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ADVANCES IN GENE-BASED THERAPIES FOR LEBER CONGENITAL AMAUROSIS: A REVIEW OF CLINICAL TRIALS

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ABSTRACT
Leber congenital amaurosis (LCA) is characterized by early-onset significant vision loss in infancy. Conventional therapeutic strategies offered limited benefits, thus escalating the focus on research into gene-based therapies. This review aimed to explore the clinical trials focusing on gene-based therapies for LCA. This literature review identified clinical trials on gene-based therapies for LCA registered on ClinicalTrials.gov using the keyword "Leber congenital amaurosis OR LCA," with no restriction on year of registration. Trials not involving gene therapy were excluded. For each eligible trial, the corresponding National Clinical Trial (NCT) number was used to search the PubMed database for peer-reviewed publications, and grey literature was sourced when no publications were available. Extracted data included patient inclusion criteria, sample size, intervention dosage, safety profiles, adverse events, and efficacy outcomes. Numerous gene-based therapies for LCA have been reported, especially those targeting mutations in RPE65, CEP290, GUCY2D, AIPL1, and LCA5. Adeno-associated virus (AAV)-mediated gene replacement therapies, CRISPR/Cas9 gene editing, and antisense oligonucleotides (AONs) have been reported to deliver promising outcomes for LCA. Luxturna (voretigene neparvovec) has been FDA-approved for RPE65-LCA, while trials on emerging therapies like EDIT-101 and sepofarsen hold therapeutic promise for CEP290-LCA. The review underscores emerging strategies in gene therapy that lay the foundation for tailored, mutation-specific treatments. Several challenges remain in optimizing delivery vectors, preserving long-term efficacy, and minimizing adverse events.

Keywords: gene-based therapy; genetic mutations; inherited retinal dystrophy; leber congenital amaurosis

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INTRODUCTION

Leber congenital amaurosis (LCA), along with early-onset severe retinal dystrophy (EOSRD), belong a group of monogenic inherited retinal dystrophies (IRDs) associated with early vision loss.(Balbirsingh et al., 2025) LCA was originally classified by a German ophthalmologist, Theodor Leber, in 1869 as a cluster of pigmentary retinal dystrophy in a child with vision loss, amaurotic pupils, wandering nystagmus, and congenital retinitis pigmentosa (RP). This disease predominantly exihibits autosomal recessive inheritance.(Kondkar & Abu-Amero, 2019). The prevalence of LCA ranges between 1:30000 and 1:80000. Approximately 5% of all IRDs and 20% of childhood blindness are caused by LCA. The earliest presentation of LCA occurs within 6 months to 1 year of life, often resulting in legal blindness. Therefore, it is considered as one of the most severe forms of IRDs.(Upadhyaya et al., 2025).

The conservative management of patients with LCA consists of symptomatic relief and supportive treatment, including a balanced and healthy diet. Supplementation with Vitamin A, minerals, and amino acids has shown no clear advantage in patients with LCA and is therefore not advised.(Daich Varela et al., 2022) Based on a bibliometric study covering 2002–2022, research focusing on LCA increased continuously, reaching its peak in 2015 and 2018, with studies consistenly exploring development of gene therapy for LCA.(Huang et al., 2024) LCA often interrelates clinically and

genetically with EOSRD. To date, 26 genes have been identified as pathogenic for LCA/EOSRD.(Bouzia et al., 2020; Huang et al., 2024).

The most commonly implicated genes associated with LCA include CEP290, CRB1, GUCY2D, RDH12, RPE65, and RPGRIP1. Mutations in these genes impact several retinal processes, such as the phototransduction, the visual cycle and the development and integrity of the photoreceptor. As a result, LCA exhibits phenotypic variability, comprising differences in the age of onset and progression of vision loss, involvement of the macula, structural alterations within the retina, and the degree of residual photoreceptor function.(Balbirsingh et al., 2025; Zobor et al., 2023). Recently, with the rapid advances in the field of information technology, substantial amount of research has focused on genes potentially causing LCA and on gene-based therapies, novel therapeutic strategies with promising prospects for LCA treatment. The purpose of this review is to provide a comprehensive description of clinical trials investigating the gene-based therapies for LCA.

METHOD

This study is a literature review focused on clinical trials investigating gene-based therapies for Leber congenital amaurosis (LCA). A comprehensive search was conducted on ClinicalTrials.gov using the keyword "Leber congenital amaurosis OR LCA" for the condition/disease field. The search was last performed on July 18, 2025. All identified trials were screened. Studies that were observational or did not involve LCA or gene-based therapies were excluded. No restrictions were applied regarding the year of trial registration or publication. For each eligible trial, the corresponding National Clinical Trial (NCT) number was used to search the PubMed database for peer-reviewed publications. When no peer-reviewed publications were available, grey literature such as conference presentations and abstracts were searched and included. Data extracted from each source consisted of participant numbers, intervention dosage, safety profiles, adverse events, and efficacy outcomes.

