented when the Lange scale was used for off-chart scoring. The Commentary noted the submission did not address the clinically meaningful threshold for VA, however the CSR for Study 301 stated that an “Improvement of 0.3 LogMAR (15 letters or 3 lines on an ETDRS chart) is considered clinically meaningful (equivalent to a halving of the visual angle, e.g. 20/80 to 20/40)” (p. 38-3495, Study 301 CSR Addendum 2018). It was noted from a previous PBAC submission that assessed the use of ranibizumab for the treatment of diabetic macular oedema, that the PBAC had agreed that an increase of ≥ 5 letters might represent a clinically meaningful difference for some patients in this particular population. It was also stated that the clinical importance will depend on the baseline VA of each eye (p. 5, ranibizumab PSD, March 2013) which is considerably lower in patients with IRDs compared to patients with diabetic macular oedema.

Table 10 Summary of secondary outcomes and analyses in the direct randomised trials

Trial ID	Secondary outcome	Method of statistical analysis	Comment (from Commentary)
Trial 301	<ul style="list-style-type: none"> • Change in white light FST averaged over both eyes at Year 1 relative to baseline; • Change in assigned first eye MLMT performance at Year 1 relative to baseline; • Change in BCVA averaged over both eyes at Year 1 relative to baseline. 	<ul style="list-style-type: none"> • Monocular mobility testing: same method as for the primary endpoint; • FST and VA: longitudinal models that provided estimates of the difference between baseline and Year 1. 	Pre-specified analysis A post-hoc analysis was presented for the outcome VA using the Lange scale.
Trial 101	Change in visual function from baseline as measured by subjective, psychophysical tests and objective, physiologic tests: VA, VF (Goldmann perimetry), ERG, Contrast sensitivity, Colour vision testing, Pupil function testing, Mobility testing, Ocular motility measurements	<ul style="list-style-type: none"> • Descriptive statistics. • Number and percentage by dose cohort for categorical data; mean, median, range, SD and N for continuous data. • Values and changes from baseline at each time point were tabulated. 	Pre-specified analysis and a post hoc analysis for FST (outcome was added over the course of Study 101). The latter was conducted using mixed effects linear regression models accounting for correlations arising from repeated measures taken from two eyes of an individual to compare the 102-injected and 101-injected eyes at baseline and year 1 visit.
Trial 102	Evaluation of the efficacy of the study drug by assessing change in visual/retinal function through subjective, psychophysical and objective, physiological tests: Mobility testing, PLR, FST, VA, VF (Goldmann perimetry), Contrast sensitivity.	<ul style="list-style-type: none"> • Descriptive statistics. • Number and percentage by dose cohort for categorical data; mean, median, range, SD and N for continuous data. • AEs and SAEs. • Values and changes from baseline at each time point were tabulated. 	

Abbreviations: AEs = adverse events; PLR = pupillary light response; VA = visual acuity; VF= visual field.

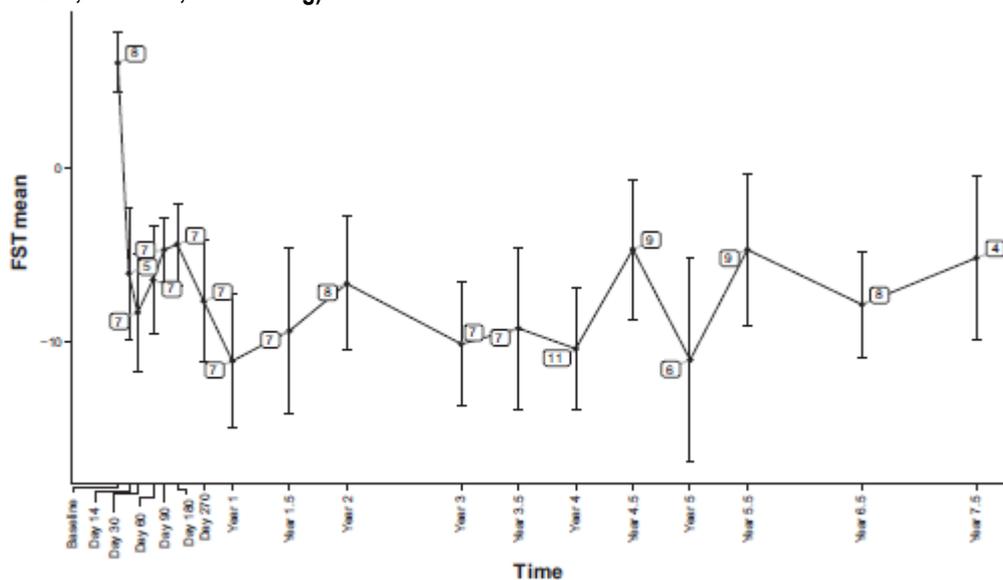
Source: Table 34, Section B.5.2 of the submission.

Results of Secondary Outcome(s)

Study 101/102

The results for FST (white light) were available for only some patients from Study 101 (n=7 in year 1). Of these evaluable patients, 57% showed a significant improvement in FST change. In Study 102, the average decrease from baseline to Year 1 was 18.04 (p<0.0001) which reflects improved retinal sensitivity (Figure 6). The improvement was higher in Study 102 (Figure 7) compared to Study 101 due to differences in doses (all patients were treated with the high dose of VN). This difference (between Study 101 and Study 102) was found to be statistically significant (p=0.0067). Most of evaluated subjects in Study 101 and 102 developed increased light sensitivity which was maintained over the follow-up period (7.5 and 4 years respectively).

