AAV-Based Gene Therapy Products: Ongoing Clinical Trials

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BioPharmAnalyses
40, rue du petit bois
78370 Plaisir
France
Phone: 33 (0)686 683 220
Contact: alb@biopharmanalyses.fr/

OctopusyX BioConsulting
Centre Atlas
24, avenue du Prado
13006 Marseille. France
Phone: 33 (0)668 071 907
Contact:olivier@octopusyx.fr

BioPharmAnalyses

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We are happy to propose you an update on ongoing approved clinical trials on AAV-based gene therapy products.

The publication provides an accurate overview to explore the latest trials using AAV vectors for the treatment of: Cardiovascular Diseases, Hematological Diseases, Hepatic Diseases, Infectious Diseases, inherited Metabolic Diseases, Lysosomal Diseases, Neurological Diseases, Neuromuscular Diseases and Ophthalmological Diseases.

Diseases and trials mentioned have been put in context with the most relevant and recent publications and informations selected by our experts.

The trials presented here have been registered and/or updated on Clinicaltrials.gov until 04/30/2020.

GLOBAL CONTENT

DISEASES MENTIONED

HIGHLIGHTS

- **Two AAV-based gene therapy products have already obtained the go-ahead from US and European health authorities:**

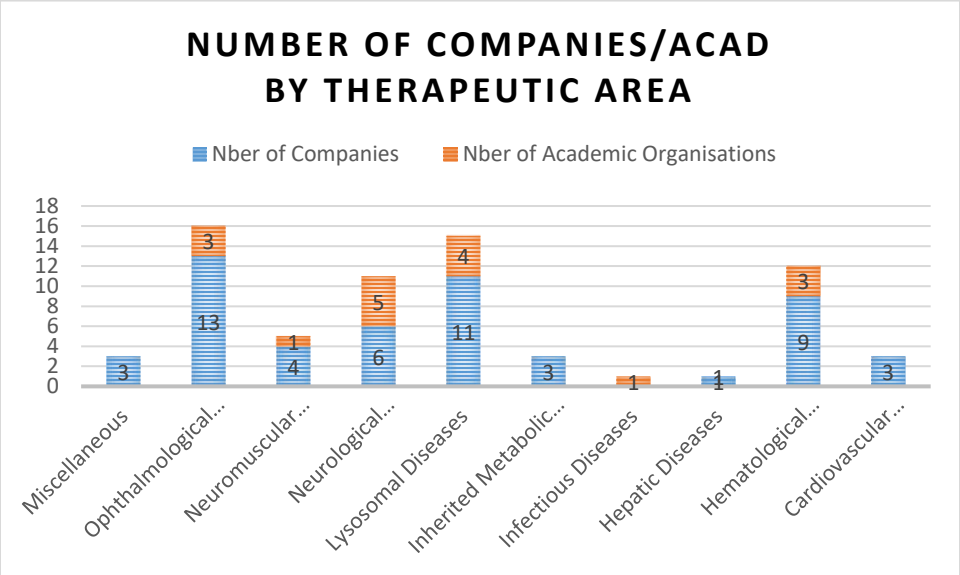
  Luxturna® received FDA approval in December 2017 as a one-time gene therapy to restore functional vision in children and adult patients with biallelic mutations of the RPE65 gene (Leber congenital amaurosis, retinitis pigmentosa). The European Commission approved Luxturna® in December 2018.
  This gene therapy was developed by Children's Hospital of Philadelphia and Spark Therapeutics, now a Roche company.

  Zolgensma® has been approved by the FDA in May 2019 for the treatment of pediatric patients less than 2 years of age with SMA type I with bi-allelic mutations in the SMN1 gene. This gene therapy has been approved in the EU in May 2020.
  This gene therapy was developed by Avexis, now a Novartis company.

- **116 clinical trials using AAV-based gene products are currently ongoing**

- **These 116 clinical trials involve 81 products for the treatment of 40 diseases.**

- **Ophthalmological diseases and lysosomal diseases are the most represented therapeutic areas.**



Examples of Ongoing Clinical Trials Presented in the Study

Hematological Diseases

Hemophilia

Hemophilia is an X-linked genetic disease in which blood doesn't clot properly. Hemophilia A is a deficiency of coagulation factor VIII (FVIII) and Hemophilia B is a deficiency of coagulation factor IX (FIX).

