Emerging treatments for Leber Hereditary Optic Neuropathy and Retinitis Pigmentosa

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MARTA ZUCCARELLI

Department of Pharmacy

University of Malta

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Abstract

Leber Hereditary Optic Neuropathy (LHON) and Retinitis Pigmentosa (RP) are rare inherited diseases which can lead to blindness, with limited treatment available.

The aim of this study was to understand emerging patterns in clinical development programs (CDPs) being pursued by pharmaceutical companies when developing safe and effective innovative medicines to treat LHON and RP.

Medicinal products (MPs) authorised within the EU to treat LHON and RP were retrieved from the European Medicines Agency (EMA) website. Investigational medicinal products (IMPs) to treat LHON and RP were retrieved from the EU Clinical Trials (EudraCT) Register and from the United States national library of medicines (USNML) database of clinical trials (CTs). CTs included in the study were those which were (i) carried out between 2006 and 2018, (ii) interventional and (iii) performed on MPs. Prospective treatment protocols were proposed for LHON and RP based on emerging MPs. Emerging patterns in primary endpoints of CTs were identified and compared. Regulatory pathways available within the EU to support the development and authorisation of orphan MPs were reviewed.

Idebenone (Raxone) is the only small molecule MP authorised in the EU to treat LHON. Voretigene neparvovec-rzyl (Luxturna) is the only gene therapy MP authorised in the EU to treat RP caused by mutation RPE65. Twenty-three CTs for 9 IMPs for LHON were included. Out of 9 IMPs, 6 were small molecules and 3 were advanced therapy medicinal products (ATMPs) (2 gene therapy and 1 somatic therapy).

Forty-nine CTs for 24 IMPs for RP were included. Out of 24 IMPs, 14 were ATMPs (8 gene therapy and 6 somatic therapy), 8 were small molecules and 2 were growth factors. IMPs in phase II and phase III stage of development were included in the treatment protocols. Five MPs (3 small molecules and 2 ATMPs) were included in the proposed

treatment protocol for LHON. The included MPs for LHON were idebenone (Raxone), cysteamine bitartrate, EPI-743, autologous bone marrow stem cells and GS010. Twelve MPs (5 small molecules, 6 ATMPs and 1 growth factors) were included in the proposed treatment protocol for RP. The included MPs for RP were QLT091001, valproic acid, brimonidine tartrate, levodopa-carbidopa, fluocinolone acetonide, voretigene neparvovec-rzyl (Luxturna), CPK850, AAV-RPGR, jCell, bone marrow-derived mesenchymal stem cells, autologous bone marrow-derived mononuclear stem cells and NT-501. The most common endpoints studied in CTs were change in visual acuity (N=6) for LHON and change in visual field (N=8) for RP. Raxone was authorised under exceptional circumstances for LHON in 2015 and protocol assistance was requested during its development. Luxturna was granted a full marketing authorisation for RP in 2018 after protocol assistance was requested two times during its development.

Three main patterns have been observed (i) the number of CTs carried out to evaluate ATMPs is increasing from 2009, when the first CT was carried out to evaluate ATMPs for both LHON and RP (ii) specific mutations are being addressed through the development of gene therapy MPs (e.g. $rAAV_2$-ND_4 for LHON and voretigene neparvovec-rzyl for RP) and small molecules (e.g. QLT091001 for RP) (iii) the number of regulatory pathways to support companies developing orphan MPs is increasing to help speed the authorisation of drugs for unmet medical needs.

Advances in research of MPs to treat LHON and RP are being made, but an unmet medical need is still present.

Keywords

Leber Hereditary Optic Neuropathy; LHON; Retinitis Pigmentosa; RP; Rare Disease; Clinical Development Program

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Glossary

Term	*Definition*	*Reference*
Advanced Therapy Medicinal Product	Medicinal products for human use, based on tissues, cells or gene	EMA website[1]
Committee for Medicinal Products for Human Use	Committee, within the European Medicines Agency (EMA), responsible for preparing the agency's opinion on questions concerning medicinal products for human use	Pignatti et al, 2011
Committee for Orphan Medicinal Products	Committee, within the EMA, responsible for adopting decisions on orphan designation	Rinaldi, 2005
Early Treatment Diabetic Retinopathy Study chart	Tool to measure visual acuity (decimal and LogMAR) formed by 11 rows with 5 characters per row	Shamir et al, 2016
Investigational Medicinal Product	Medicinal product being tested or used as reference (including being used as placebo), in a clinical trial	European Commission (EC) Regulation No 536/2014 Article 2 (5)
Leber Hereditary Optic Neuropathy	Rare, maternally-inherited optic neuropathy, caused by mitochondrial dysfunction	Yu-Wai-Man et al, 2009
Legal Blindness	Visual acuity below 1/10 (20/200 feet, 6/60 meters) from the best eye and with the best correction (glasses or contact lenses), in both eyes measured with a Snellen chart or visual field restriction	Lee and Mesfin, 2017[2]

[1] European Medicines Agency. Advanced therapy medicinal products: Overview [Internet]. London (UK). ©1995-2019 [cited May 9, 2019]. Available from URL: https://www.ema.europa.eu/en/human-regulatory/overview/advanced-therapy-medicinal-products-overview

[2] Lee SY, Mesfin FB. Blindness [Intenet]. StatPearls. Treasure Island (FL): StatPearls Publishing; last update Jan, 2019 [cited Apr 20, 2019]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK448182/

Term	*Definition*	*Reference*
	where the widest diameter is 20 degrees or less in the better-seeing eye	
Non-syndromic retinitis pigmentosa	Forms of retinitis pigmentosa where only retinal degeneration occurs, without systemic involvement	Pierrotet et al, 2014
Open Label clinical trial	Type of clinical trial where the intervention is known from both the participant and the healthcare professional	Kahan et al, 2014
Optical Computed Tomography	High resolution, non-invasive optic imaging technology through which real, two dimensional images can be seen	Podoleanu, 2012
Placebo-controlled clinical trial	Type of clinical trial where patients are randomly assigned to two (or more) groups. One group is administered with the treatment and the other group is with an inactive substance similar to the substance under evaluation, the placebo. The effect of treatments on groups are evaluated at the end of the trial	Chiodo et al, 2000; Evans, 2010
Randomised controlled clinical trials	Type of clinical trial where individuals are randomly assigned to two or more groups to test a treatment or a drug (assigned to one or more group) compared with an alternative intervention	Kendall, 2003
Sham-controlled clinical trials	Type of clinical trial where patients are randomly assigned to two (or more) groups. One group is administered with the treatment and the other group is administered with a sham treatment, to evaluate the efficacy of a drug. The effect of treatments on the groups are evaluated at the end of the trial	Sutherland, 2007

Term	*Definition*	*Reference*
Single Arm Assignment	Patient assignment where a group of individuals with targeted conditions is treated with an experimental treatment and followed by researchers during the follow-up period	Evans, 2010
Small Molecule Medicinal Product	Low weight molecule, able to easily enter inside cells, affecting other molecules (such as proteins) and causing changes in targeted cells	National Cancer Institute[3]
Snellen Chart	Tool to measure visual acuity formed by 8 rows with an increasing number of characters from the top (1 character) to the bottom (8 characters)	Shamir et al, 2016
Syndromic retinitis pigmentosa	Form of retinitis pigmentosa in which retinal degeneration is associated to other symptoms due to systemic diseases	Pierrotet et al, 2014
Visual Acuity	Spatial resolving capacity of the eye	Kaiser, 2009
Visual Field	Portion of space where objects are visible at the same moment during steady fixation of gaze in one direction	Spector, 1990[4]

[3] National Cancer Institute. NCI Dictionary of Cancer Terms: small molecule [Internet]. Bethesda, MD. Last update January 16, 2019 [cited May 9, 2019]. Available from URL: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/small-molecule-drug

[4] Spector RH. Visual Fields [Internet]. Walker HK, Hall WD, Hurst JW, editors. Clinical Methods: The History, Physical, and Laboratory Examinations. 3rd edition. Boston: Butterworth; 1990. [cited Apr 30, 2019]. Chapter 116. Available from: https://www.ncbi.nlm.nih.gov/books/NBK220/

List of Abbreviations

ATMP	Advanced Therapy Medicinal Product
ATP	Adenosine Triphosphate
BCVA	Best Corrected Visual Acuity
BDNF	Brain-Derived Neurotrophic Factor
bFGF	Basic Fibroblast Growth Factor
BMMSCs	Bone Marrow-Derived Mononuclear Stem Cells
CAP	Centrally Authorised Product
CAT	Committee for Advanced Therapies
CDP	Clinical Development Program
CHMP	Committee for Medicinal Products for Human Use
CMO	Cystoid Macular Oedema
CNTF	Ciliary Neurotrophic Factor
COMP	Committee for Orphan Medicinal Products
DHA	Docosahexaenoic Acid
EC	European Committee
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ETC	Electron Transport Chain
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
GDNF	Glial Cell-Derived Neurotrophic Factor
GPR143	G-protein-coupled receptor
IMP	Investigational Medicinal Product
LHON	Leber Hereditary Optic Neuropathy
MP	Medicinal Product
mtDNA	Mitochondrial DNA
NCA	National Competent Authority
OCT	Optic Computed Tomography
OMP	Orphan Medicinal Product
OXPHOS	Oxidative Phosphorylation
NAION	Non-Arteritic Anterior Ischemic Optic Neuropathy

PMB	Papillo-macular Bundle
QoL	Quality of Life
RGCs	Retinal Ganglion Cells
RNFL	Retinal Nerve Fiber Layer
ROS	Reactive Oxygen Species
RP	Retinitis Pigmentosa
RPE	Retinal Pigment Epithelium
RPGR	Retinitis Pigmentosa GTPase regulator
SAWP	Scientific Advice Working Party
SmPC	Summary of Product Characteristics
USNML	United States National Library of Medicines
VA	Visual Acuity
VF	Visual Field
VF-14	Visual Function Index

Chapter 1
Introduction

1.1 Background

Leber Hereditary Optic Neuropathy (LHON) and Retinitis Pigmentosa (RP), are rare diseases affecting the eye. LHON is a neuropathy which affects the optic nerve and can lead to blindness. RP is a retinal dystrophy, which affects photoreceptors (both rods and cones), and can lead to blindness.

LHON is a rare, mitochondrial, maternal-inherited optic neuropathy (Newman, 2005; Yu-Wai-Man et al, 2009), described for the first time by the ophthalmologist Theodor Leber during the second half of 19th century (Leber, 1871; Piotrowska et al, 2014). LHON is caused by three mitochondrial DNA (mtDNA) point mutations which affect mitochondria in retinal ganglion cells (RGCs) (Yu-Wai-Man et al, 2002; Kirches, 2011; Meyerson, 2015). RGCs project their axons from the retina in three different directions, forming three different retinal nerve fiber layers (RNFL). One of these RNFL is the papillomacular bundle (PMB), formed by the RGCs which project their axons directly from the fovea to the optic disc (Barton and Benatar, 2005). The PMB is severely affected in LHON, as indicated by the manifestation of central and cecocentral scotoma (Yu-Wai-Man, 2009; Fraser et al, 2010; Majander et al, 2017).

In LHON, RGCs undergo an apoptotic process due to mitochondrial dysfunction, affecting the eyes which have high energy requirement (Cohen and Gold, 2001). Mitochondrial dysfunction causes decreased adenosine triphosphate (ATP) production and an increase in reactive oxygen species (ROS) (Lemonde and Rahman, 2015). RGCs apoptosis causes optic nerve atrophy and typically manifests as blindness.

Raxone (idebenone) is currently the only authorised medicine within the European Union (EU) with the indication for LHON. Alternative treatments for LHON are needed and an unmet medical need is still present[5].

Retinitis Pigmentosa (RP) is a class of rare-inherited retinal dystrophy (or degeneration), which can lead to blindness, characterised by pigment deposits predominantly present in the peripheral retina (Frasson et al, 1999; Herse, 2005; Hamel, 2006). RP was initially characterised in 1857 by the Dutch ophthalmologist F.C. Donders (Naz et al, 2010).

Retinal dystrophies have heterogeneous genetic and clinical features (Nash et al, 2015). Genetically, the transmission of RP follows a Mendelian inheritance pattern, with autosomal recessive, autosomal dominant and X-linked RP (Venturini et al, 2014; Bravo-Gil et al, 2017). In about 30% of the cases, RP has been associated to other different syndromes, leading to the distinction between syndromic and non-syndromic RP (Hartong et al, 2006). Sixty-six genes have been associated to non-syndromic RP and 31 genes have been associated with syndromic RP[6] (Daiger et al, 2014).

The different transmission patterns in RP lead to different clinical manifestations, which can present differently among members of the same family. The affected cell types are the photoreceptors, both rods and cones. RP is also known as rods and cones dystrophy (Mohand-Said et al, 1998; Hartong et al, 2006). The time between symptom manifestation and blindness can differ from patient to patient, but all patients affected from RP will eventually develop blindness.

[5] European Commission. Regulation (EC) No 507/2006 of the EU Parliament and of the Council of 29 March 2006 on the conditional marketing authorisation for medicinal products for human use. Official Journal of the European Community 2006; L92 (6). [cited November 13, 2018]. Available from URL: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32006R0507

[6]Retinal Information Network (RetNet). Diseases:Genes and Mapped Loci Causing Retinal Diseases. [Internet]. Houston: The University of Texas Health Science Center (Texas). ©1996-2018 [cited November 14, 2018]. Available from URL: https://sph.uth.edu/retnet/

RP is a severe disease which affects patients' quality of life (QoL). To date, one medicinal product, Luxturna, is authorised to treat RP which remains an unmet medical need (Yerba, 2018).

1.1.1 Epidemiology of Leber Hereditary Optic Neuropathy

LHON is a rare disease with estimated prevalence worldwide of between 1 in 15,000 and 1 in 50,000 (Fraser et al, 2010; Jurkute and Yu-Wai-Man; 2017). A rare disease is defined within the EU as a life-threatening or chronically debilitating condition affecting no more than 5 in 10,000 persons[7]. LHON predominantly affects young adult males, with the peak age of onset between 15 and 30 years old (Riordan-Eva, 1995; Dimitriadis et al, 2014).

LHON is thought to be caused by several mtDNA point mutations (Kirches, 2011) which affect the complex I of the electron transport chain (ETC). The three most prevalent mtDNA point mutations, that account for about 97% of LHON cases, are m.11778G>A (associated with about 70% of LHON cases), m. 14484T>C (associated with about 14% of LHON cases) and m.3460G>A (associated with about 13% of LHON cases) (Newman, 2005; Yu-Wai-Man et al, 2011). These three genes encode respectively for the subunit ND4, ND6 and ND1 of the mitochondrial complex I (Patsi et al, 2008).

Affecting complex I, the mutations m.11778G>A, m. 14484T>C, m.3460G>A, lead to oxidative phosphorylation (OXPHOS) deficiency (Guy et al, 2002). OXPHOS is a crucial process for ATP synthesis which occurs in the electron transport chain (ETC) (Lieberman, 2009). The ETC is situated in the inner mitochondrial membrane (Stewart and Chinnery, 2015). The ETC is constituted by 5 protein complexes (complex I – complex V) in which oxidative and reductive reactions give the energy needed to reduce

[7] European Medicines Agency. Orphan drugs and rare diseases at a glance [Internet]. London (UK): European Medicines Agency; cEMEA2007 [cited February 24, 2018]. Available from (URL): http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/01/WC500069805.pdf

a molecule of O_2 into H_2O and ensure the energy to form 4 molecules of ATP (Nelson and Cox, 2010). During this process ROS are generated. ROS are unstable molecules with an unpaired electron which is potentially damaging for cells (Roth, 1997).

In normal conditions, reactive species are detoxified by scavengers: glutathione peroxidase, superoxide dismutase and catalase. Scavengers convert ROS into less reactive and toxic products, avoiding cellular damage (Menna et al, 2002).

In LHON, the detoxification system is not sufficient (Floreani et al, 2005). The increase of ROS and the decrease in energy production leads to cellular damage and to cellular apoptosis (Fulda et al, 2010; Pallepati and Averill-Bates, 2012, Redza-Dutordoir and Averill-Bates, 2016)

In addition to genetic factors, environmental factors play an important role in visual loss due to LHON (Jurkute and Yu-Wai-Man, 2017). Studies show that cigarette smoking might be related to the increased incidence among patients carrying one of three most common LHON mtDNA point mutations (Kirkman et al, 2009; Giordano et al, 2015). Lipophilic substances present in cigarette smoking (*e.g.* aldehydes and aromatic compounds) are thought to have an impact in affecting mitochondria, interacting with the ETC and reducing the ATP production (Miró et al, 1999; van der Toorn et al, 2007; Yang et al, 2007; Tan et al, 2008; Salem et al, 2013). Cigarette smoking is related to an increase in ROS and to a decrease in mitochondrial membrane function (), factors associated with cell apoptosis (Kim et al, 2010; Aravamudan et al, 2014).

1.1.2 Clinical manifestations of Leber Hereditary Optic Neuropathy

LHON usually manifests as a rapid, painless loss of central vision in one eye, followed by similar loss of vision in the other eye within days to months (Yu-Wai-Man et al, 2009; Fraser et al, 2010). The delay of the onset of symptoms in the second eye is of

approximately 6-8 weeks (Harding et al, 1995; Yu-Wai-Man et al, 2009, Meyerson et al, 2015). The involvement of the second eye usually occurs within 1 year (Miller et al, 1998) in 97% of cases and in 25% of cases, vision loss occurs simultaneously in both eyes (Yu-Wai-Man et al, 2014; Jurkute and Yu-Wai-Man, 2017).

Central visual function is primarily affected, with visual acuity (VA) typically deteriorating to worse than 20/200 on the logarithm of the minimal angle of resolution (logMAR) scale (Newman et al, 2006). VA is defined as the "spatial resolving capacity of the eye", the capacity of the eye in image resolution and it is considered as "the gold standard" for primary outcomes in clinical trials of LHON (Kaiser, 2009). VA 20/200 is the threshold to define legal blindness, which corresponds to VA below 1/10 (20/200 feet, 6/60 meters) in both eyes. If a non-visually impaired individual can see an object from a 60 meters' distance with a certain grade of clarity, an individual defined as legally blind can see the same object with the same clarity at a distance of not more than 6 meters from the best eye and with the best correction (Klaver et al, 1998; Bron et al, 2010).

Due to the sudden loss of vision, the QoL in patients experiencing LHON is decreased. To date, only one study has been carried out to specifically assess the QoL of LHON patients. The study was conducted by Kirkman et al, who used the visual function index (VF-14) questionnaire, validated for the formal assessment of ocular diseases. Kirkman et al concluded that legal blindness associated with LHON contributes to the decrease of QoL in LHON patients and this was reflected by the low average of VF-14 score (Kirkman et al, 2009).

The onset of LHON symptoms is due to the damage in the optic nerve. Different clinical features are present during the acute and the chronic phase. During the acute phase of LHON, optic disc hyperaemia, peripherally telangiectatic blood vessels, vascular tortuosity and swelling of the RNFL might be noticed on fundus examination (Newman

and Biousse, 2004). Mitochondrial dysfunction leads to axonal swelling and a noticeable sign is the thickening of RNFL. In 20-40% of cases fundus examinations do not show any change, leading to a delayed diagnosis (Yu-Wai-Man et al, 2008; Meyerson, et al, 2015). After six months from the onset of visual loss, characteristics on fundus examination change with the development of optic disc pallor accompanied by cupping of the optic disc, defining the start of the chronic phase of LHON. The chronic phase of LHON is characterised by the death of RGCs due to apoptotic mechanisms. Death of RGCs causes a thinning of RNFL (Carelli et al, 2009). To detect all these changes within the retina, optic computed tomography (OCT) is used as a non-invasive diagnostic tool (McLellan and Rasmussen, 2012). Using OCT, it has been observed that the less RNFL is compromised, the more is the likelihood of patients to spontaneously recover (Lam et al, 2014).

Cases of spontaneous recovery have been registered in LHON (Newman, 2011). The rate of this clinical manifestation is associated with the type of mutation. The m.14484 T>C has the highest rate of spontaneous recovery, which ranges from 37 to 71%, while the most common m. 11778 G>A has the lowest rate of spontaneous recovery rate, which usually is at around 4% (Johns et al, 1992; Johns et al, 1993); 20% likelihood of spontaneous recovery is associated with the m. 3460G>A (Carelli et al, 2011). Spontaneous recoveries usually occur within two years after the onset of symptoms (Hsu, 2014) and present as small islands of vision within the central defect bilaterally (Yu-Wai-Man et al 2014). The age of symptom onset plays a pivotal role in spontaneous recovery. Patients who experience LHON symptoms during the first two decades of life have a better prognosis when compared with elder patients (Newman, 2011). The best prognosis associated with spontaneous visual recovery in LHON is attributable to young patients carrying the m.14484 T>C (Carelli et al, 2009).

1.1.3 Treatment modalities and challenges in Leber Hereditary Optic Neuropathy

Raxone (idebenone) was the first medicinal product which obtained the marketing authorisation with the indication for LHON (Catarino and Klopstock, 2017). Raxone is a synthetic analogue of coenzyme Q_{10} (Gueven et al, 2015). Before the approval of Raxone, the most commonly used products to treat LHON were coenzyme Q_{10} (ubiquinone)-analogues. The use of Coenzyme-Q-analogue products finds its rationale in the fact that coenzyme Q_{10} is an endogenous compound with antioxidant properties, physiologically present in the ETC (Cooke et al, 2008).

LHON therapy is mainly based on the use of antioxidant compounds, anti-apoptotic agents and ROS modulators (Frantz and Wipf, 2010). Antioxidant compounds, anti-apoptotic agents and ROS modulators are used to slow down disease progression, limiting the increase of ROS and consequently, limiting the rate of cellular death due to apoptosis. Antioxidant compounds, anti-apoptotic agents and ROS modulators used during the acute phase of the disease, may slow down the disease progression and promote a certain grade of recovery (Qi, et al, 2007). When avoiding ROS formation and apoptotic mechanisms, the number of inactive but still viable RGCs increases, allowing for a possible partial sight recovery (Gueven and Faldu, 2013; Thomas et al, 2017). Advanced therapy medicinal products, including gene therapy and somatic cell therapy have been recently introduced in clinical trials to evaluate the likelihood of their use in prospective treatments (Mansergh et al, 2014).

Medicinal products (MPs) to treat LHON have been studied through time, but only few of them demonstrated to be effective therapy agents (Parikh et al, 2009; Iyer, 2013). Challenges to develop MPs to treat LHON are present. Recruitment of naive patients in clinical trials has been reported as a slow process since there are few LHON patients in the EU. Researchers have to consider an added complexity that patients with the

m.14484T>C point mutation have a 37-71% chance of spontaneous recovery of their VA introducing biases in the primary end point that are used to study LHON in clinical trials (best recovery in visual acuity determined with the Early Treatment Diabetic Retinopathy Study (ETDRS) charts measured by a logMAR) (Carelli et al, 2011).

1.1.4 Epidemiology of Retinitis Pigmentosa

RP is a rare disease with an estimated worldwide prevalence between 1 in 2500 and 1 in 7000 (Parmeggiani, 2011; Srilekha et al, 2015; Bryan et al, 2018). The onset of RP typically occurs during the early teenage years, but can span from childhood to adulthood, depending on the form of the disease (Ayuso and Millan, 2010). Except for X-linked RP, which affects only males, autosomal dominant RP and autosomal recessive RP are not sex-specific, affecting both females and males (Ferrari et al, 2011)

In 65-70% of cases, RP occurs alone, being defined as non-syndromic; in 30% of cases, RP occurs as part of a more complex group of syndromes with other organs involved, being defined as syndromic (Verbakel et al, 2018). Among non-syndromic syndromes, almost 30% are autosomal dominant RP, 20% are autosomal recessive RP, 15% are X-linked RP. The remaining 35% are represented by isolated or simple cases with different mutations (Daiger et al, 2007). Depending on the inherited pattern of RP, different genes are affected. Genes affected are reported on RetNet[8]. RetNet is a database containing information on genes and loci affected in inherited retinal diseases, including RP.

In the RetNet database, 94 genes associated to cause RP, have been identified. Twenty-seven autosomal dominant, 58 autosomal recessive, and three X-linked RP genes have been reported. Six more genes have been identified for causing both autosomal dominant

[8]Retinal Information Network (RetNet). Diseases: Genes and Mapped Loci Causing Retinal Diseases [Internet]. Houston: The University of Texas Health Science Center (Texas). ©1996-2018 [cited November 14, 2018]. Available from URL: https://sph.uth.edu/retnet/

and autosomal recessive RP (Huang et al, 2017). Seventy of the 94 genes are associated to non-syndromic RP (Abeshi et al, 2017). The three most common mutations are RHO for autosomal dominant RP, USH2A, for autosomal recessive RP and RP GTPase regulator (RPGR) for X-linked RP[9] (Givre et al, 2017)

Depending on the gene mutation, different molecular mechanisms have been identified. In RP, mutated genes encode for proteins having a key role in phototransduction, maintenance of photoreceptor structure, gene transcription and ciliary function (Scholl et al, 2015). The affected cell type is represented by photoreceptors. In the early stage of RP, rods are affected, undergoing cell death due to apoptosis, followed by cones cell death (Rattner et al, 1999; Murakami et al, 2015).

1.1.5 Clinical manifestations of Retinitis Pigmentosa

RP usually manifests with difficulties in dark adaptation with concurrent nyctalopia, reduced visual field (VF) which leads to tunnel vision and gradual reduction in central vision, leading to affected patients being blind (Chang et al, 2011; Fahim et al, 2017). The age of onset and the severity of RP are variable depending on the RP subtype. Symptoms caused by autosomal recessive RP are less severe than symptoms caused by X-linked RP. The best prognosis in relation to long-term central vision is attributable to individuals affected from autosomal dominant RP (Verbakel et al, 2018).

In the classic manifestation of RP, symptoms start during adolescence with difficulties in dark adaptation and nyctalopia progressing to mid-periphery vision loss in young adulthood. VA loss occurs only in the late stage of the disease, eventually leading to blindness (Hartong et al, 2006).

[9]U.S National Library of Medicine. Genetics Home Reference: Retinitis Pigmentosa [Internet]. Rockville Pike, Bethesda, MD 20894. Last review05 July 2018 [cited November 22, 2018]. Available from URL: https://ghr.nlm.nih.gov/condition/retinitis-pigmentosa#genes

Initial clinical manifestations of RP are the result of processes happening within the retina which can be observed when performing fundus examination. On fundus examination three clinical features are characteristic in the retina (i) bone spicule pigmentation, (ii) pallor of the optic nerve head and (iii) arteriolar narrowing (Konieczka et al, 2012).

As a consequence of photoreceptor degeneration, the retina undergoes a rearrangement. Retinal vessels move close to the retinal pigment epithelium (RPE) layer and create vascular contact with RPE cells. This vascular contact is a stimulus for RPE cells to detach from the Bruch's membrane and migrate to intraretinal perivascular sites, forming melanin deposits with a bone-spicule configuration (Li et al, 1995; Jaissle et al, 2010; Zanzottera et al, 2015). Bone spicule pigmentation arises in the mid-periphery of the retina, where the rod concentration is higher (Konieczka et al, 2012).

The characteristics of fundus examination do not simplify the recognition of RP, which sometimes can remain unnoticed for a long time before being diagnosed leading to difficulties in treatment choice.

1.1.6 Treatment modalities and challenges in Retinitis Pigmentosa

To date, no standard treatment for RP is available (Garg et al, 2018; O'Neil and Luther, 2018). Currently, treatment for RP includes nutritional supplementations vitamin A, lutein, and docosahexaenoic acid (DHA) and the neuroprotective agents, ciliary neurotrophic factor (CNTF), glial cell-derived neurotrophic factor (GDNF) and basic fibroblast growth factor (bFGF) (Huang, 2017).

Nutritional supplements have been proposed for their potential ability to protect photoreceptor function (Berson, 2000; Aleman et al, 2001; Pawlyk et al, 2002; Berson et al, 2018). The most widely used nutritional supplements are represented by vitamin A

palmitate, DHA and lutein, which are able to decrease the rate of retinal degeneration through their antioxidant properties (Shintani et al, 2009; Lin et al, 2015).

The use of vitamin A and DHA in RP patients has been a matter of debate for a long time (Musarella and MacDonald, 2011). Rayapudi et al, carried out a review aiming to evaluate the safety and efficacy of vitamin A and DHA based on the available results from clinical trials. The results of the study show no evidence of the efficacy of vitamin A and DHA in RP patients (Rayapudi et al, 2013). Lutein was tested in a clinical trial (NCT00029289) where it is shown to be safe and effective in preserving VF, but not VA (Bahrami et al, 2006).

CNTF, GDNF and bFGF are neurotrophic factors with a role to promote maturation, survival, growth and maintenance of neurons. The use of neurotrophic factors in RP treatment is related to their ability to provide protective action towards photoreceptors (Dias et al, 2017).

Different treatment approaches have been studied through time, but several challenges are present. RP is a class of rare retinal degeneration, with different mutations and different features, creating challenges to develop MPs. Another issue is related to the high costs that research and development of MPs for rare diseases have, especially when compared to the low economic return for pharmaceutical companies (Giannuzzi et al, 2017).

1.2 The EU framework to develop and authorise orphan medicinal products

Medicinal products developed to treat rare conditions such as LHON and RP are categorised as orphan medicinal products (OMPs). OMPs are defined as "*medicinal*

products intended for the diagnosis, prevention or treatment of life-threatening or very serious conditions that affect no more than 5 in 10,000 people in the European Union"[10].

Costs to develop OMPs are high when compared to the market they can account for. To incentivise pharmaceutical companies to carry out studies on drugs with indications for rare diseases, incentives have been introduced in EU law to improve the availability of innovative medicines on the market (Tambuyzer, 2010).

1.2.1 European Regulation on Orphan Medicinal Products

In the EU, the designation of OMPs is related to the Regulation EC No 141/2000 and the Regulation EC No 847/2000 which came into force in 2000 (Hollak et al, 2011).