Figure 6 Mean (+/- SE) FST over time in the first injected eye Study 101 (pooled data of the 3 different VN doses: 1.5x10¹⁰, 4.8x10¹⁰, 1.5x10¹¹ vg)



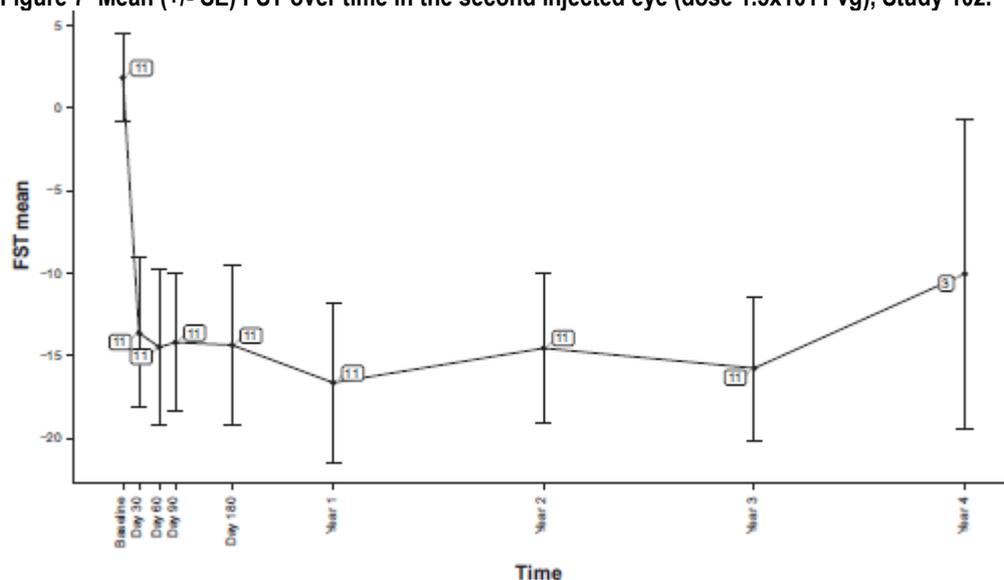
Note: The numbers within the boxes represent the numbers of patients at each time points; time points with less than 3 observations and without Baseline data were excluded from the analysis.

FST, full-field light sensitivity threshold test; SE, standard error; vg, vector genomes

Abbreviations: FST = Full-field light sensitivity threshold; vg = vector genomes; VN = voretigene neparovec.

Source: Figure 1, Chung, D.C., et al., Long-term effect of voretigene neparovec on the full-field light sensitivity threshold test of patients with RPE65 mutation-associated inherited retinal dystrophy: post-hoc analysis of Phase I trial data, in Abstract submitted to ARVO 2019 Annual Meeting.

Figure 7 Mean (+/- SE) FST over time in the second injected eye (dose 1.5x10¹¹ vg), Study 102.



Note: The numbers within the boxes represent the number of patients at each time point; Time points with less than three observations and without Baseline data were excluded from the analysis

FST, full-field light sensitivity threshold test; SE, standard error; vg, vector genomes

Abbreviations: FST = Full-field light sensitivity threshold; vg = vector genomes; VN = voretigene neparovec.

Source: Figure 2, Chung, D.C., et al., Long-term effect of voretigene neparovec on the full-field light sensitivity threshold test of patients with RPE65 mutation-associated inherited retinal dystrophy: post-hoc analysis of Phase I trial data, in Abstract submitted to ARVO 2019 Annual Meeting.

The change in LogMAR value for VA from baseline to Year 1 was greater for injected eyes than for uninjected eyes (-0.4233 versus -0.1525) in Study 101; however, this difference (-0.2708) was not statistically significant ($p=0.1019$). Although the change was improved in Study 102 (due to the higher VN dose used), the difference remained not statistically significant.

