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« BRIEFING ON…. »

RNA TRIALS

FEBRUARY 2020

AND

***BioPharmAnalyses* and OctopusyX BioConsulting are happy to propose you the latest issue of their « BRIEFING ON RNA TRIALS ».**

This new publication provides you an accurate overview to explore the *latest trials* in the *RNA therapeutics* area.

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 from 01/01/2018 to 12/31/2019.

Each Technical Datasheet includes for every trial: Identification number, Sponsor, Product, Status, Start/Planned Completion, Estimated Enrollment, Collaborations, Number of sites, Updated, Contact, Latest Related Informations/Publications.

RNA science is now translated into new therapies…

Seven RNA-based products are now approved and more than one hundred candidates have reached the clinical stage…

FOUR REASONS TO BUY:

Wishing to identify hot research topics in this highly competitive field ?

Looking for an update on the clinical portfolio ?

Needing insights to assist you in your decision-making in RNA drug or to identify the most advanced companies in the field ?

Searching for new candidates to in-license ?

« BRIEFING ON RNA TRIALS » is the up-dated tool you need to have

- **220 pages detailing more than 160 clinical trials conducted in 45 countries**
- **48 companies and academic institutions developing more than one hundred RNA therapeutics (antisense oligonucleotides, RNAi/siRNA, microRNA, mRNA...)**
- **58 targets and 62 diseases in a wide range of therapeutic areas** (cancers, cardiovascular and metabolic diseases, infectious diseases, genetic diseases, ophthalmological diseases....).

CONTENTS

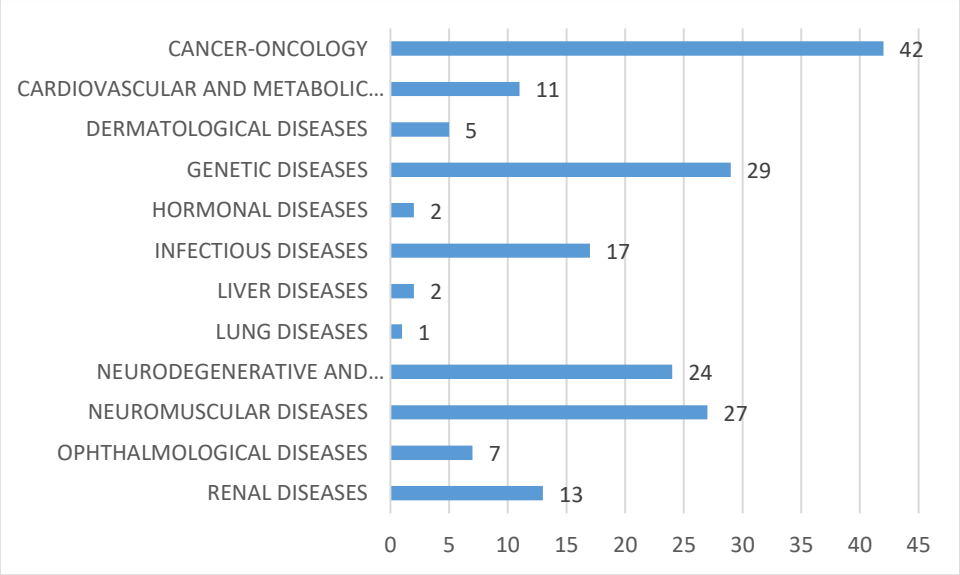
RNA THERAPEUTICS TRIALS BY NUMBERS

112 products are currently in the clinical phase of development

58 targets and 62 diseases

48 companies and academic insitutions involved in
177 clinical trials in **45 countries**

NUMBER OF STUDIES BY THERAPEUTIC AREA



DISEASES MENTIONED

Cancer - Oncology
Acute Myeloid Leukemia
Advanced lymphoid malignancies
Ewing sarcoma
Head and neck cancer
Liver cancer
Lymphoma
Melanoma
Mycosis fungoides
Non small cell lung cancer
Ovarian cancer
Pancreatic cancer
Solid tumors
Triple Negative Breast Cancer

Cardiovascular diseases and metabolic diseases
Dyslipidemias
Familial partial lipodystrophy
Heart failure
Heterozygous Familial Hypercholesterolemia (HeFH)
Homozygous Familial Hypercholesterolemia (HoFH)
Hypertension
Hypertriglyceridemia
Thrombosis