RESULT

The search strategy identified 46 clinical trials registered on ClinicalTrials.gov. Of these, eleven trials were observational studies, nine were unrelated to LCA, four did not involve gene-based therapies as the intervention, one lacked sufficient methodological detail and clear efficacy standpoint, and one was diagnostic interventional study. These trials were excluded from this review. Among the 20 included trials, the majority investigated gene augmentation therapy, followed by antisense oligonucleotides and one modifier gene therapy trial. Trial registrations ranged from 2007 to 2025, with studies conducted across North America, Europe, and Asia, including several multi-center, international collaborations. Further details of the characteristics and findings of the included trials are described in the Discussion section.

DISCUSSION

The distinctive immune-privileged properties of the eyes, combined with constant breakthroughs in the identification of contributing genes, provide great opportunities for the development of treatments for LCA.(Chiu et al., 2021) Several genes that are commonly associated with LCA include the retinal pigment epithelium-specific 65 kDa protein (RPE65), guanylate cyclase 2D (GUCY2D), centrosomal protein 290 kDa (CEP290), and aryl hydrocarbon receptor-interacting protein-like 1 (AIPL1).(Bouzia et al., 2020) The following sections outline relevant clinical trials for the treatment of LCA, categorized by the genetic mutation targeted by each therapy.

a. RPE65- LCA2

The retinal pigment epithelium 65 kDa protein (RPE65) is a critical component of the vertebrate visual system that plays a non-redundant role in the visual cycle by catalyzing the isomerization of all-trans-retinyl esters into 11-cis-retinol within the retinal pigment epithelium (RPE). This reaction is a critical step in the regeneration of 11-cis-retinal, the visual chromophore required for the

function of both rod and cone photoreceptors.(Kiser, 2022) RPE65 also contributes to the function and survival of human cone photoreceptors.(Kolesnikov et al., 2018). Mutations in the RPE65 gene have been identified in conditions such as Leber congenital amaurosis type 2 (LCA2), severe early childhood-onset retinal dystrophy (SECORD), and non-syndromic retinitis pigmentosa (RP20). The prevalence of LCA or SECORD is estimated to range from 1 in 30,000 to 1 in 80,000 births, with RPE65 mutations accounting for approximately 3–16% of these cases. Although LCA and SECORD share similar features, they can be distinguished by the age of onset and severity. LCA typically presents within the first few months of life and is characterized by profound visual impairment, night blindness, involuntary eye movements (nystagmus), reduced pupillary reflexes, light sensitivity (photophobia), and markedly diminished responses on electroretinography (ERG). The condition is progressive and may lead to complete blindness by the third or fourth decade of life. In contrast, SECORD usually manifests between ages 4 and 6 with a relatively less severe clinical course.(Aoun et al., 2021; Sinim Kahraman et al., 2022)

The advent of gene therapy for RPE-related LCA was reported as early as the year of 2007 when three independent trials (NCT00643747, NCT00481546, NCT00516477) were concurrently conducted.(Testa et al., 2013) Bainbridge et al. conducted a Phase 1/2 open-label, single-center study (NCT00643747) in which a sngle subretinal injection of recombinant adeno-associated virus 2/2 (rAAV2/2) vector, rAAV2/2.hRPE65p.hRPE65, carrying the RPE65 complementary DNA (cDNA). was administered to 12 participants at two dose levels. The first four participants received the lower dose (1×1011 vector genomes) while the subsequent eight participants received the higher dose (1×1012 vector genomes). Three-year follow-up data were available for all participants. Improvements in retinal sensitivity were observed, to varying degrees, in six participants for up to three years, reaching the peak at 6 to 12 months after treatment and then declining. No associated improvement in retinal function was detected via electroretinography (ERG). The ocular adverse events observed in this study were mild or transient intraocular inflammation in three participants who received the higher dose. Two participants experienced clinically significant deterioration in visual acuity. Macular thinning and a decline in visual acuity were also evident after subfoveal vector administration. Systemic adverse events reported including those known to be associated with oral glucocorticoids.(Bainbridge et al., 2008, 2015).

Hauswirth et al. utilized the AAV2-CBSB-hRPE65 vector in an open-label, dose-escalation Phase 1 clinical trial (NCT00481546) involving 15 patients (8 females and 7 males, aged 11-30 years) with RPE65-associated Leber congenital amaurosis (LCA).(Hauswirth et al., 2008) The vector consisted of two AAV2 inverted terminal repeats (ITR) that flank a regulatory element composed of the cytomegalovirus (CMV) immediate early enhancer and chicken β-actin promoter with first intron/exon junction, hybrid chicken β-actin and rabbit β-globin intron/exon junction followed by a human RPE65 cDNA and the SV40 polyadenylation signal. The total length of the transgene cassette was approximately 3921 base pairs (bp).(Jacobson et al., 2006) The participants were divided into five cohorts based on age and dosing regimen and received either one or two subretinal injections. No systemic safety concerns were detected; certain ocular adverse events that occurred, such as retinal detachment and inflammation, were attributable to the surgical procedure. Visual function, measured with full-field sensitivity testing (FST) and transient pupillary light reflex (TPLR), showed significant improvement compared to baseline in study eyes and remained stable for up to three years. However, visual acuity did not improve significantly and showed no meaningful difference between study eyes and control eyes.(Hauswirth et al., 2008; Jacobson et al., 2012).