Latest Publications on the Disease

■ « A Molecular Revolution in the Treatment of Hemophilia ».
Butterfield JSS et al. Department of Pediatrics, University of Florida, Gainesville, FL, USA.

Diverse molecular medicines, ranging from antibody to gene to RNA therapy, are transforming treatment of monogenetic bleeding disorders hemophilia A and B .The article provides an overview of these approaches, explains how they differ from standard therapies, and predicts how the hemophilia treatment landscape will be reshaped.

Mol Ther. 2020 Apr 8;28(4):997-1015. doi: 10.1016/j.ymthe.2019.11.006. (Abstract)

■ « Towards a global multidisciplinary consensus framework on haemophilia gene therapy: Report of the 2nd World Federation of Haemophilia Gene Therapy Round Table. » Pierce GF et al. World Federation of Hemophilia, Montreal, QC, Canada.

Haemophilia. 2020 Mar 23. doi: 10.1111/hae.13971. (Abstract)

■ « Investigational drugs to treat hemophilia. »
Franchini M et al. Italian National Blood Centre, National Institute of Health, Rome, Italy.

This review describes the preclinical and phase 1/2 studies investigating the innovative products, including factor concentrates and non-clotting factor-based therapies with extended half-life, for the management of hemophilia patients with or without coagulation factor inhibitors. Among replacement therapies for hemophilia A, these results indicate that the most interesting products are those bioengineered using XTEN fusion technology. The anti-tissue factor pathway inhibitor antibody concizumab is the most innovative and interesting agent among non-clotting factor products.

Expert Opin Investig Drugs. 2020 Feb 3:1-7. (Abstract)

■ « Gene therapy for hemophilia ».
Nathwani AC. Department of Haematology, UCL Cancer Institute, Katharine Dormandy Haemophilia and Thrombosis Unit, Royal Free London NHS Foundation Trust, London,UK; and Freeline Therapeutics.

Hemophilias are ideally suited for gene therapy because a small increment in blood factor levels (≥5% of normal) is associated with significant amelioration of bleeding phenotype in severely affected patients. This review explores recent progress and the remaining limitations that need to be overcome for wider availability of this novel treatment of inherited bleeding disorders.

Hematology Am Soc Hematol Educ Program. 2019 Dec 6;2019(1):1-8. (Abstract)

SB-525

Sangamo Therapeutics (USA)
Pfizer (USA)

SB-525 is an AAV2/6 vector encoding the cDNA for the B-domain deleted human Factor VIII (FVIII) for the treatment of hemophilia A. The secreted FVIII has the same amino acid sequence as approved recombinant anti hemophilic factors (Refacto® and Xyntha®). The SB-525 vector encodes a liver-specific promotor module and AAV2/6 exhibits liver tropism, thus providing the potential for long-term hepatic production of FVIII in hemophilia A subjects.
SB-525 is developed by Sangamo Therapeutics in collaboration with Pfizer since May 2017. Sangamo led Phase 1/2 clinical trials. In December 2019, the biotech company has completed the transfer to Pfizer of the SB-525 Investigational New Drug application (IND). Pfizer is now advancing SB-525 into a Phase 3 registrational clinical study in 2020 and has already commenced enrolling patients into a Phase 3 lead-in study.
The FDA has granted Orphan Drug, Fast Track, and regenerative medicine advanced therapy (RMAT) designations to SB-525, which also received Orphan Medicinal Product designation from the EMA.

Latest Informations/Publications on the Product

■ **JULY 2019**
Sangamo and Pfizer announce updated Phase 1/2 results for SB-525 showing sustained increased Factor VIII levels. The Phase 1/2 Alta study has been designed to assess the safety and tolerability of SB-525 in ten male patients with severe hemophilia A. The data showed that SB-525 was generally well-tolerated and demonstrated a dose-dependent increase in FVIII activity levels.
The first two patients treated at the 3e13 vg/kg dose rapidly achieved normal levels of FVIII activity as measured using a chromogenic assay, with no reported bleeding events.
The response continues to be durable for as long as 24 weeks, the extent of follow-up. The two patients more recently treated at the 3e13 vg/kg dose level are demonstrating FVIII activity kinetics that appear consistent with the first two patients treated in this dose cohort at similar early time points. Across the dose cohorts, patients demonstrated a dose-dependent increase in FVIII levels and a dose-dependent reduction in the use of FVIII replacement therapy. (Press Release)

