Rare eyes diseases: progress continues with authorised orphan medicines and breakthrough technologies

BY ROD MCNEIL

An update on the development of orphan medicines, recent regulatory treatment approvals for rare eye conditions and advances in retinal prosthetic technologies for blinding diseases.

The prevalence of a rare disease is based usually on a range of estimates and may change over time. In the European Union (EU), a disease is considered rare if fewer than five in 10,000 people have the condition. Around 30 million people in the EU are likely to suffer from a debilitating rare disease, according to estimates from the European Medicines Agency (EMA), i.e. one in 17 based on a population of 510 million. A rare disease in the United States is defined officially as a condition that affects fewer than 200,000 people and it has been estimated that between 25-30 million Americans are living with a rare disease. Inherited gene defects account for approximately 80% of rare diseases, many of which affect vision, according to the National Eye Institute.

Orphan designation

Obtaining orphan designation for an investigational treatment provides financial incentives for companies to research and develop medicines for rare diseases, which includes development support through scientific advice on study protocols, fee reductions and access to EU grants. The Committee for Orphan Medicinal Products (COMP) is responsible for reviewing applications for orphan designation. Criteria for orphan designation are: the medicine must treat, prevent or diagnose a disease which is life-threatening or chronically debilitating, or it is unlikely that the medicine will generate sufficient returns to justify the investment needed for its development; the disease must not affect more than five in 10,000 people across the EU; no satisfactory method of diagnosis, prevention or treatment exists, or if such a method does exist, the medicine must be of significant additional benefit to those affected by the condition [1].

Orphan-designated medicines that achieve marketing authorisation following evaluation by the Committee for Human Medicinal Products (CHMP) and which demonstrate that they maintain the criteria for designation secure a 10-year market exclusivity period. This blocks similar competitor medicines from entering the market for 10 years but does not necessarily block medicines which are used for the same rare disease but differ in molecular structure, mechanism of action or the way they are used, or work better than the orphan product [1].

Since 2001 through 2017, over 140 orphan medicines have been authorised for marketing in all EU member states, around 8% of all medicines granted orphan designation during the same period (Figures 1 and 2) [2]. EMA evaluations are based on a scientific assessment of all available evidence on medicines but do not consider their costs [1]. Therefore, the availability and reimbursement of a European Commission (EC)-authorised orphan medicine is subject to review by the relevant national competent authorities.

Regulatory drug approvals for rare eye diseases

Currently, there are three orphan medicines authorised by EMA in the field of ophthalmology: cenegermin (Oxervate, Dompé) for neurotropic keratitis (NK); idebenone (Raxone, Santhera Pharmaceuticals) for Leber's hereditary optic neuropathy (LHON); and ciclosporin (Verkazia, Santen Oy) for vernal keratoconjunctivitis (VKC). Ophthalmological gene therapy voretigene neparvovec (Luxturna, Spark Therapeutics Inc) is currently under evaluation by EMA.

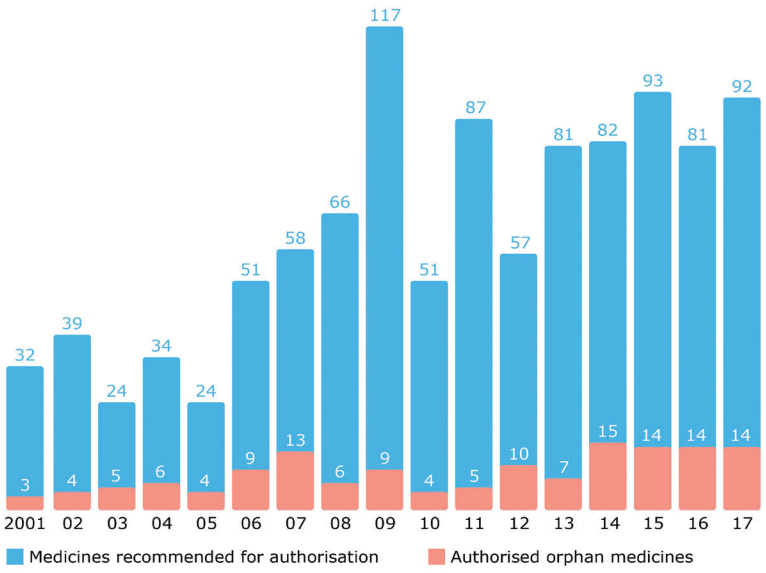


Figure 1: Over 140 orphan medicines authorised in the EU since 2001. Source: EMA.