Regulation EC No 141/2000[11], which sets the rules to grant an orphan designation, defines the role of the Committee for Orphan Medicinal Products (COMP)[12] and describes the incentives for developing and placing onto the market an OMP. Incentives to develop an OMP, result in a 10-year market exclusivity of the MP and direct access to a centralised procedure for a marketing authorisation, scientific advice procedures to help applicants in developing their products and fee reductions (Hollak et al, 2011; Nistico, 2011; Farkas et al, 2017). Regulation EC No 847/2000[13] implements Regulation EC No

[10] European Commission. Public Heath: Orphan Medicinal Products [Internet]. Directorate-General for Health and Food Safety, European Commission, Bruxelles/Brussel (Belgium). Last updated: November 27, 2017 [cited on February 27, 2018]. Available from URL: https://ec.europa.eu/health/human-use/orphan-medicines_en

[11] European Commission. Regulation (EC) No 141/2000 of the EU Parliament and the Council of 16 December 1999 on orphan medicinal products. Official Journal of the European Communities 2000; L18(1) [Internet]. [cited February 27, 2018]. Available from URL: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32000R0141

[12] European Medicines Agency. Committee for Orphan Medicinal Products: Role [Internet]. London (UK): European Medicines Agency; ©1995-2017 [cited February 27, 2018]. Available from URL: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000263.jsp

[13] European Commission. Regulation EC No 847/2000 of 27 April 2000 on laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product and definitions of the concepts 'similar medicinal product' and 'clinical superiority'. Official Journal of the European Communities 2000; L103(5) [Internet]. [cited February 27, 2018]. Available from URL: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32000R0847

141/2000 through the explanation of the criteria to grant an orphan designation (Article 3 Regulation EC No 141/2000) and market exclusivity (Article 8 Regulation EC No 141/2000).

In 2004 Regulation EC No 726/2004[14] came into force, setting the legal framework for the granting of a centralised marketing authorisation for OMPs and enabling the Committee for Medicinal Products for Human Use (CHMP)[15] to issue guidelines for the compassionate use program. OMPs are also regulated by the Regulation EC 2049/2005 which sets the rules for assistance that the European Medicines Agency (EMA) can provide pharmaceutical companies, including scientific advice and the fees payable to the EMA by the pharmaceutical companies.

An OMP which falls within the scope of the Regulation EC No 726/2004 might obtain a conditional marketing authorisation as set by the Regulation EC 507/2006[16].

[14] European Commission. Regulation (EC) 726/2004 of the EU Parliament and the Council of 31 March 2004 on laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. Official Journal of the European Community 2004; L 136(1) [Internet]. [cited on February 27, 2018]. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32004R0726

[15] European Medicines Agency. Committee for Medicinal Products for Human Use: Role [Internet]. London (UK): European Medicines Agency; c1995-2017 [cited February 27, 2018]. Available from URL: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000094.jsp&mid=WC0b01ac0580028c79

[16]European Commission. Regulation (EC) 507/2006 of the EU Parliament and the Council of 29 March 2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004 of the European Parliament and of the Council. Official Journal of the European Community 2006; L 92(6) [Internet]. [cited February 27, 2018]. Available from URL: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32006R0507

1.2.2 Marketing Authorisation for Orphan Medicinal Products

In the EU a marketing authorisation is required for a product to be placed on the market (Borg et al, 2014). Since both LHON and RP are classified as rare diseases, all medicinal products developed have access to the centralised authorisation procedure (Regnstrom et al, 2010).

A centralised authorisation procedure allows the marketing of a MP within the EU on the basis of a single EU-wide assessment[17], thus a single application to the EMA, a single evaluation by the Committee for Medicinal Products for Human Use (CHMP)[18] within the EMA and a single marketing authorisation granted by the European Commission (EC) and marketing authorisation (Tambuyzer 2010; Friedrich and Olejniczak, 2011).

To support a centralised marketing authorisation application, data about quality, safety and efficacy of a MP are requested (Lorenz et al, 2008). Obtaining data needed to grant the marketing authorisation for an OMP might be a complex process and when data is not complete a marketing authorisation can be issued as a conditional marketing authorisation[19] (Picavet et al, 2013; Martinalbo et al, 2016).

A conditional marketing authorisation is issued by CHMP when the presence on the market of a MP is essential for patients' health (*e.g.* OMPs or products that might be crucial during an emergency health situation) (Härmark and Grootheest, 2008). Since an unmet medical need should be fulfilled, a comprehensive clinical development program (CDP) is not required to grant a conditional marketing authorisation, but it is crucial that

[17] European Medicines Agency. Authorisation of medicines: Centralised authorisation procedure [Internet]. London (UK): European Medicines Agency; c1995-2017 [cited February 27, 2018]. Available from URL: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000109.jsp

[18] European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP) [Internet]. London (UK): European Medicines Agency; c1995-2017 [cited May 17, 2018]. Available from URL: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000094.jsp

[19] European Commission. Regulation (EC) No 527/2006 of 29 March 2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004 of the European Parliament and of the Council. Official Journal of the European Community 2004; L92(6) [Internet]. [cited February 27, 2018]. Available URL: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32006R0507

data presented to support an application includes a positive risk/benefit balance of a MP (Vella Bonanno et al, 2017). Once granted, the conditional marketing authorisation lasts for one year after which it can be renewed; the holder is expected to complete or carry out new studies to confirm the positive risk/benefit balance to grant a normal marketing authorisation.

In cases where it is obvious that the CDP for a MP cannot be completed (*e.g.* in case of rare conditions) a marketing authorisation under exceptional circumstances can be issued by the CHMP[20] (Martinalbo et al, 2016).

The Committee for Orphan Medicinal Products (COMP) and CHMP have different roles in the OMP framework (Figure 1.1 and Figure 1.2). Decisions related to the granting of an orphan designation are made by the COMP, while decisions related to the granting of a marketing authorisation are made by the CHMP (Gammie et al, 2015). The marketing authorisation is granted following the evaluation of the dossier submitted by applicants to support the risk/benefit profile of the claimed indication of the MP.

The risks and benefits of MPs are evaluated on data generated through CDPs, where clinical trials are carried out to prove the efficacy and safety of a MP in the claimed indication by prospective applicants.

Figure 1.1 shows the procedure through which an orphan designation is granted. After the identification of a molecule by researchers (input), the sponsor (usually a pharmaceutical company) starts funding pre-clinical tests to evaluate if the molecule might be effective to treat a certain condition (sponsor – pharmaceutical company). When pre-clinical results are promising, an orphan application can be sent from the sponsor to

[20] European Commission. Regulation (EC) No 527/2006 of 29 March 2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004 of the European Parliament and of the Council. Official Journal of the European Community 2004; L92(6) [Internet]. [cited February 27, 2018]. Available URL: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32006R0507

the European Medicines Agency (EMA). The COMP, one of the EMA committees, evaluates the dossier sent from the sponsor. If results are positive and the COMP evaluation is positive, an orphan designation can be granted for an OMP (output).

Figure 1.2 shows the procedure through which a centralised marketing authorisation for an OMP is granted. After an orphan designation is granted, incentives for the industries are given to perform further studies on an OMP (input). The sponsor (usually a pharmaceutical company), starts funding clinical trials to evaluate the safety and efficacy of an OMP (sponsor). When clinical results are promising, an application for the grant of a marketing authorisation (input) can be sent from the sponsor to the EMA (EMA). The CHMP, a committee of the EMA, evaluates the dossier sent from the sponsor. If the CHMP evaluation is positive, a centralised marketing authorisation can be granted for an OMP (output).

1.3 Clinical Development Programs

A well-developed CDP is essential to demonstrate the safety and efficacy of a new MP, increasing the probability of its approval. CDPs are created to collect clinical information related to the indication of a MP. A well-planned CDP leads to the understanding of the major risk areas, the posology and route of administration and all information related to a safe and efficacious use of a MP under study (Lai et al, 2015).

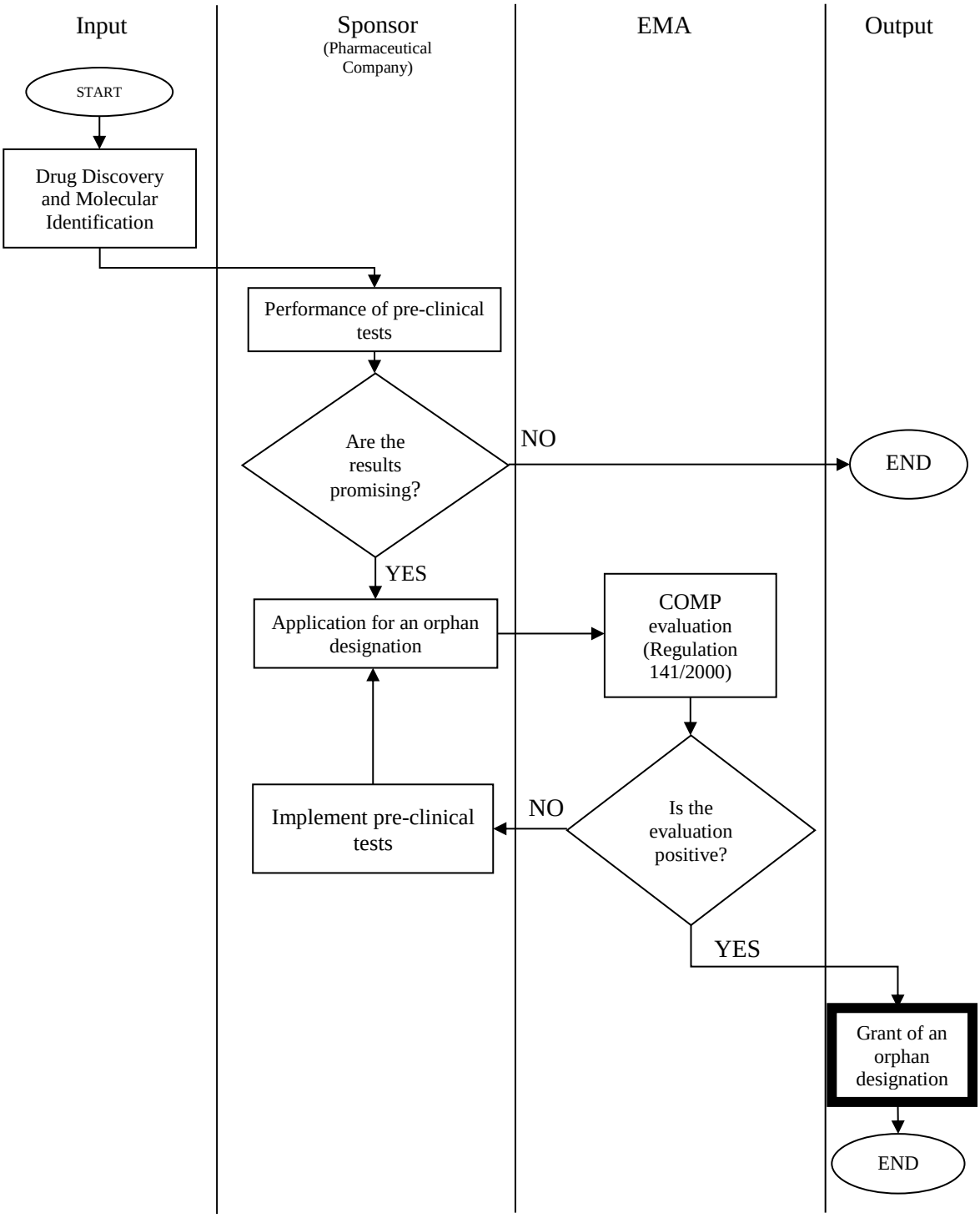


Figure 1.1 Overview of the procedure to obtain an orphan designation.
COMP: committee for Orphan Medicinal Products; EMA: European Medicines Agency

When creating a CDP, the number and types of clinical trials and their aims and objectives should be defined in the correct time sequence. Modalities to carry out a clinical trial have been harmonised throughout the European Economic Area (EEA) through the Directive (EC) 20/2001[21], the international good clinical practice (GCP)[22] and the declaration of Helsinki (World Health Organisation, 2001).

Important criteria to consider before starting a clinical trial are:

- the endpoints, to help ensure they are compatible with the intended claims;
- the studied population, intended as number and choice of population to treat;
- the statistical method, to ensure significance of the results;
- the study design, which is linked to the robustness of the results.

A multidisciplinary approach, performed by regulators, clinicians and statisticians, ensures the fulfilment of these criteria. Before starting the development of a CDP, the sponsor of the studies can ask for scientific advice and protocol assistance[23] given by either the EMA or the National Competent Authority (NCA) (Hofer et al, 2015; Milmo, 2015). The scientific advice ensures that all the appropriate tests and studies on a MP are carried out before submitting an application, so that the possibilities of reaching the market in a timely fashion are increased. Once these procedures have been completed, clinical trials are started.

[21] European Commission. Directive (EC) 20/2001 of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. Official Journal of the European Communities. 2001; L 121/34 [Internet]. [cited February 27, 2018]. Available URL: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32001L0020

[22] ICH harmonised tripartite guideline. Guideline for Good Clinical Practice E6(R1) on clinical trial protocol and protocol amendment(s) of 10 June 1996 [Internet]. [cited February 28, 2018]. Available from URL: https://apps.who.int/medicinedocs/en/m/abstract/Js22154en/

[23] European Medicines Agency. Human Regulatory: Scientific Advice and Protocol assistance [Internet]. London (UK): European Medicines Agency; c1995-2017 [cited March 2, 2018]. Available from URL http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000049.jsp&mid=WC0b01ac05800229b9

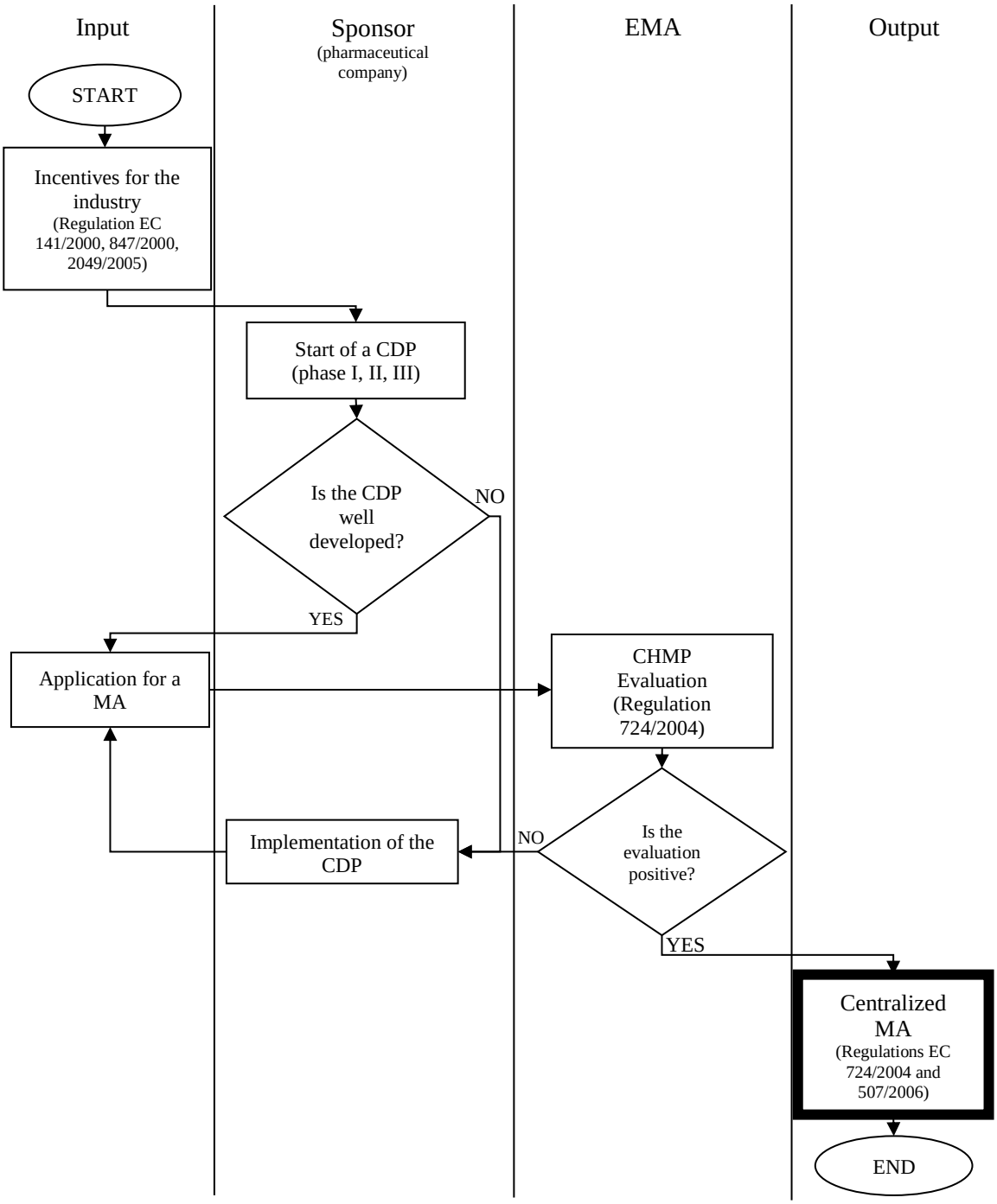


Figure 1.2 Overview of the procedure to obtain a marketing authorisation.
CDP: Clinical Development Program; CHMP: Committee for Medicinal Products for Human Use; EMA: European Medicines Agency; MA: Marketing Authorisation

Clinical trials consist of four different phases (phase I- phase IV), which are performed to evaluate different characteristics of a MP[24].

Phase I clinical trials aim to evaluate the safety and tolerability profile of a MP in addition to the pharmacokinetics and pharmacodynamics profile; for this phase healthy volunteers can be tested. Phase II clinical trials are the studies which aim to investigate safety and efficacy of a MP. During phase II studies the preliminary efficacy, the dose regimen and side effect profile of the MP are evaluated. Phase III clinical trials are confirmatory studies, in which the beneficial use of a certain medicinal product is affirmed for the indicated population. For phase III studies a bigger patient population is evaluated. Phase IV clinical trials are post approval studies in which safety, efficacy and dose evaluated in the previous phases are assessed[25].

The approval of a non-orphan medicinal product is granted after a robust CDP is presented, with consistent data showing safety and efficacy of the product demonstrated in a studied population. The CDP for OMPs, such as those to treat LHON or RP, conversely, may present a lack of data related to the efficacy, but not safety, of the MP and studied population can be smaller than normally required. There is an unmet medical need for which it is acceptable to have a product on the market for which safety data are present, but efficacy has not been completely understood. The early access to the market of these MPs ensures a benefit for patients experiencing a disease with an unmet medical need, such as LHON and RP.

[24] European Medicine Agency. ICH Topic E8: General Considerations for Clinical Trials. Note for guidance on general considerations for clinical trials (CPMP/ICH/291/95) [Internet]. London (UK): European Medicines Agency; c1995-2017 [cited January 4, 2018]. Available from URL http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002877.pdf

[25] European Medicine Agency. ICH Topic E8: General Considerations for Clinical Trials. Note for guidance on general considerations for clinical trials (CPMP/ICH/291/95) [Internet]. London (UK): European Medicines Agency; c1995-2017 [cited January 4, 2019]. Available from URL: https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-8-general-considerations-clinical-trials-step-5_en.pdf

1.4 Aims and Objectives

The aim of the study is to understand emerging patterns in clinical development programs (CDPs) being pursued by pharmaceutical companies when developing safe and effective innovative medicines to treat the rare eye diseases LHON and RP.

The objectives of this study are:

1. To propose prospective treatment protocols for LHON and RP and to understand prospective innovative medicines that are being developed so that gaps in the treatment armamentarium of LHON and RP are addressed.
2. To review the regulatory pathways available to obtain a marketing authorisation for orphan drugs and to understand the challenges faced by decision-makers (such as the EMA) when granting a marketing authorisation for LHON and RP.
3. To understand and identify patterns in CDPs being pursued by pharmaceutical companies to support the risk-benefit balance of innovative medicines to treat LHON and RP.

Chapter 2

Method

2.1 Development of prospective treatment protocols

Prospective treatment protocols for LHON and RP included (i) Centrally Authorised Products (CAPs) and Investigational Medicinal Products (IMPs).

MPs authorised within the EU were retrieved from the EMA database[26]. If MPs were in the development phase, these were incorporated in the list of authorised treatments and analysed based on their mechanism of action, number of studies and, whether present, study results. MPs accounting for an orphan designation with clinical trials in place were considered.

Prospective treatment protocols for LHON and RP were proposed using data retrieved from clinical trials. Data extracted from clinical trials consisted of (i) drugs used to treat LHON and RP, (ii) study phase and (iii) endpoints considered by researchers. Protocols proposed included IMPs with a safe profile and for which efficacy was evaluated or under evaluation. Protocols were proposed according to the subtype of LHON (if the drug was being studied against one specific mutation or for all the mutations causing LHON) and RP (if the drug was being studied for a specific mutation or to treat RP caused by all mutations).

2.1.1 Centrally authorised medicinal products

MPs centrally authorised to treat LHON or RP within the EU were retrieved from the EMA database. The European Public Assessment Report (EPAR) for authorised MPs was analysed. The EPAR is a scientific assessment report of medicines authorised within the EU[27]. Data retrieved from the EPARs was related to the CDP of authorised medicines.

[26]European Medicines Agency. Medicines [Internet]. London (UK): European Medicines Agency; ©1995-2018 [cited March 4, 2018]. Available from URL: https://www.ema.europa.eu/en/medicines
[27]European Medicines Agency. Medicines [Internet]. London (UK): European Medicines Agency; ©1995-2018 [cited March 4, 2018]. Available from URL: https://www.ema.europa.eu/en/medicines/download-medicine-data

The nature of the active substances was reviewed to understand whether the MPs were of chemical origin or advanced therapy medicinal products (ATMPs).

Information on the therapeutic indication of CAPs, pharmaceutical form and method of administration were retrieved in section 4.1 of the Summary of Product Characteristics (SmPC) of each MP. CAPs marketed within the EU for LHON and RP were included in the proposed prospective treatment protocols.

2.1.2 Medicinal products in the development phase

Two different data sources were selected to provide comprehensive information on clinical trials for IMPs currently being developed for LHON and RP. Data was retrieved from the EU Clinical Trials Register[28] and from the United States national library of medicines (USNML) database of clinical trials[29]. Keywords used to search into the databases were "Leber hereditary Optic Neuropathy", "LHON" and "Retinitis Pigmentosa".

Information on interventional clinical trials carried out in the EU and European Economic Area (EEA), started after May 2004, is present in the EU Clinical Trials Register. Information on clinical trials conducted outside the EU/EEA can be retrieved from EU Clinical Trials Register if the clinical trial is part of a paediatric investigational plan or if sponsored by a marketing authorisation holder and involved the use of a medicine in the paediatric population as part of an EU marketing authorisation[30]. The USNML database

[28]European Medicines Agency. EU clinical trials register [Internet]. London (UK): European Medicines Agency; ©1995-2018 [cited December 4, 2018]. Available from URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=retinitis+pigmentosa

[29]U.S National Library of Medicines. Clinical trials.gov [Internet]. National Institutes of Health, Bethesda, Maryland; Last updated 26 November 2012 [cited on February 28, 2018]. Available from URL: https://clinicaltrials.gov/

[30]European Medicines Agency. EU clinical trials register [online]. London (UK): European Medicines Agency; ©1995-2018 [cited December 4, 2018]. Available from URL: https://www.clinicaltrialsregister.eu/about.html

of clinical trials contains information on observational and interventional clinical trials publicly and privately supported.

A PubMed literature search was carried out searching with the keywords “LHON”, “Leber Hereditary Optic Neuropathy”, “Optic Neuropathy”, “Retinitis Pigmentosa”, “non-syndromic retinitis pigmentosa”, “treatment for retinitis pigmentosa/LHON”.

2.1.3 Inclusion and Exclusion criteria to select investigational medicinal products

When searching for studies conducted for LHON and RP, the filter function for “condition/disease” was used to retrieve relevant studies. The keywords used were “Leber Hereditary Optic Neuropathy”, “LHON” and “retinitis pigmentosa”. The elements captured were (i) active substance, (ii) pharmaceutical form, (iii) aim(s) of each clinical trial, (iv) endpoints (both primary and secondary), (v) patient population and (vi) study phase.

All clinical trials which fulfilled criteria (i)-(vi), registered from January 2006 to November 2018, were included in the current study. A timeframe of 13 years was chosen to evaluate any difference in drug development over time (*e.g.* differences in primary endpoints used). Studies carried out before January 2006 and after November 2018 were excluded from this study. Inclusion and exclusion criteria are summarised in Table 2.1.

MPs selected according to the inclusion and exclusion criteria were listed and classified according to the nature of the active substance in (i) medicinal products of chemical origin (ii) Advanced Therapy Medicinal Products (ATMPs) and (iii) Growth factor medicinal products. ATMPs were further sub-classified as gene therapy medicinal product and somatic cells medicinal products.

2.1.4 Literature Review of Investigational Medicinal Products

A literature review for each selected IMP was carried out for inclusion of IMP as prospective treatment. Product-related literature was retrieved from PubMed, pharmaceutical companies' websites and independent websites. Different sources were selected to have a better understanding of the development and marketing of the concerned IMP, where applicable.

A literature review was carried out to have a better understanding of the drug category of each IMP. IMPs in the development phase were included in the prospective treatment protocols proposed in this study according to the drug category of each selected IMP.

A brief description of each IMP was performed. Details captured were (i) mechanism of action of each IMP, (ii) site of action, (iii) subtype of LHON/RP, whether present and (iv) status, if authorised or orphan designated, for IMPs related to both LHON and RP. To have a more comprehensive overview, data related to dosage form(s) available and route of administration was retrieved.

IMPs not included in the prospective treatment protocols for LHON and RP were reviewed separately. The review on the excluded MPs was carried out to understand in which direction research is moving. Data captured mainly focused on the drug category and the mechanism of action; in particular, it was observed whether the excluded IMPs addressed a specific mutation.

Table 2.1 Inclusion and Exclusion criteria for selecting medicinal products to treat Leber Hereditary Optic Neuropathy and Retinitis Pigmentosa

Inclusion Criteria	Exclusion Criteria
• Clinical trials carried out between 1st January 2006 and 30th November 2018 • Interventional clinical trials • Clinical trials evaluating medicinal products • Clinical trials evaluating efficacy primary endpoints	• Clinical trials studying conditions other than LHON or non-syndromic RP, such as clinical trials evaluating Leber Congenital Amaurosis or other eye-related conditions • Behavioural clinical trials, such as clinical trials where the efficacy of cognitive-behavioural therapy was evaluated • Clinical trials evaluating medical devices, such as devices to perform trans corneal electrostimulation or retinal implant systems • Clinical trials evaluating supplementary products, such as trials to test Alga *Dunaliella bardawill*. • Clinical trials registered as terminated, withdrawn, no longer available. • Clinical trials evaluating safety of the studied medicinal product as primary endpoints. These included, for example, clinical trials evaluating the Adverse Drug Reactions during the treatment with a medicinal product.

2.1.5 Prospective Treatment Protocols for Leber Hereditary Optic Neuropathy and Retinitis Pigmentosa

Drugs in development phase were considered suitable to be proposed as part of prospective treatment protocols according to the development phase and if trials were carried out between January 2006 and November 2018.

On average, the clinical development phase takes six or seven years and it would be unlikely that products studied in the clinical trials initiated before January 2006 would reach the market[31]. Clinical trials that were prematurely terminated, no-longer available or withdrawn were excluded.

IMPs with clinical trials aiming to study the safety rather than the efficacy were excluded from the prospective treatment protocols. Safety endpoints were not considered suitable as these are studied during phase I and phase I/II of development of IMPs, so during its early stage.

Prospective treatment protocols were developed according to the genotyping of LHON and RP. IMPs were grouped in different categories, depending on whether they were studied to treat a specific mutation or whether they were non-mutation specific. Considering the differences encountered while analysing IMPs, proposed prospective treatment protocols were divided according to the active substance nature (chemical, ATMPs and growth factors).

[31] PhRMA: Biopharmaceutical Research & Development:The Process Behind New Medicines [Internet]. Pharmaceutical Research and Manufacturers of America: 2015 [cited December 29, 2018]. Available from URL: http://phrma-docs.phrma.org/sites/default/files/pdf/rd_brochure.pdf

2.2 Review of Clinical Development Programs

CDPs of drugs indicated for LHON and RP were analysed and reviewed. For CAPs, the EPAR was used for the identification of the number and nature of studies carried out to support the marketing authorisation application. Data included was (i) number of studies carried out, (ii) study title, (iii) study design, (iv) study aims, (v) administration and duration of the treatment, (vi) number and age of patients and (vii) primary and secondary endpoints.

The legal basis of the authorisation, such as if it was a full marketing authorisation or other type of marketing authorisation, were considered. The start date of each clinical trial was noted to perform a comparison of requirements for clinical development through time.

A stratification of IMPs in relation to the study phase and indication area, such as products addressing a specific subtype of LHON or RP, was performed. The main focus was the understanding of the number of IMPs studied to treat one specific mutation for LHON and RP, and the number of IMPs studied to treat all the mutations. Information related to the clinical trials status was retrieved from USNML database of clinical trials and EudraCT. Differences between the two databases were noticed in the description of the clinical trials status. USNML database of clinical trials uses 9 terms to define the status of clinical trials[32]. In EudraCT database 8 terms are used to indicate clinical trials status[33]. To simplify the analyses of clinical trials, 6 representative terms were selected to describe the status of clinical trials, which were grouped as (i) completed, (ii) no longer available,

[32]U.S National Library of Medicines. Clinical trials.gov: Protocol Registration Data Element Definitions for Interventional and Observational Studies [Internet]. National Institutes of Health, Bethesda, Maryland; Last review 27 June 2018 [cited on January 25, 2019]. Available from URL: https://prsinfo.clinicaltrials.gov/definitions.html

[33]European Medicines Agency. EU clinical trials register: Home and Search [Internet]. London (UK): European Medicines Agency; ©1995-2018 [cited January 25, 2019]. Available from URL: https://www.clinicaltrialsregister.eu/ctr-search/search

(iii) not yet recruiting, (iv) ongoing, (v) recruiting and (vi) unknown. This grouping exercise was performed to simplify and standardise data retrieved from the two different data sources. The other terms found to describe the status of clinical trials were incorporated; for example, clinical trials registered as "enrolling by invitation" were considered as "recruiting" clinical trials. No longer available clinical trials status describes clinical trials no longer available and which will not be available in the future. "Unknown" is a description of clinical trials status specifically used by the USNML database. The unknown status describes clinical trials previously registered as ongoing, which passed the expected completion date, but for which no verification of the real status has been performed in the past two years.

