

## 2022

### FLAGSHIP PROJECT

#### SQY-Therapeutics

*SQY-Therapeutics is the technological instrument in the hands of the AMM and allied parents for the development of a new class of drugs for the treatment of DMD.*

Treasury advance was requested to finance the mandatory preclinical regulatory studies (GLP) required to apply for clinical trial authorisation from health agencies (ANSM – EMA), Fill & Finish of the drug product 'SQY51', and the organisation of the trial logistics.

- Preclinical short-term studies in two species (13-week treatment plus recovery)
- Long-term studies in two species (28- and 44-week treatment plus recoveries)

Authorisation was granted on 21 November 2022: 'AVANCE 1'

EUCT N° 2022-500703-49-01 [clinicaltrials.gov NCT05753462](https://clinicaltrials.gov/ct2/show/study/NCT05753462)

Phase 1/2a, Monocentric, Open Label Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of SQY51 in Pediatric and Adult Patients with Duchenne Muscular Dystrophy, including : i) a 16-week Phase 1 Multiple Dose Escalation Phase, and ii) a 33-week 2a Phase.

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### GRANTS and FELLOWSHIPS

- [1] € 200'000 '**Paul Pettavino Fellowship**' for PhD Student Clémence Alibert, whose thesis project under Pr. Christophe Marcelle leadership aims to study/develop an innovative strategy for repairing dystrophic muscles by using engineered blood born cells capable to fuse with regenerating muscle fibres.  
**CNRS / NeuroMyoGene Institute (INMG), Lyon1 University Faculty of Medicine and Pharmacy**
- [2] € 226'520 '**Paul Pettavino Grant**' for Dr. Marisa Jaconi, whose project entitled "Immortal Immune-privileged myogenic stem cells for gene therapy of muscular Dystrophy" aims to enhance the therapeutic efficiency of so-called mesangioblasts, a population of vessel-associated cells that can cross the vessel walls and contribute to muscle regeneration.  
**Peer review FSRMM (Fondation Suisse de Recherche sur les Maladies Musculaires)  
Dept Basic Neurosciences, Faculty of Medicine, Geneva University**
- [3] € 51'500 to cover the salary of an **Assistant Head of Clinic** (Dr. Angely Mendoza Cardozo - from 1<sup>st</sup> November 2022 to 31 October 2024) as part of the support to AVANCE 1 clinical research project lead by Pr. Helge Amthor at the CHU (Centre Hospitalo-Universitaire) Raymond Poincaré of Garches.  
**Université Versailles St-Quentin en Yvelines**
- [4] € 8'660 for supplies for 'Monégasque-French team LIA-BAHN' located at the Monaco Scientific Center (CSM). This partnership aims to create project synergies between the CSM and the teams of the University of Versailles in the field of biotherapies applied to neuromuscular disorders. LIA-BAHN is supported by the AMM since its creation in 2013.  
**Centre Scientifique de Monaco**
- [5] € 36'000 to finance PART-2 of Jean-Paul Carta's 3D simulator to study neuromuscular and neurological diseases in an innovative way. The device consists of a sensory platform coupled to a virtual reality headset and fun sequences (rapids, stunts, etc.) to assess the motor skills (reflexes) of disable patients according to their level of ability.  
**Smart Mobilities & Devices SARL, les Mureaux – France**

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### LOCAL PATIENT SUPPORT

€ 29'000 to help with home adaptation and independency for Philippe Ferreyrolles, an adult DMD patient living in Monaco.

## 2021

### FLAGSHIP PROJECT

#### **SQY-Therapeutics: regrouped in 2022**

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### GRANTS and FELLOWSHIPS

- [1] € 160'800 'Paul Pettavino Grant'** for Dr. Daniela Latorre, whose project is entitled "Characterization of autoreactive T cells in Guillain-Barré syndrome". The reason for selecting a project not relating DMD but another rare autoimmune disease that affects the peripheral nerve was the outstanding and innovative proposal itself and the fact that Daniela is a young, excellent scientist who just recently was awarded an independent position (PRIMA fellowship) and the money for one PhD student would allow her to expand her group. In any case, the outcomes of this project may have medical implications for the development of new therapeutic options for a large spectrum of neuromuscular disorders.  
**Peer review FSRMM** (Fondation Suisse de Recherche sur les Maladies Musculaires)  
**Institute of Microbiology, ETH Zurich**
- [2] € 50'000** to cover 12-month salary of a **Clinical Research Associate** for the "Centre de Référence des Maladies Neuromusculaires" North/Est Ile-de-France.  
**Institute Necker, Paris**
- [3] € 100'000** to cover 24-month salary for an **Engineer/Postdoc** (Dr. Olga Petkova in the Team of Pr. Helge Amthor) to study dystrophin rescue in a novel transgenic mouse model of DMD (i.e., where a fluorescent tag is genetically linked to the nascent dystrophin) after systemic administration of tcDNA antisense oligonucleotides: focus being on the role of dystrophin in muscle precursor cells, the subcellular localisation of the *de novo* rescued dystrophin, the nuclear domain of dystrophin expression within muscle fibers, and the minimum level of dystrophin needed to protect muscle fibers.  
**Université Versailles St-Quentin en Yvelines**
- [4] € 150'000** to cover Team expansion of Dr. Aurélie Goyenvallé who develops 'Biotherapies for Neuromuscular Diseases' in collaboration with the CSM (LIA-BAHN) and study novel antisense molecules for the treatment of DMD with a focus on the cognitive aspects linked to the lack of dystrophin in the CNS of DMD patients.  
**Université Versailles St-Quentin en Yvelines**
- [5] € 9'048** for supplies for the 'Monégasque-French team LIA-BAHN' located at the Monaco Scientific Center (CSM). This partnership aims to create project synergies between the CSM and the teams of the University of Versailles in the field of biotherapies applied to neuromuscular disorders. LIA-BAHN is supported by the AMM since its creation in 2013.  
**Centre Scientifique de Monaco**
- [6] € 36'130** to finance PART-1 of Jean-Paul Carta's 3D simulator to study neuromuscular and neurological diseases in an innovative way. The device consists of a sensory platform coupled to a virtual reality headset and fun sequences (rapids, stunts, etc.) to assess the motor skills (reflexes) of disabled patients according to their level of ability.  
**Smart Mobilities & Devices SARL, les Mureaux – France**