Topical nerve growth factor for moderate to severe neurotrophic keratitis

Neuroptrophic keratitis is a rare, degenerative corneal disease, with an estimated prevalence of less than 4.1 per 10,000 patients [3]. Patients with moderate and severe disease constitute approximately one third of the total affected population [3]. According to Versura et al, management of NK is based on clinical severity, the aim of therapy focused on halting the progression of corneal damage and promoting epithelial healing [4].

Topical recombinant human nerve growth factor (rhNGF) treatment cenegermin was granted marketing authorisation for the treatment of moderate to severe neurotrophic keratitis by the EC in July 2017, representing the first biotechnology orphan drug worldwide authorised for this indication. Cenegermin is indicated for the treatment of moderate (persistent epithelial defect) or severe (corneal ulcer) neurotrophic keratitis in adults. More recently, in August 2018 the US Food and Drug Administration approved cenegermin for the treatment of neurotrophic keratitis, estimated to affect fewer than 65,000 people in the United States.

A positive recommendation from the EMA's CHMP was based on data from two phase II clinical trials involving 204 patients with moderate to severe NK. Both studies demonstrated that after eight weeks of treatment, a higher number of cenegermin-treated patients reached a complete corneal healing vs. patients on placebo. In the REPARO phase II study (n=156), topical rhNGF was found to be safe and more effective than vehicle in promoting corneal healing, defined as <0.5-mm maximum diameter of fluorescein staining in the lesion area [5]. At the primary efficacy endpoint at week four, corneal healing was achieved in 54.9-58.0% of rhNTG-treated patients compared with 19.6% of vehicle-treated patients.

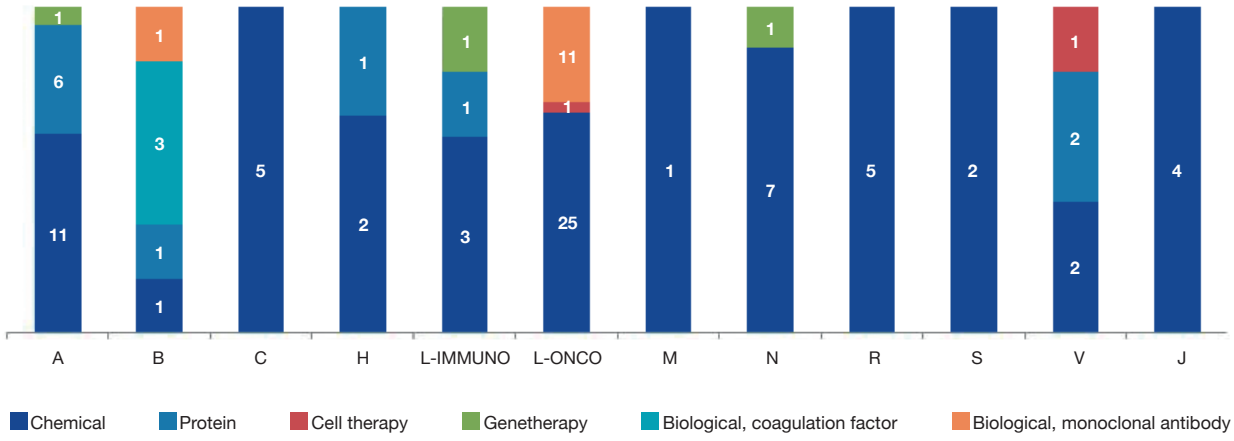
The EMA observed that the available clinical data demonstrate a clear benefit of an eight-week treatment course with cenegermin in re-establishing ocular surface integrity in patients with moderate and severe NK [3]. It noted that the observed difference of 30-40% in the rate of corneal healing with respect to vehicle control represents "robust proof of a clinically meaningful treatment benefit, as corneal health reduces the risk of eye perforation and potential sight loss". Long-term data showed maintenance of the treatment effect in the vast majority of patients (>96%) up to one year. The CHMP recommended that Dompé pursue plans for a further study to evaluate long-term outcomes, including functional outcomes, and possible additional benefit of prolonged treatment.