Dermatological diseases
Hypertrophic scars/ Keloid
Incisional complications
Recessive Dystrophic Epidermolysis Bullosa (RDEB)

Genetic diseases
Acute hepatic porphyria
Alpha 1-Antitrypsin Deficiency
Alport Syndrome
Cystic Fibrosis
Familial Chylomicronemia Syndrome
Methylmalonic acidemia
Ornithine Transcarbamylase Deficiency

Hematological diseases
β-thalassemia
Hemophilia

Hormonal diseases
Acromegaly

Infectious diseases
Chikungunya
Cytomegalovirus infection
Hepatitis B
Influenza
Rabies infection
Zika virus

Liver diseases
Hepatic fibrosis
Non Alcoholic Steatohepatitis (NASH)

Lung diseases
Idiopathic Pulmonary Fibrosis

Neurodegenerative and neurological diseases
Alzheimer’s disease
Amyotrophic Lateral Sclerosis
Chronic migraine
Hereditary transthyretin amyloidosis
Familial Amyloid Polyneuropathy
Huntington’s disease

Neuromuscular diseases
Duchenne Muscular Dystrophy
Spinal muscular atrophy

Ophthalmological diseases
Acute Nonarteritic Anterior Ischemic Optic Neuropathy
Dry Eye Disease
Leber’s Congenital Amaurosis
Retinitis pigmentosa
Usher syndrome

Renal diseases
Acute kidney injury
End-stage renal disease
IgA nephropathy
Primary hyperoxaluria

ALPORT SYNDROME

Alport syndrome is a rare genetic disorder characterized by progressive kidney disease and abnormalities of the ears and eyes. The disease is caused by mutations in the type IV collagen genes (Col4A3, Col4A4 and Col4A5). There are three genetic types: X-linked Alport syndrome (XLAS) that is caused by mutations in the COL4A5 gene, autosomal recessive Alport syndrome (ARAS) that is caused by mutations in both copies of either the COL4A3 or the COL4A4 gene, and autosomal dominant form (ADAS) that is caused by mutations in one copy of the COL4A3 or COL4A4 gene. The first sign of kidney disease is the appearance of blood in the urine early in life, with progressive decline in kidney function that ultimately results in kidney failure, especially in affected males. Progressive hearing loss occurs frequently in people with Alport syndrome. Patients may also develop abnormalities in several parts of the eyes including the lens, retina and cornea.

Latest Publications

* *Kidney Int.* 2020 Feb;97(2):426..
X-linked Alport syndrome with "empty capsule sign".
Kudose S et al. Department of Pathology and Cell Biology, Columbia University Irving Medical Center, New York, New York, USA. (Abstract)

* *Kidney Dis* (Basel). 2020 Jan;6(1):43-49.
A Novel COL4A5 Splicing Mutation Causes Skipping of Exon 14 in a Chinese Family with Alport Syndrome.
Gao E et al. National Clinical Research Center of Kidney Diseases, Jinling Hospital, Nanjing University School of Medicine, Nanjing, China. (Abstract)

* *Sci Rep*. 2019 Dec 31;9(1):20398. doi: 10.1038/s41598-019-56837-6.
Modification of an aggressive model of Alport Syndrome reveals early differences in disease pathogenesis due to genetic background.
Falcone S et al. Mammalian Genetics Unit, Medical Research Council, Harwell science and innovation campus, Oxford, OX11 0RD, UK. (Abstract – Full Text)

*_Eur J Hum Genet_. 2019 Nov 21. doi: 10.1038/s41431-019-0537-8.
New frontiers to cure Alport syndrome: COL4A3 and COL4A5 gene editing in podocyte-lineage cells.
Daga S et al. Medical Genetics, University of Siena, Siena, Italy.
The authors employed a two-plasmid approach in order to achieve a beneficial and stable variant-specific correction using CRISPR/Cas9 genome editing. One plasmid carries a Donor DNA and a reporter system mCherry/GFP to track the activity of Cas9 in cells. The other plasmid carries a self-cleaving SpCas9 and the variant-specific sgRNA. They have achieved reversion of variants greater than 40% with undesired insertions/deletions lower than 15%. Overall, these researcgers have demonstrated a new gene therapy approach directly on patients' cells, key players of Alport pathogenesis, and they have reverted COL4 causative variants towards the wild type state. These results, in combination with preclinical models, could open new frontiers in the management and the treatment of the disorder. (Abstract)