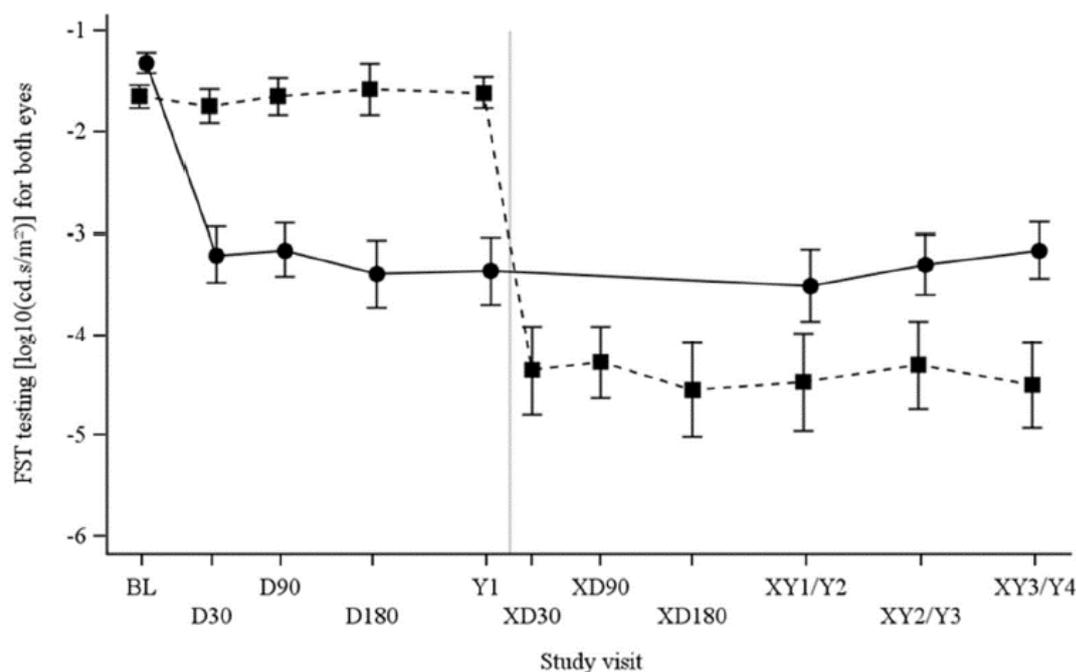
Study 301

The original intervention (OI) group showed a 2 log units' improvement in FST at day 30 compared to the control arm. At year 1 this difference was maintained and shown to be statistically significant ($-2.11 \log_{10}(\text{cd.s/m}^2)$; 95% CI: -3.91, -1.04; $p = 0.0004$).

Furthermore, at year 4 the effect of VN was maintained (Figure 8). For both treatment groups, OI and delayed intervention (DI), the gain in FST performance was -1.90 and -3.02 respectively (Table 11.2, p. 31-3495 of the Study 301 CSR Addendum 2018). The ADAR did not specify a clinically meaningful change threshold for this outcome.

The ADAR argued that there was a linear relationship (high correlation) between the MLMT scores and FST, which showed that subjects who had an improvement in the mobility test also showed improvements in FST results. A post-hoc analysis that assessed this relationship found a strong correlation between these two measures (-0.74 ; $p < 0.001$). The Commentary considered this analysis may be informative for determining whether FST is useful for following up this patient population in the event that VN is recommended for public funding. However, these results should be interpreted with caution as they result from a post-hoc analysis (not a pre-specified analysis), and hence are prone to bias.

Figure 8 Year 4 FST results (Study 301)



Abbreviations: FST = Full-field light sensitivity threshold.

Note: Circles represent the intervention arm while the squares (dotted line) represents the control group.

Source: Figure 23, Section B.6.2 of the submission.

By Year 1, in the OI group the mean change of BCVA was -0.16 (95% CI: -0.41, 0.08; $p = 0.17$) showing no statistically significant differences. In addition, the results were not considered clinically meaningful as the reported change did not reach the suggested threshold of 0.3 LogMAR defined in Study 301.

The submission also provided a post hoc analysis using the Lange scale for off-chart scoring. The results showed a mean improvement of 9 letters compared to a 1.6 letter improvement in the control group (mITT population), a 7.4 letter gain and a treatment difference of -0.16 (95% CI: -0.31, -0.01; $p = 0.035$). The Commentary noted that these results did not meet the clinically meaningful threshold and should be interpreted with caution given their post-hoc nature.

The submission did not present VA results for the period beyond year 1, hence it is uncertain whether the numerical improvement observed was maintained. Given the nature of VA, which aims to measure central visual function and is primarily cone-mediated, it is unlikely to be an appropriate effect measure to be used to model the long-term effect in patients with IRD due to biallelic RPE65 pathogenic variants (primarily a rod-cone disease). The submission stated that VA is often impaired and gets progressively worse over the course of the disease depending on the severity of the patient (Chung et al. 2019). Given that VA decline is likely dependant on disease severity and is not generally linear in nature, the Commentary considered its use in monitoring response to VN treatment may be limited.

Additional (exploratory) outcomes

Additional efficacy endpoints in Study 301 were: (1) VF testing using Humphrey and Goldmann scores, (2) the visual function questionnaire (VFQ), (3) contrast sensitivity, (4) pupillary light reflex (PLR), and (5) in-home orientation and mobility assessments. Both kinetic and static VF field tests were chosen as exploratory endpoints to evaluate alterations in function of different regions of the retina. The VFQ was a patient-reported outcome

(administered separately to subjects and to parents/guardians of younger subjects) designed to assess activities of daily living relevant to visual deficits due to RPE65 gene pathogenic variants.

Results

The mean sum total degrees of Goldmann VF (III4e) almost doubled in the intervention group (from 332.9 to 673.9) by Year 1, indicating improved peripheral vision. No such improvement was observed in the control arm, in which mean sum total degrees fell from 427.1 to 397.8, with a mean difference between arms of 378.7 (95% CI: 145.5, 612.0; post-hoc $p = 0.0059$). The results for this post-hoc analysis were found to be statistically significant; however, a clinically meaningful difference was not specified in the ADAR or the CSR. According to the ADAR, the improvement in peripheral vision observed by Year 1 was sustained through to Year 4. A longer follow-up period is needed to understand long-term trends. This exploratory outcome was used to capture short and long-term treatment effect in the economic model, which the Commentary considered may be inappropriate.

The ADAR noted that the VFQ scores of patients who received treatment, as rated by their parents, increased significantly, indicating a reduction in the perceived difficulty of daily living activities which was sustained through follow-up (up to year 4). The mean scores of controls did not change. However, the VFQ used in the trial removed certain items of HRQoL from the original version, hence the utilised questionnaire was an adapted version and was not validated. For this reason, the results should be interpreted with caution. The ADAR did not address the potential implications of patients adapting to their condition.

13. Economic evaluation

November 2020 MSAC

The applicant revised the inputs into the economic model as follows:

- Acquisition price reduced to **\$redacted** (from **\$redacted**).
- Health care perspective applied (rather than societal perspective)
- Sensitivity to different utility values investigated: HUI3 adjusted and unadjusted; EQ5D(L) unadjusted.

The applicant maintained a 40 year treatment effect was appropriate, but claimed that even if the treatment effect was reduced to 20 years, the ICER is below **\$redacted** per QALY.