Ongoing Clinical Trials

Six Month lead-in Study to Evaluate Prospective Efficacy and Safety Data of Current FIX Prophylaxis Replacement Therapy in Adult Hemophilia B Subjects (FIX:C≤2%) or Current FVIII Prophylaxis Replacement Therapy in Adult Hemophilia A Subjects (FIX:C≤1%)

PHASE 3
ID: NCT03587116
Recruitment Status: Recruiting
Start/Planned completion:
JUL 2018/OCT 2021
Estimated Enrollment: 250
Sites: 64 (AU, AT, BE, BR, CA, DE, ES, FR, GR, IL, IT, JP, KR, SA, SW, TK, TW, UK)
Updated: February 28, 2020
Contact:
Pfizer CT.gov Call Center - 1-800-718-1021 - ClinicalTrials.gov_Inquiries@pfizer.com

The study is an open-label, non-investigational product, multi-center, lead-in study to evaluate at least 6 months of prospective efficacy and selected safety data of current factor IX (FIX) or factor VIII (FVIII) prophylaxis replacement therapy in the usual care setting of moderately severe to severe adult hemophilia b subjects (FIX:c≤2%) who are negative for neutralizing antibodies to adeno-associated virus vector-Spark100 (benegene-1) and moderately severe to severe hemophilia a adult subjects (FVIII:c≤1%) who are negative for neutralizing antibodies to adeno-associated virus vector SB-525 capsid (aav6), prior to the respective therapeutic phase 3 gene therapy studies.

Dose-Ranging Study of Recombinant AAV2/6 Human Factor 8 Gene Therapy SB-525 in Subjects With Severe Hemophilia A

PHASE 2
ID: NCT03061201
Recruitment Status: Recruiting
Start/Planned completion:
JUN 2017/JUL 2024
Estimated Enrollment: 13
Sites: 8 (USA)
Updated: February 27, 2020
Contact:
Pfizer CT.gov Call Center - 1-800-718-1021 - ClinicalTrials.gov_Inquiries@pfizer.com

The purpose of the study is to evaluate the safety, tolerability and time-course profile of FVIII activity levels with adaptive doses of SB-525. The objective of the study is to reduce or eliminate the need for FVIII replacement therapy.

Valoctocogene Roxaparvovec (BMN 270 - AAV5-hFVIII-SQ)

BioMarin (USA)

Valoctocogene Roxaparvovec (BMN 270) is an investigational AAV5 [10] containing a B-domain deleted variant of FVIII gene. In February 2020, the FDA has accepted for Priority Review the Biologics License Application (BLA) for valoctocogene roxaparvovec, for the treatment of adults with hemophilia A. The agency has granted priority review designation to valoctocogene roxaparvovecand the Prescription Drug User Fee Act (PDUFA) action date is **August 21, 2020**.

The FDA has already granted valoctocogene roxaparvovec Breakthrough Therapy designation and Orphan Drug designation.

The EMA also validated BioMarin's Marketing Authorization Application (MAA) for, valoctocogene roxaparvovec, for adults with severe hemophilia A. The MAA review commenced in January 2020 under accelerated assessment. Valoctocogene roxaparvovec has Orphan Drug designation from the EMA that also granted access to its Priority Medicines (PRIME) regulatory initiative in 2017.

This submission marks the first marketing application under review in Europe for a gene therapy product for any type of hemophilia. If approved by the FDA, valoctocogene roxaparvovec will be the first gene therapy in the US for the treatment of any hemophilia.

Ongoing Clinical Trials

Gene Therapy Study in Severe Haemophilia A Patients – A Phase 1/2, Dose-Escalation, Safety, Tolerability and Efficacy Study of Valoctocogene Roxaparvovec, an Adenovirus-Associated Virus Vector-Mediated Gene Transfer of Human Factor VIII in Patients With Severe Haemophilia A

PHASE 1-2
ID: NCT02576795
Recruitment Status: Active, not recruiting
Start/Planned completion: **AUG 2015/FEB 2022**
Estimated Enrollment: 15
Sites: 9 (UK)
Updated: April 17, 2019
Contact: -

This study is being conducted by Biomarin Pharmaceutical as an open label, dose escalation study in order to determine the safety and efficacy of valoctocogene roxaparvovec (an Adenovirus-Associated Virus based gene therapy vector in participants with severe Haemophilia A.