Maguire et al. conducted a Phase 1 clinical trial (NCT00516477) to assess the safety and efficacy of the AAV.hRPE65v2 (Voretigene neparvovec-rzyl, Luxturna) vector. This vector also utilized the hybrid chicken-β-actin promoter, but with a modified Kozak sequence engineered at the translational start site to enhance transgene expression.(Bennicelli et al., 2008; Maguire et al., 2008)

Within the Italian arm of the Phase 1 clinical trial, five patients received unilateral subretinal injections of AAV2-hRPE65v2 and were followed for three years. Results showed statistically significant improvements in best-corrected visual acuity (BCVA) in treated eyes ($p < 0.001$), with maximal gains typically observed within six months post-injection and maintained through the final follow-up. The mean visual field area expanded from 1058 deg² at baseline to 4630 deg² at three years. A reduction in nystagmus frequency was also observed, with strong correlation to BCVA improvements. Pupillometry revealed significantly enhanced pupillary constriction in treated eyes at both 1- and 3-year follow-ups ($p < 0.05$). Additionally, all participants demonstrated marked improvements in mobility testing, with the gains sustained through three years post-injection. No serious adverse events related to the vector were reported, and retinal structure remained stable in all but one patient, who developed a non-progressive macular hole.(Maguire et al., 2008; Testa et al., 2013).

Following the initial trial, a follow-on Phase 1 study (NCT01208389) was conducted to evaluate the safety and efficacy of bilateral subretinal injections of AAV2-hRPE65v2 in participants who had previously received unilateral treatment. Eleven participants (aged 11–46 years) from the previous trial (NCT00516477) received a second subretinal injection in the contralateral eye 1.7 to 4.6 years after the first. The procedure was well tolerated, with no serious vector- or surgery-related adverse events. Mild and self-limiting events, including transient ocular inflammation and intraocular pressure elevation, were the most commonly reported. Functional outcomes mirrored those observed after the first injection: full-field light sensitivity threshold (FST) testing showed improved retinal sensitivity, and multi-luminance mobility testing demonstrated better functional vision, with participants navigating mobility courses under lower light conditions. Qualitative pupillary light reflex assessment also showed improved responses in all second-treated eyes. Additionally, comparison of MRI data at baseline and one year post-treatment revealed significantly increased bilateral activation across the visual cortex, extending from medial to lateral and from posterior to anterior regions of the occipital cortex.(Bennett et al., 2016)

A Phase 3 multicenter, open-label randomized controlled trial (NCT00999609) was conducted to evaluate the efficacy and safety of AAV2-hRPE65v2 (voretigene neparvovec, Luxturna) in individuals with RPE65-mediated inherited retinal dystrophy. A total of 31 participants (aged 4–44 years) were enrolled and randomized in a 2:1 ratio to receive bilateral subretinal injections of 1.5 x 1011 vector genomes of voretigene neparvovec in 0.3 mL total volume. or remain in the control group. The primary efficacy endpoint was performance on a multi-luminance mobility test (MLMT) at one year. At baseline, all participants had severely reduced vision and met specific inclusion criteria, including biallelic RPE65 mutations and measurable visual function. Participants in the treatment group showed a statistically significant improvement in functional vision, mean bilateral MLMT change score was 1.8 (SD 1.1) light levels in the intervention group versus 0.2 (1/0) in the control group (difference of 1.6, 95% CI 0.72-2.41, p=0.0013). And 13 of 20 participants in the treatment group passed MLMT at the lowest luminance level tested 91 lux, achieving the maximum possible improvement, compared to none in the control group. Secondary endpoints, including full-field light sensitivity threshold (FST) testing, also demonstrated significant improvements in the treatment group. No product-related serious adverse events were reported, and the overall safety profile was favorable, with most ocular events being mild and related to the surgical procedure.(S. Russell et al., 2017) This trial was the first randomized, controlled Phase 3 study of a gene therapy targeting a genetic disorder.(S. Russell et al., 2017) The results contributed to the subsequent approval of Luxturna by the U.S. Food and Drug Administration (FDA) in December 2017, making it the first gene therapy approved in the United States for an inherited disease.(Darrow, 2019)

Several trials have been conducted to investigate other types and configuration of vectors. An open-label, non-randomized, multicenter, sequential, two-arm Phase 1/2 clinical trial (NCT00749957) was conducted involving 12 participants (8 adults and 4 children, aged 6–39 years) diagnosed with