* *J Biol Regul Homeost Agents*. 2019 Sep-Oct;33(5 Suppl. 1):19-24.
Alport's syndrome. special issue: “Focus on pediatric nephrology”, Bruni V et al. Department of Medical and Surgical Sciences, Pediatric Unit, "Magna Graecia" University, Catanzaro, Italy. (Abstract)

TARGET: miR-21

PRODUCT: SAR339375 (RG-012) – SANOFI (FR)

RG-012 is an investigational, single stranded, chemically modified oligonucleotide that binds to and inhibits the function of microRNA-21 (miR-21). In preclinical studies, RG-012 has demonstrated potent inhibition of miR-21 *in vitro* and *in vivo*, a decrease in the rate of progression of renal fibrosis, an increase in the lifespan of the Col4A3 deficient mice by up to fifty percent. RG-012 has received orphan designation in both the US and in the EU.

In November 2018, Regulus transitioned development responsibilities for RG-012 to its partner Genzyme, a Sanofi company, for the treatment of Alport Syndrome. The initial strategic alliance has been concluded with Sanofi in June 2010.

■ PHASE 2

Study of SAR339375 in Patients With Alport Syndrome (HERA)

ID: NCT02855268 - ACT16248 - 2019-004394-10 (EudraCT Number) - U1111-1223-4466 (Other Identifier: UTN)
Recruitment Status: Recruiting
Start/Planned completion: NOV 2017/MAR 2023
Estimated Enrollment: 45
Sites: 2 (AU –USA)
Updated: January 8, 2020
Contact: Trial Transparency email recommended (Toll free number for US & Canada) 800-633-1610 ext option 6 - Contact-US@sanofi.com

The study will assess the safety and tolerability of SAR339375 and the efficacy of this compound in reducing the decline in renal function. Secondary objectives include the assessment of plasma pharmacokinetic (PK) parameters of the parent compound and its metabolites and the assessment of the immunogenicity of the SAR339375. The planned length of participation in the study for each subject is up to approximately 106 weeks (from screening through completion of follow-up).

■ PHASE 1

A Study of RG-012 in Subjects With Alport Syndrome

ID: NCT03373786 - PDY16327 - RG012-06 (Other Identifier: Regulus Therapeutics)
Recruitment Status: Completed
Start/Planned completion: DEC 2017/MAY 2019
Actual Enrollment: 4
Sites: 7 (USA)
Updated: May 24, 2019

This is a Phase 1, multi-center study of the safety, pharmacodynamics, and pharmacokinetics of RG-012 administered to subjects with Alport syndrome. During this open-label study, all eligible subjects will receive RG-012. The study consists of two parts (Part A and Part B). During Part A, half of the participants will receive a single dose of RG-012 and half will receive 4 doses of RG-012 (one dose every other week for 6 weeks). All subjects will undergo two renal biopsies, one before and one after receiving RG-012, to assess the effect of RG-012 on the kidney. After completing Part A, subjects will be able to enter Part B of the study. During Part B, all subjects will receive RG-012 every other week for 48 weeks

EWING' SARCOMA

Ewing sarcoma is a type of tumor that forms in bone or soft tissue. It predominantly affects the young population, with a worldwide incidence of three cases per million. It may be found in the bones of the legs, arms, feet, hands, chest, pelvis, spine, or skull. Ewing sarcoma also may be found in the soft tissue of the trunk, arms, legs, head, neck, retroperitoneum (area in the back of the abdomen behind the tissue that lines the abdominal wall and covers most of the organs in the abdomen), or other areas. It is most common in adolescents and young adults.

Latest Publications

* *Clin Pract*. 2019 Sep 17;9(3):1111.

Ewing's sarcoma with distant metastasis: A brief note on management and emerging therapies. Meshram GG et al. Department of Pharmacology, Postgraduate Institute of Medical Education and Research and Dr. Ram Manohar Lohia Hospital, New Delhi, India.

The researchers present a case of massive Ewing's sarcoma of the right femur with metastasis to bones and lungs. The patient was treated with chemotherapy. However, he succumbed to his illness before completion of therapy. In conclusion, Ewing's sarcoma with distant metastasis is a high risk case with poor prognosis. Integrating novel molecular targets with conventional chemotherapeutic agents holds a promise for high-risk Ewing's sarcoma patients.(Abstract - Full Text)

* *Onco Targets Ther*. 2019 May 27;12:4153-4165.