The applicant applied a 5% discount rate, but continued to assert that a lower discount rate is appropriate. The applicant also claimed that use of a 5% and a shorter time horizon arguably leads to double counting of longer term uncertainty.

The results of the economic analysis are summarised in Table 11.

Table 11: Results of revised economic analysis

Inputs	ICER/QALY
July 2020	
Applicant: Acquisition cost \$redacted, duration of effect 40 years, discounting 5%, HUI3 utility values with adjustment; health care perspective	\$redacted
MSAC: Acquisition cost \$redacted, duration of effect 15 years, discounting 5%, EQ5d(L) utilities; health care perspective	\$redacted
November 2020	
Acquisition cost \$redacted	
Acquisition cost \$redacted, duration of effect 40 years, discounting 5%, HUI3 utility values with adjustment; health care perspective	\$redacted
Acquisition cost \$redacted, duration of effect 40 years, discounting 5%, HUI3 utility values without adjustment; health care perspective	\$redacted
Acquisition cost \$redacted, duration of effect 40 years, discounting 5%, EQ5D(L) utility values without adjustment; health care perspective	\$redacted
Acquisition cost \$redacted, duration of effect 20 years , discounting 5%, EQ5D(L) utility values without adjustment; health care perspective	\$redacted
Acquisition cost \$redacted, duration of effect 15 years , discounting 5%, EQ5D(L) utility values without adjustment; health care perspective	\$redacted

Source: calculated by Department

July 2020 MSAC

The economic evaluation is summarised in Table 12.

Table 12 Summary of the economic evaluation

Perspective	Societal perspective (Australian healthcare system + selected patient/ carer cost implications). Revised base case conducted during the evaluation adopts a healthcare perspective. <i>The ESC considered this revised perspective was appropriate.</i>
Comparator	BSC
Type of economic evaluation	Cost-utility
Sources of evidence	Clinical evidence: Study 301 and the natural history of the disease study. Utility scores: time trade-off valuation study using the HUI-3 and EQ-5D-5L
Time horizon	Lifetime
Outcomes	QALYs Blindness free years
Methods used to generate results	Markov cohort model
Health states	Moderate VI Severe VI Profound VI Count Fingers Hand Motion, Light Perception to No Light Perception Death
Cycle length	One year
Discount rate	5%
Software packages used	Microsoft excel

Abbreviations: BSC = best supportive care; EQ-5D-5L = Euroqol five dimensions five levels; HUI-3 = health utility index mark 3; QALY = quality adjusted life year; VI = vision impairment. Source: Table D.3.1 of the Commentary.

Table 13 Break-down of the model time horizon by data sources and assumptions

Treatment arms	Voretigene neparvovec	BSC
Initial phase	To 3 years; informed by Study 301 data	To 1 year; informed by Study 301 data
Stabilisation phase	For 40 years (variable); assumed treatment effects persist (= no transitions except for death)	Not applicable (jump to long-term phase after 1 year)
Long-term phase	To model end; disease progression (i.e., deterioration of vision) informed by natural history data, adjusted for assumed treatment effect.	To model end; disease progression (i.e., deterioration of vision) informed by natural history data.

Abbreviation: BSC, best supportive care. Source: Table 62 of Application

The Commentary noted that defining the health states using VA and VF was not consistent with the primary outcome of Study 301 (change in MLMT performance). The argument for this approach was that no data are available linking MLMT to costs, utilities or mortality. The MSAC agreed with the Commentary and considered this was reasonable, however noted the following limitations:

- The results of Study 301 did not show statistically significant or clinically meaningful differences in VA using the Holladay scale (as used in the economic model).
- Statistically significant differences were observed in VF however, the submission did not present clinically meaningful difference thresholds for this outcome. Analyses relating to VF were post-hoc in nature and should be interpreted with caution.
- The submission did not provide justification for not using FST to define health states and inform health state transitions within the model.

Table 14 Effectiveness measures used in the economic model

	MLMT	FST (white light)	VA (visual acuity)	VF (visual function)
Outcomes from Study 301	1.6 (0.72, 2.41), p-value =0.001 (lux score)	-2.11(-3.19, -1.04) p<0.001 (log score)	-0.16 (-0.41, 0.08) p=0.17 (Holladay) -0.16 (-0.31,-0.01) p=0.035 (Lange)	378.7 (95% CI: 145.5, 612.0; post- hoc p = 0.0059). (VF score)
Outcomes used in economic model			HS1 Better than 1.0 HS1 1.0-1.4 HS3 1.4-1.8 HS4 1.8 – 3.0 HS5 Worse than 3.0 or an indication of HM, LP, or NLP	>240 ≤ 240 and >144 ≤ 144 and >48 ≤ 48

The overall costs and outcomes, and incremental costs and outcomes as calculated for the intervention and comparator in the model, and using the revised base case assumptions, are shown in Table 15. The revised base case restricts the analysis to the healthcare perspective only, excluding productivity costs, and considers two time-frames, 40 years (submission base case) and 7.5 years (length of available follow-up data).

Table 15 Costs and outcomes in the base case revised by the evaluation^a

	Cost	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness (QALY)	ICER (\$/QALY)
40-year time horizon					
VN	\$redacted	\$redacted	11.2	7.5	\$redacted
BSC	\$redacted		3.7		
7.5-year time horizon (available follow-up data)					
VN	\$redacted	\$redacted	8.0	4.3	\$redacted
BSC	\$redacted		3.7		

Abbreviations: BSC = best supportive care, ICER = Incremental Cost Effectiveness Ratio, QALY = quality adjusted life years, VN = voretigene neparvovec

Note: ^a Revised base case considers the healthcare perspective; excluding productivity losses

Source: Table D.5.3 of the Commentary.