LCA or SECORD. Participants were divided into two groups of six, each receiving a single subretinal injection of 450 µL containing either 1.8×10^{11} vector genomes (Group 1) or 6×10^{11} vector genomes (Group 2) of rAAV2-CB-hRPE65 in the poorer seeing eye. This vector is structurally similar to the rAAV2-CBSB-hRPE65 vector but includes an additional 152 base pairs at the 5′ end of the CMV immediate early enhancer. At two years, all patients tolerated the surgical procedure and vector administration without any treatment-related serious adverse events. The most frequently reported adverse events were those related to the surgical procedure, including subconjunctival hemorrhage, ocular hyperemia, reduced visual acuity, eye pain, eye irritation, elevated intraocular pressure, headache, or back pain. These were mild to moderate in severity and resolved within 1–30 days. Adverse events possibly related to the vector included ocular hyperemia in two patients and photopsia in one. Improvements in BCVA were observed in five patients; static perimetry (V30) improved in six patients, total visual field hill of vision (VTOT) in five, and kinetic visual field area in three. However, one participant experienced a decline in BCVA, and two demonstrated a reduction kinetic visual field area. Within year 3-5 follow-up, only minor unrelated illnesses were reported. Pediatric subjects demonstrated sustained improvements in BCVA and static perimetry in treated eyes, along with reduced nystagmus observed on clinical examination. Most adult patients showed no consistent change in visual acuity and static perimetry, though modest and transient improvements in kinetic fields were observed in a few cases. The greatest improvements in visual acuity were observed in younger patients with better baseline visual acuity, suggesting that treatment at an early age may help prevent progression of photoreceptor degeneration.(Pennesi et al., 2018; Weleber et al., 2016)

Le Meur et al. conducted a Phase 1/2 clinical trial of rAAV2/4.RPE65.RPE65 (NCT01496040) in 9 participants aged 9-42 years. The AAV2/4 serotype was selected over AAV2/2 due to its specific tropism toward RPE cells. Patients received either low (1.22 x 1010 to 2 x 1010 vector genomes [vg]) or high (between 3.27 x 1010 and 4.8 x 1010 vg) vector doses. Subretinal injections were administered simultaneously in two to five injection sites, primarily targeting the extra-foveal and peripheral retinal regions. All patients showed good systemic and ocular tolerance to the treatment, with no clinically relevant changes in hematological or biochemical parameters observed during follow-up. Ophthalmological follow-up revealed no deleterious effects. At one-year post-injection, the average improvement in visual acuity was not statistically significant, although greater improvements were observed in eyes with pre-existing nystagmus. Microperimetry analysis showed that the average sensitivity and the number of microscotomas in both treated and untreated eyes remained stable for up to three years. No improvements were observed in electroretinography (ERG), pupillometry, or retinal autofluorescence. Mobility testing showed no significant differences between the treated and untreated eyes one year post-injection.(Le Meur et al., 2018)

A UK-based company, MeiraGTx funded a Phase 1/2 clinical trial of AAV2/5-OPTIRPE65 (NCT02781480). The trial included 15 participants across three dose-escalation cohorts and one pediatric expansion cohort. The dose-escalation cohorts each included 3 adults in each cohort and the pediatric expansion cohorts consisted of 6 children. Each participant received a subretinal injection of AAV2/5-OPTIRPE65 in the eye with poorer baseline vision, as determined by the participant. Doses administered were 1.0×10^{11} vg/ml (Cohort 1), 3.0×10^{11} vg/mL (Cohort 2), 1.0×10^{12} vg/mL (Cohort 3), and 1.0×10^{11} vg/mL (pediatric expansion cohort). In this trial, the AAV5 was selected over AAV2 capsid due to its approximately fourfold transduction efficiency in human RPE cells. The treatment was generally well tolerated, with most adverse events being transient and mild to moderate in severity. Inflammation occurred in three of six participants in Cohorts 2 and 3 but was effectively managed by extended corticosteroid use. No instances of acute retinal thinning were reported in the postoperative period, and no significant changes in retinal thickness or macular volume were observed after 36 months. Among the nine participants who received the 1.0×10^{11} vg/mL dose, statistically significant improvements were observed at 24 weeks post-treatment in multiple assessments of visual function and functional vision including vision-guided mobility

(maze navigation), retinal sensitivity (static perimetry), and foveal-driven visual function (ETDRS letters read, contrast sensitivity, and reading speed.(Forbes & Michaelides, 2020)