Identification of key genes and pathways in Ewing's sarcoma patients associated with metastasis and poor prognosis. Li G et al. Department of Orthopedic Surgery, The Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, Zhejiang 310009, People's Republic of China.

This study intended to identify the relationship between key genes/pathways and metastasis/poor prognosis in Ewing's sarcoma patients by using bioinformatic method. Differentially expressed genes (DEGs) were identified between primary and metastasis ES samples by the GEO2R online tool. Gene ontology (Go) and Kyoto encyclopedia of genes and genomes (KEGG) pathway enrichment analyses of DEGs were performed and PPI network analyses were conducted. The ES patient's prognostic information was employed for survival analysis, and the potential relationship between miRNAs and key genes was analyzed. The results showed that a total of 298 and 428 DEGs were screened out in metastasis samples based on GSE17618 and GSE12102 dataset compared to primary samples respectively. The most significantly enriched KEGG pathway was the mismatch repair (MMR) pathway. MSH2, MSH6, RPA2, and RFC2 that belong to the MMR pathway were identified as key genes. Moreover, the expression of key genes was increased in metastasis samples compared with primary ones and was associated with poor event-free and overall survival of ES patients. The negative correlation of the expression level of the key genes with patients prognosis also supported by TCGA sarcoma database. Furthermore, knockdown of EWSR/FLI1 fusion in ES cell line A673 down-regulates the expression of the 4 key genes was revealed by GDS4962. The present study indicated that the key genes might be used as molecular targets and diagnostic biomarkers for the treatment of ES. (Abstract - Full Text)

TARGET: Furin

PRODUCT: VIGIL® - GRADALIS (USA)

Vigil® utilizes the patient's own cancer cells to elicit an immune response that is specially targeted and relevant to each patient's unique tumor neoantigens. Patient's cancer cells are genetically modified through the introduction of a proprietary gene plasmid. This plasmid carries the vectors of two genetic modifications.

The first gene sequence involves the **introduction of a bi-functional shRNA targeting the knockdown of furin**. One of the functions of the furin enzyme is to convert immunosuppressive TGFβ1 and TGFβ2 into active isoforms. Thus, inhibiting furin production in the patient's cancer cells results in the reduction in the expression of TGFβ1 and TGFβ2 in these cells.

The **second gene sequence expresses Granulocyte Macrophage Colony Stimulating Factor, or GM-CSF**, a potent stimulator of the immune system.

When the cells are injected into the patient's arm, modified autologous tumor cells are designed to activate the immune system. GM-CSF expression enhances cell surface antigen expression and recruits dendritic cells to the injection site; while the inhibition of TGFβ1 and TGFβ2 production allows cancer cells to now be "visible" to the patient's antigen-presenting cells (APCs).

Ewing's sarcoma characterized by the t(11; 22) (q24; q12) translocation at several but prioritized breakpoint sites, resulting in the EWS/FLI1 fusion gene is the second most frequently diagnosed primary malignant bone tumor in the US with an annual incidence, from birth to age 20, of 2.9 cases per million population. The EWS/FLI1 gene is well known as the driver gene of Ewing's sarcoma. Gradalis designed a novel pbi-shRNA™ EWS/FLI1 Type 1 LPX which has demonstrated sufficient specificity, safety and efficacy in animal testing to justify Phase I testing. Clinical safety (no ≥ grade 3 product related toxic effect) and target specific activity has been observed with other bi-shRNA products involving 147 cancer patients (698 separate dose administrations) (BB-IND 14205; BB-IND 14938). Moreover, safety has been observed with IV delivery of pbi-shRNA™ EWS/FLI1 Type 1 LPX in murine and swine testing via multidose IV administration.

■ PHASE 3

Vigil + Irinotecan and Temozolomide in Ewing's Sarcoma (VITA)

ID: NCT03495921 - CL-PTL-130
Recruitment Status: Recruiting
Start/Planned completion: AUG 2018/JUL 2022
Estimatedu Enrollment: 114
Sites: 16 (USA)
Updated: **November 18, 2019**
Contact: Gladice Wallraven - 214-442-8124 - info@gradalisinc.com

This is a multicenter, 1:1 randomized Phase III study of intradermal autologous Vigil immunotherapy (1.0 x 10^6 cells/injection; minimum of 4 to a maximum of 12 administrations) in combination with irinotecan and temozolomide in subjects with metastatic Ewing's sarcoma Family of Tumors (ESFT) refractory/intolerant or recurrent to 1 prior line of chemotherapy. Participants undergoing a standard surgical procedure (e.g., tumor biopsy or palliative resection) may have tumor tissue harvested for manufacture of the investigational product.