The assumptions underlying the selection of utility values and the duration of VN efficacy are highly uncertain. The ICER was also moderately sensitive to the use of cross-over data in the generation of transition probabilities in the VN arm (up to year one), the age of entry into the model and the application of healthcare costs (Table 16).

Table 16 Key drivers of the economic model

Description	Method/Value	Impact
Selection of utility values	Base case: utility data sourced from Lloyd et al.2019 using the adjusted HUI-3 for HS1. Sensitivity analysis: Alternate utility values presented in Table D.6.1; ICER ranges from \$redacted/QALY to \$redacted/QALY.	High, favours intervention
Assumed duration of VN efficacy	Base case: 40 years Sensitivity analysis: 30 years, ICER increases to \$redacted 15 years: ICER increases to \$redacted/QALY 7.5 years: ICER increases to \$redacted/QALY	High; favours intervention
Cross-over data in TPs	Base case: not included Sensitivity analysis: included, ICER increases to \$redacted/QALY	Moderate; favours intervention
Age of entry into the model ^a	Base case: 15.1 years Sensitivity analysis: 5 years, ICER decreases to \$redacted/QALY 30 years, ICER increases to \$redacted/QALY. 50 years, ICER increases to \$redacted/QALY.	Moderate; favours intervention
Application of healthcare costs	Base case; sourced from Wright et al. 2000 Sensitivity analysis: No healthcare costs applied 50 years, ICER increases to \$redacted/QALY.	Moderate; favours intervention
<i>Multivariate</i>		
Duration of VN efficacy + data source (VF)	7.5 years + VF data only. ICER increases to ICER \$redacted	High; favours intervention
Utility values+ duration of VN efficacy + data source (VF)	Alternate utility values (Brown et al (2003), 7.5 years + VF data only. ICER increases to ICER \$redacted	Very high: favours intervention

Abbreviations: HS1 = health state 1; HUI = health utility index; ICER = incremental cost-effectiveness ratio, TP = transition probabilities; VN; voretigene neparvovec.

Notes: ^a Sensitivity analyses conducted by the evaluation using the revised base case.

Source: ble D.6.2 of the Commentary.

Table 17 Alternative utility values (bold text indicates values used in applicant's base case)

Method of elicitation	EQ-5D (L) by proxies	HUI-3 by proxies	TTO in patients
Source	Lloyd 2019	Lloyd 2019	Brown 1999
Health states			
HS1 – Moderate vision impairment	0.71	0.52	0.75*
HS2 – Severe vision impairment	0.62	0.36	0.65
HS3 – Profound vision impairment	0.52	0.22	0.54
HS4 – Counting fingers	0.35	0.14	0.52
HS5 – Hand motion/ Light perception/ No light perception	0.15	-0.04	0.35

* Calculated by applicant from 4 vignettes in publication

14. Financial/budgetary impacts

November 2020

The applicant's revised estimate of the financial implications for Government health budgets is presented in Table 18.

Table 18: Revised estimated financial implications for Government health budgets over Years 1-6

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Number of patients accessing treatment	redacted	redacted	redacted	redacted	redacted	redacted
Total cost of VN at acquisition price	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Total cost of medical and other services	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Total cost to Gov't health budgets	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Impact of Pay for Performance over 3 year funding agreement	\$redacted	\$redacted	\$redacted			

The applicant proposes the acquisition price be paid in two instalments, with the first instalment (50%) due upon order and the second instalment (50%) due upon demonstration of response at 60 days. Based on the clinical trial outcomes, the estimated response rate is 93%.

July 2020

The application utilised an epidemiological approach to estimate the market size and financial implications of the introduction of VN for the treatment of biallelic RPE-65-mediated IRD. One key assumption in the model was using only the prevalent rate of RP to estimate the number of VN eligible patients. The ESC agreed with the Commentary which considered this was reasonable, however, an approach that considered both the prevalence of LCA and RP would have provided a better representation of patients likely to use VN as per the requested population. This is particularly important as the clinical data on which the ADAR relied for the effectiveness measure used for the economic analysis, was based on the use of VN in LCA patients only. It was noted that the submission presented to NICE UK and the EMA considered the prevalence of both RP and LCA.

In line with the proposed funding arrangement, the subsidy of VN for the treatment of biallelic RPE65 mediated RP will have financial implications for other parts of the Australian Government's health budget, most notably, the State and territory Government health budgets, including public hospitals. The submission noted the proportions of the overall costs to be borne by different governments falls outside the scope of the MSAC assessment. The

overall financial implications to the government (Commonwealth and States) resulting from the public funding of VN are summarised in Table 19.

Overall, a total of **redacted** patients were estimated by the applicant to receive VN treatment over the 6 year period. It is expected that the largest number of patients will receive treatment in the first three years of VN becoming available. While this was considered reasonable, the Commentary noted there was significantly high uncertainty surrounding the number of prevalent RP patients with biallelic RPE65 pathogenic variant. The number of eligible patients as per the submission was **redacted**, although it was acknowledged that to date only three patients eligible for VN have been identified in Australia. Moreover, the calculation resulting in the prevalent cases of biallelic RPE65 pathogenic variant in Australia could not be replicated from the one presented in the submission. The cost per patient for a VN treatment was estimated as **\$redacted**. The submission did not provide further detail justifying the proposed price of acquisition.

