BioPharmAnalyses

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BRIEFING ON RNA TRIALS

***BioPharmAnalyses* is happy to propose you**
the first issue of it « BRIEFING ON RNA TRIALS ».

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

« BRIEFING ON RNA TRIALS » gives you a breakdown of trials

- **by phase**
- **by disease**
- **by product**
- **by target**
- **by company**
- **by trial location**
- **by licensing agreement.**

The trials presented have been registered and updated on Clinicaltrials.gov from 01/01/2017 to 12/31/2018.

RNA therapeutics trials by numbers

78 products

(including 25 antisense oligonucleotides, 20 RNAi/siRNA and 17 mRNA)

55 targets and 65 diseases

(cancers, cardiovascular and metabolic diseases,
infectious diseases, genetic diseases, ophthalmological diseases....)

42 companies and academic insitutions involved in
101 clinical trials in **44 countries**

BREAKDOWN BY PHASE

Phase III trials:	**XX**
Phase II-III:	**XX**
Phase II trials:	**XX**
Phase I-II trials:	**XX**
Phase I trials:	**XX**
Observational trials:	**XX**

BREAKDOWN BY DISEASE

Cancer - Oncology
Ewing sarcoma
Head and neck cancer
Gynecological cancers
Liver cancer
Lymphoma
Melanoma
Metastatic Castration-Resistant Prostate Cancer
Mycosis fungoides
Non Small Cell Lung 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
Non Alcoholic Fatty Liver Disease
Primary Hyperoxaluria and Primary Hyperoxaluria type 1
Type 2 diabetes mellitus

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

Hematological diseases
Clotting disorders
β-thalassemia
Hemophilia A
Hemophilia B
Sickle cell disease

Hormonal diseases
Acromegaly

Genetic diseases
Acute hepatic porphyria
Acute intermittent porphyria (AIP)
Alpha 1-Antitrypsin Deficiency
Alport Syndrome
Cystic Fibrosis
Familial Chylomicronemia Syndrome
Ornithine Transcarbamylase Deficiency

Infectious diseases
Chikungunya
Cytomegalovirus
Hepatitis B
Influenza
Rabies infection
Zika virus

Lung diseases
Idiopathic Pulmonary Fibrosis

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

Neurological diseases
Chronic migraine

Neuromuscular diseases
Duchenne Muscular Dystrophy
Spinal muscular atrophy

Ophthalmological diseases
Acute Nonarteritic Anterior Ischemic Optic Neuropathy
Dry Eye Disease
Leber’s Congenital Amaurosis
Neovascular age-related macular degeneration

Renal diseases
Acute kidney injury
End-stage renal disease
Renal impairment

Transplantation
Prevention of Delayed Graft Function

BREAKDOWN BY TARGET

Aminolevulinic acid synthase 1 (ALAS-1)
Androgen receptor
Angiopoietin-like protein 3 (ANGPTL3)
Angiotensinogen (AGT)
Antithrombin
Apolipoprotein C-III
BCL11a
Caspase 2 gene
CD40
CEBPA gene
CFTR
Connect Tissue Growth Factor (CTGF)
COX-2 mRNA
Cbl-b
(Casitas B-lineage lymphoma-b)
EGFR
EnaC (epithelial sodidum channel)
Ephrin type-A receptor 2 (EphA2)
Exon 45
Exon 51
Exon 53
Exon 73 from the COL7A1 RNA
Factor XI
Glycolate oxydase
Growth hormone receptor (GHR)
H10N8 antigen
Heat shock protein 47 (HSP 47)
Hepatitis B surface antigen (HbsAg)
Human lipoprotein A
Huntingtin mRNA
KRAS
Lactate dehydrogenase A gene
miR-21
miR-29
miR-92a
miR-155
mutant alpha-1 antitrypsin (Z-AAT)
Neoantigens expressed by the autologous cancer protein
OX40L
OX40L+IL23+IL36gamma
p53 gene
p.Cys998X mutation in the CEP290 gene
prekallikrein
SMN2 pre-mRNA
STAT3 pathway
superoxide dismutase (SOD1)
Tau protein
TGF-β1 mRNA
Toll-like receptors (TLRs) and retinoic acid-inducible gene I
TMPRSS6 (Transmembrane protease, serine 6 or matriptase-2)
Transthyretin
TRPV1
Tumor-associated antigens
Tumor-associated antigens NY-ESO-1, tyrosinase, MAGE-A3, and TPTE
Tumor-associated antigens NY-ESO-1, MAGE C2, TPBG (5T4), Survivin, MUC1
VEGF-A
Viral proteins associated with hepatitis B virus (HBV) infection and replication, including hepatitis B surface antigen