2.2.1 Analysis of Endpoints

Primary and secondary endpoints studied during clinical trials for IMPs for LHON/RP were analysed to detect possible changes in studied endpoints through time. The effects table to summarise the efficacy of trials was used. The effects table is used by CHMP members when assessing the risk/benefit of a certain medicine. The effects table has been integrated into the EPAR in 2015, in the section related to the efficacy of trials performed for centrally approved medicinal products.

The most common endpoints studied through time were grouped. Safety and efficacy primary and secondary endpoints were divided and analysed separately. Efficacy endpoints studied through time were notably heterogeneous when compared to safety endpoints, thus were sub-grouped. Descriptive statistics analysis was carried out to analyse the most common endpoints studied in the 13-year timeframe considered.

Analysis of the most common endpoints for IMPs in development to treat LHON and RP was performed.

2.2.2 Comparative analysis to detect emerging patterns

Emerging patterns in the development of IMPs to treat LHON and RP were detected through the analysis of CDPs. Considering the status of rare diseases of LHON and RP and the scarcity of medicines available for treatment, the comparison of CDPs was based on the highest study phase (where possible) or on the available MPs. IMPs were categorised, and the phase study of each IMP was considered. Post-authorisation studies were excluded from the comparison.

For LHON, CDPs of two MPs were considered suitable to be compared. For RP, CDPs of MPs to treat mutation RPE65 and CDPs of somatic therapy medicinal products (stem cells) were considered suitable to be compared.

The comparison aimed to detect patterns pursued by pharmaceutical companies when developing medicines to treat LHON and RP. Endpoints, aims and objectives studied when developing a CDP were considered. Population studied while carrying out clinical trials was considered (healthy volunteers or affected patients). The number of interventional and observational clinical trials carried out was evaluated. Follow-up clinical trials were considered.

The analysis to detect patterns used by pharmaceutical companies when developing medicines to treat LHON and RP was performed using descriptive statistics (such as average, median and mode).

2.3 Regulatory pathways

Incentives for pharmaceutical companies to develop OMPs are well established. Regulators have a delicate position in granting an orphan designation considering the limited data on safety and efficacy on OMPs is usually provided by pharmaceutical

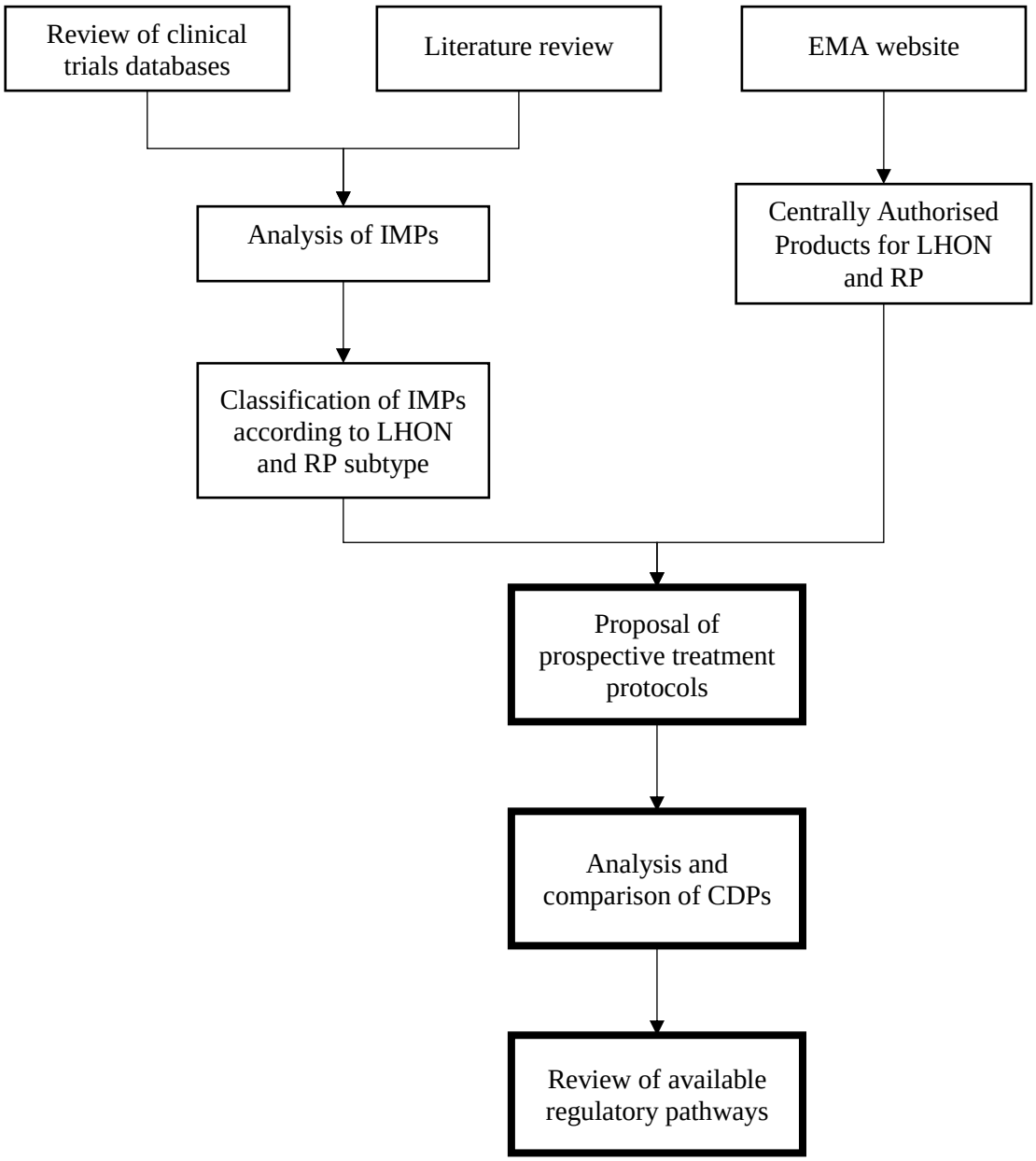
companies. The process to authorise an OMP can be slow and difficult. Regulatory pathways to speed the process to market an OMP are available within the EU. Regulatory pathways available within the EU were retrieved from the EMA website and peer-reviewed literature. The number of CAPs and OMPs was retrieved from the EMA website.

The EPAR of CAPs was reviewed to understand the regulatory pathways pursued by pharmaceutical companies when following the process to market innovative drugs. The EPAR was searched to understand whether suggestions from regulators were considered while marketing medicines to treat LHON and RP or to speed this process.

Medicinal products currently accounting for an orphan designation were retrieved from the register of designated orphan medicinal products[34]. The number of clinical trials available for each product at the moment of the designation was analysed.

Figure 2.1 shows the methodology used to carry out this study.

[34] European Commission. Register of designated Orphan Medicinal Products [Internet]. © European Union, 1995-2019 [cited March 1, 2019]. Available from URL: http://ec.europa.eu/health/documents/community-register/html/alforphreg.htm



CDP: Clinical Development Program
EMA: European Medicines Agency
IMPs: Investigational Medicinal Products
LHON: Leber Hereditary Optic Neuropathy
RP: Retinitis Pigmentosa

Figure 2.1 Flowchart of the methodology used.
The methods were divided into three phases which have been highlighted

2.4 Poster publications

Three posters related to the study were accepted for published at local and international conferences.

(i) "Developing safe and effective medicinal products to treat Leber Hereditary Optic Neuropathy (LHON). Clinical and Regulatory challenges" which was presented at the ACCP Global Conference on Clinical Pharmacy, Seattle (USA) (October 2018)

(ii) "Developing safe and effective medicinal products to treat Leber Hereditary Optic Neuropathy. Clinical and Regulatory challenges" which was presented at the 10th Malta Medical School Conference (November 2018)

(iii) "Emerging Treatment for Leber Hereditary Optic Neuropathy and Retinitis Pigmentosa" which will be presented at 79th FIP World Congress of Pharmacy and Pharmaceutical Sciences (September 2019)

The abstracts are available on Appendix VI.

Chapter 3

Results

3.1 Centrally authorised products for Leber Hereditary Optic Neuropathy and Retinitis Pigmentosa

One MP is currently authorised within the EU to treat LHON and one MP is currently authorised within the EU to treat RP. Raxone, is a small molecule authorised through a marketing authorisation under exceptional circumstances since September 2015 to treat LHON. Luxturna is a gene therapy medicinal product authorised through a full marketing authorisation, granted in September 2018 to treat RP.

3.1.1 Centrally authorised medicinal products to treat Leber Hereditary Optic Neuropathy

Raxone (Idebenone), is the only MP approved to treat LHON within the EU (Table 3.1).

Table 3.1 Idebenone, centrally authorised to treat Leber Hereditary Optic neuropathy

Name of medicinal product	Date of initial approval	Indication	Drug Category
Idebenone (Raxone)	8 September 2015	Treatment of adolescent and adult patients with visual impairment due to Leber Hereditary Optic Neuropathy	Small Molecule

Section 4.1 of the EU- Summary of Product Characteristics (SmPC) showed that Raxone is indicated for patients with visual impairment due to Leber Hereditary Optic Neuropathy. Raxone is formulated as 150mg film-coated tablets to be administered orally at a daily dose of 900mg per day, in three divided doses.

3.1.2 Centrally authorised medicinal products to treat Retinitis Pigmentosa

Luxturna (voretigene neparvovec-rzyl), is the only MP approved to treat RP within the EU (Table 3.2)

Table 3.2 Voretigene neparvovec-rzyl, centrally authorised to treat Retinitis Pigmentosa

Name of medicinal product	Date of initial approval	Indication	Drug Category
Voretigene neparvovec-rzyl (Luxturna)	20 September 2018	Treatment of patients with confirmed biallelic RPE65 mutation causing vision loss inherited retinal dystrophy	Gene therapy

Section 4.1 of the EU-SmPC showed that Luxturna is specifically indicated for patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic RPE65 mutations and who have sufficient viable retinal cells. Luxturna is a concentrate and solvent for solution to be administered as subretinal injection after vitrectomy.

3.1.3 Drugs in development for Leber Hereditary Optic Neuropathy

Twenty-nine clinical trials were retrieved from the USNML database and 9 clinical trials were retrieved from the EudraCT database using the keyword “Leber Hereditary Optic Neuropathy”. Data retrieved from the two clinical databases was combined and analysed. Sixteen clinical trials were excluded prior to review in line with the exclusion criteria; in 2 clinical trials the intervention was a device, 7 were observational clinical trials, 2 were post-authorisation expanded access programs and 1 was performed before 2006 or after 2018. More information about the criteria applied in excluding studies is reported in Figure 3.1. More information on excluded clinical trials are available on Appendix I.

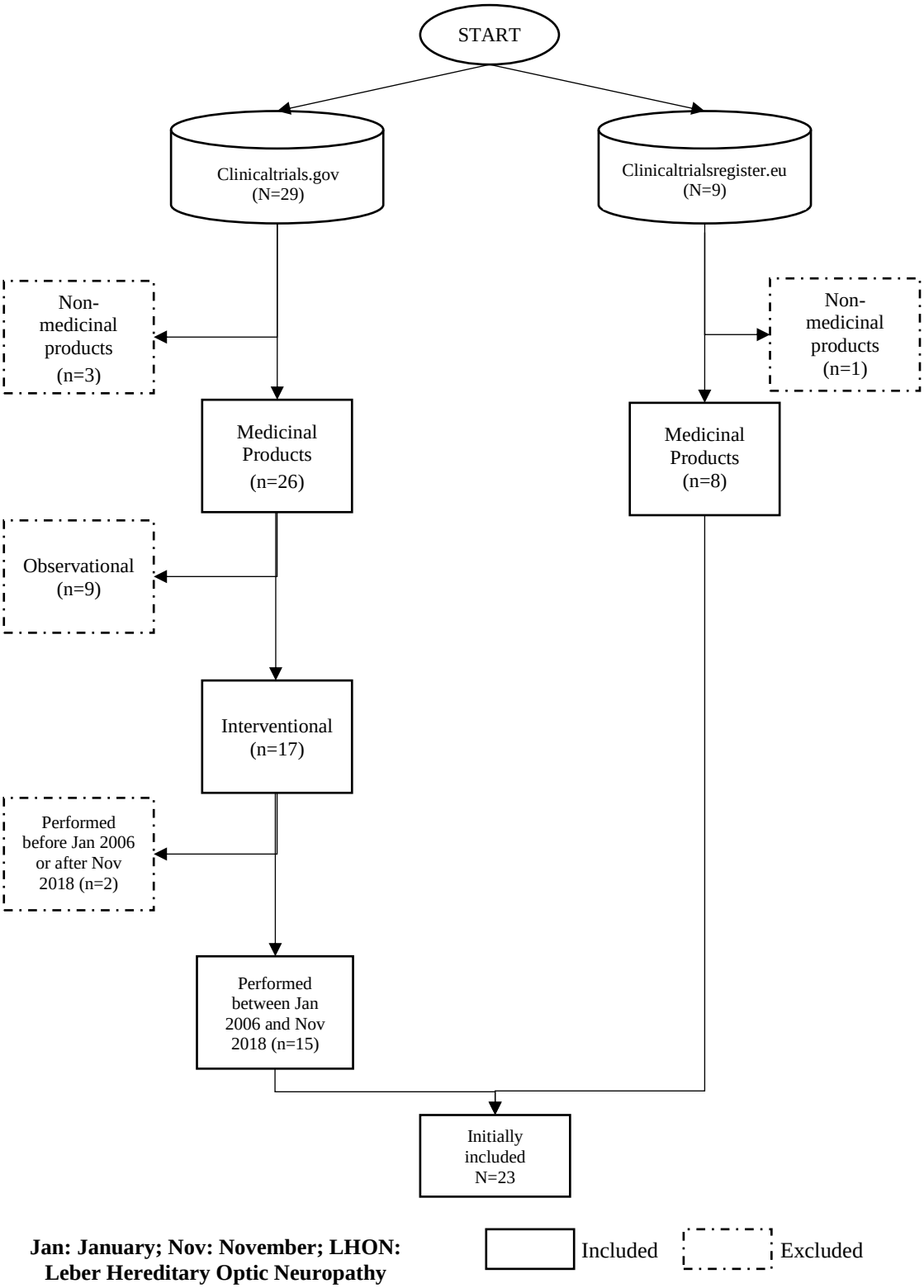


Figure 3.1 Clinical trials initially included for Leber Hereditary Optic Neuropathy

3.1.4 Drugs in development for Retinitis Pigmentosa

One-hundred and forty-six clinical trials were retrieved from the USNML database and 17 clinical trials were retrieved from the EudraCT database searching for the keyword "Retinitis Pigmentosa". Data retrieved from the two clinical databases were combined and analysed. One hundred and seven clinical trials were excluded prior to review in line with the exclusion criteria; in 63 clinical trials the intervention was either a device (26), a drug supplement (13), a procedure (8), dietary supplement (5), diagnostic tests and genetic analysis (4) or behavioural (2) others (5). Thirty-nine were observational clinical trials, 5 were performed before January 2006 or after November 2018 and 7 were investigating conditions other than RP. More information about the criteria applied in excluding studies is reported in Figure 3.2.

More information on excluded clinical trials is available on Appendix II.

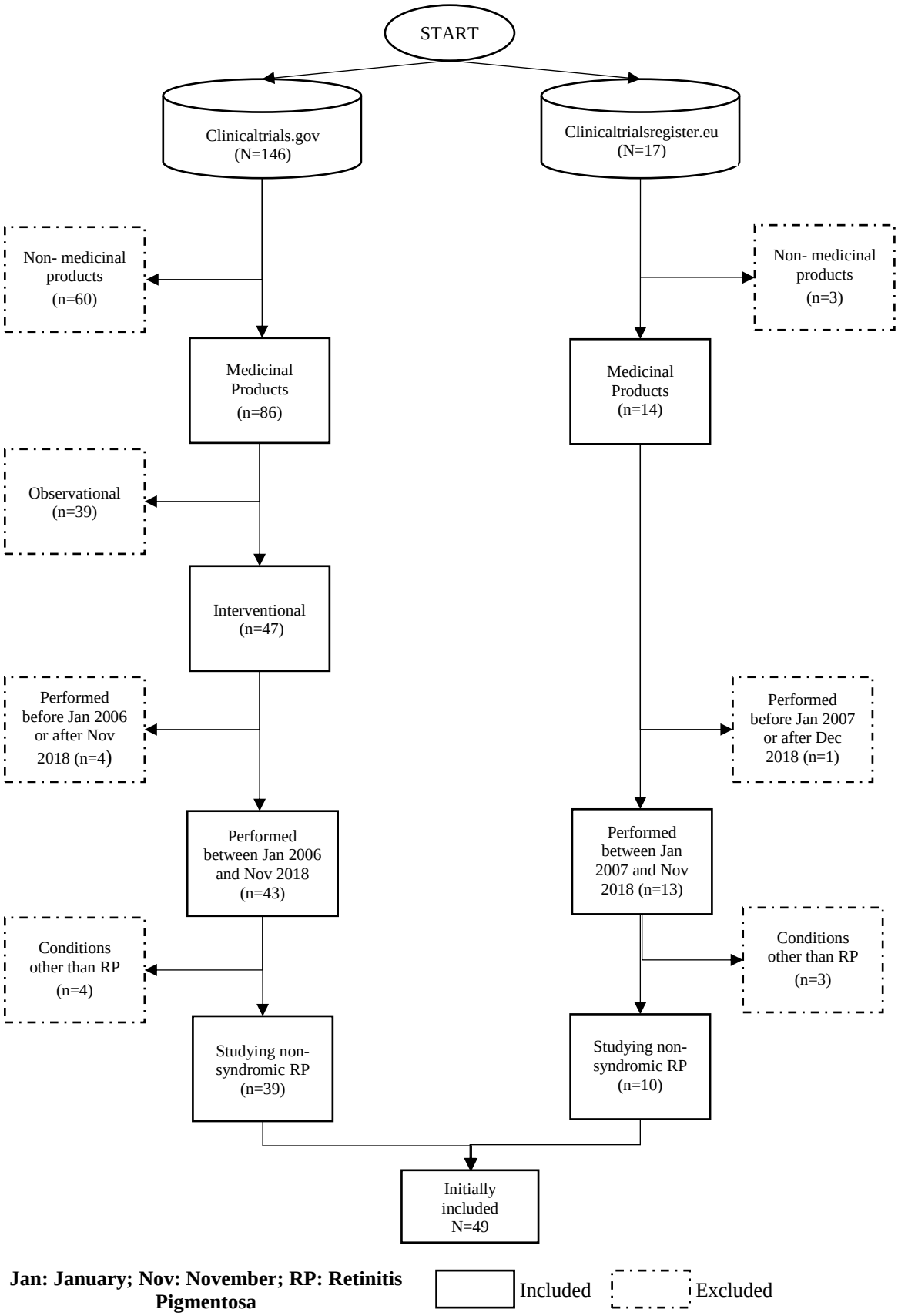


Figure 3.2 Clinical trials initially included for Retinitis Pigmentosa

3.2 Analysis of clinical trials

The number of clinical trials carried out between 2006 and 2018 for LHON and RP was analysed. Since a 13-year timeframe was considered, years were grouped unequally. Twenty-three clinical trials to evaluate new treatments for LHON and 49 clinical trials to evaluate new treatments for RP, carried out between January 2006 and November 2018, were included. In table 3.3 and 3.4 the number of included clinical trials performed over time is shown.

Table 3.3 Number of clinical trials performed between 2006 and 2018 for Leber Hereditary Optic Neuropathy (N=23)

	2006-2010	2011-2014	2015-2018
Number of clinical trials	**3**	**7**	**13**
Average number of clinical trials/Year	**0.6**	**1.75**	**3.25**

Table 3.4 Number of clinical trials performed between 2006 and 2018 for Retinitis Pigmentosa (N=49)

	2006-2010	2011-2014	2015-2018
Number of clinical trials	**10**	**17**	**22**
Average number of clinical trials/Year	**2**	**4.25**	**5.5**

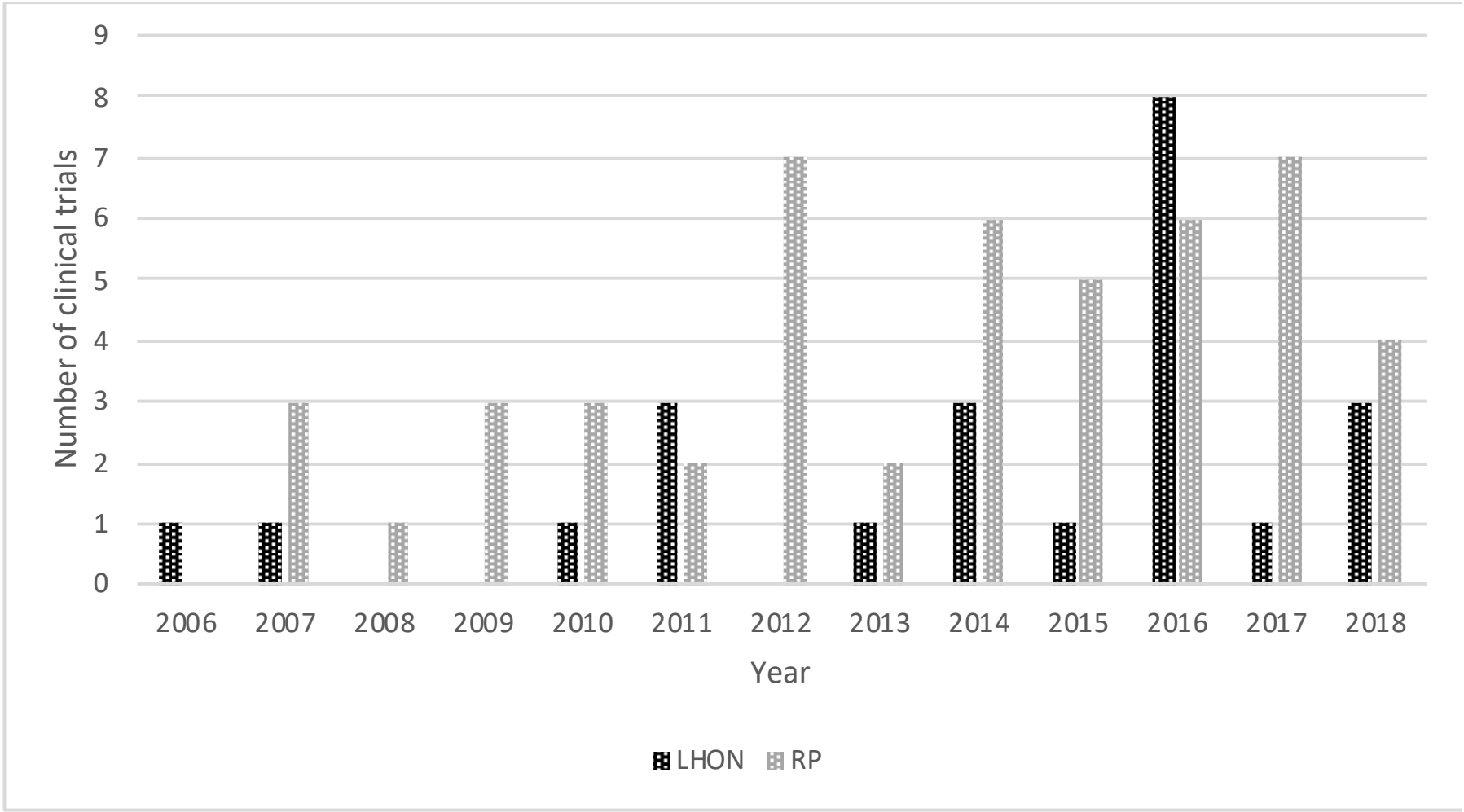


Figure 3.3 Clinical trials carried out through time to evaluate the included clinical trials for Leber Hereditary Optic Neuropathy (N=23) and Retinitis Pigmentosa (N=49)

3.2.1 Study phase of clinical trials

Prior to start of the analysis of the study phase, 2 phase IV clinical trials were excluded (2015-004405-16 and NCT02774005A). Three more clinical trials were excluded because the study phase was not provided in the two data sources (NCT01920867, NCT01267422 and NCT03011541). A total of 67 clinical trials for LHON and RP were analysed.

Thirty-two out of 67 clinical trials were early development phase clinical trials, thus phase I and phase I/II (Table 3.5).

Table 3.5 Phase I and Phase I/II clinical trials carried out between 2006-2018 for Leber Hereditary Optic Neuropathy (N=4) and Retinitis Pigmentosa (N=28)

LHON				
Years	**2006-2010**	**2011-2014**	**2015-2018**	**Total**
Number of Trials	1	3	0	4
Average number of clinical trials/Year	0.25	0.75	0	0.33
Number of completed clinical trials	0	1	0	1
RP				
Years	**2006-2010**	**2011-2014**	**2015-2018**	**Total**
Number of Trials	5	10	13	28
Average number of clinical trials /Year	1.25	2.75	3.25	2.33
Number of completed clinical trials	3	5	1	9

Twelve out of 32 were phase I clinical trials, 19 out of 32 were phase I/II clinical trials. Out of 12 phase I clinical trials, 2 investigated medicines for the treatment of LHON and 10 investigated medicines for the treatment of RP. Out of 19 phase I/II clinical trials, 2 investigated medicines to treat LHON and 17 investigated medicines to treat RP.

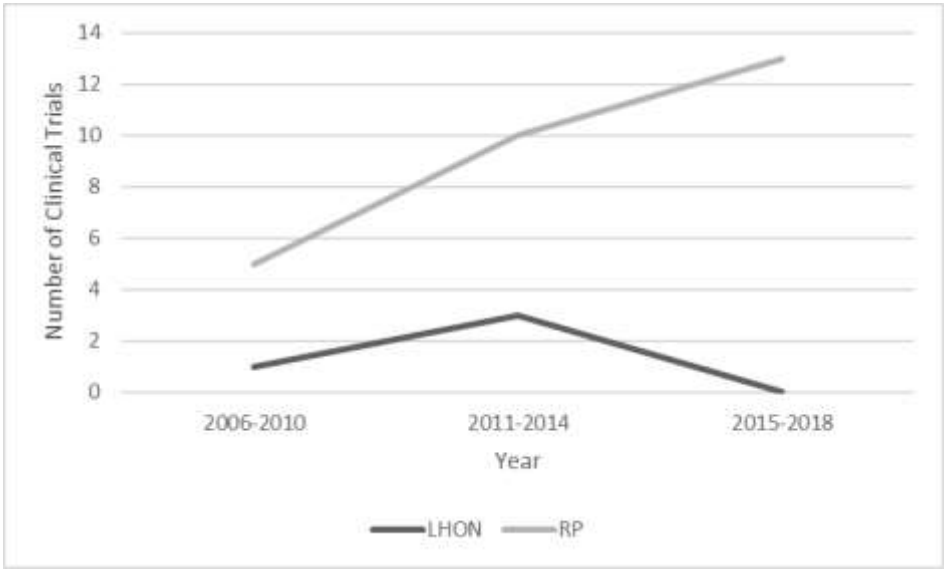


Figure 3.4 Phase I and Phase I/II clinical trials carried out between 2006-2018 for Leber Hereditary Optic Neuropathy (N=4) and Retinitis Pigmentosa (N=28)

Thirty-five out of 67 clinical trials for LHON and RP were phase II, phase II/III and phase III (Table 3.6). Out of 35 clinical trials, 23 were phase II, 11 were phase III, 1 was phase II/III.

Table 3.6 Phase II and Phase II/III and Phase III clinical trials carried out between 2006-2018 for Leber Hereditary Optic Neuropathy (N=15) and Retinitis Pigmentosa (N=20)

LHON				
Years	**2006-2010**	**2011-2014**	**2015-2018**	**Total**
Number of Trials	2	3	10	15
Average/Year	0.5	0.8	2.5	1.3
Number of completed clinical trials	3	3	0	6
RP				
Years	**2006-2010**	**2011-2014**	**2015-2018**	**Total**
Number of Trials	6	6	8	20
Average/Year	1.2	1.2	2	1.7
Number of completed clinical trials	4	2	1	7

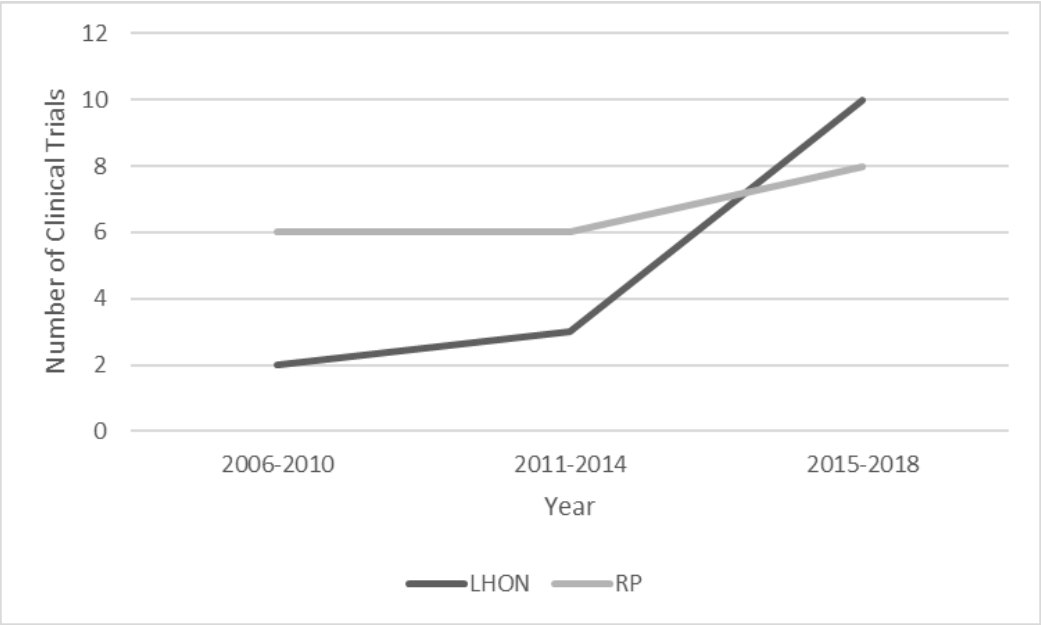


Figure 3.5 Phase II and Phase II/III and Phase III clinical trials carried out between 2006-2018 for Leber Hereditary Optic Neuropathy (N=15) and Retinitis Pigmentosa (N=20)

Out of 23 phase II clinical trials, 7 investigated medicines were to treat LHON and 16 investigated medicines were to treat RP. Out of 11 phase III clinical trials, 7 investigated medicines were to treat LHON and 4 investigated medicines were to treat RP. Phase II/III clinical trial investigated medicines to treat LHON.