■ PHASE 2

A Two-part Phase IIb Trial of Vigil in Ewing's Sarcoma

ID: NCT02511132 - CL-PTL-121
Recruitment Status : Active, not recruiting
Start/Planned completion: MAR 2017/DEC 2019
Estimated Enrollment: 22
Sites: 6 (USA)
Updated: March 20, 2019

Based on the limited accrual to Part 1 of this study, Gradalis is opening Part 2 of this clinical protocol to assess the safety of Vigil immunotherapy in combination with irinotecan and temozolimidetemozolomide. Part 2 will be conducted at the same centers as Part 1, studying intradermal autologous Vigil cancer vaccine (1.0 x 10^7 cells/injection; minimum of 4 to a maximum of 12 administrations) in patients with metastatic Ewing's sarcoma Family of Tumors (ESFT) refractory or intolerant to at least 1 prior line of chemotherapy. Patients undergoing a standard surgical procedure (e.g., tumor biopsy or palliative resection) may have tumor tissue harvested for manufacture of investigational product. Patients meeting eligibility criteria including manufacture of a minimum of 4 immunotherapy doses of Vigil will be registered to receive: (i) oral temozolimide temozolomide 100 mg/m2 daily (Days 1 - 5, total dose 500 mg/m2/cycle), (ii) irinotecan 50 mg/m2 daily (Days 1 - 5, total dose 250mg/m2/cycle), orally or irinotecan 20mg/m2 daily (Days 1 - 5, total dose 100mg/m2/cycle), intravenously (iii) peg-filgrastim 100µg/kg (Day 6) subcutaneously (optional and may be administered at home), and (iv) Vigil 1.0 x 10^7 cells/injection, intradermally on Day 15 and every 3 weeks thereafter.

■ PHASE 1

Pbi-shRNA™ EWS/FLI1 Type 1 LPX in Subjects With Advanced Ewing's Sarcoma

ID: NCT02736565 - CL-PTL-001
Recruitment Status: Recruiting
Start/Planned completion: OCT 2016/FEB 2020
Estimated Enrollment: 28
Sites: 2 (USA)
Updated: June 17, 2019
Contact: Gladice Wallraven - 214-442-8124 - info@gradalisinc.com

FAMILIAL PARTIAL LIPODYSTROPHY (FPL)

Familial partial lipodystrophy is a rare genetic disorder characterized by generalized or partial loss adipose tissue. Six different subtypes of FPL have been identified. Each subtype is caused by a mutation in a different gene. Mutations in five genes that cause FPL have been identified including the LMNA gene, that codes for lamin A and lamin C; the PPARG gene, that codes for the transcription factor PPAR gamma; the PLIN1 gene, that codes for perilipin; the AKT2 gene that codes for protein kinase B beta; and the CIDEC gene that codes for the CIDEC protein that plays a role in storage of fat within lipid droplets.

Latest Publications

* *J Clin Endocrinol Metab*. 2019 Dec 1;104(12):6025-6032.
Diagnostic Challenge in PLIN1-Associated Familial Partial Lipodystrophy.
Jéru I et al. Sorbonne University, Inserm U938, Saint-Antoine Research Centre and Institute of CardioMetabolism and Nutrition, Paris, France.
(Abstract – Full Text)

* *Acta Diabetol.* 2019 Dec 20. doi: 10.1007/s00592-019-01462-y.
The novel loss of function Ile354Val mutation in PPARG causes familial partial lipodystrophy.
Padova G et al. Endocrinology Unit, Garibaldi Hospital, Catania, Italy.
Familial partial lipodystrophy (FPLD) is a rare autosomal dominant disorder, mostly due to mutations in lamin A (LMNA) or in peroxisome proliferator-activated receptor gamma (PPARG) genes. In the present study, the authors aimed to identify and functionally characterize the genetic defect underlying FPLD in an Italian family presenting with several affected individuals in three consecutive generations. (Abstract)

TARGET: APOLIPOPROTEIN C-III

PRODUCT: WAYLIVRA® (VOLANESORSEN - ISIS-APOCIIIRX - ISIS 304801) - IONIS PHARMACEUTICALS (USA)

Volanesorsen is an antisense oligonucleotide that targets mRNA for apolipoprotein C-III (ApoC-III). By blocking the production of this protein, this ASO reduces the level of triglycerides in the blood and, as a result, fat accumulation in the body. The drug has received market authorization in the EU in May 2019 for the treatment of familial chylomicronaemia syndrome.