There is continued interest in advancing gene therapy approaches for RPE65-associated LCA. This includes the development of HG004, an AAV9-based gene therapy, for the RPE65-LCA. AAV9 was selected over AAV2 due to its superior tropism for the human RPE. In the ongoing LIGHT study (NCT06088992), an interim analysis of six patients aged 8 to 35 years who received subretinal injections of low or middle doses of HG004 in their worse-seeing eye showed improvements in visual function, including BCVA, retinal sensitivity, and visual field area. No serious adverse events or dose-limiting toxicities were observed, and most adverse events were mild and self-resolving.(Luk et al., 2024) A comparative analysis of clinical outcomes suggested that HG004 may reduce the risk of foveal thinning compared to AAV2-based therapy. The absence of progressive atrophy in HG004-treated eyes may be attributed to differences in vector design, dosage, and injection technique. The use of AAV9 and the lower vector dose were attributed to a reduction in inflammation and metabolic stress. Furthermore, the smaller injection volume in the HG004-treated eyes (200 µL versus the 300 µL in the Luxturna study) and controlled bleb formation may help to minimize retinal stretch injuries.(Luk et al., 2025) A separate multi-regional Phase 1/2 trial (NCT05906953) is currently recruiting to further investigate HG004's clinical potential, with estimated study completion in 2028. This therapy has received both Orphan Drug Designation and Rare Pediatric Disease Designation from the U.S. Food and Drug Administration.(HuidaGene Therapeutics Co., Ltd., 2024; Luk et al., 2025)

b. CEP290-LCA10

One of the most frequently mutated genes in LCA patients is the CEP290, which causes a condition known as LCA10 and accounts for up to 15% of all LCA cases. The CEP290 gene is located in the connecting cilium of photoreceptors, and is essential for the process of cilium assembly and ciliary protein trafficking. This mutation occurs deep within intron 26 of the CEP290 gene, causing a cryptic splice donor site that elicits inclusion of a cryptic exon carrying a premature stop codon (p.C998X) into around half of cellular CEP290 transcripts, leading to partial activity of CEP290 in patients with IVS26 mutations.(Ruan et al., 2017).

Gene augmentation therapy using viral gene delivery vectors (AAV) was initially proposed. However, the large size of the CEP290 coding sequence (~7.5kb), compared to the packaging capacity of AAV (~4.7 kb), limits the applicability of this strategy. A breakthrough in genetic engineering allows the ability to conduct gene-editing for *CEP290* IVS26 mutation using the clustered regularly interspaced short palindromic repeats (CRISPR) and CRISPR-associated (Cas) protein 9 system (CRISPR/Cas9). This technology utilizes the AAV5 as a vector to deliver bacteria *Staphylococcus aureus* Cas9 with *CEP290*-specific guide RNAs (gRNAs) to the photoreceptor cells via injection to the subretinal tissue, known as the EDIT-101. The pair of gRNAs stimulates removal or inversion of the mutated IVS26, thus resulting in normal splicing followed by restoration of functional CEP290 expression. Injection into the subretinal area, along with natural tropism of AAV5 toward the photoreceptor cells and the use of the photoreceptor specific GRK1 promoter, collaboratively serve to limit the expression of CRISPR/CAS9 system specifically to the target tissues and cells.(Maeder et al., 2019; Ruan et al., 2017).

Editas Medicine sponsored a Phase 1/2, open-label, single-increasing-dose clinical trial (NCT03872479) including 12 adults (aged 17 – 63 years; median 37 years old) and 2 children (aged 9 and 14 years old) with CEP290 IVS26 mutation. Participants received a subretinal injection of EDIT-101 in the worse (study) eye with varying dosage (low, medium, high). Six participants showed a significant improvement of at least 0.6 log cd-sec/m^2 in cone-mediated vision based on full-field stimulus testing (FST). Overall, nine participants (64%) exhibited meaningful gains from baseline in either best-corrected visual acuity, red light sensitivity as assessed by FST, or mobility

test performance. Additionally, six participants experienced notable improvements in vision-related quality of life scores. No serious adverse events were recorded in relation to the treatment or procedure, and no dose-limiting toxic effects were reported. This finding support further research of in vivo CRISPR/CAS9 gene editing is encouraged to further assess the efficacy and safety of treatment in LCA as well as a potential therapeutic strategy for other IRD due to CEP290- IVS26 and other genetic causes.(Pierce et al., 2024)

Alternative approach currently under investigation for the treatment of CEP290-associated LCA10 is the use of antisense oligonucleotides (AONs), novel therapeutic agents designed to bind specific RNA sequences. The primary mechanism of action of AONs is to silence either a splice site or a mutant sequence at the mRNA level, leading to exon skipping or variant silencing, respectively. One AON currently undergoing investigation for LCA10 is Sepofarsen (QR110), a 17-mer 2′-O-methyl-modified phosphorothioate antisense RNA oligonucleotide. Sepofarsen specifically binds to the pseudoexon region introduced by the deep intronic c.2991+1655A>G mutation in intron 26 of the CEP290 gene. This binding prevents the cryptic splice donor site from being recognized by splice factors. As a result, normal splicing of the pre-mRNA is restored, allowing the cell to produce full-length, functional CEP290 protein. In the Phase 1b/2 open-label, multicenter clinical trial (NCT03140969) evaluating sepofarsen in patients with CEP290-associated LCA10, 11 participants aged 8–44 years were enrolled and divided into two cohorts based on dosing regimens. Six participants received 160 µg loading and 80 µg maintenance doses, while five participants received 320 µg loading and 160 µg maintenance doses. All participants received intravitreal injections in one eye and were followed for one year. The result of this trial showed clinically meaningful improvements in visual function, with nearly half of participants gaining at least 15 letters in BCVA on the ETDRS chart. These gains were generally supported by improvements in full-field stimulus testing (FST) and mobility test performance. However, dose-dependent ocular adverse events were observed, with 10 of 11 participants developing adverse events in the treated eye. Cataract development was observed in 8 participants (three in the 160 µg/80 µg group and all five in the 320 µg/160 µg group). Cataracts in the higher-dose group occurred earlier and were more severe, but visual acuity was restored after lens replacement without complications. Additional adverse events in the higher-dose group included cases of cystoid macular edema, parafoveal intraretinal cysts, and retinal thinning, which generally stabilized or resolved with topical treatment. There were no reports of systemic adverse events.(S. R. Russell et al., 2022) Nine participants were enrolled in a long-term extension study (NCT03913130), but the study was prematurely terminated due to sponsor decision for reasons unrelated to safety.(Laboratoires Thea, 2019)