■ « Multiyear Follow-up of AAV5-hFVIII-SQ Gene Therapy for Hemophilia A ».
K. John Pasi et al.

This article demonstrated that a single infusion of valoctocogene roxaparvovec resulted in sustained, clinically relevant benefit, as measured by a substantial reduction in annualized rates of bleeding events and complete cessation of prophylactic factor VIII use in all 13 participants who had received 4e13vg/kg or 6e13 vg/kg.

Twelve of these participants also experienced a full resolution of target joints.
(Funded by BioMarin Pharmaceutical; ClinicalTrials.gov number, NCT02576795; EudraCT number, 2014-003880-38.).

N Engl J Med 2020; 382:29-40 (Abstract)

Gene Therapy Study in Severe Haemophilia A Patients With Antibodies Against AAV5 (270-203)

PHASE 1-2
ID: NCT03520712
Recruitment Status:
Enrolling by invitation
Start/Planned completion:
APR 2018/JUN 2024
Estimated Enrollment: 10
Sites: 2 (UK)
Updated: April 8, 2019
Contact: -

This study is being conducted as an open label, single dose study in order to determine the safety of valoctocogene roxaparvovec in participants with severe hemophilia A who also have pre-existing antibodies against AAV5.

Fidanacogene elaparvovec (PF-06838435 - SPK-9001)

Pfizer
Spark Therapeutics (USA)

Fidanacogene elaparvovec (PF-06838435 - SPK-9001) is an AAV-based gene therapy that contains a high-activity human coagulation factor IX gene. The product received orphan drug designation from the FDA in September 2015 and breakthrough therapy designation in July 2016. It has been granted support through the European Medicines Agency (EMA) PRIority MEdicines (PRIME) program in February 2017. ODD status has been granted in the EU in November 2018.[12]

Ongoing Clinical Trials

A Study to Evaluate the Efficacy and Safety of Factor IX Gene Therapy With PF-06838435 in Adult Males With Moderately Severe to Severe Hemophilia B (BENEGENE-2)

PHASE 3
ID: NCT03861273 - BENEGENE-2
Recruitment Status: Recruiting
Start/Planned completion:
JUL 2019/NOV 2026
Estimated Enrollment: 55
Sites: 31 (AU, CA, GR, JP, SA, TK, TW, UK, USA)
Updated: April 10, 2020
Contact:
Pfizer CT.gov Call Center - 1-800-718-1021 - ClinicalTrials.gov_Inquiries@pfizer.com

This study will evaluate the efficacy and safety of PF-06838435 in adult male participants with moderately severe to severe hemophilia B (Factor IX circulating activity of 2% or less). Eligible study participants will have completed a minimum 6 months of routine Factor IX prophylaxis therapy during the lead in study (C0371004). Participants will be dosed once and will be evaluated over the course of 6 years. The main objectives of the study are to compare the annualized bleeding rate of the gene therapy to routine prophylaxis from the lead-in study and to evaluate the impact that it may have on participant's Factor IX circulating activity.

Long-term Safety and Efficacy Study of SPK-9001 in Individuals With Hemophilia B

PHASE 2
ID: NCT03307980
Recruitment Status: Recruiting
Start/Planned completion:
JUN 2017/OCT 2026
Estimated Enrollment: 20
Sites: 7 (USA)
Updated: December 4, 2019
Contact:
Pfizer CT.gov Call Center - 1-800-718-1021 -
ClinicalTrials.gov_Inquiries@pfizer.com

The study is a long term follow up (LTFU) study designed to evaluate the overall long term safety, durability of transgene expression, and effect on clinical outcomes of SPK 9001 mediated gene transfer. While safety will be monitored in general, new onset of oncologic, hematologic, neurologic, or auto immune events will be of particular interest. This trial will last for 5 years providing a minimum of 6 years of follow up post vector administration.

Lysosomal Diseases

Danon Disease

Danon disease is a rare X-linked genetic disorder characterized by cardiomyopathy, skeletal muscles myopathy and intellectual disability. This lysosomal-associated disorder is leading to early death due to heart failure. Danon disease is caused by mutations in the LAMP2 gene that provides instructions for making lysosomal associated membrane protein-2 (LAMP-2). The absence or reduction of LAMP2 protein leads to disruption of intracytoplasmic trafficking with an accumulation of autophagic material and glycogen in cardiac muscle and skeletal muscle cells.
There are no therapies available for the treatment of Danon disease.