Related Informations/Publications

* *Drugs*. 2019 Aug;79(12):1349-1354.
Volanesorsen: First Global Approval.
Paik J, Duggan S. Springer Nature, Private Bag 65901, Mairangi Bay, 0754, Auckland, New Zealand.
This article summarizes the milestones in the development of volanesorsen leading to its first approval in the EU as an adjunct to diet in adult patients with genetically confirmed familial chylomicronaemia syndrome and at high risk for pancreatitis, in whom response to diet and triglyceride lowering therapy has been inadequate. (Abstract)

■ PHASE 2-3

The BROADEN Study: A Study of Volanesorsen (Formerly ISIS-APOCIIIRx) in Patients With Familial Partial Lipodystrophy

ID: NCT02527343 - ISIS 304801-CS17 - BROADEN
Recruitment Status: Active, not recruiting
Start/Planned completion: OCT 2015/SEP 2021
Estimated Enrollment: 60
Sites: 30 (BE, BR, CA, DE, ES, GR, IL, IT, NL, PO, RU, TR, UK, US)
Updated: August 23, 2018

The purpose of this study is to evaluate the efficacy and safety of volanesorsen (IONIS-APOCIIIRx) given for 52 weeks in patients with Familial Partial Lipodystrophy. Patients will then be allowed to continue in a 2 year Open Label Extension of the study.

■ PHASE 2

Efficacy, Safety and Tolerability of ISIS 304801 in People With Partial Lipodystrophy With an Open-Label Extension

ID: NCT02639286 - 160038
Recruitment Status: Completed
Start/Planned completion: DEC 2015/SEP 2019
Actual Enrollment: 6
Collaboration: National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) (USA)
Sites: 1 (US)
Updated: October 2, 2019

The purpose of this study is to determine if apoC-III reduction using an ASO to apoC-III (ISIS 304801) will reduce triglycerides and improve insulin resistance, diabetes, and hepatic steatosis in patients with lipodystrophy.

TARGET: ANGIOPOIETIN-LIKE 3 (ANGPTL3)

PRODUCT: AKCEA-ANGPTL3-LRX (VUPANORSEN - ISIS 703802) – AKCEA THERAPEUTICS (USA) – IONIS PHARMACEUTICALS (USA)

AKCEA-ANGPTL3-LRx is a ligand conjugated antisense (LICA) drug designed to reduce the production of angiopoietin-like 3 (ANGPTL3). The absence of ANGPTL3 has been shown to be cardioprotective and associated with reduced risk of insulin resistance and diabetes mellitus. Ionis and Akcea are developing AKCEA-ANGPTL3-LRx to treat multiple lipid disorders including rare hyperlipidemias and NAFLD with metabolic complications. The AKCEA-ANGPTL3-LRx Phase 2 program is designed to include three clinical studies in patients with one of three rare hyperlipidemias, including familial chylomicronemia syndrome (FCS), familial partial lipodystrophy (FPL), and homozygous familial hypercholesterolemia (HoFH). In October 2019, Akcea Therapeutics and Pfizer have entered into a worldwide exclusive licensing agreement for AKCEA-ANGPTL3-LRx. Under terms of the agreement,

Akcea and Ionis will receive a $250 million upfront license fee, which will be split equally between the two companies.

Related Informations/Publications

* **JANUARY 2020** - Akcea Therapeutics announced positive topline results from the Phase 2 study of AKCEA-ANGPTL3-LRx in patients with hypertriglyceridemia, type 2 diabetes and non-alcoholic fatty liver disease (NAFLD). The study met the primary endpoint of significant triglyceride lowering and multiple secondary endpoints with a favorable safety and tolerability profile. (Press Release)

■ PHASE 2

Study of AKCEA-ANGPTL3-LRX (ISIS 703802) in Patients With Familial Partial Lipodystrophy (FPL)

ID: NCT03514420 - ISIS 703802-CS5
Recruitment Status: Completed
Start/Planned completion: MAY 2018/AUG 2019
Estimated Enrollment: 4
Collaboration: Ionis Pharmaceuticals (USA)
Sites: 1 (US)
Updated: September 13, 2019

This is a multi-center, open-label study to evaluate the efficacy of AKCEA-ANGPTL3-LRX for reduction of fasting triglycerides in patients with Familial Partial Lipodystrophy.