The National Institute for Health and Care Excellence (NICE) issued single technology appraisal guidance in July this year advising that cenegermin is not recommended, within the terms of its marketing authorisation, for treating moderate or severe NK in adults in the NHS [6]. Nonetheless, NICE stated that evidence suggests that when used for eight weeks, cenegermin is an effective treatment compared with vehicle in terms of corneal healing. However, the longer-term corneal healing effects are not known because there are no data available about this, noted NICE. Moreover, based on the evidence presented, the most likely cost-effectiveness estimate would be higher than the range that NICE normally considers to be an acceptable use of NHS resources (i.e. £20,000 to £30,000 per Quality Adjusted Life Year gained).

Leber's hereditary optic neuropathy

Leber's hereditary optic neuropathy is a maternally inherited disease characterised by acute or sub-acute painless vision loss in one eye, generally followed by a similar vision loss in the second eye in a matter of weeks or few months (typically 2-4 months) [7]. The prevalence of LHON is estimated at between one in 15,000 to one in 50,000 worldwide [7]. Idebenone (Raxone, Santhera Pharmaceuticals) has EC marketing authorisation for the treatment of visual impairment in adolescent and adult patients with LHON [7]. The proposed mechanism of action in LHON is that idebenone mitigates inactive-but-viable retinal ganglion cell dysfunction by shuttling electrons onto complex III of the mitochondrial transport chain, thereby bypassing the deficient complex I, restoring production of cellular energy and decreasing oxidative stress in affected cells [8].

In April 2017 the Scottish Medicines Consortium accepted idebenone for restricted use within NHS Scotland to patients with LHON who are not yet blind, i.e. they do not meet the UK criteria to be registered as severely sight impaired [9]. It cited data from the RHODOS 24-week double-masked randomised placebo-



Therapeutic area

A - alimentary tract & metabolism
B - blood & blood forming organs
C - cardiovascular system
H - systemic hormonal preparations
L - antineoplastic agents
L - immunomodulating agents
M & N - musculoskeletal & nervous system
R - respiratory system
S - sensory organs
V - various
J & P - antiinfectives & antiparasitic

Figure 2: Authorisations of orphan medicines by type and therapeutic class, 2000-2017. Source: EMA.

controlled study, in which patients who received idebenone had numerical improvements in visual acuity over placebo. The advice also took account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of idebenone.

Verkazia approved under accelerated assessment for rare eye allergy

In July 2017, the EMA recommended granting a marketing authorisation in the EU for Verkazia, a medicine that treats severe vernal keratoconjunctivitis, a rare form of chronic eye allergy that can lead to corneal ulcers and loss of sight, in children from four years of age and adolescents. It is estimated to affect one to three people out of 10,000 in the EU, according to Eurostat. In a press statement, EMA noted that there is a need for additional treatments because currently authorised therapies are not always effective or adequate to control severe VKC.

The recommendation of EMA's CHMP is mainly based on data from one phase III clinical trial in 169 patients with severe VKC [10]. The study showed that, after four months, more patients treated with Verkazia than with placebo had an improvement in corneal health while requiring no additional corticosteroid medication. After four months of treatment, all main VKC symptoms studied (light sensitivity, itching, tearing and mucous discharge) improved. Following review, the COMP has recommended that the orphan designation of the medicine be maintained as it still meets the criteria for designation as an orphan medicinal product. It also concluded that Verkazia is of significant benefit over corticosteroids because these medicines cannot be used long-term due to their side-effects. It also considered that the combined use of Verkazia with antihistamines may improve the outcome of patients with severe VKC.