Latest Publications on the Disease

■ « Danon Disease ».
Matthew RG Taylor Adult Medical Genetics Program, University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA.
Eric D Adler, Division of Cardiology, University of California San Diego, San Diego, California, USA.

GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2020. 2020 Mar 5.
(Abstract - Full Text)

■ « Lysosomal Abnormalities in Cardiovascular Disease ».
Congwu Chi et al
Division of Cardiology, Department of Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO 80045, USA.

In this review, the authors highlighted studies that have improved our understanding of the connection between lysosome function and cardiovascular diseases with an emphasis on a recent breakthrough that characterized a unique autophagosome-lysosome fusion mechanism employed by cardiomyocytes through a lysosomal membrane protein LAMP-2B. This finding may impact the development of future therapeutic applications.

Int J Mol Sci. 2020 Jan 27;21(3):811.
(Abstract - Full Text)

■ « Danon Disease: Review of Natural History and Recent Advances ».
G Cenacchi et al.
Department of Biomedical and Neuromotor Sciences, "Alma Mater" University of Bologna, Bologna, Italy)

The authors surveyed over 500 Danon disease patients reported in the literature from the first description to the present, in order to summarize the clinical, pathological and molecular data and treatment perspectives. An early molecular diagnosis is of crucial importance for genetic counselling and for therapeutic interventions: in male patients, the prognosis is poor due to rapid progression towards heart failure, and only heart transplantation modifies the disease course.

Neuropathol Appl Neurobiol. 2019 Nov 7.
(Abstract

RP-A501

Rocket Pharmaceuticals (USA)

RP-A501 (AAV9.LAMP2B) is a recombinant AAV9 containing the human lysosome-associated membrane protein 2 isoform B (LAMP2B) transgene.[15] The LAMP2 gene, a key mediator of autophagy, has three isoforms: LAMP2A, LAMP2B, and LAMP2C. LAMP2B is the predominant isoform expressed in cardiomyocytes. In February 2019 Rocket Pharmaceuticals was notified by the FDA that the company was granted Fast Track designation for RP-A501.

Latest Informations/Publications on the Product

■ « Systemic AAV9.LAMP2B Injection Reverses Metabolic and Physiologic Multiorgan Dysfunction in a Murine Model of Danon Disease ».
Ana Maria Manso, Division of Cardiology, Department of Medicine, UC San Diego, San Diego, CA 92037, USA.

This study evaluates the efficacy of human LAMP2B gene transfer using a recombinant adeno-associated virus 9 carrying human LAMP2B (AAV9.LAMP2B) in a Lamp2 knockout (KO) mouse, a Danon disease model. AAV9.LAMP2B was intravenously injected into 2- and 6-month-old Lamp2 KO male mice to assess efficacy in adolescent and adult phenotypes. Lamp2 KO mice receiving AAV9.LAMP2B demonstrated dose-dependent restoration of human LAMP2B protein in the heart, liver, and skeletal muscle tissue. Impaired autophagic flux, evidenced by increased LC3-II, was abrogated by LAMP2B gene transfer in all tissues in both cohorts. Cardiac function was also improved, and transaminases were reduced in AAV9.LAMP2B-treated KO mice, indicating favorable effects on the heart and liver. Survival was also higher in the older cohort receiving high vector doses. In summary, LAMP2B gene transfer improves metabolic and physiologic function in a DD murine model, suggesting that a similar therapeutic approach may be effective for treating patients with this highly morbid disease.

Sci Transl Med. 2020 Mar 18;12(535):eaax1744 (Abstract)

■ **MAY 2019**
Rocket Pharmaceuticals has presented preclinical data of RP-A501 at the American Society of Gene and Cell Therapy 2019 Annual Meeting in Washington, D.C. IND-enabling toxicology studies were conducted in wild-type mice and non-human primates. Three dose levels were tested in mice, including 3×10^{13} vg/kg, 1×10^{14} vg/kg, and 3×10^{14} vg/kg. The highest dose level from the murine study, 3×10 vg/kg, was tested in non-human primates. No dose-Latest adverse events were observed at all tested doses in both mice and non-human primates. Vector genomes, mRNA and protein expression were widely distributed across key tissues with high levels of transduction, transcription and translation detected in the heart, skeletal muscle, diaphragm and liver. (Press Release)