RETINITIS PIGMENTOSA (RP)

Retinitis pigmentosa is a group of rare, genetic disorders that involve a breakdown and loss of cells in the retina. Common symptoms include difficulty seeing at night and a loss of peripheral vision. This inherited disorder results from harmful changes in any one of more than 50 genes that carry the instructions for producing photoreceptors in cells within the retina. Forms of RP and related diseases include Bardet-Biedl syndrome, Leber congenital amaurosis, Usher syndrome, among others.

Symptoms of RP typically appear in childhood. Children often have difficulty getting around in the dark. Their visual field becomes restricted and patients with RP often find bright lights uncomfortable. Because there are many gene mutations that cause the disorder, its progression can differ greatly from person to person. Some people retain central vision and a restricted visual field into their 50s, while others experience significant vision loss in early adulthood. Eventually, most individuals with RP will lose most of their sight.

Gene therapy for several different types of RP has shown promise in the laboratory. In a landmark clinical trial, gene therapy for a retinal disorder called Leber congenital amaurosis (LCA) led to improved vision for people with that disorder. This and other gene therapy clinical trials for LCA are ongoing to establish a maximally safe dosage and determine the long-term benefits of treatment.

Latest Publications

* *Sci Rep*. 2020 Jan 31;10(1):1603.

Retinitis Pigmentosa Due to Rp1 Biallelic Variants.

Silva RS et al. Department of Ophthalmology, Ophthalmology Institute Dr. Gama Pinto, Lisbon, Portugal.

In the present study, the authors screened 529 Brazilian individuals affected by inherited retinal disorders. A total of seven unrelated and nonsyndromic patients with RP1 biallelic variants (OMIM # 180100) were diagnosed in their centre and included in the study. They had classic retinitis pigmentosa with diagnosis at the first decade of life. All patients had molecular diagnosis, with six different RP1 variants. This study reports two new pathogenic variants - two frameshift duplications (c.1234dupA p.Met412Asnfs*7 and c.1265dupC p.Ala423Cysfs*2) and reinforces other four known pathogenic variants - two frameshift deletions (c.469delG p.Val157Trpfs*16 and c.3843delT p.Pro1282Leufs*12) and two stop gain mutations (c.1186 C > T p.Arg396* and c.1625C > G p.Ser542*). These findings broaden the spectrum of RP1 variants. This study also reviewed the fundus characteristics that clinically could raise the hypothesis of a retinitis pigmentosa due to RP1 gene. It is worthwhile to try to identify the disease-causing variants in each patient since it can provide prognostic information and be useful in genetic consultation and diagnosis in the future. (Abstract)

* *Int J Mol Sci*. 2020 Jan 25;21(3). pii: E777. doi: 10.3390/ijms21030777.

RNA editing as a therapeutic approach for retinal gene therapy requiring long coding sequences.

Fry LE et al. Nuffield Laboratory of Ophthalmology, Nuffield Department of Clinical Neurosciences & NIHR Oxford Biomedical Research Centre, University of Oxford, Oxford OX3 9DU, UK.

Pairing site-directed RNA-targeting mechanisms with engineered deaminase enzymes allows for the programmable correction of G>A and T>C mutations in RNA. This offers a promising therapeutic approach for a range of genetic diseases. For inherited retinal degenerations caused by point mutations in large genes not amenable to single-adeno-

associated viral (AAV) gene therapy such as USH2A and ABCA4, correcting RNA offers an alternative to gene replacement. Genome editing of RNA rather than DNA may offer an improved safety profile, due to the transient and potentially reversible nature of edits made to RNA. This review considers the current site-directing RNA editing systems, and the potential to translate these to the clinic for the treatment of inherited retinal degeneration. (Abstract – Full Text)

* *J Med Genet*. 2019 Dec 19. pii: jmedgenet-2019-106473

Gene editing prospects for treating inherited retinal diseases.

Benati D, Patrizi C, Recchia A Life Sciences, University of Modena and Reggio Emilia, Modena, Italy.