A randomized, double-masked, sham-controlled Phase 2/3 clinical trial (NCT03913143, ILLUMINATE) was conducted to evaluate the efficacy and safety of sepofarsen. Thirty-six participants at 14 sited across Europe, North America, and Latin America were included in this trial and were randomized into three arms: sepofarsen 160/80 µg, sepofarsen 80/40 µg, or sham. The primary endpoint of this trial was the mean change in BCVA in the treated eye from baseline compared with sham at Month 12. Secondary endpoints included full-field stimulus testing threshold (FST; red, blue, white), a mobility course composite score, and safety. The did not meet both its primary and secondary endpoints. The improvements in BCVA, FST, and mobility course composite score was not significantly different from the sham group. However, post hoc analyses comparing the treated eye to the contralateral eye revealed a positive treatment effect consistent with earlier Phase 1/2 results. Approximately a third of participants experienced improvements across multiple endpoints (BCVA, FST, mobility, and patient-reported outcomes such as VFQ25- and PGI-C). From a safety standpoint, although sepofarsen was generally well tolerated and the Treatment Emergent Adverse Events (TEAEs) were consistent with the findings of the Phase 1/2 trial, three serious adverse events were reported: acute angle closure glaucoma, foveal thinning, and transient epileptic seizures. Another Phase 2/3 trial (NCT04855045, BRIGHTEN) investigated the

safety and tolerability of sepofarsen in pediatric subjects. However, its results have not been made publicly available. (Leroy et al., 2022; ProQR Therapeutics, 2019, 2022).

While the primary endpoint was not met, the trial demonstrated beneficial effects at the individual level and a favorable safety profile, supporting continued investigation. Accordingly, a double-masked, randomized, placebo-controlled, paired-eye Phase 3 trial (NCT06891443, HYPERION) is currently ongoing. At the beginning of the study, each participant will have one eye randomly assigned to receive sepofarsen and the other eye assigned to placebo during the first year. In the second year, the eye initially assigned to sepofarsen will continue the treatment. For the eye initially assigned to placebo, the treatment will be reallocated: 50% of the eyes will continue to receive placebo, and 50% of the eyes will switch to sepofarsen. Sepofarsen and placebo will be administered via intravitreal injection every six months. The trial is currently recruiting participants, with estimated primary and study completion dates in 2027 and 2028, respectively.(Laboratoires Thea, 2025).

Another novel therapeutic approach currently being evaluated for inherited retinal diseases such as retinitis pigmentosa (RP) and Leber congenital amaurosis (LCA) is OCU400 (AAV-hNR2E3), a modifier gene therapy that targets the master regulatory gene NR2E3 via adeno-associated virus (AAV) delivery. NR2E3 is a retina-specific nuclear hormone receptor that regulates key processes including retinal cell homeostasis, metabolism, and the visual cycle. Rather than replacing a specific mutated gene, OCU400 utilizes an adeno-associated virus (AAV)-based delivery of the NR2E3 nuclear hormone receptor gene to modulate downstream gene networks and stabilize retinal homeostasis. This approach is designed to be gene-agnostic and can potentially address multiple genetic defects with a single intervention.(Upadhyay et al., 2024).

A multi-center, open-label, Phase 1/2 trial (NCT05203939) was conducted to assess the safety and efficacy of OCU400 for retinitis pigmentosa (RP) and Leber congenital amaurosis (LCA). The study consisted of three dose-escalation cohorts and three dose-expansion. A total of 22 participants were enrolled (18 individuals with RP and 4 with CEP290-LCA). Safety and efficacy outcomes were reported only for the RP cohort. The results for the LCA subgroup were not available. Among the RP participants, 16 of 18 subjects demonstrated either preservation or improvement in the treated eye based on either BCVA, low-luminance visual acuity (LLVA) or MLMT scores from baseline. Reported ocular adverse events included panuveitis and decreased BCVA. No serious adverse events (SAEs) related to OCU400 were recorded in the low- and medium-dose groups. In the high dose and open-enrollment cohorts, two participants experienced SAEs unrelated to OCU400, attributed to surgical technique with cases resolved within days or weeks.(Ocugen, 2021; Upadhyay et al., 2024) Following this trial, a Phase 3 multicenter, randomized, double-masked, placebo-controlled study (NCT06388200, liMeliGhT) is underway to further evaluate the efficacy, safety, and tolerability of OCU400 for retinitis pigmentosa. The primary endpoint is the proportion of responders, defined as participants achieving improvement of at least two lux levels from baseline on the Luminance Dependent Navigation Assessment (LDNA). The trial began dosing its first patient in June 2024 with an estimated study completion date in 2026.(Ocugen, 2024)