Four out of 23 clinical trials for LHON were in early development phase, thus phase I and phase I/II clinical trials. Out of 23, 7 clinical trials were phase II, 7 clinical trials were phase III and 1 clinical trial was phase II/III. Two clinical trials out of 23 were phase IV and in 2 out of 23 clinical trials, the study phase was not reported (Table 3.7).

Table 3.7 Number of clinical trials performed for Leber Hereditary Optic Neuropathy between 2006 and 2018 according to the study phase and status (N=23)

Phase	Number of Studies	Trials Status					
		Recruiting	Active, not recruiting	Ongoing	Completed	Terminated	Unknown
Not Provided	2	1	-	-	1	-	-
Phase I	2	1	-	-	1	-	-
Phase I/II	2	-	1	1	-	-	-
Phase II	7	-	1	-	4	1	1
Phase II/III	1	-	1	-	-	-	-
Phase III	7	1	2	4	-	-	-
Phase IV	2	1	-	1	-	-	-
Total	23	4	5	6	6	1	1

Twenty-seven out of 49 clinical trials carried out for RP were early in development phase, thus phase I and phase I/II clinical trials. Out of 49 clinical trials, 16 were phase II, and 4 were phase III clinical trials. In 2 out of 49 clinical trials the study phase was not provided in the data sources (Table 3.8).

Table 3.8 Number of clinical trials performed for Retinitis Pigmentosa between 2006 and 2018 according to the study phase and status
(N=49)

Phase	Number of Studies	Trials Status					
		Recruiting	Active, not recruiting	Ongoing	Completed	Terminated	Unknown
Not Provided	2	2	-	-	-	-	-
Phase I	10	3	-	1	5	1	-
Phase I/II	17	6	3	2	4	1	1
Phase II	16	1	2	5	7	-	1
Phase II/III	0	-	-	-	-	-	-
Phase III	4	-	1	1	-	1	1
Phase IV	0	-	-	-	-	-	-
Total	49	12	6	9	16	3	3

3.2.2 Analysis of recruited patients

Between 2006 and 2018, a total of 911 patients were recruited in clinical trials for LHON. Two phase IV clinical trials (NCT02774005 and 2015-004405-16) were excluded from the data collection due to the post authorisation phase study. Patients enrolled in clinical trial NCT03011541 were not considered in the analysis due to the phase not reported in the data source. Seventeen out of 20 clinical trials enrolled patients affected from LHON. Clinical trials NCT02023866 and NCT02473445 enrolled patients with inherited mitochondrial diseases (including LHON), clinical trial NCT01064505 enrolled patients with NAION/chronic optic nerve atrophy (including LHON) and clinical trials NCT03011541 enrolled patients with damage to the optic nerve or retina. The average

number of patients recruited was 45.6 patients per clinical trial, the median was of 38 patients, with a range of between 9 and 90 patients recruited.

A total of 2238 patients were recruited in clinical trials for RP. All the clinical trials were enrolling patients affected from RP. Patients enrolled in clinical trials NCT03011541 and NCT01920867 were not considered in this analysis due to the study phase not reported in the data sources. The average number of recruited patients was 52.9 patients per clinical trials, with a median of 30 patients. The range of recruited patients was between 4 and 300.

For phase I and I/II clinical trials a total of 118 patients and 590 patients were recruited for LHON and RP respectively. No phase I and phase I/II clinical trials for LHON were carried out between 2015-2018, thus no analysis was performed. During the period between 2006-2010, only 1 phase I and phase I/II clinical trial for LHON was carried out, so descriptive statistics was not used to describe patient enrolment (Table 3.9).

For phase II, phase II/III and phase III clinical trials a total of 784 and 1648 patients for LHON and RP respectively, were recruited (Table 3.10). In clinical trials carried out for LHON, both sexes were considered eligible to be enrolled in all considered clinical trials.

Table 3.9 Recruited patients for phase I and phase I/II clinical trials for Leber Hereditary Optic Neuropathy (N=118) and Retinitis Pigmentosa (N=590)

Phase I and Phase I/II								
	LHON				RP			
	2006-2010	2011-2014	2015-2018	TOTAL	2006-2010	2011-2014	2015-2018	TOTAL
Total number of patients recruited	48	70	0	118	65	218	307	590
Average number of patients recruited	Only one clinical trial was performed	23.3	0	29.5	16.2	21.8	23.6	21.8
Median number of patients recruited		22	0	24.5	14	15	21	18
Range of patients recruited		21-27	0	21-48	5-32	5-50	4-71	4-71
Number of clinical trials	1	3	0	4	4	10	13	27

In 4 phase I/ II (NCT03316560, NCT03116113, NCT03252847, 2016-003967-21) and 1 phase II (2016-003852-60) clinical trials, performed for X-linked RP, only male patients were considered eligible to be recruited.

3.2.3 Analysis of clinical trials design

Open label (unblinded), single group assignment, was most common clinical trial design for phase I and phase I/II clinical trials. Open label, single group clinical trial design was found in 16 out of 31 phase I and phase I/II clinical trials (LHON: n=2; RP: n=14). The second most common clinical trial design was represented by non-randomised, single group, open label clinical trials, found in 4 out of 31 clinical trials (LHON: n=0; RP: n=4). Three out of 31 clinical trials were only registered as open label clinical trials (LHON: n=0; RP: n=3), 2 out of 31 clinical trials were randomised parallel assignment and one

was non-randomised parallel assignment (LHON: n=1; RP: n=2). Other designs present in LHON and RP clinical trials were non-randomised, escalating dose, open label clinical trial (LHON: n=1), non-randomised, sequential assignment, open label clinical trials (RP: n=3).

Table 3.10 Recruited patients for phase II and phase III clinical trials for Leber Hereditary Optic Neuropathy (N=784) and Retinitis Pigmentosa (N=1648)

Phase II, Phase II/III and Phase III								
	LHON				RP			
	2006-2010	2011-2014	2015-2018	TOTAL	2006-2010	2011-2014	2015-2018	TOTAL
Total number of patients recruited	169	133	482	784	720	558	370	1648
Average number of patients recruited	84.5	44.3	48.2	52.3	120	93	46.2	82.4
Median number of patients recruited	84.5	36	40	40	79	47.5	46.5	50
Range of patients recruited	84-85	12-85	12-90	12-90	27-290	30-202	20-84	20-290
Number of clinical trials	2	3	10	15	6	6	6	20

The most common clinical trial design for phase II clinical trials was represented by randomised, parallel assignment, double masking clinical trials, present in 7 out of 23 (LHON: n=1; RP: n=6) clinical trials, followed by single group, open label clinical trials design present in 6 out of 23 clinical trials (LHON: n=3 RP: n=3). Randomised, parallel assignment, quadruple masking clinical trials was present in 4 out of 23 clinical trials (LHON: n=2; RP: n=2). Three out of 23 clinical trials were non-randomised (LHON: n=0; RP: n=3), and 1 out of 3 was non-randomised, parallel assignment, open label. In 2 out of 23 clinical trails the study design was not present in the data source and 1 out of 23 clinical trials, performed for RP, was a randomised crossover clinical trial.

Phase II/III and phase III clinical trials design were evaluated together. The most common clinical trial design was represented by randomised, parallel assignment, double blind, present in 5 out of 10 phase III clinical trials (LHON: n=4; RP: n=1), followed by randomised, parallel assignment, quadruple masking design of 3 out of 10 clinical trials (LHON: n=2; RP: n=1). Two out of 10 phase III clinical trials were randomised, open label, parallel assignment design (LHON: n=0; RP: n=2).

3.2.4 Analysis of the endpoints

Endpoints studied through time to evaluate treatments for LHON and RP were analysed. Prior to analysis, 1 clinical trial (2008-004561-26) was excluded because primary endpoints were not reported in the database. Two phase IV clinical trials carried out for LHON were not considered in the analysis of the endpoints (2015-004405-16 and NCT02774005A). A total of 21 clinical trials were analysed for LHON and 48 clinical trials were analysed for RP.

The average number of primary endpoints studied in LHON clinical trials was 1.1, with a range of 1 to 2 primary endpoints studied per each clinical trial and a median and mode equal to 1.

Table 3.11 Most common safety and efficacy endpoints studied between 2006 and 2018 for Leber Hereditary Optic Neuropathy

	LHON
Safety Endpoints	Incidence of adverse events (n=4)
	Safety and tolerability (n=2)
	Dose limiting toxicity (n=1)
	Immune tests (n=1)
Efficacy Endpoints	Change in VA (n=6)
	BCVA (n=5)
	Best recovery in VA (n=2)
	Change from Baseline in Newcastle Paediatric Mitochondrial Disease Scale (n=2)
	VF (n=1)

The average number of primary endpoints studied for RP was 1.6 per clinical trial, with a range of 1 to 8 primary endpoints studied per each clinical trial and a median and a mode equal to 1. The most common safety-related primary endpoint studied for LHON was the incidence of adverse drug reactions, studied in 3 out of 7 clinical trials. The most common safety-related primary endpoint studied for RP was the occurrence of adverse events, studied in 12 out of 18 clinical trials.

The most common efficacy-related primary endpoint studied for LHON was change in visual acuity measured with a LogMAR studied in 6 out of 16 clinical trials, followed by the measurement of the BCVA, studied in 5 out of 16 clinical trials. The most common efficacy-related primary endpoint studied for RP was change in visual field. The other primary endpoints studied through time are summarised in table 3.11 and table 3.12.

Table 3.12 Most common safety and efficacy endpoints studied between 2006 and 2018 for Retinitis Pigmentosa

	RP
Safety Endpoints	Incidence of adverse events (n=15)
	Immune tests (n=3)
	Visual loss (n=3)
	Dose limiting toxicity (n=2)
	Ocular inflammation (n=2)
Efficacy Endpoints	VF (n=8)
	BCVA (n=6)
	Change in VA (n=5)
	Change in cystoid macular oedema (n=5)
	Mobility testing (n=2)
	Change from baseline in the macula (n=2)
	Change from baseline in laser flare and cell measurements (n=1)
	Change in Electroretinogram (n=1)
	Change in Retinal Sensitivity (n=1)
	Choroidal thickness (n=1)
	Cone photoreceptor preservation (n=1)
	Improvement from Baseline in microperimetry (n=1)
	Number of responders in dark adaptation (n=1)
	Retinal thickness (n=1)
	Visual function (n=1)

Four out of 21 clinical trials carried out for LHON did not study secondary endpoints. The most common safety-related secondary endpoint for LHON was the immune response (n=7). The most common efficacy-related secondary endpoint for LHON was the change in LogMAR VA (n=20), followed by colour contrast sensitivity (n=13) and VF (n=12).

Seven out of 48 trials carried out for RP did not study secondary endpoints. The most common safety-related secondary endpoint for RP was the incidence of serious and non-serious adverse drug reactions (n=17). The most common efficacy-related secondary endpoint for RP was the VF (n=19), followed by BCVA (n=18).

3.3 Prospective treatment protocols and literature review for Leber Hereditary Optic Neuropathy

Three medicinal products retrieved from clinical trials database were proposed as part of the prospective treatment protocol for LHON (Table 3.13).

Table 3.13 Medicinal products included in the prospective treatment protocol for Leber Hereditary Optic Neuropathy (N=4)

Active Substance	Number of clinical trials performed	Year	Clinical trials ID
Cysteamine bitartrate	2	2014	NCT02023866
		2015	NCT02473445
Bone Marrow Stem Cells	1	2016	NCT03011541
$rAAV_2$-ND_4	8	2011	NCT01267422
		2016	2015-001265-11
		2016	2015-001266-26
		2016	NCT02652780
		2016	NCT02652767
		2017	NCT03153293
		2018	NCT03293524
		2018	2017-002187-40

Products included in the prospective treatment protocols were at a stage of the development where efficacy was being studied as the primary endpoint. Cyclosporine A was not proposed as part of the prospective treatment protocol due to the results of clinical trial NCT02176733, where it was shown its inefficacy as prophylactic agent in preventing second-eye involvement in LHON patients (Leruez et al, 2018).

Included MPs were grouped according to the drug category and their mechanism of action. Results of drug category and mechanism of action of selected MPs are shown in Table 3.14.

Table 3.14 Overview of the selected medicinal products studied to treat Leber Hereditary Optic Neuropathy divided by category and mechanism of action
(N=3)

Category		Mechanism of action	Active Substance	Number of Products
Small Molecules		Modulating agent of mitochondrial electron transport chain	Cysteamine bitartrate	n=1
Advanced Therapy	Gene Therapy	Gene transference	$rAAV_2$-ND_4	n=2
	Somatic Therapy	Retinal tissues regeneration	Bone-marrow derived stem cells	

With regards to IMPs studied which were related to a specific LHON mutation, 1 out of 3 IMPs was studied related to LHON caused by a specific mutation. $rAAV_2$-ND_4 (GS010) is being studied to specifically treat the mtDNA point mutation 11778G>A which encodes for the subunit ND_4 of complex I. Two out of 3 IMPs were studied to treat LHON caused by all three mtDNA point mutations.

For each selected substance, the route of administration and dosage form were analysed (Table 3.15). Bone marrow derived stem cells was the only product for which different

routes of administration were explored. Different routes were explored according to (i) degree of visual loss (ii) aetiology of visual loss (iii) associated risk factors for the treatment arms and (iv) patient's medical risk status[35].

Table 3.15 Route of administration and dosage form of selected investigational medicinal products for Leber Hereditary Optic Neuropathy (N=3)

Active Substance	Route of administration	Dosage form
Cysteamine bitartrate	Oral	Delayed-release capsules
$rAAV_2$-ND_4	Intravitreal injection	Suspension for injection
Bone-marrow derived stem cells	Retrobulbar injection, Subtenon injection and Intravitreal injection	Suspension for injection
	Retrobulbar injection, Subtenon injection, Intravitreal injection and Intravenous injection	
	Subretinal or intra-optic nerve injection of BMSC concentrate followed by intravenous infusion of stem cells	

One additional medicinal product, EPI-743, was included following literature review.

3.3.1 Literature review of medicinal products to treat Leber Hereditary Optic Neuropathy

In this section results of literature review on IMPs studied to treat LHON have been reported.

Cysteamine Bitartrate

The use of cysteamine bitartrate to treat LHON (or more generally, mitochondrial diseases) is related to its antioxidant properties. The antioxidant properties of cysteamine

[35] US National Library of Medicines. Clinical trials.gov [Internet]. National Institute of Health, Bethesda, Maryland; last update 26 November 2018 [cited February 11, 2018]. Available from URL https://clinicaltrials.gov/ct2/show/NCT01920867

bitartrate are related to its ability of increase the production of glutathione, a super antioxidant[36]. Glutathione may reduce the oxidative stress and prolong mitochondrial survival, delaying the occurrence of blindness in patients affected from LHON.

GS010 (rAAV$_2$-ND$_4$)

rAAV$_2$-ND$_4$ is a recombinant viral vector able to transduce non-dividing cells, resulting in long term transgene expression (Daya and Berns, 2008). rAAV$_2$-ND$_4$ has been studied to specifically treat the mutation m.11778G>A, affecting the mitochondrial gene ND$_4$. The adeno-associated viral vector type 2 (AAV$_2$) acts by carrying the wildtype gene ND$_4$, which substitutes the mutated gene, producing a normal protein (Manickam et al, 2017). The integration of the wild-type gene into the mitochondrial genome is a crucial, but complicated step in the success of gene therapy. To overcome this issue, the allotopic expression technique is used. In the allotropic expression technique, a nuclear version of the mitochondrial gene codes for proteins expressed in cytoplasm. The synthesised proteins have a mitochondrial targeting sequence, which allows for effective trafficking to their target site in the mitochondria (Koilkonda et al, 2014; Ratican et al, 2018).

Eight clinical trials have been registered in both EudraCT database and USNLM database to prove the safety and efficacy of rAAV$_2$-ND$_4$ in LHON patients.

Bone Marrow Stem Cells

New treatment approaches for LHON include autologous bone marrow-derived stem cells. Bone marrow stem cells (BMSCs) are being tested for two main reasons (i) ability to differentiate into neuron-like cells and (ii) production of neutrophic factors. The

[36]Rare Mitochondrial Disorders Service. Are there any treatments in development? [Internet]. United Kingdom. RARE MITOCHONDRIAL DISORDERS SERVICE © 2019 [cited March 1, 2019]. Available from URL: http://mitochondrialdisease.nhs.uk/patient-area/questions-answers/52/

provision of neutrophic factors promotes axons regeneration and protects RGCs, potentially restoring visual loss in LHON patients.

EPI-743

EPI-743 is a catalytic small molecule, structurally similar to idebenone. EPI-743 chemical structure presents a modified benzene ring which increases its antioxidant properties. EPI-743 acts by increasing the synthesis of glutathione and, as a consequence, reducing oxidative stress (Peragallo and Newman, 2015; Theodorou-Kanari et al, 2018). To date, the efficacy of EPI-743 has been tested in one proof of concept study, in which 4 out of 5 patients showed improvements of signs and symptoms (Sadun et al, 2012).

3.3.2 Other products in development

Three more MPs are currently in development to treat LHON, Elamipretride, scAAV$_2$-P$_1$ND$_4$ and QPI-1007. Elamipretride, scAAV$_2$-P$_1$ND$_4$ and QPI-1007 were excluded from the prospective treatment protocols due to the early stage of their development. At the moment of this study, no clinical trials assessing the efficacy of Elamipretride, scAAV$_2$-P$_1$ND$_4$ and QPI-1007 were carried out, leading to their exclusion. A summary of the characteristics of Elamipretride, scAAV$_2$-P$_1$ND$_4$ and QPI-1007 was considered important to understand which molecules are being studied to treat LHON (Table 3.16).

Elamipretride

Elamipretride is a small molecule under study to treat LHON. Elamipretride is part of the Szeto-Schiller peptide family which attenuates ROS production in mitochondria and cytochrome C release (Szeto, 2014; Koopman et al, 2016).

Elamipretride acts by protecting the structure of the cristae and preventing mitochondrial swelling under ischemic conditions through its high affinity to cardiolipin (Birk et al, 2013; Mileykovskaya et Dowhan, 2014; Ren et al, 2014).

QPI-1007

QPI-1007 is a synthetic small interfering RNA which targets the caspase-2 mRNA and temporarily inhibits its expression via the RNA interference pathway[37], providing a neuroprotective effect in the retina. QPI-1007 was granted an orphan designation for non-arteritic anterior ischemic optic neuropathy (NAION), due its mechanism of action which can reduce apoptosis. QPI-1007 acts by reducing apoptosis through the downregulation of caspase-2 expression, responsible for starting the apoptotic process.

scAAV$_2$-P$_1$ND$_4$

scAAV$_2$-P$_1$ND$_4$is a gene therapy medicinal product which targets the mitochondrial gene ND$_4$. scAAV$_2$-P$_1$ND$_4$ is a self-complementary viral vector which contains a double strand of DNA, increasing the speed and the efficiency of transgene expression (McCarty, 2008).

Table 3.16 Summary of medicinal products currently under evaluation to treat Leber Hereditary Optic Neuropathy (N=3)

Active Substance	Clinical trial ID	Phase	Route of Administration	Sponsor
Elamipretride	NCT02693119	Phase II	Topical	Stealth BioTherapeutics Inc.
QPI-1007	NCT01064505	Phase I	Intravitreal injection	Quark Pharmaceuticals
scAAV$_2$-P$_1$ND$_4$	NCT02161380	Phase I	Intravitreal injection	John Guy

[37]Quark Pharmaceuticals, Inc. Pipeline: QPI-1007 [Internet]. Newark, CA. Copyright 2015 Quark [cited March 1, 2019]. Available from URL: http://quarkpharma.com/?page_id=23

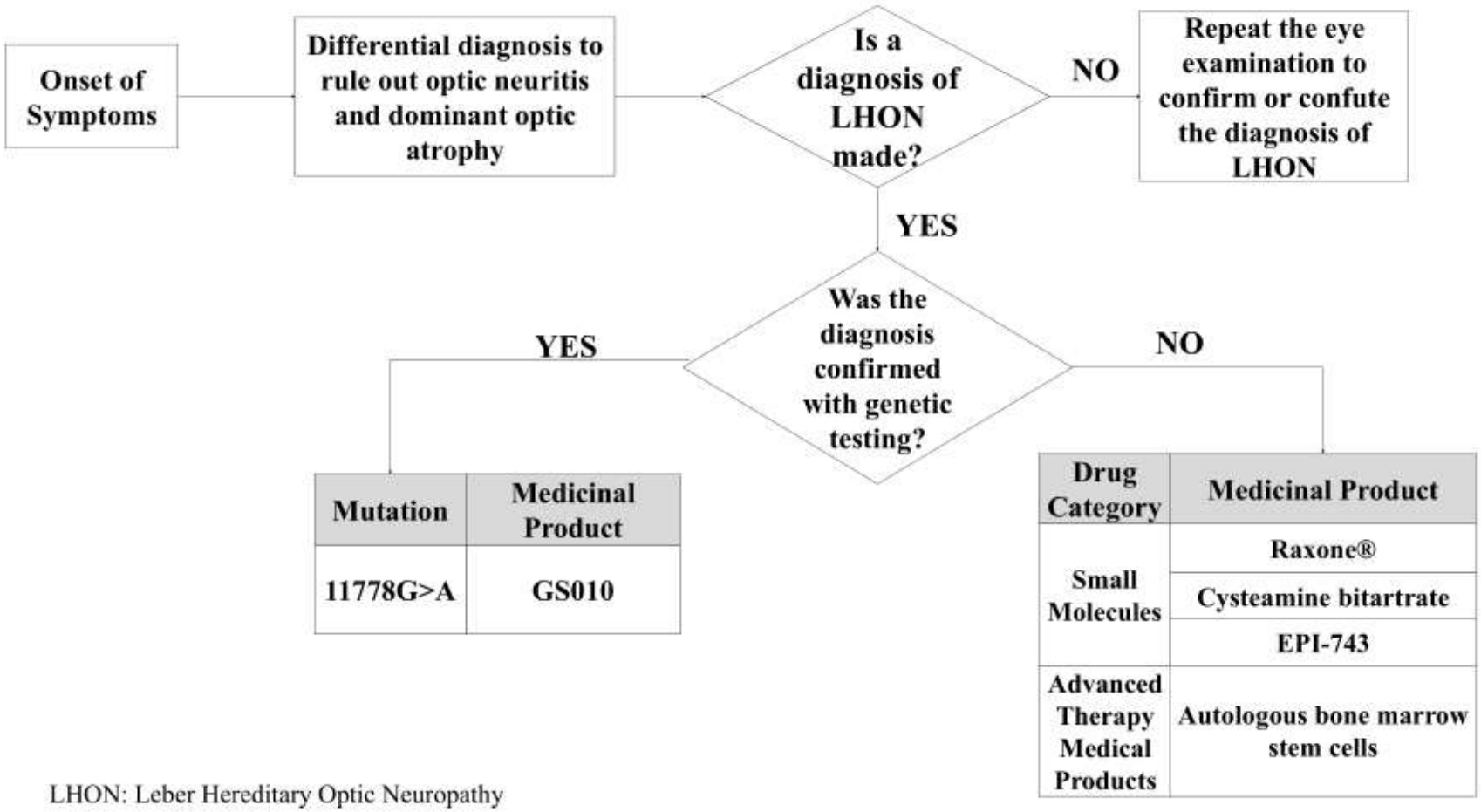


Figure 3.6 Proposed prospective treatment protocol with relevant medicines considered suitable to treat Leber Hereditary Optic Neuropathy

3.4 Prospective treatment protocols and literature review for Retinitis Pigmentosa

Eleven MPs were selected as part of the prospective treatment protocol for RP. Table 3.17 describes the included MPs with the relevant studies.

Table 3.17 Medicinal products included in prospective treatment protocols for Retinitis Pigmentosa (N=11)

Active Substance	Number of clinical trials performed	Start of clinical trial (year)	Clinical trials ID
Brimonidine Tartrate	2	2008	NCT00661479
		2010	2010-019079-32
Levodopa-Carbidopa	1	2016	NCT02837640
Fluocinolone Acetonide	1	2016	2016-002523-28
Valproic Acid	2	2010	NCT01233609
		2011	NCT01399515
QLT091001	5	2009	NCT01014052
		2012	NCT01543906
		2012	NCT01521793
		2012	2011-004214-42
		2016	2013-005393-22
scAAV8/RLBP1	1	2018	NCT03374657
AAV8-RPGR	2	2017	2016-003852-60
		2017	NCT03116113
Autologous Bone Marrow-derived mononuclear stem cells	4	2009	NCT01068561
		2011	NCT01560715
		2014	NCT01914913
		2017	NCT02280135
Bone Marrow derived mesenchymal Stem Cells	3	2012	NCT01531348
		2013	NCT01920867
		2017	NCT03011541
Human Retinal Progenitor Cells	3	2014	NCT02320812
		2015	NCT02464436
		2017	NCT03073733
NT-501	3	2007	NCT00447993
		2007	NCT00447980
		2012	NCT01530659

Products included in the prospective treatment protocols were at a stage of the development where efficacy was being studied as primary endpoint.

Included MPs were grouped according to the drug category and their mechanism of action. Results of drug category and mechanism of action of selected medicinal products are shown in Table 3.18.

Table 3.18 Overview of the selected medicinal products studied to treat Retinitis Pigmentosa divided by category and mechanism of action
(N=11)

Category		Mechanism of action		Medicinal Product	Number of Products
Small Molecules		Neuroprotection	Photoreceptors	Brimonidine Tartrate	n= 5
			RPE	Levodopa-Carbidopa	
			Photoreceptors and RPE	Fluocinolone acetonide	
		Pharmacological chaperons		Valproic Acid	
		Replacement of missing chromophore		QLT091001	
Advanced Therapy	Gene Therapy	Gene transference		scAAV8/RLBP1	n=2
				AAV-RPGR	
	Somatic Therapy	Photoreceptors/retinal tissues regeneration		Autologous bone marrow-derived mononuclear stem cells	n=3
				Bone-marrow derived stem cells	
				Human Retinal Progenitor Cells	
Growth Factors		Neurogenesis stimulants		NT-501	n=1

Three more MPs, Aflibercept, Minocycline and recombinant human nerve growth factor (rhNGF) were retrieved from the data selection. These three MPs were not included due to their proposed mechanism of action addressed to treat cystoid macular oedema (CMO), a condition which may occur in association with RP. More information on Aflibercept, Minocycline and rhNGF can be retrieved on Appendix VII.

With regards to IMPs studied related to a specific RP subtype, 7 out of 11 IMPs were related to RP no specific subtype, 3 out of 11 IMPs were studied to treat RP caused by a specific mutation and 1 out of 11 IMPs was studied to treat autosomal dominant forms of RP (Table 3.19).

Table 3.19 Overview of prospective products for the treatment of Retinitis Pigmentosa according to drug category (N=11)

Active Substance	Retinitis Pigmentosa Subtype Treatment	Drug Category
Brimonidine Tartrate	No specific subtype proposed	Small Molecule
Levodopa-Carbidopa	No specific subtype proposed	Small Molecule
Fluocinolone acetonide	No specific subtype proposed	Small Molecule
Valproic Acid	Autosomal dominant form of RP	Small Molecule
QLT091001	Retinitis Pigmentosa caused by RPE65 mutation	Small Molecule
scAAV8/RLBP1	Retinitis Pigmentosa caused by RLBP1 mutation	Gene Therapy
AAV-RPGR	Retinitis Pigmentosa caused by RPGR mutation	Gene Therapy
Autologous bone marrow-derived mononuclear stem cells	No specific subtype proposed	Somatic Therapy
Bone-marrow derived stem cells	No specific subtype proposed	Somatic Therapy
Human Retinal Progenitor Cells	No specific subtype proposed	Somatic Therapy
NT-501	No specific subtype proposed	Growth Factors

For each selected substance, the route of administration and dosage form were analysed (Table 3.20). Out of 11 IMPs, 4 were studied to be administered through intravitreal injection, 2 were studied to be administered through subretinal injection, 2 were studied to be administered orally, 1 was studied to be administered via drops and 1 to be implanted.

Bone-marrow derived stem cells were studied to be administered through intravitreal, intraneuronal or subretinal injection.

Table 3.20 Route of administration and dosage form of selected investigational medicinal products for Retinitis Pigmentosa (N=11)

Active Substance	Route of administration	Dosage form
Brimonidine Tartrate	Intravitreal injection	Implant
Levodopa-Carbidopa	Oral	Tablet
Fluocinolone acetonide	Intravitreal injection	Implant
Valproic Acid	Oral	Tablets, Soft gel capsules
Minocycline	Oral	Tablets, Capsules
QLT091001	Oral	Oral Solution
Aflibercept	Intravitreal injection	Solution for injection
scAAV8/RLBP1	Subretinal injection	Solution for injection
AAV-RPGR	Subretinal injection	Suspension for injection
Autologous bone marrow-derived mononuclear stem cells	Intravitreal injection	Suspension for injection
Bone-marrow derived stem cells	Intravitreal, intraneuronal or subretinal injection	Solution for injection
Human Retinal Progenitor Cells	Intravitreal injection	Suspension for injection
rhGNF	Ocular	Eye drops
NT-501	Ocular	Implant

3.4.1 Literature Review

In this section results of literature review on IMPs studied to treat RP have been reported.

Brimonidine Tartrate

Brimonidine tartrate is a high selective α2-agonist administered topically on the eyes (Wheeler and Woldemussie, 2001). Brimonidine tartrate has a well-established neuroprotective effect on RGCs probably caused by the upregulation of neuronal survival factors (Burke and Schwartz 1996; Woldemussie, 2001). The rationale to use brimonidine

tartrate to treat RP is the improvement of photoreceptor survival due to the induction of basic fibroblast growth factor (bFGF) mRNA (Wen et al, 1996; Merin et al, 2008).