CANCER - ONCOLOGY

EWING'S SARCOMA

Vigil + Irinotecan and Temozolomide in Ewing's Sarcoma

ID: NCT03495921 - CL-PTL-130

Gradalis (USA - TX)

Product: **Vigil (Pbi-shRNA™ EWS/FLI1 Type 1 LPX)**
Phase: 3
Status: Recruiting
Start/Planned completion: AUG 2018/JUL 2022
Estimated Enrollment: 140
Sites: 10 (US)
Updated: November 16, 2018
Contact: info@gradalisinc.com

This is a multicenter, 1:1 randomized Phase III study of intradermal autologous Vigil immunotherapy (1.0 x 10e6 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, Vigil.

Vigil utilizes the patient's own cancer cells to create a fully personalized cancer immunotherapy. Patient's cancer cells are genetically modified. These modifications are achieved through the introduction of a proprietary gene plasmid into the patient's cancer cells. The 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. It has been demonstrated that GM-CSF enhances surface antigen expression, making the cancer cells more visible to the patient's immune system. GM-CSF also further stimulates the patient's immune system by actively recruiting and maturing antigen-presenting cells, such as dendritic cells.

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).

HEAD AND NECK CANCER

Target: EGFR

A Study of BB-401 in Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma

ID : NCT03433027
Benitec BioPharma (AU)
Product: **BB-401**
Phase: 2
Status: Active, not recruiting
Start/Planned completion: MAR 2018/OCT 2019
Estimated Enrollment: 16
Sites: 6 (AU, RU)
Updated: November 9, 2018
The purpose of this study is to evaluate the safety, tolerability and efficacy of intratumoral injections with an Epidermal Growth Factor Receptor (EGFR) AntiSense DNA (BB-401) in patients with metastatic/recurrent head and neck squamous cell cancer (HNSCC).
Related Informations/Publications :
* *Br J Cancer* . 2018 Dec 26. doi: 10.1038/s41416-018-0351-z. Co-targeting EGFR and IKKβ/NF-κB signalling pathways in head and neck squamous cell carcinoma: a potential novel therapy for head and neck squamous cell cancer. Li Z et al. Marlene and Stewart Greenebaum Comprehensive Cancer Center, University of Maryland School of Medicine, Baltimore, MD, US.
Results/Comment s: Epidermal growth factor receptor (EGFR) plays an important role in HNSCC proliferation and therapy resistance, but the efficacy of targeting of EGFR for therapy has been limited. This article explores the molecular link between EGFR and inhibitor of κB kinase β/nuclear factor-κB (IKKβ/NF-κB) signalling pathways in the regulation of HNSCC EGFR inhibitor resistance. Link: Abstract

LIVER CANCER

Target : CEBPA gene

First-in-Human Safety and Tolerability Study of MTL-CEBPA in Patients With Advanced Liver Cancer

ID : NCT02716012 - MNA-3521-011 - 2015-003051-21 EudraCT Number) - 20332 (Other Identifier: UK NIHR CRN) - OUTREACH
Mina Therapeutics (UK)
Product: **MTL-CEBPA** (Small activating RNA (saRNA) – short double stranded RNA designed to activate CCAAT enhancer binding protein alpha (CEBPA) gene)
Phase: I
Status: Recruiting
Start/Planned completion: MAR 2016/DEC 2019

Estimated Enrollment: 51
Sites: 9 (SG, TW, UK)
Updated: September 10, 2018
Contact: clinicaltrials@minatx.com
The study is in two parts: dose escalation followed by a dose expansion; both parts of the study will recruit advanced hepatocellular carcinoma patients with cirrhosis. All participants will be refractory to or ineligible for loco-regional therapy including surgery, radiofrequency tumour ablation, transarterial chemoembolisation or sorafenib.

Related Informations/Publications

* **DEC 2018** - MiNA Therapeutics announced enrolment of the first patients treated with MTL-CEBPA in combination with Sorafenib in OUTREACH
Link: Press Release

* *Oncol Rep.* 2018 Dec 13. doi: 10.3892/or.2018.6930.
MicroRNA-486-5p functions as a tumor suppressor of proliferation and cancer stem-like cell properties by targeting Sirt1 in liver cancer. Yan X et al. College of Life Science and Bioengineering, Beijing University of Technology, Beijing, CN.
- *Results/Comments* : MicroRNAs are small non-coding RNAs that target the 3'untranslated region of mRNAs. Their dysregulation has been implicated in several types of cancer including liver cancer, but it still remains unknown if they play a role in targeting liver cancer stem-like cells (CSCs). These researchers compared the miRNA profiles between liver cancer samples and adjacent non-tumor tissues using The Cancer Genome Atlas (TCGA) datasets. The results of their study indicated that the miR-486-Sirt1 axis was involved in suppressing CSC traits and tumor progression.
Link: Abstract