c. GUCY2D- LCA1

GUCY2D, the first gene reported to be associated with LCA, accounts for 10–20% of all LCA cases.(Boye, 2015; Kumaran et al., 2017) This gene is responsible for encoding the retinal guanylyl cyclase 1 (RetGC1), an enzyme expressed in the outer segment of the photoreceptors, predominantly in the cones. RetGC1 is a key component of phototransduction involved in restoring cytoplasmic cGMP levels that decrease upon light stimulation. Restoration of cytoplasmic cGMP levels allows the influx of intracellular Ca^{2+} and consequently facilitates the recovery of photoreceptor dark-adapted state.(Rodilla et al., 2023) Mutations in the GUCY2D gene can reduce

or abolish the ability of GC1 to replenish cGMP in photoreceptors, resulting in the biochemical state equivalent to chronic light exposure in these cells.(Boye, 2015).

GUCY2D-associated LCA is characterized as a severe congenital stationary cone-rod dystrophy with high hyperopia, panretinal degeneration, and diminished visual acuity. Biallelic variants in GUCY2D also have been more rarely associated with rod-predominant dysfunction. Patients with biallelic GUCY2D mutations appear to be good candidates for gene augmentation therapy due to the preservation of their retinal structure and residual rod fucntion throughout most of their lives, thereby providing an extended window for treatement and the potential for long-term outcomes.(Rodilla et al., 2023).

Recently published Phase 1/2 clinical trial (NCT03920007) on 15 LCA patients who were genetically confirmed having biallelic mutations in GUCY2D shown great tolerability with 300 µL of ATSN-101 (a recombinant adeno-associated virus serotype 5 (AAV5) vector containing the human GUCY2D cDNA under the transcriptional control of the human rhodopsin kinase (hGRK1) promoter). ATSN-101 was administered by injection into the subretinal to the macula in the study eye. Study participants also received periprocedural corticosteroids and antibiotics to minimize the inflammation. Nine study participants were included in dose escalation with 3 cohort studies, each cohort study were assigned with 3 participants being given low dose (cohort 1), middle dose (cohort 2), and high dose (cohort 3) of ATSN-101. The other six study participants were included in dose expansion group with 2 cohort studies, 3 adult participants were assigned into high dose of ASTN-101 group (cohort 4) and the other 3 pediatric participants were assigned with high dose of ASTN-101 group (cohort 5). The main study was completed within the 12-month period, and an additional four years follow-up to further assess the safety and efficacy of ATSN-101. No serious treatment-emergent adverse effects (TEAEs) were reported in the study, however some mild ocular inflammation and reversible with steroid was reported. In groups receiving high dose of ATSN-101, mean change in dark adapted FST on month 12 was 20.3 decibels (dB; 95% CI 6.6 to 34.0) in the treated eyes compared to 1.1 dB (–3.7 to 5.9) in the untreated eyes. BCVA improvements were modest (p=0.10). The MLMT was conducted on three of six patients in the high dose group with maximum score achieved in the treated eye.(Yang et al., 2024)

d. AIPL1-LCA4

Biallelic mutations in the AIPL1 gene, responsible for Type 4 LCA (LCA4) and estimated to account for only about 5% of LCA, are associated with autosomal recessive LCA. AIPL1 serves as a photoreceptor-specific co-chaperone that collaborates with the molecular chaperone heat shock protein 90 (HSP90) to promote the proper and stable assembly of the retinal cyclic GMP (cGMP) phosphodiesterase (PDE6) holoenzyme in both cones and rods. The absence of AIPL1 markedly reduces the PDE6 levels in cone and rods due to misassembly of PDE6 subunits. These misassembled subunits are targeted for degradation by the proteasomes. Elevated cGMP levels cause rapid photoreceptor degeneration, and electroretinography (ERG) responses are extinguished. Similarly, disease-causing variants of PDE6 also cause elevated cGMP levels and subsequent retinal degeneration..(Aboshiha et al., 2015; Sacristan-Reviriego et al., 2018).