Table 19 Submission estimated financial implications for Government health budgets over Years 1-6

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Intervention						
Number of treated patients ^a	redacted	redacted	redacted	redacted	redacted	redacted
Sub-total cost: VN	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Co-administered services						
Specialist visits	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Sub-total cost: MBS/PBS	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
OCT tests	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Genetic testing	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Procedure costs	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Prednisone	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Treatment of AEs	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Travel and accommodation	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Total cost: other services	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Total cost to Gov'ts	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted

Abbreviations: AEs, adverse events; VN = voretigene neparvovec

Notes: ^a Each patient requires the procedure to be carried out separately on each eye. The cost of the intervention is a cost per patient and includes sufficient VN to treat both eyes.

Source: Table E.5.1 and E.5.2 of the Commentary.

The Commentary considered that there is potential for the net cost/year to the government to be less than estimated in the submission due to an overestimated number of prevalent patients applied in the financial estimates.

The Commentary particularly noted that the submission's calculation yielding a 3.16% prevalence of the biallelic RPE65 pathogenic variant in RP patients could not be replicated. The pre-ESC response acknowledged that this prevalence figure had been incorrectly calculated, and presented a revised prevalence estimate of 2.45%.

Revised financial estimates based on this new prevalence estimate are presented in Table 20.

Table 20 Pre-ESC revised estimated financial implications for Government health budgets over Years 1-6

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Intervention						
Number of treated patients ^a	redacted	redacted	redacted	redacted	redacted	redacted
Sub-total cost: VN	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Co-administered services						
Total cost: other services	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Total cost to Gov'ts	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Previous total cost to Gov'ts	<i>\$redacted</i>	<i>\$redacted</i>	<i>\$redacted</i>	<i>\$redacted</i>	<i>\$redacted</i>	<i>\$redacted</i>

Abbreviations: AEs, adverse events; VN = voretigene neparvovec

Notes: ^a Each patient requires the procedure to be carried out separately on each eye. The cost of the intervention is a cost per patient and includes sufficient VN to treat both eyes.

Source: Table 1, Pre ESC response

15. Key issues from ESC for MSAC

Key Issues for MSAC
<ul style="list-style-type: none"> • Whether the criteria for access to VN should: <ul style="list-style-type: none"> • take account of retinal cell viability and whether an assessment method and thresholds be defined • have a starting age of 2 years (proposed TGA label) or 3 years (clinical trial entry criteria). • Whether the proposed STC model, although appropriate in view of the likely number of eligible patients and necessary clinical and product handling expertise, will ensure equity of access, particularly given current access to genetic testing is variable across jurisdictions. • The clinical evidence shows that voretigene neparvovec (VN) treatment was associated with statistically significant and, based on expert opinion, clinically relevant differences in the change in the multi luminance mobility test (MLMT). However, this measure was developed for use in VN clinical trials and is not be suitable as a performance measure in routine clinical practice. Change in light sensitivity (FST) was statistically significant, but no clinically meaningful threshold was proposed for this measure. The change in visual field (VF), although statistically significant, showed important inter-test variability, was not a pre-specified outcome and no clinically meaningful threshold was proposed. Finally, the change in visual acuity (VA) did not show statistically significant differences and did not reach the proposed clinically meaningful threshold. Despite several limitations around these two outcomes, VA and VF were used to account for treatment effect in the economic model. The latter may be inappropriate. The submission did not justify why FST was not used to define health states and inform transition probabilities. • The health states in the economic model were defined by a combination of VA and VF, with vision impairment cut-off points based in principle on American Medical Association (AMA) guidelines (AMA, 2007). Moderate vision impairment (HS1) represents a wide visual function range where some patients may have near normal vision and others are close to 'legal blindness' (23% of baseline, 57% if using natural history data of VA and VF). After Year 1, 70% of patients (VN) are in HS1 and remain in this health state for 40 years. Therefore, the ESC considered one of the

Key Issues for MSAC

main issues present in the economic evaluation is whether HS1 is sensitive enough to capture patient difference. The ESC noted that the application attempted to address the wide visual function range in HS1, by adjusting the utility values in HS1 (to 0.75). The ESC considered this was appropriate given the limitations of the model structure, however considered a significant amount of uncertainty remained. This change increased the revised base case ICER from ~\$redacted/QALY to ~\$redacted/QALY. Furthermore, the use of the EQ-5D 5L increased the ICER from ~\$redacted/QALY to ~\$redacted/QALY for the adjusted and unadjusted utilities respectively.

- The justification for the selection of the base case utility values was not well supported by the submission and these are an important driver of the cost-effectiveness results. The base case utilities were obtained from a study that relied on the expertise of six retina specialists with expertise in inherited retinal dystrophies (IRDs) who provided a proxy valuation of vignettes using the EQ-5D-5L and HUI-3.
- The sample size informing the transition probabilities in the first year (derived from Study 301) and beyond year 1 for the BSC arm and beyond year 40 for the VN arm (derived from the natural history of RPE65 study), were small, hence considered highly uncertain. The pre-ESC response asserts the sample size reflects the ultra-rare nature of the condition.
- The model assumed that treatment effect was maintained for 40 years based on 1 year of data. Extrapolation seems reasonable but the extent to 40 years is highly uncertain. Reducing the duration of treatment effect to 7.5 years (period for which follow-up evidence is available) increases the ICER from ~\$redacted/QALY in the revised base case to ~\$redacted/QALY.
- The number of eligible patients was likely overestimated in the initial submission and in the pre-ESC response. This is mainly explained from the uncertainty around the prevalence estimate of retinitis pigmentosa (RP) which was used as a proxy for all IRDs caused by a RPE605 biallelic pathogenic variants. This contrasts with the estimate presented to the NICE UK and the EMA which considered both the RP and Leber congenital amaurosis (LCA) prevalence. This may be particularly important, as the clinical data were generated in LCA patients only.
- Additionally, there is uncertainty that all patients in the prevalent pool will be identified, given only redacted (from an estimated redacted) have been identified so far, or that identified patients will have sufficient viable retinal cells. These sources of uncertainty have large financial implications.
- ESC noted additional costs such as, the likely increase in cataract surgery among this patient population and the costs of cascade testing for family members, were not considered.