Levodopa-Carbidopa

The combination levodopa-carbidopa is commonly used to treat Parkinson's disease. The use of levodopa-carbidopa in ocular diseases had been investigated on patients suffering from age-related macular degeneration and albinism (Brilliant et al, 2016). The combination levodopa-carbidopa is thought to have a protective effect on the retinal pigment epithelium (RPE) where a G-protein-coupled receptor (GPR143) is expressed. GPR143 is activated by L-dopa and controls neurotrophic factors release by the RPE (De Filippo et al, 2017). Through the activation of GPR143, levodopa-carbidopa is thought to slow down the progression of RP.

Fluocinolone acetonide

Fluocinolone acetonide is a synthetic corticosteroid delivered through a non-erodible implant (Ghasemi Falavarjani, 2009; Sarao et al, 2014). The use of fluocinolone acetonide is related to its corticosteroid nature which allows in reducing microglial-related neuroinflammation and protecting photoreceptors (Glybina et al, 2010).

Valproic Acid

Valproic acid is used to treat epilepsy and mood disorders, but this drug accounts for a multitude of therapeutic effects (Peterson and Naunton, 2005; Dragunow et al, 2006). In 2011, Clemson et al, carried out a pilot study to evaluate the short-term efficacy of valproic acid in RP patients, obtaining improvement in VA in 9 out of 13 eyes (Clemson et al,2011; Todd and Zelinka, 2017). Valproic acid acts by upregulating the expression of growth

factors by inhibiting a histone deacetylase (Chiu et al, 2013). Valproic acid is currently being studied to treat autosomal dominant RP (Birch et al, 2018).

QLT091001

QLT091001 (9-cis-retinyl acetate) is an oral synthetic retinoid being studied to treat RP caused by two mutations (i) the RPE65 and (ii) the LRAT mutation (Koenekoop et al, 2014). Mutations in RPE65 and LRAT result in absence of 11-cis-retinal, fundamental in vision cycle. QLT091001 is preferred to 11-cis-retinal due its higher stability (Maeda et al, 2012; Scholl et al, 2015).

scAAV8/RLBP1

scAAv8/RLBP1 is a self-complementary vector able to deliver the RLPB1 gene promoter[38] (Choi et al, 2015; MacLachlan et al, 2018). The treatment with scAAv8/RLBP1is addressed to x-linked RP caused by the mutation RLBP1.

AAV-RPGR

AVV-RPGR is a viral vector for the treatment of RP caused by a mutation in the RPGR gene which is a GTPase regulator[39] (Fischer et al, 2017). The RPGR mutation causes X-linked RP.

[38] Novartis. Nonclinical safety evaluation of scAAV8-RLBP1 (CPK850) for treatment of RLBP1 retinitis pigmentosa [Internet]. © 2018 Novartis AG [cited March 20, 2019]. Available from URL: https://oak.novartis.com/35113/

[39] MeiraGTx. MeiraGTx Announces AAV-RPGR Granted Fast Track Designation by U.S. FDA for Treatment of X-Linked Retinitis Pigmentosa Due to RPGR Deficiency [Internet]. London (UK). © 2019 MeiraGTx Limited [cited March 22, 2019]. Available from URL: https://investors.meiragtx.com/news-releases/news-release-details/meiragtx-announces-aav-rpgr-granted-fast-track-designation-us/

Autologous bone marrow-derived mononuclear stem cells

Autologous bone marrow-derived mononuclear stem cells (BMMSCs) are cellular fractions isolated from human adult bone marrow. These stem cells include hematopoietic lineage cells, progenitor cells and mesenchymal stromal cells (Cuende et al, 2012). BMMSCs are under evaluation to treat eye-related diseases such as RP, but also dry age-related macular degeneration and ischemic retinopathy (Siqueira, 2012). A phase II clinical trial carried by Siqueira et al, showed an improvement in microperimetry in the enrolled patients associated with an improvement in patients' QoL (Siquira et al, 2015).

Bone marrow-derived mesenchymal stem cells

Pluripotent autologous bone marrow-derived mesenchymal stem cells are able to differentiate into different phenotypes (Caplan, 2009). Animal studies showed that autologous bone marrow stem cells protect photoreceptor cells (Cislo-Pakuluk and Marycz, 2017) by secreting growth factors, such as brain-derived neurotrophic factor (BDNF), bFGF and CTNF, which is thought to increase photoreceptors survival (Wang et al, 2010).

Human Retinal Progenitor Cells

Retinal Progenitor stem cells are immature cells which have already initiated the differentiation process to become retinal cells, such as photoreceptors[40]. Retinal progenitor stem cells act by integrating into the diseased retinal and then differentiating into retinal cells (Canola et al, 2007). The hypothesised mechanism of action of retinal progenitor stem

[40] jCyte. Retinal Progenitor Cells [Internet]. Newport Beach (CA). © 2019 jCyte [cited March 22, 2019]. Available from URL: http://jcyte.com/jcell-therapy/retinal-progenitor-cells/

cells is the release of trophic factors and the delaying of blindness by increasing the survival of cone cells[41]

NT-501

Encapsulate cell therapy NT-501 is constituted by genetically modified human cells which secrete ciliary neurotrophic factor (CNTF) (Sieving et al, 2006). CNTF is a nerve growth factor which accounts for a wide range of neuroprotective effects, including protection and rescuing of dying photoreceptors (Do Rhee et al, 2013). NT-501 is delivered in the retina, where it promotes the production of CNTF.

3.4.2 Other products in development

Nine more medicinal products are currently in development to treat RP, AAV2/5-hPDE6B, RST-001, GS030, rAAV2tYF-GRK1-RPGR, AAV2/5-hRKp.RPGR, Human Primary Retinal Pigment Epithelial, Autologous Bone Marrow-Derived CD34+, CD133+ and CD271+ and Cyclosporine. The MPs listed were excluded from the prospective treatment protocols due to the early stage of their development. At the time of this study, no clinical trials assessing the efficacy of AAV2/5-hPDE6B, RST-001, GS030, rAAV2tYF-GRK1-RPGR, AAV2/5-hRKp.RPGR, Human Primary Retinal Pigment Epithelial, Autologous Bone Marrow-Derived CD34+, CD133+ and CD271+ and Cyclosporine were carried out, leading to their exclusion. A summary of the characteristics of these products was considered important to understand which molecules are being studied to treat RP (Table 3.21).

[41] National Institutes of Health. Use of Retinal Progenitor Cells for the Treatment of Retinitis Pigmentosa [Internet]. Bethesda MD. Last updated October 26, 2018 [cited March 22, 2019]. Available from URL: https://ncats.nih.gov/trnd/projects/complete/progenitor-cells-treatment-retinitis-pigmentosa

AAV2/5-hPDE6B

AVV2/5-hPDE6B is a viral vector for the treatment of RP caused by a mutation in the PDE6B gene. PDE6B is an indirect regulator of apoptosis, regulating the cytoplasmic level of cyclic guanosine monophosphate (cGMP).

A dysfunction in the PDE6B gene leads to an increase of cGMP, creating the hyperpolarisation of the rod's membrane, a high concentration of cGMP and apoptosis (Cheng et al, 2016). The PDE6B is an autosomal recessive mutation (Ali et al, 2011; Kim et al, 2012; Tatour et al, 2019).

RST-001

RST-001is a viral vector (AVV2) delivering the channelrhodopsin-2. Channelrhodopsin-2 is an optical neuromodulator, able to bind with the retinal chromophore forming a directly light-gated cation channel (Bi et al, 2006; Ivanova et al, 2010). Through the use of RST-001 vision can be restored by introducing new photosensors in RGCs. RST-001 is potentially suitable to be used in all mutations causing RP[42]

GS030

GS030 (AAV2.7m8-ChrimsonR-tdTomato) is a gene therapy MP composed by two components. The gene therapy is represented by a viral vector (AVV2.7m8) which delivers photoactivatable channel-rhodopsin protein into RGCs. Biomimetic goggles are present, to stimulate the engineered retinal cells and mimicking the normal retinal activity[43].

[42] Allergan. A Novel Eye Care Development Program for Potential Treatment of Retinal Disease [Internet]. Dublin, Ireland. ©Allergan2019 [cited April 30, 2019]. Available from URL: file:///Users/Marta/Downloads/Retrosense%20Acquisition%20Investor%20Deck%209-5-16%20FINAL%20(2).PDF

[43] GenSight Biologics S.A. GS030 for Retinitis Pigmentosa: Product Overview [Internet]. Paris (France). © 2019 Gensight Biologics [cited Apr 30, 2019]. Available from URL: https://www.gensight-biologics.com/product/gs030-for-retinitis-pigmentosa/

rAAV2tYF-GRK1-RPGR

rAAV2tYF-GRK1-RPGR is a viral vector expressing the gene RPGR-ORF15. This viral vector addresses a mutation causing X-linked RP (DiCarlo et al, 2018).

AAV2/5-hRKp.RPGR

AAV2/5-hRKp.RPGR is a gene therapy medicinal product able to deliver the gene RPGR-ORF15, causing X-linked RP[44]

Human Primary Retinal Pigment Epithelium

Retinal pigment epithelium (RPE) is a layer of cells which supports metabolic and cellular processes of retinal photoreceptors, which undergo degeneration in patients suffering from RP (Strauss, 2005; Salero et al, 2012). Subretinal transplantation of RPE stem cells is currently under evaluation to repair the degenerating RPE by substituting damaged cells (Canto-Soler et al, 2016).

Autologous Bone Marrow-Derived CD34+, CD133+, and CD271+

Autologous Bone Marrow-Derived CD34+, CD133+, and CD271+ are mesenchymal stem cells expressing on their membrane markers CD34, CD133, and CD271. These three specific cell types were selected by the researchers due to the diverse potentialities to differentiate into specific functional cell types to regenerate damaged retinal tissue (NCT02709876).

[44] MeiraGTx. Efficacy and safety of AAV2/5-hRKp.RPGR to treat X-linked retinitis pigmentosa [Internet]. London (UK): © 2018 MeiraGTx Limited. All Rights Reserved [cited Apr 30, 2019]. Available from URL: https://meiragtx.com/wp-content/uploads/2018/08/ESGCT-2017-RPGR-poster1-1.pdf

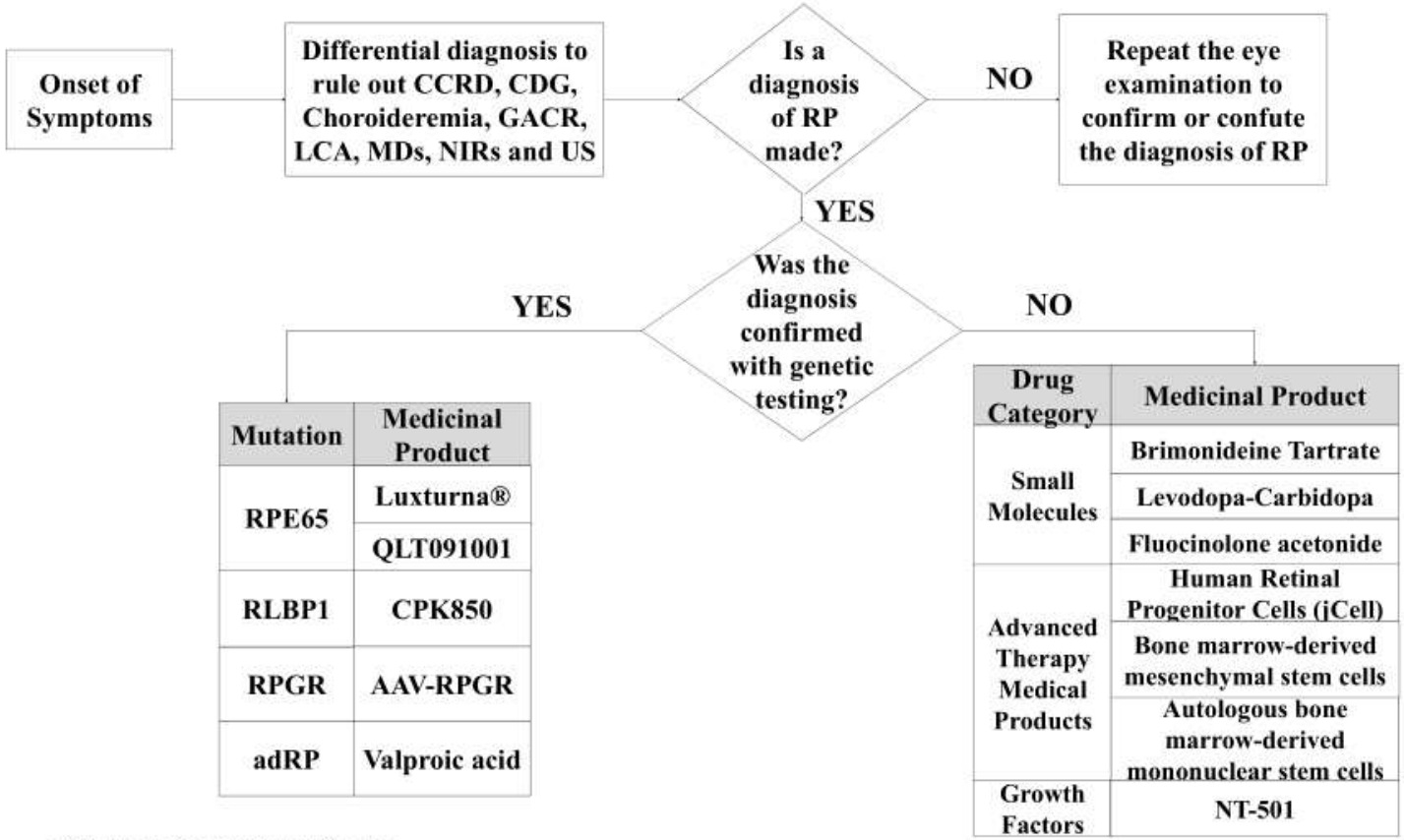


Figure 3.7 Proposed prospective treatment protocol with relevant medicines considered suitable to treat retinitis pigmentosa

CD34+ bone marrow stem cells

CD34+ bone marrow stem cells are the hematopoietic fraction product that underwent purification using a monoclonal antibody to CD34 (Fung et al, 2017). CD34+ stem cells can repair the damaged retina and retinal vasculature by homing in the retina after being injected (Park et al, 2017). A phase I clinical trial was carried out to evaluate safety of stem cells in several retinal diseases among which RP was present.

Table 3.21 Summary of medicinal products currently under evaluation to treat retinitis pigmentosa (N=9)

Active substance	Clinical trial ID	Phase	Route of Administration	Sponsor
AAV2/5-hPDE6B	2016-001429-16 and NCT03328130	I/II	Subretinal injection	Horama S.A.
RST-001	NCT02556736	I/II	Intravitreal injection	Allergan
GS030	2017-002204-27 and NCT03326336	I/II	Intravitreal injection (gene therapy) and repeated light stimulation (stimulating glasses)	GenSight Biologics
rAAV2tYF-GRK1-RPGR	NCT03316560	I/II	Subretinal injection	Applied Genetic Technologies Corp
AAV2/5-hRKp.RPGR	NCT03252847	I/II	Subretinal injection	MeiraGTx UK II Ltd
Human Primary Retinal Pigment Epithelial	NCT03566147	I	Subretinal transplantation	Eyecure Therapeutics Inc.
Autologous Bone Marrow-Derived CD34+, CD133+, and CD271+	NCT02709876	I/II	Intravitreal injection	Stem Cells Arabia
CD34+ bone marrow stem cells intravitreal	NCT01736059	I	Intravitreal injection	University of California, Davis
Cyclosporine	NCT00433277	N/A	Topical	Semmelweis University

Cyclosporine A

Cyclosporine A is an immunosuppressive agent which acts by inhibiting the development of cell-mediated reactions. Due to its mechanism of action, cyclosporine A is a treatment for several autoimmune diseases (e.g psoriasis or rheumatoid arthritis) and in cases of organ transplant. Cyclosporine A was evaluated following the thought that RP has an autoimmune pathomechanism.

3.5 Clinical Development Programs

Ongoing CDPs of prospective products and CAPs to treat LHON and RP were analysed.

3.5.1 Clinical development programs of centrally authorised products

Two medicinal products are currently authorised within the EU to treat LHON and RP. More information on CDPs submitted to support the application of CAPs have been reported in the following sections.

3.5.1.1 Clinical development program of Raxone

Raxone (idebenone) was issued a marketing authorisation under exceptional circumstances (Article 14(8) of Regulation 726/2004). The application submitted for the approval of Raxone, was a hybrid application, which is defined in Article 10(3) of Directive No 2001/83/EC. A hybrid application is submitted when a MP does not meet the definition of generic medicinal product or when bioequivalence cannot be demonstrated through bioavailability studies. Due to changes in the active substance(s), therapeutic indications strength, dosage form or route of administration of the concerned product when compared to a reference product, the results of appropriate pre-clinical trials are deemed necessary to be provided. The reference product used to issue the

marketing authorisation for Raxone was Mnesis 45 mg tablets (Takeda Italia Farmaceutici S.p.A).

The European Commission, on 8th September 2015, granted a marketing authorisation under exceptional circumstances for Raxone. A marketing authorisation under exceptional circumstances is granted when data on safety and efficacy of a medicinal product cannot be provided by the applicants. According to the EMA, there are three main reasons why data cannot be provided (i) the indication is too rare, (ii) the collection of further data to support an application is considered unethical, (iii) comprehensive information cannot be provided in the current state of scientific knowledge[45].

The application of Raxone was supported by quality, non-clinical and clinical data. Non-clinical data was partially retrieved from the non-CDP of the reference product Mnesis and published scientific literature. Data retrieved from Mnesis non-CDP was related to (i) secondary pharmacodynamic studies, (ii) safety pharmacology, (iii) pharmacodynamic drug interactions, (iv) carcinogenic properties and (v) local tolerance. Data retrieved from the non-CDP of Mnesis and published scientific literature were related to (i) metabolism, excretion and pharmacokinetics drug interactions and (ii) genotoxicity and reproduction toxicity. Data on pharmacokinetics was retrieved from 4 phase I clinical trials carried out on healthy volunteers, 3 phase II and phase III clinical trials carried out on LHON patients (RHODOS) and Friedreich ataxia (FRDA) patients (MICONOS and IONIA) and Mnesis data.

The CDP supporting the application was composed of a phase II, double-blind, randomised, placebo-controlled clinical trial, investigating safety and efficacy of Raxone (RHODOS), one observational follow-up study (RHODOS-OFU), on expanded access

[45] European Medicines Agency. Pre-authorisation guidance: types of applications and applicants [Online]. London (UK): European Medicines Agency; ©1995-2019 [cited March 25, 2019]. Available from URL: https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/pre-authorisation-guidance

program (EAP), one natural history case record study and 4 phase I clinical trials on healthy volunteers. Additional safety data on Raxone was retrieved from 3 phase II and phase III double-blind randomised, placebo-controlled clinical trials carried out on FRDA patients. More information on the CDP of Raxone can be retrieved from Appendix III.

3.5.1.2 Clinical development program of Luxturna

Luxturna (voretigene neparvovec) was issued a full marketing authorisation (Article 8(3) of Directive 2001/83). A full marketing authorisation (also referred as complete and independent application) should include the results of (i) physico-chemical, biological or microbiological (pharmaceutical tests), (ii) toxicological and pharmacological tests (pre-clinical tests) and (iii) clinical trials.

On 22nd November 2018 Luxturna was authorised by the European Commission with the indication for Leber's congenital amaurosis type 2 and RP, inherited retinal dystrophy caused by confirmed biallelic RPE65 mutations.

The CDP supporting the application for Luxturna was composed of 1 phase I clinical trial, 1 phase II clinical trial, 1 phase III clinical trial, 1 natural history study and 1 clinical trial to validate the mobility testing tool validated by the company. The main study presented was a phase III, open-label, randomised to evaluate safety and efficacy of Luxturna in patients suffering from Leber's congenital amaurosis (AAV2-hRPE65v2-301/302). Luxturna was approved with the indication for "inherited retinal dystrophy caused by confirmed biallelic RPE65 mutations" due to the similarity between Leber's congenital amaurosis type II and RP caused by biallelic RPE65 mutation. More information on the CDP of Luxturna can be retrieved in Appendix III.

3.5.2 Clinical development programs of selected prospective products

Ongoing clinical trials of MPs included in the prospective treatment protocols have been described in table 3.22 (LHON) and table 3.23 (RP).

Table 3.22 Ongoing clinical trials of medicinal products selected as prospective treatment for Leber Hereditary Optic Neuropathy

Medicinal product	Clinical Trial number	Clinical Trial Description
GS010 ($rAAV_2$-ND_4)	NCT01267422	SC, proof of concept, OL, SD, S and E study of $rAAV_2$-ND_4 in patients ≥8yo, affected from LHON due to m.11778G>A
	2013-001405-90	SC, phase I/II, NR, escalating dose, OL, S and E study of GS010 in patients of ≥18 yo, affected from LHON due to m.11778G>A
	NCT02064569	Phase I/II, OL, DE, S and T study of GS010 in patients of ≥18yo, affected from LHON due to m.11778G>A
	NCT03153293	MC, phase II/III, prospective, OL, S and E study of GS010 in patients of ≥10yo, affected from LHON due to m.11778G>A
	NCT02652767 and 2015-001265-11	MC, phase III, R, double-masked, sham-controlled, pivotal, E study of GS010 in patients of ≥12yo affected from LHON for less than 6 months due to m.11778G>A
	NCT02652780 and 2015-001266-26	MC, phase III, R, double-masked, sham-controlled, pivotal, E study of GS010 in patients of ≥12yo affected from LHON for more than 6 months due to m.11778G>A
	NCT03406104 and 2017-002153-11	Long-term follow-up of LHON subjects treated with GS010 Ocular Gene Therapy in the NCT02652767 or NCT02652780 Phase III clinical trials
	NCT03293524 and 2017-002187-40	MC, phase III, R, double-masked, placebo-controlled, E and S study of GS010 in patients ≥12yo affected from LHON due to m.11778G>A for Up to One Year
Cysteamine Bitartrate	NCT02023866	OL, phase II, DE, S, E, T, PK and PD of cysteamine bitartrate in patients 6 to 17 yo affected from inherited mitochondrial disease
	NCT02473445	Long-term extension, OL study to assess the S, T and E of cysteamine bitartrate delayed-release capsules in patients 6 to 17yo with inherited mitochondrial diseases who previously enrolled into study NCT02023866
Bone marrow-derived mesenchymal stem cells	NCT03011541	SC, OL, NR, E study in patients of ≥18yo affected from optic nerve or retinal conditions including LHON

DE: Dose Escalation; E: Efficacy; LHON: Leber Hereditary Optic Neuropathy; MC: Multi Centre; NR: non/randomised; OL: Open Label; PM: Patient Masked; R: randomised; S: safety; SC: Single Centre; SD: single dose; T: Tolerability; yo: years/old

Clinical trials have been described according to the study phase and in chronological order.

GS010 was the most studied product to treat LHON. Eight clinical trials investigating safety and efficacy of GS010 were carried out between 2013 and 2018. Four out of 8 clinical trials were retrieved from both the EudraCT database and clinicaltrials.gov, being carried out both in the EU and US.

The most common clinical trial design adopted in LHON trials was the open label design, observed in 7 out of 11 clinical trials evaluated for MPs studied to treat LHON. Three out of 11 clinical trials were randomised, clinical trials. One out of 11 clinical trials was a long-term follow-up.

Stem cells were the most common products studied to treat RP. Ten clinical trials were carried out to evaluate safety and efficacy of stem cells; 4 out of 10 clinical trials were carried out to evaluate autologous bone marrow-derived mononuclear stem cells, 3 out of 10 clinical trials were carried out to evaluate safety and efficacy of bone marrow-derived mesenchymal stem cells and human retinal progenitor cells.

The most common clinical trial design adopted in RP trials was the open label design, observed in 16 out of 34 clinical trials. Twelve out of 34 clinical trials were randomised clinical trials and 9 out of 34 were non-randomised clinical trials.

Comprehensive ongoing CDPs for each MP can be found in Appendix IV.

Table 3.23 Ongoing clinical trials of medicinal products selected as prospective treatment for Retinitis Pigmentosa

Medicinal product	Clinical Trial ID	Clinical Trial Description
Brimonidine Tartrate	NCT00661479	MC, exploratory, phase I/II, NR, single injection, ascending-dose S, E study to evaluate Brimonidine intravitreal implant in one eye of patients of ≥18 yo
	2010-019079-32	MC, phase II, NR, PM S, extension study in patients of ≥18yo previously enrolled into study NCT00661479
Levodopa-Carbidopa	NCT02837640	SC, phase II, OL, E study of levodopa-carbidopa tablets in patients of ≥10 yo
Fluocinolone acetonide	2016-002523-28	SC, phase II, pilot, NR, S and E study in patients of ≥18yo affected from RP
Valproic acid	NCT01233609	MC, phase II, R, placebo-controlled, E study in patients ≥18yo affected from autosomal dominant RP
	NCT01399515	SC, phase II, prospective, NR, S and E study in patients ≥18 yo affected from RP
QLT091001	NCT01543906	MC, phase I, OL, proof of concept, S and E study in patients of ≥12yo affected from autosomal dominant RP caused by mutation in RPE65
	NCT01521793 And 2011-004214-42	MC, phase I, OL, S and E extension study of NCT01543906 in patients of ≥5yo affected from autosomal dominant RP caused by mutation in RPE65 or LRAT
	NCT01014052	MC, phase I, proof of concept, S study in patients of ≥18yo affected from autosomal dominant RP caused by mutation in RPE65 or LRAT
	2013-005393-22	MC, phase III, R, double-blind, placebo-controlled, S, E, PK, dose-response study in patients ≥2yo affected from autosomal dominant RP caused by mutation in RPE65 or LRAT
scAAV8/RLBP1	NCT03374657	SC, phase I/II, OL, single-ascending dose, S, T and E in patients of ≥18yo affected from RP due to mutation RLBP1
AVV_8-RPGR	NCT03116113 and 2016-003852-60	MC, phase I (DE), phase II/III (dose-expansion), R, non-masked, S and E study in patients of ≥10yo affected from RP due to mutation RPGR
Autologous bone marrow-derived mononuclear stem cells	NCT01068561	SC, phase I, OL, NR, S study in patients of ≥18yo affected from RP
	NCT01914913	SC, phase I, OL, S and E study in patients of ≥18yo affected from RP
	NCT02280135	SC, phase I, R, parallel, double-blind, placebo-controlled, S study in patients of ≥18yo affected from RP
	NCT01560715	SC, phase II, OL, NR, short-term S and E study in patients of ≥18yo affected from RP
Bone marrow-derived mesenchymal stem cells	NCT01531348	SC, phase I, OL, feasibility and S study in patients of ≥18yo affected from RP
	NCT01920867	SC, OL, NR, E study in patients of ≥18yo affected from optic nerve or retinal conditions including RP
	NCT03011541	SC, OL, NR, E study in patients of ≥18yo affected from optic nerve or retinal conditions including RP

Medicinal product	Clinical Trial ID	Clinical Trial Description
Human Retinal Progenitor Cells	NCT02320812	MC, phase I/II, OL, SD, T and S study in patients of ≥18yo affected from RP
	NCT02464436	MC, phase I/II, OL, DE, T and S study in patients of ≥18yo affected from RP
	NCT03073733	MC, phase II, prospective, R, double-masked, S and E study in patients of ≥18yo affected from RP
NT-501	NCT01530659	SC, phase II, R, double-masked, sham-controlled, S and E study in patients ≥18yo affected from RP
	NCT00447993	MC, phase II/III, R, double-masked, E study in patients of ≥18yo affected from RP
	NCT00447980	MC, phase II/III, R, double-masked, S and E study in patients of ≥18yo affected from RP

DE: Dose Escalation; E: Efficacy; LHON: Leber Hereditary Optic Neuropathy; MC: Multi Centre; NR: non/randomised; OL: Open Label; PM: Patient Masked; R: randomised; S: safety; SC: Single Centre; SD: single dose; T: Tolerability; yo: years/old

3.5.3 Comparison of clinical development programs

A comparison of CDPs of MPs suitable for the treatment of LHON and RP is presented in this section. In table 3.24 a comparison of the CDPs of Raxone and GS010 is presented. An authorised MP and a prospective MP were selected to be compared based on completeness of CDPs. The CDP of Raxone was retrieved from the EPAR and trials registered in EudraCT. The CDP of GS010 was retrieved from clinical trials registered on EudraCT and USNLM database of clinical trials.

The CDP supporting the application of Raxone consisted of a phase II clinical trial and a follow-up clinical trial. Results from an EAP and a Natural History Case Record Survey were submitted as additional data. Pharmacokinetics was investigated in 4 phase I clinical trials in healthy volunteers. Eighty-five patients affected from m.11778G>A, m.14484T>C, m.3460G>A were enrolled in the RHODOS study. Sixty patients previously enrolled in the RHODOS study participated in the 30-month follow-up RHODOS-OFU.

The CDP of GS010 consisted of 5 clinical trials; 1 phase I/II, 1 follow-up clinical trial and 3 phase III clinical trials. A total of 182 patients affected from LHON due to m.11778G>A were enrolled in clinical trials part of the CDP of GS010. Seventy-four patients previously enrolled in NCT02652767 and NCT02652780 participated to the 5-year follow-up study NCT03406104.

A proof of concept study (NCT01267422) and a phase II/III (NCT03153293) were retrieved from clinicaltrials.gov, sponsored by Huazhong University of Science and Technology. In both clinical trials the primary endpoint was the evaluation of change in BCVA from baseline. Safety endpoints were evaluated as secondary endpoints. No studies in healthy volunteers were carried out.

Comparison of CDPs was based on phase II and phase III clinical trials (Table. 3.24).