Cystinosis

Cystinosis is a rare genetic autosomal recessive disease, caused by a lyposomal transport defect resulting in the intracellular accumulation of cystine. Cystinosis affects approximately 0.15 in 10,000 people, equivalent to a total of around 7600 people in the EU [11]. Mercaptamine (Cystadrops, Orphan Europe S.A.R.L.) eye drops solution, designated as an orphan medicine in 2008, is indicated for the treatment of corneal cystine crystal deposits in adults and children from two years of age with cystinosis. The European Public Assessment Report notes that, in the pivotal CHOC study, the absolute reduction in corneal crystals from baseline to month three as measured with in-vivo confocal microscopy (primary efficacy) was 4.6±3.1 units (-40.4%) in the Cystadrops treatment arm and 0.5±3.4 units (-0.8%) in the cysteamine HCl eye drops solution 0.10% (CH 0.10%) comparator arm (a standard of care, ex tempore formulation of 0.10% cysteamine) [11]. The difference between treatment arms was 3.8±0.9 (95% CI 2.1 to 5.6, $p<0.0001$). The observed 30 to 40% reduction in corneal crystals is supported by a similar mean relative reduction in key clinical endpoint, photophobia [11].

Voretigene neparvovec for inherited form of retinal dystrophy

Promising progress continues to be made with initiation of gene therapy clinical trials for inherited retinal disease, including Leber's congenital amaurosis, choroideraemia, Stargardt disease, achromatopsia and X-linked retinitis pigmentosa (RP) [12,13].

New gene therapy voretigene neparvovec, an adeno-associated virus vector-based gene therapy, was approved in December 2017 by the US FDA to treat children and adult patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy and viable retinal cells. This represents the first directly administered gene therapy approved in the US that targets a disease caused by mutations in a specific gene. The condition, which leads to vision loss and may cause complete blindness in certain patients, affects approximately 1000 to 2000 patients in the US. Mutations in the RPE65 gene are associated with several clinical manifestations including nyctalopia, decreased visual field and decreased visual acuity [14]. Symptoms include early childhood blindness, nystagmus, night blindness, progressive visual field and visual acuity loss, and progression to inevitable blindness in early adulthood [15].

Voretigene neparvovec uses a non-pathogenic recombinant adeno-associated virus vector serotype 2 (AAV2) to deliver cDNA encoding RPE65 protein to target cells in the retina. Voretigene neparvovec is administered to each eye via subretinal injection. A phase 3 study evaluated the efficacy of voretigene neparvovec in 31 participants. The primary efficacy endpoint was the change from baseline to one year in a subject's ability to navigate an obstacle course at various light levels (measured by using multi-luminance mobility test (MLMT) score). The group treated with voretigene neparvovec demonstrated significant improvements in their ability to complete the obstacle course at low light levels as compared to the control group. At year one, an MLMT score change of two or greater occurred in 52% of subjects in the treatment group compared with 10% of the subjects in the control group when using both eyes [10]. An MLMT score change of two or more is considered a clinically meaningful benefit in functional vision. Twenty paediatric subjects were evaluated in the phase 3 study and showed similar efficacy treatment responses as the overall study population.

Spark Therapeutics submitted a market authorisation application with the EMA for investigational voretigene neparvovec in July, 2017. Novartis agreed in January 2018 an exclusive licensing and supply agreement with Spark Therapeutics for the development and commercialisation of this novel ophthalmology gene therapy outside the US.

Prosthetic technologies for blinding disease

Argus II retinal prosthesis (Second Sight Medical Products) induces visual perception in individuals with severe to profound retinitis pigmentosa. It is described as an established technology with more than 293 implants, approved for individuals with RP (bare-light and no-light perception in the US). Second Sight is also advancing the development of a visual cortical prosthesis system called Orion, a transformational technology with a six subject feasibility study underway with encouraging early results, according to a recent investor conference presentation [16]. This technology platform is designed to bypass the damaged eye and / or optic nerve to directly stimulate the brain and provide the perception of patterns of light. The Orion System converts images captured by a miniature video camera mounted on glasses into a series of small electrical pulses. The company believes it has broad potential to treat many forms of blindness, including those due to glaucoma, diabetic retinopathy, optic nerve disease and trauma. Projects are underway to iterate implant design and externals in preparation for a pivotal clinical trial.

The RETINA IMPLANT Alpha AMS (Retina Implant AG) has been designed to replace the non-functioning and absent photoreceptor cells with a functional device to stimulate the remaining components of the retina to restore limited visual function and functional vision in patients with RP. Interim results of a multicentre trial in 15 patients blind from inherited retinal degenerations showed that the prosthesis was reliable, well tolerated and could restore limited visual functions in blind patients with degenerations of the outer retina [17]. Edwards et al. this year reported clinical trial results showing that

the Alpha AMS implant improved visual performance in five of six participants with end-stage RP and exhibited ongoing function for up to 24 months [18].