* *Oncol Rep* . 2018 Dec 12. doi: 10.3892/or.2018.6928.
Inhibition of PIKfyve using YM201636 suppresses the growth of liver cancer via the induction of autophagy. Hou JZ et al. Institute for Innovative Drug Design and Evaluation, School of Pharmacy, Henan University, Kaifeng, Henan, CN.
- *Results/Comments* : This study incidates that phosphatidylinositol-3-phosphate 5-kinase (PIKfyve) may be a potential therapeutic target for the treatment of liver cancer.
Link: Abstract

* **OCT 2018** - MiNA Therapeutics announces Sosei will not exercise acquisition option.
Link: Press Release

* **SEP 2018** - MiNA Therapeutics provided an update from the ongoing Phase I study of MTL-CEBPA in advanced liver cancer patients at International Liver Cancer Association Conference. Link: Press Release

HEMATOLOGICAL DISEASES

CLOTTING DISORDERS

Target: Factor IX

A Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single and Multiple Doses of IONIS FXI-LRx in up to 84 Healthy Volunteers

ID: NCT03582462 - ION 957943-CS1
Ionis Pharmaceuticals (USA –CA)
Product: **IONIS FXI-LRx**
Phase: 1
Status: Recruiting
Start/Planned completion: JUL 2018/MAY 2019
Estimated Enrollment: 84
Sites: 1 (CA)
Updated: July 23, 2018
Contact: patients@ionisph.com
Related Informations / Publications
* *Med Res Rev* . 2018 Sep;38(6):1974-2023. doi: 10.1002/med.21503. Recent advances in the discovery and development of factor XI/XIa inhibitors. Al-Horani RA, Afosah DK. Division of Basic Pharmaceutical Sciences, College of Pharmacy, Xavier University of Louisiana, New Orleans, LA, US.
Results/Comments : This review highlights various chemical, biochemical, and pharmacological aspects of FXI/FXIa inhibitors (polypeptides, active site peptidomimetic inhibitors, allosteric inhibitors, antibodies, aptamers. antisense oligonucleotides), with the goal of advancing their development toward clinical use. Link: Abstract

OPHTHALMOLOGICAL DISEASES

ACUTE NONARTERITIC ANTERIOR ISCHEMIC OPTIC NEUROPATHY (NAION)

Target: mRNA of the Caspase 2 gene

Phase 2/3, Randomized, Double-Masked, Sham-Controlled Trial of QPI-1007 in Subjects With Acute Nonarteritic Anterior Ischemic Optic Neuropathy (NAION)

ID: NCT02341560 - QRK207
Quark Pharmaceuticals (USA – MA)
Product: **QPI-1007**
Phase: 2-3
Status: Recruiting
Start/Planned completion: OCT 2015/OCT 2020
Estimated Enrollment: 800
Sites: 84 (AU, CN, DE, IL, IN, IT, SG, US)
Updated: August 3, 2018
Contact: rshopbell@quarkpharma.com
This study will determine the effect of QPI-1007 on visual function in subjects with recent-onset NAION and assess the safety and tolerability of intravitreal injections of QPI-1007 in this population. This study will also evaluate the structural changes in the retina following administration of QPI-1007.
Related Informations / Publications
* *Acta Ophthalmol* . 2018 Dec;96(8):e1018-e1024. Optic nerve head morphology in primary open-angle glaucoma and nonarteritic anterior ischaemic optic neuropathy measured with spectral domain optical coherence tomography. Resch H et al. Department of Ophthalmology and Optometry, Medical University Vienna, Vienna, Austria. Link: Abstract - Full Text
* **OCT 2018** Quark Pharmaceuticals Announces Acceptance of Presentation and Abstracts at ASN 2018 (October 23-28, 2018) and AAO 2018 (October 27-30, 2018) Annual Meetings. An abstract for QPI-1007 has been accepted for presentation at the American Academy of Ophthalmology (AAO) 2018 Annual Meeting to be held October 27–30, 2018 in Chicago. The presentation focused on an interim analysis of the baseline characteristics in patients with NAION from the QRK207 Study, a Phase 2/3, Randomized, Double-Masked, Sham-Controlled Trial of QPI-1007. Link: Press Release

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