Voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations [ID1054]

Addendum #1

Summary of Stakeholder Testimonials

31/05/2019

1 Introduction

This addendum was produced following the submission of additional stakeholder testimonials, following completion of the ERG report. These testimonials include: patient and carer viewpoints elicited in a survey for those affected by any gene-mediated IRD, conducted by Retina UK; the views of patients, carers and healthcare professionals speaking at a meeting of the FDA's Cellular, Tissue, and Gene Therapies Advisory Committee in October 2017; video evidence provided by the company showing a patient navigating the MLMT outcome measure pre- and post-treatment; and a short video produced by the company that includes the views of a patient and his carer. This addendum is provided to supplement the evidence summarised in Section 8 of the ERG report.

2 Summary of Stakeholder Testimonials

2.1 Patient and carer views elicited in Retina UK submission

While the study survey described in Retina UK's submission is large (916 responders), the ERG note that the survey was targeted generally to patients and carers affected by inherited sight loss caused by mutations in any gene i.e. which included but was not restricted to the patient population considered in the company submission for treatment by VN. In this survey, 73.51% of respondents had a diagnosis of retinitis pigmentosa while 1.05% had a diagnosis of Leber's congenital amaurosis (LCA). The ERG also note that no details are given regarding methods employed in conducting this survey or data extraction and analysis, and so it is not possible for the ERG to assess or comment on the quality of the survey or the reliability of the survey findings presented in the submission. Despite these limitations, the ERG note that many of the points presented in the submission by Retina UK are in agreement with many of the points described in the ERG's summary of patient support group submissions as presented in section 8.2 of the ERG report (and highlighted in bold below). These points of agreement are as follows:

Anxiety and worry on noticing changes to vision, leading to depression and mental health issues. Retina UK stated that 92% of respondents with vision loss conditions reported that vision loss impacted on mental health, with almost three quarters reporting that they had experienced anxiety, 62% had experienced stress, 41% had experienced depression and 33% had experienced loneliness.

People living with the condition stated the condition deprives them of opportunities in education, the labour market e.g. getting a job and/or job security. The Retina UK survey results indicate that over three quarters of respondents with vision loss conditions felt that their career / job was affected, with this being significant or extreme in 46%, while over half of respondents indicated that their condition had impacted their education.

Substantial effect on parents, carers and loved ones of people living with the condition. Retina UK agree with other stakeholder submissions that parents caring for affected children often fear for their child's future and many experience guilt due to the inherited nature of the condition. An additional point made by Retina UK is that there can be stress from managing the financial impact of reducing or giving up work to care for their child alongside additional expenses such as adaptive aids and travel to specialist appointments.

Retina UK, along with other patient stakeholders in the ERG's main report, suggested there is **unmet need for people living with RPE65-mediated IRD as there are currently no treatments for people with this condition available on the NHS**. Retina UK state in their submission that there is currently no treatment that slows or stops the progression of sight loss and cite how a 2013 James Lind Priority Setting Partnership on inherited retinal dystrophies identified the highest priority research question as: Can a treatment to slow down progression or reverse sight loss in inherited retinal diseases be developed?

In Section 8.2 of the ERG report, the patient expert expressed the view that there would be considerable benefit in stabilizing or reversing the visual deterioration of school age or younger

children, even if the effect was limited in time. Retina UK similarly noted that effective treatment for those experiencing childhood onset sight loss could provide lifetime benefit in terms of education, employment and quality of life.

Retina UK state that the progressive nature of sight loss conditions leads to a continual series of losses, with associated grief, and that **the need to continually adapt to increasing disability is stressful.** This is in alignment with the patient expert view summarised in the ERG report.

In Section 8.2 of the ERG report, the patient expert expressed the view that **reducing the effects of night blindness could improve mobility and give patients confidence, improve their safety and prevent isolation, while improved visual acuity would help patients access written material, to recognise faces and interact naturally with colleagues and stakeholders.** Retina UK confirm that sight loss affected mobility in 90% of responders with visual loss conditions and 95% of respondents said that their condition impacted on their leisure time and hobbies. The majority of respondents with visual loss conditions said that their sight loss condition affected their social life, day-to-day routines, relationships and family life, and the likelihood of falls or accidents.