Table 3.24 Comparison of clinical development programs of Raxone and GS010

	Raxone (Idebenone) Santhera Pharmaceuticals	**GS010 (rAAV2/2-ND4) GenSight Biologics**
Phase II	**SNT-II-003** - R, DB, placebo controlled, S, T and E study - Administration: one arm 900mg idebenone per day; one arm placebo - N: 84 patients affected from LHON - PE: BCVA	
	SNT-II-003-OFU - Prospective cohort, follow-up of SNT-II-003 after 30 months off treatment, single-visit study - N: 60 patients affected from LHON - Change in BCVA	
Phase III		**GS-LHON-CLIN-03A** - R, DB, Sham-Controlled, E study - Administration of single dose of GS010 (90µL) in one random eye and placebo in the other eye - N: 36 patients affected from mutation m.11778G>A - PE: change in ETDRS VA utilizing derived LogMAR acuity after 48 weeks from injection
		GS-LHON-CLIN-03B - R, DB, Sham-Controlled, E study - Administration of single dose of GS010 (90µL) in one random eye and placebo in the other eye - N: 37 patients affected from mutation m.11778G>A - PE: change in ETDRS VA utilizing derived LogMAR acuity after 48 weeks from injection
		GS-LHON-CLIN-05 - R, DB, parallel-assignment, S and E study - Administration of GS010 (dose 90µL) or placebo (dose 90 µL) - N: 90 patients affected from mutation m.11778G>A - PE: BCVA 1-year post-treatment
		GS-LHON-CLIN-06 - Prospective cohort, long-term follow-up of GS-LHON-CLIN-03A/B up to 5 years post-treatment - N: 74 patients affected from mutation m.11778G>A PE: Number of adverse events and serious adverse events

BCVA: best-corrected visual acuity; DB: double-blind; E: efficacy; ETDRS: Early Treatment Diabetic Retinopathy Study N: number of enrolled patients; R: randomised; S: safety, T: tolerability

In table 3.25 a comparison of the CDPs of MPs studied to treat mutation RPE65 is presented. An authorised MP and a prospective MP were selected to be compared based on completeness of CDPs. The CDP of Luxturna was retrieved from the EPAR and trials registered in EudraCT. The CDP of QLT091001 was retrieved from clinical trials registered on EudraCT and USNLM database of clinical trials.

The CDP supporting the application of Luxturna consisted of a one phase I study, one phase II study, one phase III study, a natural history study and a study to validate the mobility testing tool developed by the company. Traditional pharmacokinetics tests were not deemed necessary, considering the subretinal route of administration of Luxturna which considerably reduces the risk of blood dissemination. The only pharmacokinetic study carried out was to test the route of elimination of Luxturna. Thirty-one patients were enrolled in clinical trial AAV2-hRPE65v2-301 and randomised in a 2:1 ratio.

The CDP of QLT091001 is composed of 4 clinical trials, 3 phase I and 1 phase 3. Phase I clinical trials have been performed to evaluate safety and efficacy QLT091001 in patients suffering from RP or Leber Congenital Amaurosis caused by mutation RPE65 or LRAT. In the three phase I clinical trials, the duration of the study was of 7 days. QLT901001 was initially tested in a 7-day course and, following positive results, QLT091001 was tested up to 3 additional courses of oral QLT091001 administered once daily for 7 days. In all 4 clinical trials, the primary endpoint evaluated was the change in VF from baseline in 1-year time.

More information on CDPs can be retrieved in Appendix V

Table 3.25 Comparison of clinical development programs of Luxturna and QLT091001

	Luxturna **(voretigene neparvovec)** **Spark Therapeutics**	**QLT091001** **(zuretinol acetate)** **QLT Inc.**
Phase III	**AAV2-hRPE65v2-301** - R, open-label, parallel assignment, S and E study - Administration: subretinal administration of 1.5^{11} vector genomes per eye in a volume of 0.3mL in both eyes - N: 31 patients affected from mutation RPE65 - PE: changes in functional vision using the multi-luminance mobility testing	**RETIRD04** - R, cross-over, DB, placebo-controlled, E, PK, dose-response study - Administration: oral administration of a solution containing 20mg/ml of QLT091001 - N: 48 patients affected from mutation RPE65 or LRAT - PE: Percentage of VF changed from baseline to 12 months in the treated eye

DB: double-blind; E: efficacy; N: number of enrolled patients; PE: primary endpoint; PK: pharmacokinetics; R: Randomised; S: safety; VF: visual field

CDPs of somatic therapy medicinal products were compared and results are presented in table 3.26. Clinical trials carried out for Human Retinal Progenitor Cells (HRPCs) and autologous bone marrow mononuclear stem cells (BMMSCs) were retrieved from the database clinicaltrials.gov. On the database EudraCT no clinical trials carried out to evaluate somatic therapy products were found.

The current CDP of jCell consists of a phase I and phase II clinical trials. Phase I clinical trial (JC-01) evaluated safety and tolerability of jCell in 28 patients affected from RP. JC-02 was performed on 84 patients affected from RP and the primary efficacy endpoint evaluated was the best-corrected visual acuity (BCVA) measure with an ETDRS chart. Another clinical trial on HRPCs was retrieved from clinicaltrials.gov, sponsored by ReNeuron Limited. This was a phase I/II clinical trial evaluating the safety of HRPCs.

The current CDP of BMMSCs consists of a phase I and phase II clinical trials. Phase I clinical trial (CPRS) evaluated the short-term safety of a single injection of BMMSCs in 5 patients affected from RP. A phase II clinical trial was carried out to assess short-term efficacy other than safety in a wider population of 50 patients affected from RP to evaluate changes in VA. Another phase I clinical trial on BMMSCs was retrieved from clinicaltrials.gov. More information is available on Appendix V.

Two clinical trials on mesenchymal stem cells have been registered on clinicaltrials.gov (SCOTS and SCOTS 2). The aim of both SCOTS and SCOTS2 was to evaluate the efficacy of bone marrow derived stem cells in patients affected from optic nerve and retinal diseases. The BCVA measured with Snellen Eye Chart and the ETDRS was the efficacy measure used in both clinical trials. More information is available on Appendix V.

Table 3.26 Comparison of initial clinical development programs of jCell and Autologous bone marrow mononuclear stem cells

	jCell **Human Retinal Progenitor Cells** **jCyte, Inc**	**Autologous bone marrow mononuclear stem cells** **University of Sao Paulo**
Phase II	**JC-02** - R, DB, sham-controlled, S and E study - Administration: single intravitreal injection in two different doses (3.0 x 106 and 6.0 x 106) and a mock injection - N: 84 patients affected from RP - PE: BCVA measured with an ETDRS	**NCT01560715** - NR, open-label, S and E study - Administration one intravitreal injection of a 0.1 ml cell suspension containing around 10x106 - N: 50 patients affected RP - PE: Change in VA measured with an ETDRS

BCVA: best-corrected visual acuity; DB: double-blind; E: efficacy; ETDRS: Early Treatment Diabetic Retinopathy Study ; N: number of enrolled patients; NR: non-randomised; PE: primary endpoint; PK: pharmacokinetics; R: Randomised; S: safety; VA: visual acuity

3.6 Regulatory Pathways

Six regulatory pathways are available within the EU to speed the process to authorise OMPs. The available regulatory pathways are shown in table 3.27.

Table 3.27 Overview of regulatory pathways available within the European Union

Regulatory Pathway	Description
Scientific advice and Protocol assistance	To ensure an appropriate CDP, scientific advice/protocol assistance can be requested to the Scientific Advice Working Party (SAWP) during each phase of the development of a MP concerning quality, nonclinical and/or clinical issues. Protocol assistance is specific for OMPs
PRIME	The PRIME (PRIority MEdicines) scheme was launched in 2016 to help patients in benefitting from a treatment when not available. The PRIME can be requested to the CHMP and Committee for Advanced Therapies (CAT) during the early phase of a drug development to address the limited available resources to generate data necessary to complete an application. PRIME is built on scientific advice and accelerated assessment, enabling the assessment of a marketing authorisation application through an accelerated assessment.
Accelerated assessment	The accelerated assessment can be requested during a late phase of a drug development (when a marketing authorisation application is being assessed) to the CHMP and enables in the reduction of the time for assessing a marketing authorisation application for centralised procedures from 210 days to 150 days. To have access to accelerated assessment, the sponsor should justify the "major health interest" the medicinal product will target and demonstrate its therapeutic innovation. The medicinal product should show that it is either the first available treatment for a certain disease or that its therapeutic effect is superior to the existing treatment.
Adaptive Pathways	Adaptive pathways are based on existing pathways to ensure a faster access to medicines by patients and increase the positive impact of a new MP on public health. Adaptive pathways can be requested during each phase of the development to different committees which follow and advice the developer during each of the development phase of a MPs
Conditional marketing authorisation	A conditional marketing authorisation is granted by the CHMP during a late phase of a drug development (marketing authorisation application). Through a conditional marketing authorisation, a MP (especially for unmet medical needs) can be placed on the market despite the absence of comprehensive data related to its use and will be valid for one year

Regulatory Pathway	Description
Marketing authorisation under exception circumstances	A marketing authorisation under exceptional circumstances is granted by the CHMP. For the grant of a marketing authorisation under exceptional circumstances, data on the efficacy and safety under normal conditions of use cannot be provided by the applicant due to, for example, the rarity of a condition. A marketing authorisation under exceptional circumstances allows on the market a medicinal product addressing an unmet medical need, which is chronic, life threatening or for which a satisfactory treatment is not available, but comprehensive data on the efficacy and safety under normal conditions of use cannot be provided by the applicant.

Protocol assistance was used before marketing Raxone and Luxturna. The request of protocol assistance for Raxone was performed in November 2009 and was related to clinical aspects of the development. Protocol assistance for Luxturna was requested in July 2013 and December 2015, related to the clinical design of clinical trial NCT00999609.

Both Raxone and Luxturna were marketed as OMPs (Table 3.28).

Table 3.28 Overview of the orphan designation of authorised products for Leber Hereditary Optic Neuropathy and Retinitis Pigmentosa (N=2)

Medicinal product	Indication	Number of clinical trials carried out before the designation	Orphan designation date
Raxone	Treatment of Leber's hereditary optic neuropathy	0	15 February 2007
Luxturna	Treatment of retinitis pigmentosa	4	28 July 2015

Through the orphan designations, both Raxone and Luxturna obtained protocol assistance, facilitating the process for the product to reach the market. Raxone was marketed in 2015 after a marketing authorisation withdrawal in 2011 because of a negative opinion of the CHMP due to non-met primary endpoints in the principal clinical trial, RHODOS, and non-characterised mechanism of action.

One out of 3 MPs, GS010, selected as part of the prospective protocol for LHON is currently designated as OMP (Table 3.29). At the moment of the designation no clinical trials were started to evaluate the safety and efficacy of GS010, which was only evaluated in animal models.

Table 3.29 Overview of medicinal products issued with orphan designation for Leber Hereditary Optic Neuropathy (N=1)

Medicine name	Date of orphan designation	Expected mechanism of action	Drug Category
GS010	13 May 2011	Expected to deliver the gene for an enzyme called 'NADH dehydrogenase 4' in patients affected from LHON due to mutation 11778G>A	Gene therapy

From the Register of designated Orphan Medicinal Products, 26 orphan designated MPs with the indication for RP were retrieved. Three out of 26 were selected as part of prospective treatment protocols and were analysed.

Table 3.30 Overview of medicinal products issued with orphan designation for Retinitis Pigmentosa (N=3)

Medicine name	Date of orphan designation	Expected mechanism of action	Drug Category
AAV_8-RPGR	22 February 2018	Expected that the virus will carry the RPGR gene into the retinal cells, enabling them to produce the missing RPGR protein, necessary for the normal functioning of retinal cells	Gene therapy
Human Retinal Progenitor Cells	19 June 2013	Expected to develop into mature retinal cells replacing the damaged cells	Somatic Therapy
QLT091001	13 May 2011	Expected to be taken by mouth and converted into 9-cis-retinal in the retina. 9-cis-Retinal is similar to the deficient 11-cis-retinal and is expected to replace it, thus enabling the photoreceptor cells to function properly.	Small Molecule

Three out of 11 MPs selected as part of the prospective protocol for RP are currently designated as OMP (Table 3.30). At the moment of the designation, 1 clinical trial was ongoing for AAV_8-RPGR (NCT03116113), 1 clinical trial was ongoing for QLT91001 (NCT01014052) and 0 clinical trials were started for human retinal progenitor.

Chapter 4
Discussion

4.1 Emerging patterns in LHON and Retinitis Pigmentosa

The number of medicines in development for LHON and RP has increased in recent years, but an unmet medical need for these two rare diseases is still present. To date, one MP is authorised to treat LHON and one MP is authorised to treat RP within the EU. The interest of researchers on medicines to treat LHON and RP is increasing, as shown by the increased number of clinical trials performed during the considered 13-year timeframe. In 2006, at the beginning of the considered timeframe, 1 clinical trial was ongoing for a MP for LHON and no clinical trials were ongoing for MPs for RP and no treatments for LHON and RP were available on the market.

From 2006, the number of explored drug classes has increased (Zhang et al, 2017; Martinez-Fernandez De La Camara et al, 2018; Rodrigues et al, 2018; Theodorou-Kanakari et al, 2018). Small molecules, predominant in 2006, have now been juxtaposed to gene therapy MPs, which have the advantage of targeting specific mutations, increasing the likelihood to reverse the diseases. The number of gene therapy MPs is increasing noticeably, and clinical trials carried out to evaluate safety and efficacy are well-structured. GS010 is currently being evaluated to treat LHON and its CDP to show safety and efficacy is extensive; if Luxturna is taken as an example, the CDP is extensive and clearly shows the safety and efficacy of the medicine. The interest towards somatic therapies is also increasing, but more experience is still required with this drug class, since data in relation to stem cells use in LHON and RP is still limited.

Treatments are not sufficient yet but steps forward are being made. The regulatory pathways reviewed in this study showed the support given by regulatory authorities to companies while developing safe and effective medicines to treat rare diseases, as shown by the protocol assistance given during the development of both Raxone and Luxturna and the marketing authorisation under exceptional circumstances granted for Raxone.

Processes to authorise medicines for rare diseases are becoming smoother due to the help granted at EU level.

During the 13-year-time period considered, trends in the development of medicines to treat LHON and RP were observed.

Increased number of explored drug classes

Before 2006, only one clinical trial was carried out to explore a potential treatment for LHON. The trial was carried out in 2005 and evaluated the effect of curcumin in ameliorating visual outcomes[46]. From 2006 to 2018, the number of clinical trials carried out and the number of drug categories explored for LHON increased. Small molecules and advanced therapy medicinal products (ATMPs) were tested during the considered 13-year time frame and also device near-infrared light-emitting diodes therapy.

In case of RP, the first interventional clinical trial was registered in clinicaltrials.gov in 1984 to evaluate vitamin A and vitamin E as supplemental therapy. According to the data retrieved from EudraCT and USNML database of clinical trials, research was focusing on supplements, in particular vitamins A and E, lutein and docosahexaenoic acid. The first clinical trial studying a growth factor (CNTF) was registered in 2003. From 2006, new drug classes have been explored. The first clinical trial for QLT091001, a small molecule, and the first clinical trial to evaluate autologous bone marrow stem cells, belonging to ATMPs class, were registered in 2009. Research towards growth factors improved, exploring an increased number of products.

[46] US National Library of Medicines. Clinicaltrials.gov [Internet]. A Randomized, Double-blind, Placebo-controlled Trial of Curcumin in Leber's Hereditary Optic Neuropathy (LHON). National Institute of Health, Bethesda, Maryland; last update 26 November 2018 [cited May 11, 2019]. Available from URL: https://clinicaltrials.gov/ct2/show/NCT00528151?cond=lhon&draw=2&rank=19

Advanced therapy medicinal products as new window for treatment

An increased number of ATMPs has been studied during the considered time frame for both LHON and RP. Treatment approaches considered in relation to ATMPs were related to gene and cell-based therapy. In 2006, at the beginning of the considered period, no clinical trials on ATMPs were started for LHON and RP.

GS010 has been the first ATMP with a registered clinical trial to treat LHON in 2011. Since then, more clinical trials have been carried out to assess safety and efficacy of GS010, but also another gene therapy product, scAAV2-P1ND4v2, has been tested in 2014 as a potential treatment for LHON. Another approach considered was the transplantation of stem cells, for which a clinical trial was carried out in 2016. These results show the increased interest generated by ATMPs as possible treatment for LHON. For RP, autologous bone marrow-derived stem cells were tested in a clinical trial in 2009. Since 2009, clinical trials to test 13 ATMPs have been carried out.

The increased interest in gene therapy might be due mainly to two factors (i) limited systemic dissemination of the vector and (ii) limited immune response, avoiding the risk to affect retinal function and limit expression of the therapeutic gene as stated by other authors (Forrester and Xu, 2012; Taylor, 2016; Kumaran et al, 2018; Ratican et al, 2018).

Medicinal products addressing specific mutations

Specific mutations have been addressed more since gene therapy products have been studied. With advanced technology, viral vectors are to date able to deliver specific wild-type copies of the cDNA corresponding to a mutated gene. ATMPs act directly on the source of damage, restoring the physiological conditions. Reviews on treatment in LHON and RP shows the consideration of ATMPs (Yu-Wai-Man et al, 2011; Yu-Wai-Man et al, 2014; Meyerson, 2015; Pilz et al, 2017; Verbakel et al, 2018). In contrast to ATMPs,

small molecules do not usually act directly on the mutation, but on the underlying conditions caused by the mutations.

In LHON, the two gene therapy products GS010 and scAAV2-P1ND4v2 are viral vectors which address the subunit ND_4 of the ETC, affected by the mutation m.11778G>A. Since the mutation m.11778G>A is the most common, affecting about 70% of LHON patients with low rate of spontaneous recovery which accounts for almost 4% of the patients, it is not surprising that there is interest in developing medicines which specifically address this mutation.

Luxturna, the only product authorised for RP, is a viral vector which specifically address the RPE65 mutation. Since the first clinical trial in 2008, other gene-based therapy clinical trials have been started to address specific mutations. Three different gene therapy MPs (AAV-RPGR, AAV2/5-hRKp.RPGR and rAAV2tYF-GRK1-RPGR) are being investigated to treat X-linked RP caused by mutation RPGR. Other mutation-specific products to treat RP in the pipeline are CPK850 (rAAV8-RLBP1) and AAV2/5-hPDE6B which will respectively address the gene RLBP1[47] and PDE6B[48].

Small molecules addressing specific mutations have been studied through time. The cardiolipin stabiliser, elamipretride is a small molecule currently under study to treat the LHON-causing mutation m.11778G>A. Two small molecules are being studied to specifically treat the mutation RPE65 (QLT091001) and autosomal dominant mutations

[47] US National Library of Medicines. Clinicaltrials.gov [Internet]. A First-in-human, Proof of Concept Study of CPK850 in Patients with RLBP1 Retinitis Pigmentosa. National Institute of Health, Bethesda, Maryland; last update 26 November 2018 [cited May 11, 2019]. Available from URL: https://clinicaltrials.gov/ct2/show/NCT03374657

[48] US National Library of Medicines. Clinicaltrials.gov [Internet]. Safety and Efficacy Study in Patients With Retinitis Pigmentosa Due to Mutations in PDE6B Gene. National Institute of Health, Bethesda, Maryland; last update 26 November 2018 [cited May 11, 2019]. Available from URL: https://clinicaltrials.gov/ct2/show/NCT03328130?cond=retinitis+pigmentosa&rank=11

(Valproic acid[49]) in RP (Scholl et al, 2015).

Regulatory pathways for orphan medicinal products

Difficulties associated with carrying out clinical studies for OMPs have been documented (Picavet et al, 2013). Regulatory challenges are associated to clinical challenges, leading both pharmaceutical companies and regulators facing difficult decisions. OMPs, are often used to treat conditions for which no MPs are available on the market or, as in the LHON and RP case, for which few treatment options are available, but an unmet medical need is still present. To date, regulatory pathways pursued by pharmaceutical companies when developing MPs to treat rare diseases are different and can apply to each phase of the development of a MP (Hall and Carlson, 2014).

In the EU, protocol assistance[50] and PRIME[51] are two tools which can apply to the early phase of MPs development. While PRIME can be requested only during the early development stage of a MP to treat an unmet medical need, protocol assistance applies for each phase of a MP development (Sharma et al, 2010). As stated by Elsäßer et al, an early intervention by regulators leads to a pharmaceutical company developing a MP following a pathway which will increase the possibility of obtaining a marketing authorisation through the correct development of a MP (Elsäßer et al, 2014). Following recommendation given by regulators, clinical trials are carried out in line with the most

[49] US National Library of Medicines. Clinicaltrials.gov [Internet]. Trial of Oral Valproic Acid for Retinitis Pigmentosa (VPA). National Institute of Health, Bethesda, Maryland; last update 26 November 2018 [cited May 11, 2019]. Available from URL: https://clinicaltrials.gov/ct2/show/NCT01233609?cond=retinitis+pigmentosa&rank=13

[50] European Medicines Agency. Guidance for Applicants seeking scientific advice and protocol assistance [Internet]. London (UK): European Medicines Agency; c1995-2017 [cited April 15, 2018]. Available from URL: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004089.pdf

[51] European Medicines Agency. PRIME- Priority Medicines [Internet]. London (UK): European Medicines Agency; c1995-2017 [cited April 15, 2018]. Available from URL: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000660.jsp&mid=WC0b01ac05809f8439

recent regulation and the most recent scientific knowledge. The benefits related to the use of protocol assistance during the development of an orphan drug were shown by Hofer et al, who analysed the development of orphan drugs from 2008 to 2013. Hofer et al, evaluated the positive effect of protocol assistance which led to 76% of the considered orphan drugs obtaining a marketing authorisation. This may be considered in line with the results of this study (Hofer et al, 2015). For Raxone and Luxturna protocol assistance was requested while building the CDP, leading both drugs to reach the market. For Raxone®, the marketing authorisation under exceptional circumstances allowed the marketing of a MP for an unmet medical condition.

No other regulatory pathways were used while authorising Raxone and Luxturna. During the review of the regulatory pathways, other suitable regulatory pathways to speed up an authorisation for a MP which addresses an unmet medical need were individuated. According to published literature, a higher number of OMPs have been developed within the EU because of implementation of the available regulatory tools set by the EMA as well as the incentives given to pharmaceutical companies when developing MPs to treat rare conditions (Sharma et al, 2010; Hall and Carlson, 2014).

Considerations on clinical trials

The traditional pathway in drug development, forecasts studies in phase I, followed by studies in phase II and, depending on the product under investigation, studies in phase III. The majority of the products under investigation for LHON and RP followed or are following this traditional pathway.

In phase I clinical trials the main aim was the establishment of safety and toxicity of medicines in humans. The design of choice observed for phase I trials was represented by single arm, open label, non-randomised clinical trials. The most common safety

endpoints studied for LHON and RP was the number of adverse events occurring and serious adverse events, followed by the dose-limiting toxicity.

Phase II and phase III clinical trials are respectively defined as therapeutic exploratory and therapeutic confirmatory clinical trials. The design of choice observed for phase II and phase III clinical trials was represented by parallel assignment, randomised, double blind, clinical trials, where the comparison was performed with a placebo. The number of enrolled patients in phase II and phase III clinical trials did not differ, having almost the same sized clinical trials for both phases. The most common primary endpoints studied were related to efficacy, in particular it was observed that visual-acuity related endpoints were most commonly studied for LHON, but also in RP despite the most commonly studied being VF. This result is in line with the symptoms of LHON, where visual acuity is primarily affected and the symptoms of RP, where visual field is primarily affected.

Endpoints investigated during clinical trials for LHON were in line with EMA visual function endpoints suggested by the scientific advice working party (SAWP)[52]. The SAWP emphasised the study of VA as primary endpoint rather than VF. VA is considered of primary importance for patients, therefore the measurement of BCVA is often recommended. BCVA should be measured in number of letters gained in ETDRS chart with a minimal clinically relevant improvement of 10 letters. VA was extensively studied also for RP, but the most common primary endpoints were VF-related. According to Wickström and Moseley, in slowly progression diseases, such as RP, VF and BCVA are

[52] Jane Moseley (EMA Scientific Advice). Visual Function Endpoints the Regulatory Perspective [Internet]. London (UK): European Medicines Agency. ©1995-2019 [cited May 20, 2019]. Available from URL: https://www.ema.europa.eu/en/documents/presentation/presentation-day-1-visual-function-endpoints-regulatory-perspective_en.pdf

not considered sufficiently sensitive in determining efficacy due to their low sensitivity (Wickström and Moseley, 2017).

A non-traditional pathway to carry out clinical trials was noticed, where clinical trial phases were combined. Phase I/II clinical trials were observed more often than phase II/III clinical trials in both LHON and RP. In phase I/II clinical trials, phase I and phase II clinical trials are combined, leading to a faster development of a drug due to the lower number of patients enrolled (no need to enrolled patients for two different clinical trials) and also shorter time need to answer to the research question associated with the early development phase.

Patients enrolled in clinical trials were affected patients. Healthy volunteers were only enrolled in the 4 phase I clinical trials carried out to evaluate pharmacokinetics and bioavailability of Raxone. For Luxturna, a study to validate the mobility assessment tool was performed in healthy volunteers.

4.2 Limitations

This study is limited to the quality of the data sources used. Documents and databases used as data sources were publicly available. Two clinical trial databases were used to provide a comprehensive picture of MPs in the development phase. EudraCT and USNML database of clinical trials are administered by two different regulatory regions and do not have the same framework for data elements. Differences have been noticed in the classification of MPs which are identified as active substances of chemical origin biological/ biotechnological origin (other than Advanced Therapy IMP (ATIMP)) in EudraCT while in USNML database of clinical trials the active substances were classified as IMPs independently of the nature. The registration of clinical trials was also different. In EudraCT clinical trials are registered as “ongoing” or “concluded” while in

clinicaltrials.gov, ten different definitions of clinical trials were found. In clinicaltrials.gov, clinical trials could be registered as “completed”, “recruiting”, “terminated”, “not yet recruiting”, “completed”, “no longer available”, “active, not recruiting”, “withdrawing”, “unknown” and “enrolling by invitation”. Standardisation of terminology was performed by choosing common and representative terms. Within USNML database of clinical trials, differences in results were retrieved when inserting the keyword “LHON” and “Leber Hereditary Optic Neuropathy”.

The lack of published literature was also a concern due to difficulties in retrieving prior research studies and lack of published results on studies carried out on IMPs studied to treat LHON and RP.

In this study costs of developing MPs to treat LHON and RP and the affordability for patients were not considered. A cost-benefit analysis should be performed to understand how LHON and RP treatments affect both patients and, where relevant, the national health service.

4.3 Recommendations

The main focus of this study was to understand the development of medicines to treat the rare eye diseases LHON and RP. The patterns observed in this study may not necessarily apply to the development trend in other therapeutic areas.

Future work may be focused on other rare diseases affecting the eyes, such as Dominant Optic Atrophy or Leber Congenital Amaurosis. The method can be applied to other rare diseases, in particular mitochondrial disorders or retinopathies. Statistical testing can be applied to evaluate the statistical significance of the obtained results.

4.4 Conclusions

Research on MPs to treat LHON and RP is at an early stage. An unmet medical need is still present for LHON and RP. Raxone is the only available MP within the EU to treat LHON and Luxturna is the only available MP within the EU to treat RP.

At this stage, standards of care for patients affected from both LHON and RP have not been set, but research is moving forward as shown by the increased number of clinical trials and the increased number of drug classes explored, results in line with other authors.

The regulatory field is developing new strategies to meet the need of having more orphan drugs on the market, as was shown by the number of regulatory pathways which can be applied to support the development and authorisation of orphan drugs.

Important advances in research have been made, but more treatments are needed to be made available on the market to treat patients suffering from LHON and RP.

In conclusion, research is moving forward in evaluating new targeted treatments which will benefit patients suffering from LHON and RP, but development of MPs is still at an early stage.

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Appendix I

Clinical trials excluded a priori for Leber Hereditary Optic Neuropathy

Excluded Clinical Trials				
Exclusion Criteria		**Year of the clinical trial start date**	**NCT Number**	**EudraCT number**
Non-medicinal product (N=4)	Device (n=3)	Pre-2006 (n=0)		
		2006-2012 (n=1)	NCT01389817	
		2013-2019 (n=2)	NCT03475173 NCT02982499	
	Drug Supplement (n=1)	Pre-2006 (n=0)		
		2006-2012 (n=1)		2009-016982-26
		2013-2019 (n=0)		
Observational and Expanded Access Programs (N=9)		Pre-2006 (n=0)		
		2006-2012 (n=2)	NCT01694940, NCT01421381	
		2013-2018 (n=7)	NCT02796274, NCT03295071, NCT01892943, NCT02771379, NCT03406104, NCT02300753, NCT03672968	
Carried out before January 2006 or after November 2018 (N=2)		Pre-2006 (n=1)	NCT00528151	
		Post November 2018 (n=1)	NCT01495715	

Appendix II

Clinical trials excluded a priori for Retinitis Pigmentosa

Excluded Clinical Trials				
Exclusion Criteria		**Year of the clinical trial start date**	**NCT Number**	**EudraCT number**
Non-medicinal product (N=63)	**Device (n=26)**	Pre-2006 (n=3)	NCT00345917, NCT00279500, NCT00515814	
		2006-2012 (n=7)	NCT01837901, NCT01835002, NCT00407602, NCT01603576, NCT01024803, NCT00427180, NCT00804102	
		2013-2019 (n=16)	NCT03629899, NCT02548572, NCT02086890, NCT01847365, NCT03635645, NCT03444961, NCT03418116, NCT03248388, NCT02720640, NCT02303288, NCT03406416, NCT01864486, NCT02670980, NCT03057496, NCT03561922, NCT02804360	
	Drug supplement (n=13)	Pre-2006 (n=7)	NCT00346333, NCT00065455, NCT00029289, NCT00000116, NCT00000114, NCT00004827, NCT00100230	
		2006-2012 (n=2)	N/A	2012-002436-82, 2006-001727-19
		2013-2018 (n=4)	NCT02465749, NCT03078309, NCT03746522, NCT03013543	
	Procedure (n=8)	Pre-2006 (n=1)	NCT00016471	
		2006-2012 (n=5)	NCT01604356, NCT00717080, NCT00461435, NCT01415453, NCT01497379	
		2013-2018 (n=2)	NCT02614651, NCT01866371	
	Dietary supplement (n=5)	Pre-2006 (n=0)		
		2006-2012 (n=2)	NCT01680510	2007-005578-29
		2013-2018 (n=3)	NCT02244996, NCT02018692, NCT01256697	
	Diagnostic test and genetic analysis (n=4)	Pre-2006	N/A	
		2006-2012 (n=1)	NCT01235624	
		2013-2018 (n=3)	NCT02309866, NCT03322930, NCT02018692	
	Behavioural (n=2)	Pre-2006	NCT00213811	
		2006-2012	N/A	

Excluded Clinical Trials				
Exclusion Criteria		**Year of the clinical trial start date**	**NCT Number**	**EudraCT number**
		2013-2018	NCT03368027	
	Other (n=5)	Pre-2006 (n=1)	NCT02385565	
		2006-2012	N/A	
		2013-2018 (n=4)	NCT01949623, NCT03381235, NCT02575430, NCT02909985	
Observational (N=39)		Pre-2006 (n=9)	NCT00004345, NCT00254605, NCT00001347, NCT00231010, NCT00106743, NCT00004574, NCT00068224, NCT00001166, NCT00378742	
		2006-2012 (n=9)	NCT00475254, NCT00784901, NCT01021982, NCT01490827, NCT01790958, NCT00559234, NCT01793168, NCT00874783, NCT01694940	
		2013-2018 (n=21)	NCT02860520, NCT02759952, NCT03349242, NCT03314207, NCT03626207, NCT03281005, NCT02588430, NCT01999049, NCT01860092, NCT03510234, NCT03146078, NCT02014389, NCT02617966, NCT03319524, NCT01876147, NCT02435940, NCT03602820, NCT02890550, NCT01954953, NCT03597399, NCT02375438	
Carried out before January 2006 or after November 2018 (N=5)		Pre-2006 (n=2)	NCT00433277, NCT00063765	
		Post November 2018 (n=3)	NCT03780257, NCT03772938	2018-002433-38
Conditions other than retinitis pigmentosa (N=7)		Pre-2006 (n=0)		
		2006-2012 (n=2)	NCT01461213	2006-001727-19,
		2013-2018 (n=5)	NCT03184584, NCT02739217, NCT02065011	2017-000813-22, 2016-000898-20

Appendix III

Clinical development programs of the two centrally authorised products Raxone and Luxturna as described in the relevant EPARs

Raxone® (Idebenone)

Santhera Pharmaceuticals

This is a summary of the CDP in support of a centralised MA granted on 8th September 2015. The legal basis for this application refers to Article 10(3) of Directive 2001/83/EC – hybrid application using Mnesis (45mg idebenone coated tablets) as reference products (it was authorised in IT in 1993 based on a full stand-alone application).