Ongoing Clinical Trials

Gene Therapy for Male Patients With Danon Disease Using RP-A501; AAV9.LAMP2B

PHASE 1
ID: NCT03882437
Recruitment Status: Recruiting
Start/Planned completion:
APR 2019/APR 2023
Estimated Enrollment: 24
Sites: 1 (USA)
Updated: December 4, 2019
Contact:
Clinical Information - 646-901-9276 -
Danonclinicaltrial@rocketpharma.com

This non-randomized open-label Phase 1 study evaluates the safety and toxicity of gene therapy using a recombinant AAV9 containing the human lysosome-associated membrane protein 2 isoform B (LAMP2B) transgene (investigational product (IP), RP-A501) in male patients with Danon Disease (DD). RP-A501 will be administered as a single IV infusion.
Two dose levels are planned to be investigated in 4 distinct cohorts:
Cohort 1: Age 15 years and older:
Low Dose (n=3-6 subjects) ;
Cohort 2: Age 15 years and older:
High Dose (n=3-6 subjects) ;
Cohort 3: Age 8-14 years:
Low Dose (n=3-6 subjects) ;
Cohort 4: Age 8-14 years:
High Dose (n=3-6 subjects).
Clinical data read-outs are expected in the second half of 2020.

Latest Informations/Publications on Clinical Trials

▪ JUN 2019
« Rocket Pharmaceuticals Announces Patient Dosing Has Commenced for Phase 1 Clinical Trial of RP-A501, the First Gene Therapy to Treat a Monogenic Heart Failure »

Patient dosing has commenced in the open-label, Phase 1 clinical trial of RP-A501 for the treatment of Danon disease. University of California San Diego (UCSD) Health is the initial and lead center for the Phase 1 clinical trial under the leadership of Eric Adler M.D. and Barry Greenberg M.D.

Eric Adler is Director of Cardiac Transplant and Mechanical Circulatory Support at UC San Diego Health and Professor of Medicine at University of California, San Diego School of Medicine.
Barry Greenberg, is the Director of the Advanced Heart Failure Treatment Program at UCSD Health and Professor of Medicine at UC San Diego School of Medicine, and is principal investigator of the trial. (Press Release)

Ophthalmological Diseases

Latest Publications on Gene Therapy and Inherited Retinal Diseases

■ « Empowering Retinal Gene Therapy with a Specific Promoter for Human Rod and Cone ON-Bipolar Cells »
Elmar Carlos Hulliger, Simon Manuel Hostettler,and Sonja Kleinlogel. Institute of Physiology, University of Bern, 3012 Bern, Switzerland

Optogenetic gene therapy holds promise to restore high-quality vision in blind patients and recently reached clinical trials. Although the ON-bipolar cells, the first retinal interneurons, make the most attractive targets for optogenetic vision restoration, they have remained inaccessible to human gene therapy due to the lack of a robust cell-specific promoter. The authors describe the design and functional evaluation of 770En_454P(hGRM6), a human GRM6 gene-derived, short promoter that drives strong and highly specific expression in both the rod- and cone-type ON-bipolar cells of the human retina. Expression also in cone-type ON-bipolar cells is of importance, since the cone-dominated macula mediates high-acuity vision and is the primary target of gene therapies. 770En_454P(hGRM6)-driven middle-wave opsin expression in ON-bipolar cells achieved lasting restoration of high visual acuity in the rd1 mouse model of late retinal degeneration. The new promoter enables precise manipulation of the inner retinal network and paves the way for clinical application of gene therapies for high-resolution optogenetic vision restoration, raising hopes of significantly improving the life quality of people suffering from blindness.

Mol Ther Methods Clin Dev. 2020 Jun 12; 17: 505–519
(Full Text)

■ « AAV-Mediated Gene Delivery to 3D Retinal Organoids Derived from Human Induced Pluripotent Stem Cells »
Marcela Garita-Hernandez et al. Sorbonne Université,, INSERM, CNRS, Institut de la Vision, 17 rue Moreau, F-75012 Paris, France