Reported AIPL1 variants associated with LCA include missense and nonsense mutations, as well as small insertions and duplications, small deletions and splice alterations. Missense variants occurring at the very first or last nucleotides of exons, along with small insertions and duplications spanning intron-exon boundaries, have been demonstrated to induce aberrant pre-mRNA AIPL1 splicing, thus clarifying the pathogenic mechanisms of these variants. Additionally, missense and nonsense variants in the FKBP-like and tetratricopeptide repeat domains of AIPL1 lead to the loss of both HSP90 interaction and PDE6 activity leading to the occurrence of LCA.(Aboshiha et al., 2015; Sacristan-Reviriego et al., 2020) The study conducted by Aboshiha et al., using high resolution optical computed tomography (OCT) imaging, found promising evidence of relative preservation of

the foveal outer retinal structure in the very youngest AIPL1-LCA patients. Therefore, a human gene therapy-based approach might be considered in select AIPL-LCA patients with preserved outer retinal structure.(Aboshiha et al., 2015).

A non-randomized, single-arm, clinical trial in the UK was conducted including four children aged between 1.0–2.8 years with severe retinal dystrophy associated with biallelic disease-causing sequence variants in AIPL. Participants were treated with a recombinant adeno-associated viral vector comprising the human AIPL1 coding sequence driven by a human rhodopsin kinase promoter region (rAAV8.*hRKp.AIPL1*). The intervention was administered to one eye of each child via subretinal injection. Oral prednisone was prescribed to prevent inflammation. At a mean follow-up of 3.5 years (range 3.0–4·1), improvements of the visual acuity were observed in the treated eyes , with a mean of 0.9 logMAR (range 0.8–1.0). In contrast, the children's untreated eyes visual acuity became unmeasurable at the final follow-up. An objective test of visual acuity was conducted in two compliant children confirmed functional improvements. The measurement of visual evoked potentials showed enhanced activity of the visual cortex, specifically in the treated eyes. Imaging studies revealed better preservation of the sturctural lamination of the outer retina in the treated eyes of three children, and retinal thickness was better maintained in all treated eyes compared to untreated eyes. However, one child developed cystoid macular oedema in the treated eye. These results demonstrate the potential efficacy and safety of AIPL1 gene augmentation therapy in young children with severe retinal dystrophy, though ongoing monitoring and larger studies are necessary to fully assess long-term outcomes and adverse effects.(Michaelides et al., 2025)

e. LCA5-LCA5

Lebercilin, encoded by the LCA5 gene (C6ORF152) located on chromosome 6q14.1, is an 80 kDa protein expressed in the connecting cilium of photoreceptors. It is widely present in human and mouse tissues, particularly in ciliated epithelia. Lebercilin interacts with other intraflagellar transport proteins essential for the bidirectional movement of proteins from the inner segments to the outer segments of photoreceptors, particularly during photoreceptor outer segment formation. Mutations in the LCA5 gene, accounting for approximately 2% of the overall cases of LCA, disrupt the function of lebercilin. These mutations cause clinical manifestations such as nystagmus, delayed pupillary responses, photophobia, hyperopia, and severely decreased visual activity, often presenting as early in the first year of life.(Faber et al., 2023; Uyhazi et al., 2020).

Aleman et al. conducted a Phase 1b/2a clinical trial (NCT05616793) to assess the safety and tolerability subretinal OPGx-001 for LCA5-associated IRD. The trial is currently ongoing and plans to enroll 15 participants, with study completion estimated in June 2028. The therapeutic agent OPGx-001 consists of a sterile suspension of an AAV8 vector containing single-stranded DNA that encodes the native human LCA5 transgene (pAAV.hLCA5) driven by CMV immediate early enhancer and the chicken beta-actin (CβA) promoter. Preliminary safety data from three subjects receiving unilateral subretinal injections of 1×10^{10} vector genomes per eye showed no serious adverse events related to the vector or procedure. Retinal lamination assessed via spectral-domain optical coherence tomography (SD-OCT) remained stable in treated eyes compared to untreated controls. Cone-mediated vision improved by an average of 1 $\log_{10}$ unit on chromatic full-field stimulus testing, and objective pupillometry confirmed these results. Virtual reality orientation and mobility test shown better performance than baseline. The visual acuity of the treated eyes either returned to the baseline or improved in all participants. The favorable safety outcomes and treatment efficacy provide a foundation for enrolling patients with milder phenotypes while implementing careful dose escalation.(Aleman et al., 2025)

CONCLUSION

Gene-based therapies offer promising and innovative approaches for the future of LCA treatment. Numerous clinical trials have demonstrated that specific and targeted gene substitution and editing

techniques have resulted in improvements in visual function, notably in patients with mutations in the RPE65, CEP290, and GUCY2D genes. The FDA approval of Luxturna marked a pivotal moment in the landscape of therapeutic interventions for LCA, a condition once considered a progressive, irreversible disease. The development of innovative platforms such as CRISPR/Cas9 editing (EDIT-101), antisense oligonucleotides (sepofarsen), and gene-agnostic therapy (OCU400) open new possibilities for improving outcomes in patients with these conditions. Further research and refinement of vector technologies are required to promote broader application of gene-based therapies in LCA and other related IRDs.

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