Heathy Volunteers	Affected Patients
Study SNT-I-001 – Phase I • *Design:* Randomised, parallel group, cross-over, single dose, bioavailability study • *Aims:* comparison between two groups administered at different doses of Idebenone after high fat meals. • *Administration:* Idebenone (Raxone ®, 150 mg) was administere at single dose to one group (group A), while the other group was administered with 5 tablets of Idebenone (Raxone ®, 150 mg) after a high fat meal. • *Duration:* single dose administration • *Objective:* food effect on the PK of Idebenone and its metabolites at two doses strength • *N:* 28 healthy subjects • *Endpoints:* o Primary: evaluation of the bioavailability of Idebenone and its metabolites o Secondary: N/A	N/A
Study SNT-I-002 – Phase I • *Design***:** Open label, single-dose, bioavailability study • *Aims:* characterisation of the pharmacokinetics of Raxone over a seven-fold dose range (150 mg 1050mg) • *Administration***:** oral administration of different doses of Raxone • *Duration***:** single dose administration • *Objective***:** pharmacokinetics of Idebenone after a single dose of 150mg of Idebenone • *N:* 8 healthy subjects • *Endpoints:* o Primary: characterisation of the pharmacokinetics of Raxone o Secondary: N/A	N/A
Study SNT-I-003 – Phase I • *Design:* Parallel group, randomised, single and repeated t.i.d dose, bioavailability study • *Aims:* characterisation of the pharmacokinetics profile after a single oral dose and after repeated three times daily • *Administration:* Idebenone (Raxone ®, 150 mg) was administered at single dose t.i.d to one group (group A), while the other group was administered with 5 tablets of Idebenone (Raxone ®, 150 mg) t.i.d • *Duration:* 2 weeks • *Objective:* characterisation of pharmacokinetics of Idebenone at multiple doses at two doses strength • *N:* 25 healthy subjects • *Endpoints:* o Primary: assessment of plasma pharmacokinetics of Raxone and urinary excretion o Secondary: N/A	N/A

Study SNT-I-004 – Phase I • *Design*: Open-label, single dose (7x150 mg) • *Aims:* characterisation of the pharmacokinetics of Raxone over a seven-fold dose range (150 mg 1050mg) • *Administration:* Single dose (7x150mg) • *Duration*: single dose administration • *Objectives*: pharmacokinetics of Idebenone after a single oral dose of 7x150mg • *N*: 8 healthy subjects • *Endpoints*: o Primary: characterisation of the pharmacokinetics of Raxone o Secondary: N/A	N/A
N/A	**Study SNT-II-003* – RHODOS – Phase II (Main Study)** • *Design:* Prospective, randomized, placebo-controlled safety, tolerability and efficacy study • *Aims*: comparison between Idebenone and Placebo; o Two treatment groups: Idebenone or placebo, randomised in a 2:1 ratio. • *Administration:* Idebenone 900 mg/day (300 mg three times a day during meals) or placebo. • *Duration:* 24 weeks • *Objective*: to determine whether administration of Idebenone can improve visual function in patients with LHON • *N*: 85 patients were enrolled (all evaluated for safety and tolerability).7 patients prematurely abandoned the study (4 belonging to the placebo group and 3 belonging to the Idebenone group), thus the final randomisation was performed on 78 patients (52:26 respectively Idebenone and Placebo). • *Endpoints*: o Primary: best recovery of visual acuity o Secondary: - improvement in visual acuity (VA) - colour contrast sensitivity - Quality of Life (QoL) - Plasma level of Idebenone
N/A	**SNT-II-003-OFU** • *Design*: Single Visit, Observational, Follow-up Study • *Aims:* assessment of the status of the patients who participated to the RHODOS (SNT-II-003) trial in the past • *Duration*: single follow-up after 30 months off-treatment. • *N*: 60 patients who previously participated to the RHODOS study • *Endpoint:* o Primary: change in best logMAR visual acuity compared to last treatment visit of SNT-II-003 o Secondary: N/A
N/A	**SNT-EAP-001** • *Design:* Expanded Access Program on the use of Raxone • *Aims:* collection of relevant information on the risk-benefit balance of Raxone • *Administration:* Idebenone 150mg film-coated tablets, 900 mg/day • *Duration:* from 6 to 36 months • *Objectives:* to provide patients to have access to Raxone on a patient-name basis and to collect data to evaluate the risk-benefit balance of Raxone • *N:* 93 patients (safety population) and 69 patients (efficacy population) • *Endpoints:* o Primary: Proportion of patients with CRR in VA from nadir o Secondary: - Proportion of patients with CRR by mutation - Proportion of patients with CRR by gender, age at Baseline, smoking status, duration of disease at Baseline and VA at nadir - Duration of Raxone treatment at CRR - The treatment effect size in VA in patients with CRR

	SNT-IR-006 • *Design:* natural history case record survey • *Aims:* to establish the natural course of vision loss and recovery in patients with a genetically confirmed diagnosis of LHON • *Objective:* evaluation of patients treated with Raxone (on average 520mg/day) and patients not receiving raxone. • *N:* 383 records collected and analysed • *Endpoints:* o Primary: VA as a function of time since onset of symptoms o Secondary: - Proportion of patients with spontaneous clinically relevant recovery (sCRR) from VA nadir by disease history and mutation status - Proportion of patients with no clinically relevant deterioration in VA

Endpoints definitions Study SNT-II-003

Primary endpoint	Best Recovery in VA	Best Recovery of logMAR VA at week 24 in either right or left eye (whichever shows best improvement) compared to baseline
Main secondary endpoint	Change in best VA	Best VA of logMAR VA at Week 24 (best eye at week 24) compared to best VA at baseline (best VA at baseline)
Other Secondary endpoint	Responder Analysis (A): Proportion of patients with VA deterioration to ≥1.0 logMAR	In LHON patients entering the trial with an eye still less affected than 0.5 logMAR: Proportion of patients in which the visual acuity in the initially least affected eye deteriorates to 1.0 logMAR or more.
Other Secondary endpoint	Responder Analysis (A): Proportion of patients/eye with ≥0.2 logMAR VA improvement	Count of eyes/patients for which VA improves between baseline and Week 24 by at least 0.2 logMAR.
Other Secondary endpoint (*post-hoc, mITT population only)*	Responder Analysis (A): Proportion of patients/eye CRR from baseline	Proportion of patients with CRR fom Baseline (improvement of at least logMAR 0.2 for patients with "on-chart" VA at Baseline, or an improvement from "off-chart" VA at Baseline).
Other Secondary endpoint (*post-hoc, mITT population only)*	Responder Analysis (A): Proportion of patients/eye CRR from nadir	Proportion of patients with CRR from nadir (the worst VA at any time post-Baseline)

Reference submitted:

Three open-label cohort studies were submitted:

Mashima Y1, Kigasawa K, Wakakura M, Oguchi Y. Do idebenone and vitamin therapy shorten the time to achieve visual recovery in Leber hereditary optic neuropathy?. J Neuroophthalmol. 2000;20(3):166-70.
Carelli V, La Morgia C, Valentino ML, Rizzo G, Carbonelli M, De Negri AM, et al. Idebenone treatment in Leber's hereditary optic neuropathy. Brain. 2011;134(Pt 9):e188
Orssaud C, Robert M, Roche O, Dufier J. Visual function improvement after idebenone therapy in Leber hereditary optic neuropathy. Acta Ophtalmologica. 2012

Luxturna® (voretigene neparvovec-rzyl))
Novartis Europharm Limited

This is a summary of the CDP in support of the centralised MA granted on 20th September 2018. The legal basis for this application refers to Article 8.3 of Directive 2001/83/EC – complete and independent application

Heathy Volunteers	Affected Patients
N/A	**Study AAV2-hRPE65v2-101 – Phase I** • *Design:* Open-label dose-escalation safety study • *Aims:* to evaluate whether gene transfer will be safe and effective in the treatment of Leber Congenital Amaurosis • *Administration:* sub-retinal injection in three cohorts with ascending doses of AAV2-hRPE65v2 (1.5E10 vector genomes voretigene neparvovec-rzyl in 150 microliters, 4.8E10 vector genomes voretigene neparvovec-rzyl in 150 microliters and 1.5E11 vector genomes voretigene neparvovec-rzyl in 300 microliters) • *Duration:* Subjects have been followed up for 8 years • *Objective:* to evaluate safety and efficacy of subjects receiving a one-time sub-retinal injection of AAV2-hRPE65v2 into a single eye • *N:* 12 patients ≥8-year old affected from Leber Congenital Amaurosis due to confirmed biallelic RPE65 mutations • *Endpoints:* o Primary: - Safety and tolerability o Secondary: - Changes in visual function as measured by subjective, psychophysical tests and by objective, physiologic tests
N/A	**Study AAV2-hRPE65v2-102 – Phase I** • *Design:* open-label safety study • *Aims:* • *Administration:* to evaluate the safety of re-administration of adeno-associated viral vector containing the gene for human RPE65 [AAV2-hRPE65v2] to the contralateral eye in subjects with Leber Congenital Amaurosis previously enrolled in a phase 1 study duration • *Objective*: • *N:* subjects who had taken part in initial Phase 1 study (AAV2-hRPE65v2-101) with unilateral, sub-retinal administration of AAV2-hRPE65v2. • *Endpoints:* o Primary: - Adverse events as a measure of safety and tolerability o Secondary: - Visual Acuity - Visual Field - Mobility testing
N/A	**Study AAV2-hRPE65v2-302 – Phase III (Main Study)** • *Design:* open-label, randomised, parallel assignment, safety and efficacy study • *Aims:* to evaluate safety and efficacy of AAV2-hRPE65v2 • *Administration*: sub-retinal administration of gene therapy vector AAV2-hRPE65v2 (1.5E11 vector genomes per eye) to both eyes via surgical procedures on separate days • *Duration:* 12 months • *Objective*: to determine whether non-simultaneous, bilateral sub-retinal administration of AAV2-hRPE65v2 improved the ability to navigate in adults and children, three years of age or older, with RPE65 mutations and to continue to assess the safety and tolerability of AAV2-hRPE65v2. • *N:* 31 patients ≥3-year old affected from retinal dystrophy due to mutation RPE65 • *Endpoints:*

	○ Primary: - mobility test in both eyes as measured by a change score, one year following vector administration as compared to a subject's baseline bilateral mobility test performance ○ Secondary: - Full-field Light Sensitivity Threshold (FST) Testing - Monocular mobility testing change score - Visual acuity at year 1 compared to baseline
N/A	**Study RPE65 NHx (amendment 001, EU) – Natural case history** • *Design:* Retrospective medical chart review • *Aims:* to describe the natural history of retinal degenerative disease in subjects with mutations in the RPE65 *gene* • *Administration:* N/A • *Duration:* N/A • *Objective:* to obtain data on visual acuity, Goldmann kinetic visual fields and optical • *coherence tomography* • *N:* 70 cases were considered eligible to be included • *Endpoints:* N/A

Endpoints definitions study AAV2-hRPE65v2-302

Primary endpoint	Multiluminance mobility test (MLMT)	Clinic-based clinician reported outcome assessment tool where patients are asked to navigate between start and finish in an obstacle course at ambient light set at between 400 lux and 1 lux during each attempt.
Secondary endpoint	Full field sensitivity test	Average light sensitivity of the entire visual field for white light at year 1 after exposure as compared to baseline light sensitivity testing
Secondary endpoint	Visual acuity	ETDRS or HOTV charts used or description type assessment for grossly impaired acuity and conversion to LogMAR units

Appendix IV

Ongoing clinical development programs of the medicinal products selected as part of the prospective treatment protocols for LHON

GS010 (rAAV$_2$-ND4)
GenSight Biologics
This is a summary of the ongoing CDP for GS010.
Orphan Designation granted on 13th May 2015 (Procedure number: EU/3/11/860).

Heathy Volunteers	Affected Patients
N/A	**Study GS-LHON/CLIN/01– Phase I/II** • *Design*: Open label, dose escalation safety and efficacy study • *Aims:* non-randomised, open label, dose escalation clinical trial • *Administration:* escalating doses of GS010 (rAAV2) • *Objective:* Evaluation of the safety and tolerability of a single intravitreal (IVT) injections of escalating doses of GS010 (9xE09 vg, 3xE10 vg and 9xE10 vg) in patients suffering from Leber Hereditary Optic Neuropathy (LHON) due to mutation G11778A in the mitochondrial NADH Dehydrogenase 4 (ND4) gene • *Duration:* 2 years • *N*: 22 patients treated with GS010 • *Endpoints:* o Primary: incidence of local and general adverse events and serious adverse events o Secondary: - Efficacy 48 weeks after the injection (VA, Visual Field) - Measurement of RNFL - Cellular and humoral response
N/A	**Study GS-LHON-CLIN-05 – Phase III** • *Design*: Randomized, double-masked, placebo-controlled efficacy and safety study • *Aims:* comparison between GS010 and Placebo o Two treatment groups: rAAV2 or Placebo randomised in 1:1 ratio. • *Administration:* rAAV2 was administered intravitrally at a dose 90µL (9E10 viral genomes); placebo was a sterile, apyrogenic solution used for ocular surgery and administered intravitrally at a dose of 90 µL. • *Objectives:* assessment of safety and efficacy of GS010, in improving the retina functional and structural outcomes in subjects with LHON due to the m.11778 G>A • *N:* 90 patients divided in two groups, randomised in 1:1 allocation. • *Endpoints:* o Primary: Best-Corrected Visual Acuity (BCVA) reported using LogMAR o Secondary: - Best-Corrected Visual Acuity (BCVA) - Visual Field - Contrast Sensitivity - Quality of life
N/A	**Study GS-LHON-CLIN-03A – Phase III** • *Design*: Randomized, double-masked, sham-controlled, pivotal, efficacy study • *Aims:* comparison between the eye treated with GS010 and the eye treated with sham injection o One treatment group: one randomly selected eye of each participant treated with GS010 and the other eye of each participant treated with sham injection. • *Administration:* subjects received a single dose of GS010 in one of their randomly selected eyes, via intravitreal injection containing 9E10 viral genomes in 90µL balanced salt solution (BSS) plus 0.001% Pluronic F68®. In the other eye they received a standard antiseptic preparation. • *Objectives*: evaluation of the efficacy of GS010 compared with sham at week 48 in the change from baseline of the LogMAR in subjects affected by LHON for 6 months or less by LHON

Heathy Volunteers	Affected Patients
	• *N*: 36 patients, with LHON onset less than 6 months • *Endpoints*: o Primary: VA, measured by a logMAR, at Week 48 after IVT injection o Secondary: - VA over the follow-up period (after 48 and 96 weeks of the injection) - Change from the baseline of the logMAR score - Visual Field - Colour contrast sensitivity
N/A	**Study GS-LHON-CLIN-03B – Phase III** • *Design*: Randomized, double-masked, sham-controlled, pivotal, efficacy study • *Aims:* comparison between the eye treated with GS010 and the eye treated with sham injection o One treatment group: one randomly selected eye of each participant treated with GS010 and the other eye of each participant treated with sham injection. • *Administration:* subjects received a single dose of GS010 in one of their randomly selected eyes, via intravitreal injection containing 9E10 viral genomes in 90µL balanced salt solution (BSS) plus 0.001% Pluronic F68®. In the other eye they received a standard antiseptic preparation. • *Objectives*: To evaluate the efficacy of GS010 compared with sham at Week 48 in the change from baseline of the LogMAR in subjects affected by LHON for more than 6 months and to 12 months • *N*: 36 patients, with LHON onset between 6 and 12 months • *Endpoints*: o Primary: VA, measured by a logMAR, at Week 48 after IVT injection o Secondary: - VA over the follow-up period (after 48 and 96 weeks of the injection) - Change from the baseline of the logMAR score - Visual Field - Colour contrast sensitivity

Two additional clinical trials were carried out from the Huazhong University of Science and Technology

Heathy Volunteers	Affected Patients
N/A	**Study RAVCT-2 – Phase I/II** • *Design*: Prospective, open label safety and efficacy study • *Aims:* comparison before and after treatment o One treatment group • *Administration:* Single Intravitreal Injection of $rAAV_2$-ND4 at 5×10^9 vg/0.05 mL dose for patients younger than 12 years old and 1×10^{10} vg/0.05 for patients elder than 12 years old. • *Duration:* 1 year • *Objective*: assessment of the safety and efficacy of rAAV2-ND4 treatment in Leber hereditary optic neuropathy patients with 11778 LHON mutation. • *N:* 9 patients were enrolled and evaluated at month 1, 3 and 9 after intravitreal injection. • *Endpoints*: o Primary: change in visual acuity before and after treatment o

Heathy Volunteers	Affected Patients
	○ Secondary: - Measurement of intraocular pressure before and after treatment; - Neutralizing antibody essay before and after treatment; - Average RNFL Thickness; - Computerized Visual Field.
N/A	**Study Leber 2 – Phase II/III** • *Design*: Randomized, double-blind, safety and efficacy study • *Aims:* randomised comparison between a single injection of rAAV2 and placebo (normal saline) ○ Four treatment groups: rAAV2 group (24 patients), divided in 2 more groups and placebo group (24 patients) divided in 2 more groups, in a parallel randomisation. • *Administration:* rAAV2 was administered at a dose 1 × 10^10 vg/0.05 mL while the placebo was administered at a dose 0.05ml. • *Duration:* (estimated) 36 months • *Objective:* the evaluation of safety and efficacy of rAAV2-ND4 treatment for Leber hereditary optic neuropathy with the G11778A mutation • *N*: 48 enrolled patients divided in 2 groups: 24 patients were at more than 24 months after onset, and 24 were less than 24 months. Each group was randomly divided in two more groups (12 patients per each) and to one group it was administered with single IVT Injection of RAAV2 (1 × 10^10 vg/0.05 mL) while the other group was administered with normal saline (0.05 ml). • *Endpoints*: ○ Primary: - Best Recovery of Visual Acuity (BCVA) - Computerized Visual Field ○ Secondary: - visual evoked potential (VEP) - retinal nerve fiber layer (RNFL) - Liver and kidney function in plasma

Cysteamine bitartate
Horizon Pharma USA, Inc.

Healthy Volunteers	Affected Patients
N/A	**Study RP103-MITO-001 – Phase II** • *Design*: Open-label, dose-escalating safety, tolerability and efficacy study • *Aims*: evaluation of change in QoL after 24 weeks of Cysteamine bitartrate administration • *Administration*: delayed-release capsules administered up to 1.3 g/m²/day in two divided doses, every 12 hours, for up to 6 months • *Duration*: 6 months • *Objectives*: assessment of safety, tolerability, efficacy, pharmacokinetics and pharmacodynamics of cysteamine bitartrate for treatment of children with inherited mitochondrial disease • *N*: 36 patients in paediatric age (≥6 years old <18 years old) with documented genetically confirmed diagnosis of inherited mitochondrial diseases • Endpoints: o Primary: change from baseline in newcastle paediatric mitochondrial disease scale o Secondary: - change over time in pharmacodynamic biomarkers
N/A	**Study RP103-MITO-002 – Phase II** • *Design*: Long-term open-label extension study to assess safety, tolerability and efficacy • *Aims*: assessment of safety, tolerability and efficacy of cysteamine bitartate in paediatric population • *Administration*: delayed-release capsules are administered twice per day at dose dependent to tolerability • *Duration*: 2 years • *Objectives*: long-term extension study of patients with mitochondrial diseases to assess safety, tolerability and efficacy of cysteamine bitartate • *N*: 22 patients in paediatric age (≥6 years old <18 years old) with documented genetically confirmed diagnosis of inherited mitochondrial diseases • *Endpoints*: o Primary: QoL (change in Newcastle Paediatric Mitochondrial Disease scale score each three months up to 24 months) o Secondary: - Change over time in two of the most pre-eminent symptoms - Change over time in Pharmacodynamic Biomarkers

Autologous Bone Marrow Stem Cells
MD Stem Cells

Healthy Volunteers	Affected patients
N/A	**Study SCOTS2 – N/A** • *Design:* Open-label, efficacy study • *Aims*: comparison among three arms in which different routes of administration were performed • *Administration*: - Arm 1: retrobulbar, subtenon and intravenous for one or both eyes - Arm 2: retrobulbar, subtenon, intravitreal and intravenous for one or both eyes - Arm 3: intraoptic nerve or subretinal for eye with worse vision with fellow eye receiving either retrobulbar and subtenon or retrobulbar, subtenon and intravitreal; followed by intravenous • *Duration*: 12 months (estimated) • *Objectives*: assessment of the efficacy of stem cells in degenerative eye diseases. • *N*: 500 patients (estimated) with documented progressive damage to the retina or optic nerve and have less than or equal to 20/40 BCVA • *Endpoints*: o Primary: BCVA measured at first post- procedure day,then 3 months, 6 months and 12 months post-procedure day. o Secondary: - Visual field - RNFL

Appendix V

Ongoing clinical development programs of the medicinal products selected as part of the prospective treatment protocols for RP

Brimonidine Tartrate
Allergan Limited

Healthy Volunteers	Affected Patients
N/A	**Study 190342-028D – Phase I/II** • *Design:* exploratory, non-randomised, patient-masked, ascending-dose, safety and efficacy study • *Aims:* evaluation of the safety and efficacy on visual function of a single injection in one eye • *Administration*: four arms were administered three doses of Brimonidine Tartrate were administered in one eye o 100 µg Brimonidine Tartrate Implant (2 groups) o 200 µg Brimonidine Tartrate Implant (1 group) o 400 µg Brimonidine Tartrate Implant (1 group) • *Duration:* 6 months • *Objective:* to detect changes from baseline after six months from the administration of Brimonidine Tartrate • *N:* 21 patients affected from RP in both eyes were enrolled • *Endpoints:* o <u>Primary</u> - Change from baseline in BCVA in the study eye, using an eye chart o <u>Secondary:</u> - Change from baseline in contrast sensitivity in the study eye, measured using a Pelli-Robson contrast sensitivity chart at 1 meter
N/A	**Study 190342-033D – Phase II** • *Design*: non-randomised, patient-masked, sham-controlled, safety extension study of 190342-028D and 190342-032D • *Aims:* evaluation of the biodegradation and related safety profile of intravitreal brimonidine tartrate implant • *Administration:* N/A • *Duration:* N/A • *N:* 290 patients affected from RP and geographic atrophy from age-related macular degeneration previously enrolled in studies 190342-028D and 190342-032D • *Endpoints:* o <u>Primary:</u> - Number of adverse events - Vital signs (blood pressure, pulse, respiration) - Manifest refraction and BCVA by ETDRS - Biomicroscopic examination - Intraocular pressure - Indirect ophthalmoscopic examination

Levodopa-Carbidopa
Beirut Eye Specialist Hospital

Healthy Volunteers	Affected Patients
N/A	**Study NCT02837640 – Phase II** • *Design:* open label, single arm, efficacy study • *Aims:* to evaluate the effect of L-Dopa on the progression of retinitis pigmentosa • *Administration:* Sinemet 200/50 1/2 tablet (levodopa-carbidopa 100/25) b.i.d and then will be increased to t.i.d • *Duration:* 6 months • *Objective:* assessment of levodopa-carbidopa efficacy in patients affected by retinitis pigmentosa • *N:* 50 patients • *Endpoints:* o <u>Primary:</u> - Change in Electroretinogram o <u>Secondary:</u> - Change in VA - Change in VF

Iluvien
(Fluocinolone Acetonide)
Moorfields Eye Hospital

Healthy Volunteers	Affected Patients
N/A	**Study KHAK1001– Phase II** • *Design:* non-randomised, pilot, safety and efficacy study • *Aims:* to evaluate the effect of fluocinolone acetonide in RP patients • *Administration:* intravitreal • *Duration:* 36 months • *Objective:* anatomical and functional changes in treated eyes when compared with the fellow eye (non-treated), safety and efficacy of fluocinolone acetonide • *N:* 20 patients affected from intraocular inflammation associated with RP • *Endpoints:* o <u>Primary:</u> - Change in macular thickness - Change in outer retinal thickness across the macula - Change in VF size of V4e isopter area o <u>Secondary:</u> - Change in oxygen saturation and vessel calibre in retinal venules and arterioles - Change in all ISCEV electrophysiological parameters - Number of cases requiring treatment of ocular hypertension or glaucoma, cataract, retinal detachment, tear or endophthalmitis

Valproic Acid
Foundation Fighting Blindness Clinical Research Institute

Healthy Volunteers	Affected Patients
N/A	**Study NCT01233609 – Phase II** • *Design:* Randomised, placebo-controlled, non-blinded, parallel assignment, efficacy study • *Aims:* to evaluate the efficacy of Valproic Acid (VPA) to both slow the progression of visual function loss and/or to restore visual function in patients with Autosomal Dominant Retinitis Pigmentosa (RP) and to collect safety and tolerability information • *Administration:* 1 to 4 Valproic acid 250mg softgels capsules • *Duration:* N/A • *Objective:* the evaluation of efficacy, safety and tolerability of valproate acid in patients suffering from retinitis pigmentosa • *N:* 90 patients • *Endpoints:* o <u>Primary:</u> - Mean change in visual field area from baseline to 52 weeks o <u>Secondary:</u> - Mean Change in Visual Field Area from baseline to 52 Weeks--I4e Isopter; - Static Perimetry by Treatment Arm--Full Field Hill of Vision; - Static Perimetry Volume--30 Degree Hill of Vision; - Mean Change From Baseline in Best Corrected Visual Acuity
N/A	**Study NCT01399515 – Phase II** • *Design:* open-label, non-randomised, parallel assignment, safety and efficacy study • *Aims:* to evaluate the efficacy and safety of oral valproic acid to slow the progression of visual function and/or to improve the visual function in patients with retinitis pigmentosa • *Administration:* one 500mg tablet by mouth daily • *Duration:* N/A • *Objective:* evaluation of safety and efficacy of valproate acid in patients suffering from retinitis pigmentosa • *N:* 200 patients • *Endpoints:* o <u>Primary:</u> - Mean change in visual field area from baseline to 48 weeks o <u>Secondary:</u> - Mean change in best corrected visual acuity (BCVA) - Mean change in 30-Hz flicker Electroretinogram (ERG) amplitude - Mean change in central macular thickness - Mean change in fundus appearance - Mean change in total score on vision-related quality of life - Occurrence of adverse effect related to Valproic acid - Changes in clinical laboratory data (CBC, BUN, Creatinine, Liver panel (Cholesterol, Total protein, Albumin, Total bilirubin, Alkaline phosphatase, AST, ALT, GGT), Coagulation panel (PT INR, PT%, PT sec, aPTT, Fibrinogen), Electrolyte panel (Na, K, Cl, TCO2) Mean change in central macular volume

Orphan Designation granted on 13th May 2011 (Procedure number: EU/3/11/865).