Retinal diseases (RD) include inherited retinal dystrophy (IRD), for example, retinitis pigmentosa and Leber's congenital amaurosis, or multifactorial forms, for example, age-related macular degeneration (AMD). IRDs are clinically and genetically heterogeneous in nature. To date, more than 200 genes are known to cause IRDs, which perturb the development, function and survival of rod and cone photoreceptors or retinal pigment epithelial cells. Conversely, AMD, the most common cause of blindness in the developed world, is an acquired disease of the macula characterised by progressive visual impairment. To date, available therapeutic approaches for RD include nutritional supplements, neurotrophic factors, antiangiogenic drugs for wet AMD and gene augmentation/interference strategy for IRDs. However, these therapies do not aim at correcting the genetic defect and result in inefficient and expensive treatments. The genome editing technology based on clustered regularly interspaced short palindromic repeat (CRISPR)-associated protein (Cas) and an RNA that guides the Cas protein to a predetermined region of the genome, represents an attractive strategy to tackle IRDs without available cure. In this review, the authors introduce the mechanism of CRISPR/Cas system, presenting an updated panel of Cas variants and delivery systems, then they focus on applications of CRISPR/Cas genome editing in the retina, and, as emerging treatment options, in patient-derived induced pluripotent stem cells followed by transplantation of retinal progenitor cells into the eye. (Abstract)

TARGET: mutant P23H mRNA

PRODUCT: QR-1123 (PREVIOUSLY KNOWN AS IONIS-RHO-2.5RX) – PROQR THERAPEUTICS (NL)

QR-1123 is a first-in-class investigational antisense oligonucleotide designed to treat autosomal dominant retinitis pigmentosa (adRP) due to the P23H mutation in the rhodopsin (RHO) gene. The therapy aims to inhibit the formation of the mutated toxic version of the rhodopsin protein by specifically binding the mutated RHO mRNA. Binding of QR-1123 causes allele specific knockdown of the mutant mRNA by a mechanism called RNase H mediated cleavage without affecting the normal RHO mRNA. QR-1123 is intended to be administered through intravitreal injections in the eye.

QR-1123 was discovered and developed by Ionis Pharmaceuticals. In October 2018, ProQR Therapeutics has acquired the rights to QR-1123. Under the terms of the agreement, ProQR was granted an exclusive worldwide license to QR-1123 and relevant patents.

■ PHASE 1 - 2

A Study to Evaluate the Safety and Tolerability of QR-1123 in Subjects With Autosomal Dominant Retinitis Pigmentosa Due to the P23H Mutation in the RHO Gene (AURORA)

ID: NCT04123626 - PQ-1123-001 - AURORA
Recruitment Status: Recruiting
Start/Planned completion: OCT 2019/OCT 2021
Estimated Enrollment: 35
Sites: 3 (USA)
Updated: December 13, 2019
Contact: ProQR Clinical Trial Manager - +31(0)88 166 7000 - info@proqr.com

This study evaluates the safety, tolerability and efficacy of QR-1123 injection in the eye (intravitreal; IVT) injections (one eye/unilateral) in subjects receiving a single dose or repeat doses. Single injections will be assessed in an open label way, and repeat injections will be assessed in a double-masked, randomized, sham-controlled fashion.

The study will comprise up to 8 single dose and repeat dose cohorts. Prior to initiating a higher single dose cohort and/or prior to initiating repeat dose cohort(s), available safety and efficacy data will be reviewed by the DMC.

In the single dose cohorts subjects will receive a single, unilateral IVT injection of QR-1123 in an open label fashion. In the repeat dose cohorts subjects will be randomized to receive either a unilateral IVT injection of QR-1123 every 3 months or a unilateral sham procedure every 3 months, in a double masked fashion. Subjects will be followed for safety, tolerability and efficacy for a total period of 12 months. The trial is conducted at expert sites in North America. Initial data from the study are expected in 2021.

Related Informations/Publications

* **DECEMBER 2019** - ProQR Announces First Patient Dosed in Phase 1/2 Aurora Trial of QR-1123 for Autosomal Dominant Retinitis Pigmentosa. (Press Release)
* **NOVEMBER 2019** - ProQR Receives Orphan Drug Designation from FDA for QR-1123 for Autosomal Dominant Retinitis Pigmentosa. (Press Release)

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