An early feasibility study is underway to transfer the surgical implantation technique and evaluate the safety and effectiveness of the RETINA IMPLANT Alpha AMS to restore limited visual function and functional vision in blind RP patients who are at the light perception (LP) or no-light perception (NLP) vision level [19]. According to study investigators, the ability to restore limited vision in blind RP patients with LP or NLP vision will reduce their disability and morbidity and provide a viable option to combat their disease and improve their lives.

In September 2018, the EMA's CHMP recommended granting a marketing authorisation for the gene therapy Luxturna for the treatment of adults and children suffering from inherited retinal dystrophy caused by RPE65 gene mutations.

References

1. European Medicines Agency. Rare diseases, orphan medicines: getting the facts straight. 28 February 2018. EMA/551338/2017.
2. European Medicines Agency. Development of medicines for rare diseases: an overview of the EU's orphan designation programme. News release 31/08/2018.
3. Committee for Medicinal Products for Human Use (CHMP). European Public Assessment Report: Oxervate (cenegermin). May 2017.
4. Versura P, Giannaccare G, Pellegrini M, et al. Neurotrophic keratitis: current challenges and future prospects. *Eye Brain* 2018;**10**:37-45.
5. Bonini S, Lambiase A, Rama P, et al; REPARO Study Group. Phase II Randomized, double-masked, vehicle-controlled trial of recombinant human nerve growth factor for neurotrophic keratitis. *Ophthalmology* 2018;**125(9)**:1332-43.
6. National Institute for Health and Care Excellence. Cenegermin for treating neurotrophic keratitis. NICE Technology appraisal guidance [TA532]. July 2018. www.nice.org.uk/guidance/ta532 Last accessed September 2018.
7. Committee for Medicinal Products for Human Use (CHMP). European Public Assessment Report: Raxone (idebenone). June 2015.
8. Raxone Summary of Product Characteristics, September 2015. www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003834/WC500193836.pdf Last accessed September 2018.
9. Scottish Medicines Consortium. idebenone (Raxone®) 150mg film-coated tablets SMC No. (1226/17). April 2017.
10. Committee for Medicinal Products for Human Use (CHMP). European Public Assessment Report: Verkazia (ciclosporin). July 2017.
11. Committee for Medicinal Products for Human Use (CHMP). European Public Assessment Report: Cystadrops (mercaptamine). October 2016.
12. Campa C, Gallenga CE, Bolletta E, Perri P. The role of gene therapy in the treatment of retinal diseases: a review. *Curr Gene Ther* 2017;**17(3)**:194-213.
13. Martinez-Fernandez De La Camara C, Nanda A, Salvetti AP, et al. Gene therapy for the treatment of X-linked retinitis pigmentosa. *Expert Opin Orphan Drugs* 2018;**6(3)**:167-77.
14. ClinicalTrials.gov database. A patient registry study for patients treated with voretigene neparvovec. ClinicalTrials.gov Identifier: NCT03597399.
15. US Food and Drug Administration. BLA Clinical Review Memorandum – voretigene neparvovec [LUXTURNA]. www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM592766.pdf Last accessed September 2018.
16. Second Sight. EYES Investor Presentation 09-03-18. https://investors.secondsight.com
17. Stingl K, Schippert R, Bartz-Schmidt KU, et al. Interim results of a multicenter trial with the new electronic subretinal implant Alpha AMS in 15 patients blind from inherited retinal degenerations. *Front Neurosci* 2017;**11**:445.
18. Edwards TL, Cottriall CL, Xue K, et al. Assessment of the electronic retinal implant Alpha AMS in restoring vision to blind patients with end-stage retinitis pigmentosa. *Ophthalmology* 2018;**125(3)**:432-43.
19. ClinicalTrials.gov database. RETINA IMPLANT Alpha AMS in blind patients with retinitis pigmentosa. ClinicalTrials.gov Identifier: NCT03629899.

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