Human induced pluripotent stem cells (hiPSCs) promise a great number of future applications to investigate retinal development, pathophysiology and cell therapies for retinal degenerative diseases. Specific approaches to genetically modulate hiPSC would be valuable for all of these applications. Vectors based on AAV have shown the ability for gene delivery to retinal organoids derived from hiPSCs. Thus far, little work has been carried out to investigate mechanisms of AAV-mediated gene delivery and the potential advantages of engineered AAVs to genetically modify retinal organoids. In this study, the authors compared the early transduction efficiency of several recombinant and engineered AAVs in hiPSC-derived RPE cells and retinal organoids in relation to the availability of their cell-surface receptors and as a function of time. The genetic variant AAV2-7m8 had a superior transduction efficiency when applied at day 44 of differentiation on retinal organoids and provided long-lasting expressions for at least 4 weeks after infection without compromising cell viability. All of the capsids tested transduced the hiPSC-RPE cells, with the AAV2-7m8 variant being the most efficient. Transduction efficiency was correlated with the presence of primary cell-surface receptors on the hiPS-derived organoids.

Int J Mol Sci. 2020 Feb; 21(3): 994.
(Full Text)

Achromatopsia (ACHM)

Achromatopsia is a rare autosomal recessive inherited retinal disease (IRD) characterized by a partial or total absence of color vision. It prevents cone photoreceptors from functionning. Affected people can also have an increased sensitivity to light and glare, involuntary back-and-forth eye movements, and significantly reduced sharpness of vision. They can also have farsightedness or, less commonly, nearsightedness.

The disease results from mutations in one of several genes (CNGA3, CNGB3, GNAT2, PDE6C, PDE6H, ATF6). These mutations affect cone photoreceptors which are the specialist light-sensing cells responsible for colour vision and vision in bright light. The CNGB3 and CNGA3 genes are the two most common genes that have been identified as causing achromatopsia.

AAV-CNGA3 (AAV2/8 hG1.7 p.coCNGA3)

Meira GTx (USA - UK)

AAV- CNGA3 (AAV2/8-hG1.7p.coCNGA3) is an AAV-based gene therapy designed to restore cone function in patients with achromatopsia (ACHM) caused by mutations in the Cyclic Nucleotide Gated Channel Alpha 3 subunit (CNGA3) gene. This AAV 2/8 is carrying a proprietary engineered promoter (hG1.7p) driving a codon-optimized CNGA3 cDNA. The product is delivered via subretinal injection covering the central macula region of the eye, where most of the cones in the retina are located.
AAV-CNGA3 was granted orphan drug designation by the FDA and by the European Medicines Agency in August 2018. In January 2019, MeiraGTx has established collaboration and license agreement with Janssen with respect to three MeiraGTx's IRD pipeline, including AAV-CNGA3.

Latest Informations/Publications on the Product

■ **APR 2019**

« MeiraGTx Announces Upcoming Presentation on Achromatopsia Gene Therapy Candidate AAV-CNGA3 at ARVO 2019 »

A pre-clinical poster on safety and efficacy of AAV-CNGA3 has been presented at the Association for Research in Vision and Ophthalmology (ARVO) 2019 Annual Meeting in Vancouver, British Columbia. In pre-clinical models, treatment with AAV-CNGA3 resulted in long-term visual improvements and cone photoreceptor survival at titers planned for use in a Phase 1/2 clinical trial of AAV-CNGA3. (Press Release)

Long-Term Follow-Up Gene Therapy Study for Achromatopsia CNGB3 and CNGA3

PHASE 1-2
ID: NCT03278873
Recruitment Status: Recruiting
Start/Planned completion:
JUN 2017/AUG 2024
Estimated Enrollment: 72
Sites: 1 (UK)
Updated: September 12, 2019
Contact:
MeiraGTx UK II Ltd +44 (0)20 3866 4320 -
ocularinfo@meiragtx.com

This study is a longer-term follow-up study for patients who participated in one of the clinical trials: AAV - CNGB3 retinal gene therapy for patients with achromatopsia, or AAV - CNGA3 retinal gene therapy for patients with achromatopsia.