Healthy Volunteers	Affected Patients
N/A	**Study RET RP 01 – Phase I** • *Design:* open-label, proof of concept, safety and efficacy study • *Aims:* evaluation of visual function improvement, duration of visual function improvement and safety of QLT091001 • *Administration:* oral solution once daily for 7 days • *Duration:* 7 days • *Objective:* proof of concept on safety and efficacy of QLT091001 after 7-day treatment • *N:* 5 patients ≥18-year-old suffering from RP due to mutation RPE65 • *Endpoints:* o Primary: - Visual field o Secondary: - Safety assessed by adverse events, clinical laboratory results, ECG's and vital signs
N/A	**Study RT IRD 01– Phase I** • *Design:* open label, proof of concept, safety and efficacy study • *Aims:* evaluation of safety QLT091001 over a 7-day treatment period efficacy lasting if observed • *Administration:* N/A • *Duration:* 7 days • *Objective:* evaluation of safety and efficacy of QLT091001 over a 7-day-period • *N:* 32 patients ≥18-year-old suffering from RP due to mutation RPE65 or LRAT • *Endpoints:* o Primary - Percentage of VF changed from baseline to 12 months after treatment o Secondary - Safety assessed by adverse events, clinical laboratory results, ECG's and vital signs
N/A	**Study RET IRD 02– Phase I** • *Design:* open-label, extension of RET RP 01, safety and efficacy study of repeated doses of QLT091001 • *Aims:* evaluation of safety and efficacy of three additional courses of QLT091001 • *Administration:* administered once daily for 7 days in subjects treated previously with a single 7-day course • *Duration:* 7 days • *Objective:* evaluation of safety and efficacy of up to 3 additional courses of oral QLT091001 administered once daily for 7 days • *N:* 27 patients ≥5-year-old affected from RP and Leber's Congenital Amaurosis caused by mutations RPE65 or LRAT • *Endpoints:* o Primary - Percentage of VF changed from baseline to 12 months after treatment o Secondary - Safety assessed by adverse events, clinical laboratory results, ECG's and vital signs
N/A	**Study RETIRD04– Phase III** • *Design:* randomised, cross-over, double-blind, placebo-controlled, efficacy, pharmacokinetics, dose-response study

Healthy Volunteers	Affected Patients
	• *Aims:* evaluation of efficacy of QLT091001 in patients affected from RP or Leber's Congenital Amaurosis between 6 and 40 years old • *Administration:* oral administration • *Duration:* 12 months • *Objective:* to evaluate efficacy, tolerability, pharmacokinetics and safety of oral QLT091001 in subjects with Leber congenital amaurosis or RP due to RPE65 or LRAT mutations • *N:* 48 patients ≥6-year-old affected from RP and Leber's Congenital Amaurosis caused by mutations RPE65 or LRAT • *Endpoints:* o <u>Primary</u> - Percentage of VF changed from baseline to 12 months in the treated eye o <u>Secondary</u> - Change from baseline in visual field volume in the study eye - Visual field volume in the study eye - Proportion of subjects with increase in visual field volume in the study eye of at least 10% in Course 12, and proportion of subjects with increase in visual field volume in the study eye of at least 20% in Course 12 - Change from baseline in HLHC BCVA (ETDRS at 4 meters or 1 meter) in the study eye - Change from baseline in LLLC BCVA (ETDRS at 4 meters or 1 meter) in the study eye - Patient reported outcomes

CPK850
(scAAv$_8$-pRLBP1(short)-hRLBP1 vector)
Novartis Pharmaceuticals

Healthy Volunteers	Affected Patients
N/A	**Study NCT03374657 – Phase I/II** • *Design:* open-label, non-confirmatory, single ascending dose, safety, tolerability and efficacy study • *Aims:* to explore the maximum tolerated dose of CPK850 and to evaluate the safety and potential efficacy of CPK850 on improving visual function in patients with decreased visual function from RLBP1 retinitis pigmentosa • *Administration:* 5 different doses of CPK850 via subretinal injection • *Duration:* single dose administration of each dose • *Objective:* evaluation of tolerability, safety and efficacy of CPK850 in patients affected by retinitis pigmentosa due to biallelic mutations in the RLBP1 gene • *N:* 21 patients • *Endpoints:* o <u>Primary:</u> - Number adverse events, serious adverse events and deaths - Number of responders in dark adaptation o <u>Secondary</u>: - Number of recovery of the cone system (dark adaptation) - Number of improvement in rod function in treated eye vs untreated eye (dark adaptation) - Change from screening/baseline in visual field perimetry mean deviation - Change from screening/baseline in total contrast sensitivity score - Change from screening/baseline in light-adapted microperimetry sensitivity - Change from screening/baseline in the local electrical activity of the retina - Change from screening/baseline in the electrical activity of the retina - Change from screening/baseline in reading speed - Change from screening/baseline in eye dominance - Change from screening/baseline in Change from baseline in mobility test scores - Change from screening/baseline in the National Eye Institute - Visual function questionnaire 25 (NEI-VFQ 25) - Change from screening/baseline in the low luminance questionnaire (LLQ) responses

AVV_8-RPGR

Nightstar Therapeutics

This is a summary of the ongoing CDP for AVV_8-RPGR.

Orphan Designation granted on 22nd February 2018 (Procedure number: EU/3/18/1975).

Healthy Volunteers	Affected Patients
N/A	**Study MGT009 – Phase I/II/III** • *Design:* o Phase I (part 1): open-label, non-randomised, unmasked, dose escalation safety study o Phase II/III (part 2): randomised, double-blinded, dose-expansion efficacy study • *Aims:* to evaluate safety, tolerability and efficacy of a single sub-retinal injection of AAV8-RPGR • *Administration:* o Part 1: subretinal administration of 6 escalating doses of AVV_8-RPGR o Part 2: subretinal administration of 2 doses (high and low) of AVV_8-RPGR compared to 1 untreated group • *Duration:* o Part 1: 24 months o Part 2: 12 months • *N:* 63 male patients ≥18 years old (part 1) and ≥10 years old (part 2) affected from x-linked RP due to mutation RPGR • *Endpoints:* ***Part 1*** o <u>Primary:</u> - Incidence of dose-limiting toxicities - Incidence of treatment-emergent adverse events o <u>Secondary:</u> - Change from baseline in microperimetry at regular intervals throughout the study - Change from baseline in BCVA throughout the study ***Part 2*** o <u>Primary:</u> - Improvement from Baseline in microperimetry. o <u>Secondary</u> - Incidence of treatment-emergent adverse events over a 12-month period - Change from baseline in microperimetry at regular intervals throughout the study - Change from baseline in BCVA at regular intervals throughout the year

Autologous Bone Marrow-Derived Mononuclear Stem Cells
MD Stem Cells

Healthy Volunteers	Affected Patients
N/A	**Study ICMS-2013-0019– Phase N/A** • *Design:* open-label, non-randomised, efficacy study • *Aims:* to evaluate the efficacy of bone marrow derived stem cells in patients affected from optic nerve and retinal diseases • *Administration:* injections of autologous bone marrow derived stem cells isolated from the bone marrow using standard medical and surgical practices • *Duration:* 12 months • *N:* 300 patients ≥18 years old affected from optic nerve and retinal diseases including RP • *Endpoints:* o Primary: - BCVA measured with Snellen Eye Chart and the ETDRS o Secondary: - VF evaluated with automated perimetry
N/A	**Study NCT03011541– Phase N/A** • *Design:* open-label, non-randomised, efficacy study • *Aims:* to evaluate the efficacy of bone marrow derived stem cells in patients affected from optic nerve and retinal diseases • *Administration:* injections of autologous bone marrow derived stem cells isolated from the bone marrow using standard medical and surgical practices • *Duration:* 12 months • *N:* 500 patients ≥18 years old affected from optic nerve and retinal diseases including RP divided in three study arms • *Endpoints:* o Primary: - BCVA measured with Snellen Eye Chart and the ETDRS o Secondary: - VF evaluated with automated perimetry - Optical Coherence Tomography thickness of the retinal nerve fiber layer the optic nerve and/or macula

One additional study on autologous bone marrow-derived mononuclear stem cells was carried out

Mahidol University

Healthy Volunteers	Affected Patients
N/A	**Study RP-001 – Phase I** • *Design:* open-label, safety and feasibility study • *Aims:* to evaluate feasibility and safety of adult bone marrow-derived mesenchymal stem cells • *Administration:* intravitreal injection of 1 million stem cells in balanced salt solution of 100 microliters • *Duration:* 12 months • *N:* 10 patients ≥18 years old affected from RP • *Endpoints:* o Primary: - Change from baseline in laser flare and cell measurements o Secondary: - Change from baseline in visual function tests

Autologous bone marrow mononuclear stem cells
University of Sao Paulo

Healthy Volunteers	Affected Patients
N/A	**Study CPRS– Phase I** • *Design:* prospective, non-randomised, open-label, safety study • *Aims:* to evaluate the short-term safety of a single injection of autologous bone marrow mononuclear stem cells • *Administration:* one intravitreal injection 0.1 ml cell suspension containing around $10x10^6$ stem cells • *Duration:* 6 months • *N:* 5 patients ≥18 years old affected from RP • *Endpoints:* o <u>Primary:</u> - Severe visual loss, defined as a drop in 15 letters on ETDRS visual acuity scale o <u>Secondary:</u> - Increase in intra-ocular inflammation - Improvement in ERG response - Increase in VF - Increase > 5 letters on BCVA
N/A	**Study NCT01560715– Phase II** • *Design:* prospective, non-randomised, open-label, safety and efficacy study • *Aims:* to evaluate the short-term safety and efficacy of a single injection of autologous bone marrow mononuclear stem cells • *Administration:* one intravitreal injection of a 0.1 ml cell suspension containing around $10x10^6$ • *Duration:* 12 months • *N:* 50 patients ≥18 years old affected from RP • *Endpoints:* o <u>Primary:</u> - Change in VA measured with a ETDRS - Decrease in ERG response and in 5 square degrees on VF o <u>Secondary:</u> - Increase in intra-ocular inflammation - Improvement in ERG response - Increase in VF - Increase > 5 letters on BCVA

Autologous bone marrow mononuclear stem cells
Red de Terapia Celular

Healthy Volunteers	Affected Patients
N/A	**Study TC/RP– Phase I** • *Design:* randomized, double-blind, placebo-controlled, safety study • *Aims:* to evaluate the safety of intravitreal injection of autologous bone marrow mononuclear stem cells • *Administration:* injection of 0.1 ml of the suspension with the autologous bone marrow mononuclear stem cells in one eye and subconjunctival injection of 0.1 ml saline in the control eye • *Duration:* 12 months • *N:* 8 patients ≥18 years old affected from RP • *Endpoints:* o <u>Primary:</u> - Rate of serious and non-serious adverse events o <u>Secondary:</u> - Change in VA measured with ETDRS - Colour vision and contrast sensitivity

Healthy Volunteers	Affected Patients
	- Change in VF and macular sensitivity measured with the Humphrey perimeter

Autologous bone marrow mononuclear stem cells
Chaitanya Hospital, Pune

Healthy Volunteers	Affected Patients
N/A	**Study CSCC/BMRP/2013//01– Phase I/II** • *Design:* open-label, safety and efficacy study • *Aims:* to evaluate the efficacy of autologous bone marrow mononuclear stem cells after one-year treatment • *Administration:* N/A • *Duration:* 18 months • *N:* 15 patients ≥18 years old affected from RP • *Endpoints:* o <u>Primary:</u> - VA measured with electronic visual acuity technology o <u>Secondary:</u> - N/A

jCell

jCyte, Inc

This is a summary of the ongoing CDP for AVV_8-RPGR.

Orphan Designation granted on 19nd June 2013 (Procedure number: EU/3/18/1975).

Healthy Volunteers	Affected Patients
N/A	**Study JC-01– Phase I/II** • *Design:* prospective, open-label, single-Arm, safety and tolerability study • *Aims:* to evaluate safety and tolerability of a single dose of jCell • *Administration:* single intravitreal injection of 0.5 - 3.0 million human retinal progenitor cells in one eye • *Duration:* 12 months • *N:* 28 patients ≥18 years old affected from RP • *Endpoints:* o Primary: - Number of adverse events, related and severe treatment emergent adverse events o Secondary: - Change in BCVA in tested eye versus the untreated eye
N/A	**Study JC-02– Phase II** • *Design:* prospective, randomized, double-blind, sham-controlled, safety and efficacy study • *Aims:* to evaluate the efficacy of human retinal progenitor cells compared with sham control • *Administration:* single intravitreal injection in two different doses (3.0×10^6 and 6.0×10^6) and a mock injection • *Duration:* 12 months • *N:* 84 patients ≥18 years old affected from RP • *Endpoints:* o Primary: - BCVA measured with an ETDRS o Secondary: - Mobility test - VF measured with a Goldman test - Contrast sensitivity

One additional study was carried out from ReNeuron

Human Retinal Progenitor Cells

ReNeuron Limited

This is a summary of the ongoing CDP for Human Retinal Progenitor Cells.

Orphan Designation granted on 19nd June 2013 (Procedure number: EU/3/13/1140).

Healthy Volunteers	Affected Patients
N/A	**Study RN03-CP-0001– Phase I/II** • *Design:* prospective, open-label, dose-escalation, safety and tolerability study • *Aims:* to evaluate safety and tolerability of human retinal progenitor cells • *Administration:* single subretinal injection • *Duration:* 6 months • *N:* 21 patients ≥18 years old affected from RP • *Endpoints:* o Primary: - Safety measure by the incidence of treatment emergent adverse events o Secondary: - Change from baseline in BCVA measured with ETDRS - Change from baseline in VF measured with Goldmann visual field, microperimetry and FST - Change from baseline in retinal sensitivity

NT-501
Neurotech Pharmaceuticals

Healthy Volunteers	Affected Patients
N/A	**Study AOSLO-CNTF-FFB-01 – Phase II** • *Design:* prospective, randomized, double-masked, sham-controlled, safety and efficacy study • *Aims:* to evaluate the change in cone density and spacing in patients at a early stage of RP or Usher syndrome • *Administration:* the implant is surgically implanted into patients' eye • *Duration:* 36 months • *N:* 30 patients suffering from RP or Usher syndrome at a early stage • *Endpoints:* o <u>Primary:</u> - Cone photoreceptor preservation after 30 months post-implant measured by AOSLO technology o <u>Secondary:</u> - Presence or absence of rejection or extrusion of the implant - Changes in ocular function - Local or systemic toxicity
N/A	**Study CNTF 3– Phase II/III** • *Design:* randomised, double-masked, safety and efficacy study • *Aims:* to evaluate safety and efficacy of CNTF implants on vision in persons with late stage RP, Usher type and Choroideremia versus the sham-injected eye (comparator) • *Administration:* two implants with two different doses of CTNF surgically implanted into patients' eye • *Duration:* 12 months • *N:* 65 patients ≥18 years old affected from RP, Usher syndrome or Choroideremia • *Endpoints:* o <u>Primary:</u> - Change in BCVA using the Electronic Visual Acuity technology at month 12 o <u>Secondary:</u> - Long term observation of BCVA, OCT, inflammation and QoL
N/A	**Study CNTF 4– Phase II/III** • *Design:* randomised, double-masked, safety and efficacy study • *Aims:* to evaluate safety and efficacy of CNTF implants on vision in persons with early stage RP, Usher type and Choroideremia versus the sham-injected eye (comparator) • *Administration:* two implants with two different doses of CTNF surgically implanted into patients' eye • *Duration:* 12 months • *N:* 68 patients ≥18 years old affected from RP, Usher syndrome or Choroideremia • *Endpoints:* o <u>Primary:</u> - Change in VF using Humphrey visual field sensitivity from baseline to month 12 o <u>Secondary:</u> - Change in VF sensitivity at 24 months - Mean, median and distribution of change in BCVA at month 12 and 24 - Change in ERG, OCT, inflammation and QoL at month 12 and 24

A phase I study on NT-501 was carried out in 2003. The study ID in SNLMN is NCT00063765 and for completeness of information was decided to report it. Data related on clinical trial NCT00063765nwas partially retrieved from scientific literature (Kauper et al, 2012).

National Eye Institute (NEI)

	Study CTNF 1– Phase I • *Design:* N/A • *Aims:* evaluation of the ophthalmic and systemic safety of NT-501 a preliminary efficacy • *Administration:* 5 patients were implanted a high dose of CTNF and 5 patients were implanted with a low dose of CTNF • *Duration:* 6 months • *N:* 10 patients ≥18 years old affected from RP • *Endpoints:* o <u>Primary:</u> - Safety (NOS) o <u>Secondary:</u> - Inflammation measured by the anterior chamber cell scale and vitreous haze grading - VA, VF, ERG - Retinal thickness measured by OCT

Appendix VI

Published abstracts

Developing safe and effective medicinal products to treat Leber Hereditary Optic Neuropathy (LHON). Clinical and regulatory challenges

Zuccarelli Marta[1], John-Joseph Borg[2], Janis Vella[3] and Anthony Serracino- Inglott[3]

(1) Departement of Pharmacy, University of Malta, Msida (MSD), Malta
(2) Sir Temi Zammit Buildings, Malta Life Sciences Park, San Ġwann, SGN 3000, Malta., Medicines Authority, San Gwann, Malta
(3) Department of Pharmacy, University of Malta, Msida, Malta Abstract

Introduction:
Leber Hereditary Optic Neuropathy (LHON) is a rare maternally-inherited mitochondrial optic neuropathy caused by three mitochondrial DNA point mutations. In the EU, Raxone® (Idebenone) is the only approved medicinal product (MP) to treat LHON. There are no FDA-approved MPs for LHON in the US.

Research Question or Hypothesis:
Which MPs are in development to treat LHON? Which clinical development programs (CDPs) are being pursued by pharmaceutical companies when developing MPs to treat LHON?

Study Design: Review

Methods:
MPs to treat LHON were identified. Mechanism of action and site of action of MPs and nature of active substances were identified. A prospective treatment protocol was suggested and emerging patterns in primary endpoints studied over time were identified and compared. Regulatory pathways to obtain a licence for orphan medicinal products were analysed.

Results:
Nine MPs suitable to treat LHON are in development: 6 products are small molecules, 3 products consist of advanced therapy MPs. Three out of 9 MPs are modulating agents, 3 out of 9 are inhibitors of apoptosis, 2 out of 9 consist of gene therapy products and 1 out of 9 consists of reverse-disease therapy. Eight products out of 9 act at a mitochondrial level and 1 product out of 9 acts on retinal ganglion cells. One out of 9 products, Raxone®, has a marketing authorisation in the EU and 1 product, rAAV2, obtained the orphan designation. Comparison among CDPs shows that different primary endpoints are being studied in phase III trials.

Conclusion:
There is a need to develop adequate CDPs for the approval of MPs to treat LHON in the EU and US.

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Leber Hereditary Optic Neuropathy (LHON) is a rare maternally-inherited mitochondrial optic neuropathy, causing loss in visual acuity (VA). Within the European Union (EU), one medicinal product (MP), idebenone is approved and for one MP, rAAV2, an orphan designation was issued. The aims of this study were to propose prospective treatment protocols and to understand clinical and regulatory pathways pursued by pharmaceutical companies when developing MPs to treat LHON (LHONMPs).

Methodology included the identification LHONMPs studied from 2007 to 2017, mechanism of action, site of action of LHONMPs and the nature of active substances. Analysis of clinical development programs (CDPs). Identification and comparison of emerging patterns in primary endpoints studied using descriptive statistics. Identification of regulatory pathways pursued by pharmaceutical companies and regulators.

Nine LHONMP are in development: 6 small molecules (cyclosporine A, cysteamine bitartrate, elamipretride, idebenone, KH176 and QPI-1007) and 3 advanced therapy MPs ($rAAV_2$, $scAAV_2$ and stem cells). Cyclosporine A, Elamipretride and QPI-1007 are inhibitors of apoptosis; idebenone, KH176 and cysteamine bitartrate are modulating agents; $rAAV_2$, $scAAV_2$ are fixing gene therapy agents and stem cells is a reverse-disease therapy. Stem cells are the only LHONMP acting on retinal ganglion cells, the other 8 LHONMPs act on mitochondria. Comparison of CDPs shows improvements in quality of clinical trials performed through time. The most common primary endpoint studied was the improvement in VA. Idebenone was marketed under exceptional circumstances and protocol assistance was requested by the pharmaceutical company to the European Medicines Agency during the development.

EMERGING TREATMENTS FOR LEBER HEREDITARY OPTIC NEUROPATHY AND RETINITIS PIGMENTOSA

Marta Zuccarelli*[1], John-Joseph Borg[2], Janis Vella[1], Anthony Serracino-Inglott[1]

[1]Department of Pharmacy, Faculty of Medicine and Surgery, University of Malta, Msida,
[2]Malta Medicines Authority, Malta Life Sciences Park, San Gwann, Malta

Background: Leber Hereditary Optic Neuropathy (LHON) and Retinitis Pigmentosa (RP) are rare-inherited diseases causing blindness with few treatments available within the European Union (EU).

Purpose: To understand emerging patterns when developing medicines to treat LHON and RP.

Methods: Data on investigational medicinal products (IMPs) to treat LHON and RP was retrieved from the EU Clinical Trials (EudraCT) Register and from the United States National Library of Medicines (USNML) Database of Clinical Trials (CTs). CTs included in the study were (i) performed between January 2007 and November 2018, (ii) interventional, (iii) related to IMPs, (iv) registered as ongoing, recruiting or completed. Emerging patterns in primary endpoints of CTs were identified and compared.

Results: Twenty-three CTs for 9 IMPs for LHON were included. Out of 9 IMPs, 6 were small molecules and 3 were advanced therapy products (2 gene therapy and 1 somatic therapy). Among the small molecules, idebenone was authorised in the EU under exceptional circumstances. Forty-nine CTs for 24 IMPs studied for RP were included. Out of 24 IMPs, 14 were advanced therapy products (8 gene therapy and 6 somatic therapy), 8 were small molecules and 2 growth factors. Among the gene therapy products, voretigene neparvovec-rzyl has a marketing authorisation within the EU. The most common endpoints studied were change in visual acuity (n=6) for LHON and change in visual field (n=8) for RP.

Conclusion: An increased interest for medicines to treat LHON and RP was shown by the increased number of CTs carried out and the number of drug classes explored. Only two medicines are authorised within the EU for LHON and RP and an unmet medical need is present.

Appendix VII

Medicinal products retrieved to treat Cystoid Macular Oedema associated with retinitis pigmentosa

Aflibercept

Aflirbicept is an anti-vascular epithelial growth factor (VEGF) under evaluation for the treatment of RP associated cystoids macular oedema (Strong et al, 2017). Anti-VEGF and aflirbicept are under evaluation due to its indirect action in reducing oedema through the inhibition of vascular permeability and cellular mitosis following activation of VEGF (Steward, 2012; Moustafa and Moschos, 2015).

Minocycline

Minocycline is a tetracycline antibiotic reported to have a neuroprotective effect (Elewa et al, 2006). Minocycline is being studied to treat RP due to its inflammatory action. The inflammation in RP patients is related to the presence of macular oedema which usually appears in the advanced stage of the disease, causing decreased central vision (Shahsuvaryan, 2015).

Recombinant human nerve growth factor

The nerve growth factor (NGF) is a well-known member of the neurotrophins family, and a pleiotropic factor which exerts its activity to both the central and the peripheral nervous system, but also to the endocrine, immune and visual system (Micera et al, 2004; Ferrari et al, 2014). Recombinant human (rh) NGF is a clone of the human gene. When administered on the surface of the eyes, topically administered in eye-drops from, NGF reaches the retina, the optic nerve and the brain (Lambiase et al, 2009). The rationale for using rhNGF is its protective action in promoting photoreceptors survival as demonstrated in animal models (Lenzi et al, 2005; Sacchetti et al, 2017). The exact mechanism of photoreceptors protection exerted by rhNGF has not been understood yet (Falsini et al, 2016).

Aflibercept
Moorfields Eye Hospital NHS Foundation Trust

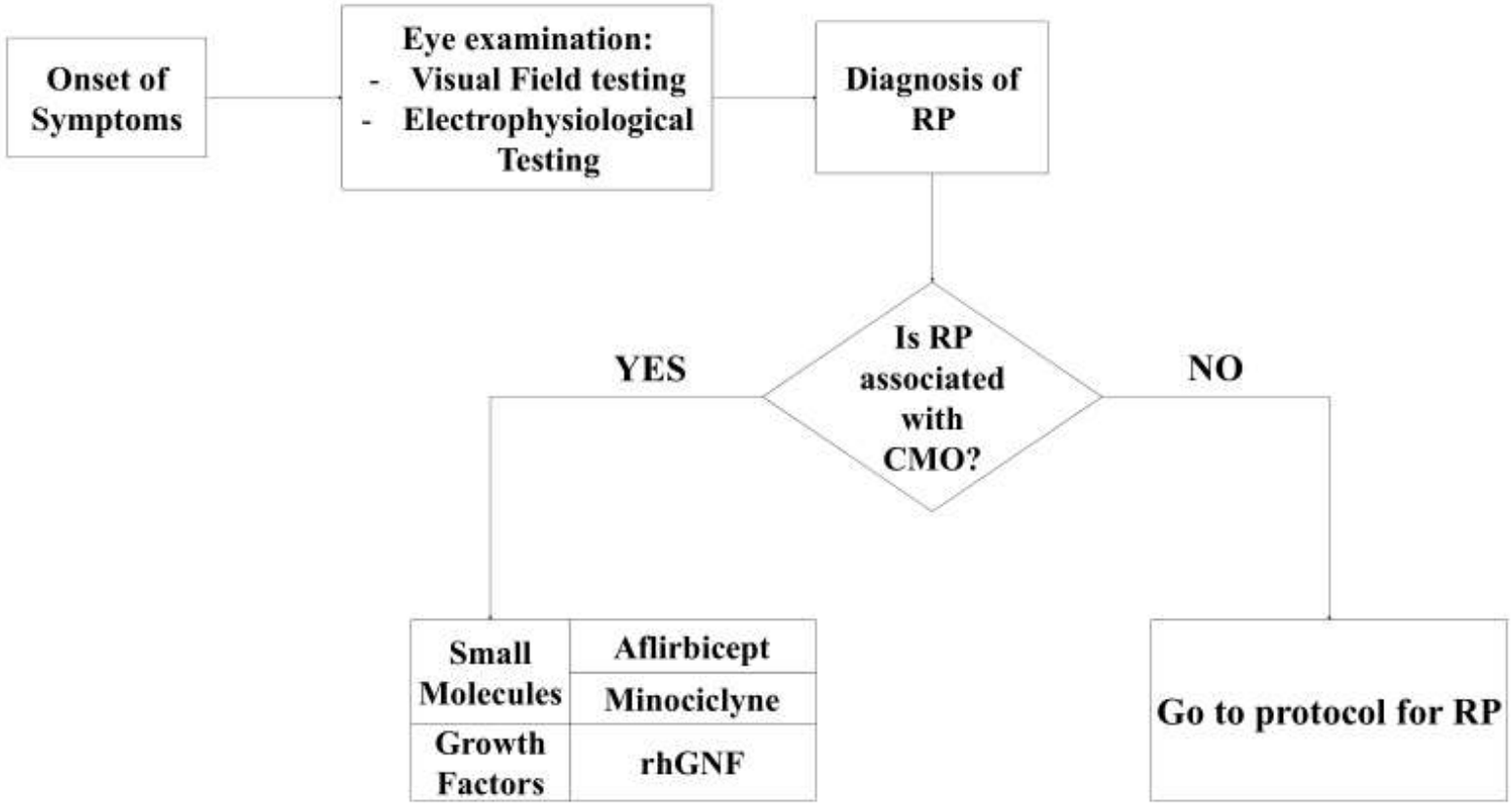
Healthy Volunteers	Affected Patients
N/A	**Study MICM1014– Phase II** • *Design:* prospective, non-randomised, therapeutic exploratory, safety and efficacy study • *Aims:* to evaluate safety and efficacy of aflibercept in treating cystoid macular oedema in patients suffering from RP • *Administration:* intravitreal injection of 2mg of 40mg/ml every 4 weeks for 3 months followed by a treat and extend protocol up to 12 months (if no reduction in macular oedema was noticed) • *Duration:* 12 months • *Objective:* to assess the efficacy of a minimum of 3 intravitreal injections of aflibercept in reducing cystoid macular oedema. Before being considered non-responders, patients were given 5 injections of aflibercept • *N:* 30 patients ≥16 years old affected from cystoid macular oedema associated with RP • *Endpoints:* o <u>Primary:</u> - Mean of central macular thickness (CMT) measured with Spectral Domain (SD) OCT 12 months post-treatment - Number of adverse events related to the treatment o <u>Secondary:</u> - mean CMT at 6 months as measured with SDOCT - mean BCVA ETDRS letter score at 6 and 12 months - mean macular volume at 6 and 12 months measured with SDOCT - Number of adverse events and serious adverse events over a period of 17 months

Minocycline
National Eye Institute (NEI)

Healthy Volunteers	Affected Patients
N/A	**Study NCT02140164 – Phase I/II** • *Design*: pilot, uncontrolled, open-label, prospective, efficacy study • *Aims*: to investigate the safety and possible efficacy of oral minocycline in participants with Cystoid Macular Oedema and Retinitis Pigmentosa • *Administration:* oral dose of 100 mg (or appropriate weight-adjusted paediatric dose) of minocycline twice daily • *Duration:* 12 months • *Objective:* evaluation of the efficacy of Minocycline in one eye with macular oedema considered the study eye. Before starting the use of Minocycline, a pre-treatment phase was performed • *N:* 7 patients • *Endpoints:* o <u>Primary:</u> - Change in cystoid macular edema based on optical coherence tomography o <u>Secondary:</u> - Change in cystoid macular edema based on optical coherence tomography - Changes in amplitude of photopic and scotopic responses on electroretinogram - Change in microperimetry - Change in visual field as measured by HVF 30-2 - Number of study eyes achieving a 15-letter or more worsening in electronic visual acuity - Number of Ocular Adverse Events - Number of non-ocular Adverse Events - Number of severe adverse events

Recombinant human nerve growth factor
Dompé Farmaceutici S.p.A

Healthy Volunteers	Affected Patients
N/A	**Study NGF0113 – Phase I/II** • *Design:* randomized, controlled, parallel group, dose ranging, safety and potential efficacy study • *Aims:* to evaluate safety and tolerability of two dose regimens versus a control • *Administration:* two different doses (60 µg/ml and 180 µg/ml) of eye drops solution versus placebo • *Duration:* 24 weeks • *N:* 50 patients ≥18 years old affected from RP • *Endpoints:* o Primary: - Number of serious and non-serious adverse events o Secondary: - Best Corrected Distance Visual Acuity measured with a ETDRS - Change in ocular tolerability measured by visual analogue scale - Presence of Anti-NGF antibodies
N/A	**Study RF-2010-2318561 – Phase II** • *Design:* randomised, double-blind, parallel group, placebo-controlled, safety and efficacy study • *Aims:* to evaluate the efficacy of recombinant human nerve growth factor over 1-month period versus placebo • *Administration:* 180 µg/ml eye drops • *Duration:* 12 months • *N:* 45 patients suffering from cystoid macular oedema associated with RP • *Endpoints:* o Primary: - Macular thickness assessed by ocular coherence tomography o Secondary: - Short and long distance BCVA - Contrast sensitivity - VF - Number of recurrence of macular oedema



CMO: Cystoid Macula Oedema
rhGNF: recombinant humant nerve growth factor
RP: Retinitis Pigmentosa

Figure 1 Proposed prospective treatment protocol with relevant medicines considered suitable to treat cystoid macular oedema associated with retinitis pigmentosa