The ERG note two points of disagreement between Retina UK and the points described in the ERG's summary of clinician expert submissions as presented in the ERG report (Section 8.1). These points of disagreement are summarised below:

Because genetic networks are in place across England, patients with known molecular diagnoses who could benefit from treatment can be identified. In their statement, Retina UK state that while treatment with VN is only suitable to those with a specific genotype (and therefore not appropriate for the majority of the inherited sight loss community), access to genetic testing to confirm genotype is not consistent across the country, so that those in areas where testing is not readily available will be unable to benefit from the treatment.

Side effects are unlikely to be a barrier to adoption of the treatment. In their submission, Retina UK state that patients and carers are aware of possible side effects including retinal damage and vision loss and that some patients may prefer not to risk their remaining vision early in the disease course.

2.2 Patient and clinician testimonials presented at the FDA's 67th meeting of the cellular, tissue, and gene therapies advisory committee

The ERG note that many of the points presented by patients and clinician experts at the 67th meeting of the cellular, tissue, and gene therapies advisory committee are in agreement with many of the points in the ERG's summary of patient support group submissions as presented in the ERG report (Section 8.2). These points of agreement are summarised below:

- Substantial effect on parents, carers and loved ones of people living with the condition.
- Successful treatment has the potential to have a huge influence at a critical stage of childhood development and learning.
- The need to continually adapt to increasing disability is highly stressful.
- Reducing the effects of night blindness could improve mobility and give patients confidence, improve their safety and prevent isolation, while improved visual acuity

would help patients access written material, to recognise faces and interact naturally with colleagues and stakeholders.

In addition, the ERG note that many of the points presented by clinician experts in the FDA's 67th meeting of the cellular, tissue, and gene therapies advisory committee are in agreement with points reported in the ERG's summary of clinician expert submissions as presented in the ERG report (Section 8.1) These points are summarised below:

- The most important outcome in the assessment of VN is gain of navigation, which will likely have a significant effect on the independence of affected patients.
- Side effects are unlikely to be a barrier to adoption of the treatment.
- Surgery is standard i.e. not significantly different to present clinical vitrectomies and is within the capabilities of specialist units.

Two additional issues were raised in the provided comments.

Eligibility for treatment with VN. A clinical expert and a service user advocate both noted that an upper age limit for treatment was inadvisable.

Durability of treatment effect. A clinical expert noted that in his view, treatment response to VN is durable over several years, citing anecdotal evidence of one patient nine years post-treatment.

2.3 Video and power point materials submitted by the company

The company provide MLMT (a novel measure of functional vision ability to conduct visually dependent activities of daily living independently) assessment videos showing evidence of successful navigation of the MLMT maze following treatment with VN at 1 year and 3 years at 1 lux (equivalent to a moonless summer night or indoor night-light), alongside a patient testimonial.

2.4 Summary

There is recognition in all submissions of an unmet need for people living with RPE65 as there are currently no treatments for people with this condition available on the NHS. There is agreement between all the received submissions that vision loss impacts on mental health, manifesting in symptoms such as stress, anxiety, depression and loneliness, and impacts on education and career / job prospects. Submissions agreed that successful treatment can support a critical stage of childhood development and learning and could provide lifetime benefit in terms of education, employment and quality of life. All submissions agreed that there is substantial impact on parents / carers / loved ones, ranging from emotional distress from raising a child with vision loss to stress arising from associated financial burden e.g. having to give up job to care for a child. There is a recognition in all the submissions that the need to continually adapt to increasing disability is stressful. All submissions agreed that reducing the effects of night blindness could improve mobility and that vision loss significantly impacted on relationships and social life.

There is agreement between clinician experts from all submissions regarding the suitability of MLMT assessment as an outcome measure for evaluating the effectiveness of VN. Clinician experts also share a view that surgery is standard i.e. not significantly different to present clinical vitrectomies and is within the capabilities of specialist units.

There are two points of disagreement between submissions. The first relates to the provision of genetic networks. In the ERG report (Section 8.1), NHS England assert that genetic networks are in place across England and that patients with known molecular diagnoses who could benefit from treatment can be identified. However, Retina UK disagree. They state in their submission that their survey indicates that access to genetic testing to confirm genotype is not consistent across the country, so that those in areas where testing is not readily available will be unable to benefit from the treatment. A second point of disagreement is that while clinician experts agree that side effects are unlikely to be a barrier to adoption of the treatment, Retinal UK states that some patients may prefer not to risk their remaining vision early in the disease course.