Gene Therapy for Achromatopsia (CNGA3) (CNGA3)

PHASE 1-2
ID: NCT03758404
Recruitment Status: Recruiting
Start/Planned completion:
JUL 2019/JAN 2022
Estimated Enrollment: 18
Sites: 2 (UK, USA)
Updated: March 12, 2020
Contact:
MeiraGTx UK II Ltd +44 (0)20 3866 4320 -
ocularinfo@meiragtx.com

AGTC-402 (rAAV2tYF-PR1.7-hCNGA3)

Applied Genetic Technologies Corp - AGTC (USA)

AGTC-402 (rAAV2tYF-PR1.7-hCNGA3) is an AAV-based gene therapy designed to restore cone function in patients with achromatopsia (ACHM) caused by mutations in the Cyclic Nucleotide Gated Channel Alpha 3 subunit (CNGA3) gene.[20]

Latest Informations/Publications on the Product

■ **MAR 2020**

« AGTC Announces Completion of Enrollment in All Adult Dose Groups of its Ongoing Phase 1/2 Clinical Trials in Patients with Achromatopsia »

The planned enrollment has been completed in all dose groups for adult patients, including the two higher dose groups, of the Phase 1/2 clinical programs with achromatopsia due to mutation in the ACHM CNGB3 or ACHM CNGA3 genes. AGTC continues to enroll pediatric patients at the higher dose groups in both trials. AGTC most recently reported interim six-month data from the dose escalation cohorts of its ongoing ACHM Phase 1/2 clinical trials in January 2020. Results from both studies demonstrated encouraging signs of biologic activity as shown by positive changes in light discomfort testing as well as encouraging patient anecdotes describing real-world improvements in visual function. A favorable safety profile with no dose-limiting inflammatory responses was observed. (Press Release)

■ « Safety and Efficacy Evaluation of rAAV2tYF-PR1.7-hCNGA3 Vector Delivered by Subretinal Injection in CNGA3 Mutant Achromatopsia Sheep »

Gootwine E et al. Agricultural Research Organization, The Volcani Center , Rishon LeZion, Israel

The results are herein reported of a study evaluating safety and efficacy of AGTC-402 in CNGA3-deficient sheep. Thirteen day-blind sheep divided into three groups of four or five animals each received a subretinal injection of an AAV vector expressing a CNGA3 gene in a volume of 500 µL in the right eye. Two groups (n = 9) received either a lower or higher dose of the AGTC-402 vector, and one efficacy control group (n = 4) received a vector similar in design to one previously shown to rescue cone photo-receptor responses in the day-blind sheep model (rAAV5-PR2.1-hCNGA3). All vector-treated eyes showed improved cone-mediated electroretinography responses with no change in rod-mediated electroretinography responses. Behavioral maze testing under photopic conditions showed significantly improved navigation times and reduced numbers of obstacle collisions in all vector-treated eyes compared to their contralateral control eyes or pre-dose results in the treated eyes.

Hum Gene Ther Clin Dev. 2017 Jun;28(2):96-107. (Abstract)

Safety and Efficacy Trial of AAV Gene Therapy in Patients With CNGA3 Achromatopsia

PHASE 1-2
ID: NCT02935517
Recruitment Status: Recruiting
Start/Planned completion:
MAY 2017/JUN 2023
Estimated Enrollment: 24
Sites: 9 (IL, USA)
Updated: January 14, 2020
Contact:
Jill Dolgin, PharmD + 1833-770-2862 - advocacy@agtc.com

This will be a non-randomized, open-label, Phase 1/2 study of the safety and efficacy of AGTC-402, administered to one eye by subretinal injection in individuals with achromatopsia caused by mutations in the CNGA3 gene. The primary study endpoint will be safety and the secondary study endpoint will be efficacy. Subjects will be enrolled sequentially in four groups. Subjects in Groups 1, 2 and 3 will be at least 18 years of age and will receive a lower, middle or higher dose of study agent. Subjects in Group 4 will be at least 6 years of age and will receive the maximum tolerated dose identified in Groups 1, 2 and 3. Safety will be monitored by evaluation of ocular and non ocular adverse events and hematology and clinical chemistry parameters. Efficacy parameters will include visual acuity, light discomfort testing, color vision, static visual field, ERG, adaptive optics retinal imaging and OCT.

Latest Informations/Publications on Clinical Trials

■ **JAN 2020**
« AGTC Reports Encouraging Interim Six-Month Data from the Dose Escalation Cohorts of its Ongoing Phase 1/2 Clinical Trials in Achromatopsia »

Interim results from the ongoing Phase 1/2 clinical programs in patients with achromatopsia due to mutation in the ACHM CNGA3 gene demonstrate encouraging signs of biologic activity and a favorable safety profile. The company plans to report data from additional dose groups, age groups and time-points in the second half of 2020. The data reported are from 9 patients in the ACHM CNGA3 trial. Additional data are expected to be available in the second half of 2020. (Press Release)