The submission does not nominate any outcome measures for the proposed managed access arrangement. Specification of the elements of a funding agreement will be critical for ensuring the cost-effectiveness of VN in clinical practice, should it be publicly funded. The applicant pre-ESC contends this can be done after MSAC recommends, but for Kymriah MSAC wanted these elements to be defined prior to recommending.

ESC discussion

ESC noted that this application is requesting public subsidy of voretigene neparvovec (Luxturna™) for the treatment of adult and paediatric patients with vision loss due to inherited retinal dystrophy (IRD) caused by confirmed biallelic *RPE65* pathogenic variants and who have sufficient viable retinal cells. ESC noted that this application seeks shared funding from the Australian and state/territory governments through the National Health Reform Agreement (NHRA).

The ESC noted IRDs are a complex group of eye disorders, with extensive genic, allelic and phenotypic heterogeneity. The ESC considered the application and Commentary did not appropriately address the fact that due to allelic heterogeneity, there is no genotype-phenotype correlation in the presentation of IRDs. The same variant can cause different phenotypes of varying severity, as other modifiers of disease that are present (genetic or environmental factors) are also thought to impact disease severity.

The ESC noted the application focused on the retinal dystrophies that are related to the *RPE65* gene; LCA, SECORD and RP. While these three conditions differ in terms of age of onset, severity of visual impairment and the rate of progression, they do share some common features such as nyctalopia, progressive visual loss and loss of central vision. The ESC noted that LCA and SECORD usually have an onset between birth and age 5, with patients usually blind by the age of 20 and no light perception left by the fourth decade of life. On the other hand, RPE is associated with a later age of onset, usually detected in childhood or adolescence. The ESC also noted that while variants in the *RPE65* gene can cause these specific retinal dystrophies, variants in hundreds of other genes can also cause the same conditions.

The ESC considered that given the complex nature of the IRDs, genetic diagnosis is also complex. The ESC considered there may be equity of access issues related to availability of genetic testing, noting that genetic testing for IRDs is funded via public hospitals, which can vary on a state by state basis. The ESC suggested the sponsor address this issue in its pre-MSAC response.

The ESC considered equity issues could also arise from the proposed STC approach to service delivery, although noting this approach may be appropriate in view of the rarity of the condition and the expertise required for treatment. The ESC queried whether the training of surgeons and pharmacists would be available in the long-term.

The ESC considered the proposed clinical management algorithm (Figure 2) and advised BSC (as defined in Figure 1) should be included as part of every pathway, given that even with VN treatment, some level of vision impairment will remain, requiring ongoing ophthalmologist review as well as vision support in some cases. The ESC considered that the VN arm of the proposed management algorithm should also include the potential for future cataract surgery, given it was a significant AE associated with the vitrectomy procedure.

The ESC noted that the Commentary stated that there is a discrepancy between the age of patients eligible for treatment in the trial, ≥ 3 years, and the proposed TGA indication, ≥ 2 years. The ESC advised further clinical advice should be sought on the appropriateness of treatment for children aged between 2 to 3 years in order to inform MSAC's consideration.

The ESC considered it may be appropriate for there to be defined criteria for retinal viability and noted the applicant had agreed to work with the Department to develop these if considered appropriate by MSAC.

The ESC noted that other treatments for IRD such as oral retinoid supplementation as monotherapy or as a synergistic treatment to gene therapy are currently being trialled. Similarly, other gene therapies for IRDs, for example, antisense oligonucleotide therapies for CEP290-associated LCA, are currently in the clinical trial phase.

The ESC noted that, as is often the case for rare conditions, there is limited clinical evidence available for VN with the key clinical trial, 301, enrolling 31 patients with LCA only.

ESC noted the application described VN as inferior in terms of safety and superior in terms of effectiveness when compared to BSC.

The ESC considered the documented change in MLMT score was statistically significant and clinically meaningful. However, the ESC also noted that although the applicant claimed a change in MLMT score of 1 was clinically meaningful, the FDA “Summary Basis for Regulatory Action – LUXTURNA” document suggests an MLMT score change of two or greater as the clinically meaningful benefit for functional vision.

The ESC also noted that MLMT could not be used to assess response in clinical practice. ESC considered that this would make assessment of effectiveness in clinical practice difficult. The ESC noted that other measures such as FST, VF and VA may be able to be used in clinical practice to assess a patient’s response to VN. The ESC considered that while use of these secondary and other outcomes to assess response to treatment maybe appropriate in clinical practice, it noted:

1. Change in FST was statistically significant and may be correlated to change in MLMT score, but no clinically meaningful threshold was proposed;
2. Change in VF was statistically significant, but showed important inter-test variability, was not a pre-specified outcome and no clinically meaningful threshold was proposed; and
3. Change in VA did not show a statistically significant difference and did not reach the proposed clinically meaningful threshold, and may not be correlated with response since VA aims to measure central visual function and is primarily cone-mediated, and IRD due to biallelic RPE65 pathogenic variants is primarily a rod-cone disease.

The ESC considered there was clinical uncertainty resulting from a lack of long-term trial data available to inform the duration of treatment effect. The ESC noted the pre-ESC response stated there has been no loss of treatment effect over the 7.5 years follow-up to date.

The ESC noted the three main issues associated with the economic evaluation, as identified in the Commentary were:

1. the translation of secondary outcomes of effectiveness;
2. the modelled results were most sensitive to the selection of utility values; and
3. the assumed duration of VN efficacy (extrapolation of treatment effect)

The ESC noted the modelled time horizon was categorised into three phases depending on the availability of clinical data and to allow varied extrapolation-related assumptions (see Table 13):

- Initial phase
- Stabilisation phase
- Long-term phase

The ESC noted that health states in the model were defined by a combination of VA and VF, with vision impairment cut-off points based in principle on American Medical Association (AMA) guidelines (AMA, 2007). The ESC further noted Moderate vision impairment (HS1) represents a wide visual function range where some patients may have near normal vision and others are close to 'legal blindness' (23% of baseline, 57% if using natural history data of VA and VF). After Year 1, 70% of patients (VN) are in HS1 and remain in this health state for 40 years. Therefore, the ESC considered one of the main issues present in the economic evaluation is whether HS1 is sensitive enough to capture patient difference. The ESC noted that the application attempted to address the wide visual function range in HS1, by adjusting the utility values in HS1 (to 0.75). The ESC considered this was appropriate given the limitations of the model structure, however considered a significant amount of uncertainty remained.

The ESC considered that if a claim of superior clinical effectiveness was accepted, consideration must then be given as to whether the VA and VF data appropriately captured the effectiveness of VN in the economic model (see Table 14). The ESC considered limitations existed in relation to:

- the wide variation of visual impairment amongst patients;
- 64% of patients are children; and
- the small sample size available (N=29) to inform the economic modelling, resulting in many of the assumptions in the model being very sensitive to change.

The ESC noted the transition probabilities were calculated based on the proportion of patients at each time point who were within pre-defined cut-offs (of VA and VF), rather than the statistically significant differences observed in the trial (Table 14). The ESC considered that given the small sample size, there was uncertainty as to whether this approach adequately captured the treatment effect. The ESC advised that a correlation measure, demonstrating that the pre-defined cut-offs correspond to the statistically significant differences observed in the trials would have helped to address this uncertainty.

The ESC considered the duration of treatment effect to be a source of uncertainty, noting the ICER almost doubles when the time horizon is revised from 40 years to 7.5 years. The ESC noted this results from most of the cost of treatment being up-front, so the assumption of a lifetime benefit has a significant impact on the ICER. The ESC considered the revised base case should use a 7.5 year time horizon, corresponding to the duration of follow up in the clinical trial. The ESC also noted that VN may be more cost-effective when given to younger children.

The ESC considered the revised based case ICER (Table 15) was high and very uncertain.

The ESC noted the modelled results were most sensitive to the selection of utility values and the assumed duration of VN efficacy (Table 16).

The ESC noted the utility values were based on a bespoke survey, designed using vignette descriptions of IRD states and relied on the expert opinion of six retinal specialists (no patients) using generic QoL instruments, the health-the 5-level version of EQ-5D-5L and Health Utility Index 3 (HUI3). The HUI3 results were used in the economic evaluation, due to the presence of a visual measure. However the ESC noted that the results of the HUI3 are lower than those seen with the EQ-5D-5L and those reported in the literature for similar conditions. The ESC considered the use of these utility values may not be appropriate.

The ESC noted the Commentary also questioned the appropriateness of using VA data to inform the economic model. Additional multivariate analysis were carried out using only the VF data and a 7.5 year time horizon. This moderately increased the ICER from \$redacted/QALY to \$redacted/QALY. However, when also adjusting for higher utility values, the ICER increased significantly to \$redacted/QALY (Table 16).

The ESC considered another economic issue for consideration was that the cost-effectiveness of VN is contingent on yet to be established clinical guidelines and treatment pathways. The ESC noted the proposed funding arrangement and structure of the key components of the clinical pathway were complex, and considered that identification of a robust and reproducible treatment eligibility criteria for genetic testing and retinal cell viability was key to ensuring VN's cost-effectiveness in clinical practice.

The ESC considered that the number of eligible patients was likely to be overestimated even after being revised downwards in the preESC response. Factors contributing to an overestimation include:

- uncertainty around the prevalence estimate of retinitis pigmentosa (RP) which was used as a proxy for all IRDs caused by a RPE65 biallelic pathogenic variants. This contrasts with the estimate presented to the NICE UK and the EMA which considered both the RP and Leber congenital amaurosis (LCA) prevalence. This may be particularly important, as the clinical data were generated in LCA patients only;
- uncertainty that all patients in the prevalent pool will be identified, given only redacted (from an estimated redacted) have been identified so far;
- uncertainty that identified patients will have sufficient viable retinal cells to benefit from treatment.

These sources of uncertainty have large financial implications.

The ESC considered the average cost of treatment for each patient was likely to be higher, as additional costs such as, the likely increase in cataract surgery among this patient population and the costs of cascade testing for family members, were not considered.

16. Other significant factors

Nil

17. Applicant comments on MSAC's Public Summary Document

Novartis will continue to work collaboratively with MSAC, the Department of Health and State/Territories and Federal Government to help ensure that Australians with vision loss due to inherited retinal dystrophy (IRD) caused by confirmed biallelic RPE65 pathogenic variants will receive access to Luxturna, funded jointly by the Commonwealth and the States through the National Health Reform Agreement (NHRA), at the earliest opportunity.

18. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: [visit the MSAC website](#)