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### LOCAL PATIENT SUPPORT

**€ 8'619** to support mobility expenses of Philippe Ferreyrolles, an adult DMD patient living in Monaco.

## 2020

### FLAGSHIP PROJECT

#### SQY-Therapeutics

*SQY-Therapeutics is the technological instrument in the hands of the AMM and allied parents for the development of a new class of drugs for the treatment of DMD.*

In 2020, SQY-Therapeutics selected/validated its first lead-compound 'SQY51' for human clinical purposes. Such validation was carried out in a variety of preclinical models, opening with in vitro analyses using patient cell lines and ending with animal models for robust evaluations of pharmacokinetics, tissue biodistribution and pharmacodynamics (i.e., skipping of exon 51 of the DMD gene in skeletal muscles, respiratory muscles, and heart) of the lead compound.

The achievement of these studies has triggered an avalanche of new commitments ahead of the forthcoming preclinical evaluations and the clinical trial to come. More specifically, to supply large quantities of raw material (i.e., tcDNA building blocks A, C, G, T for oligonucleotide synthesis), transfer our technology to a contractor for the GMP-compliant synthesis of SQY51 at large scale (i.e., to satisfy the needs of drug product for the schedule regulatory tox-studies and the clinical trial itself and eventually an extension phase if promising), mandate a CRO for the GLP-compliant toxicology study, etc.

#### Synthena

The hosting contract at UniBe coming to an end and could not be renewed, all the activities of Synthena on tcDNA manufacturing and oligonucleotide synthesis were transferred to SQY-Therapeutics. As a result, Synthena reimbursed € 2'774'380 overpayment from AMM, which were reallocated to SQY-Therapeutics.

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### GRANTS and FELLOWSHIPS

- [1] **€ 125'000** to the laboratory of Dr. Dmitri Stetsenko with the idea of preparing possible collaborative projects and/or future exchanges of researchers in the field of the chemistry behind antisense oligonucleotides. This operation enabled us to evaluate 3 researchers, one of whom, the very valuable with extensive experience in the field of oligo production for clinical purposes, has joined SQY-Therapeutics on a permanent basis.  
**Novosibirsk State University, Russia**
- [2] **€ 57'000** to cover 12-month salary of a **Postdoctoral fellow** (Dr. Amalia Stantzou) for studying, under the supervision of the Pr. Helge Amthor, the differential expression and restoration of dystrophin at critical sites in muscle fibers, as a translational research project upstream of the planned analyses of muscle biopsies from the AVANCE 1 clinical trial.  
**Université Versailles St-Quentin en Yvelines**
- [3] **€ 23'120** to support the project "REHAssist" led by Dr. Mohamed Bouri within EPFL consisting in the development of devices for mobility aids and rehabilitation.  
**Ecole Polytechnique Fédérale de Lausanne (EPFL)**
- [4] **€ 9'622** for supplies for the 'Monégasque-French team LIA-BAHN' located at the Monaco Scientific Center (CSM). This partnership aims to create project synergies between the CSM and the teams of the University of Versailles in the field of biotherapies applied to neuromuscular disorders. LIA-BAHN is supported by the AMM since its creation in 2013.  
**Centre Scientifique de Monaco**

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### LOCAL PATIENT SUPPORT

**€ 7'000** to contribute mobility expenses of Philippe Ferreyrolles, an adult DMD patient living in Monaco.

## 2019

### FLAGSHIP PROJECT

*SQY-Therapeutics and Synthena are technological instruments in the hands of the AMM and allied parents for the development of a new class of drugs for the treatment of DMD.*

#### **SQY-Therapeutics**

2019 was dedicated to consolidating the preclinical analysis platforms set up within the company, which enabled a candidate compound to be identified, modified so that it was safer while being more effective.

#### **Synthena**

Synthena has carried out the upstream work on the synthesis of the tricyclo-DNA oligonucleotides designed/proposed by SQY-Therapeutics will seeking to optimise production yields.

Of all the compounds tested, 'SQY51' proved to be the most promising. The move of Synthena's activities to SQY-Therapeutics was completed in December 2019.

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### GRANTS and FELLOWSHIPS

- [1] **€ 155'874** were awarded to Pr. Robert Kotin, a pioneer in the design of gene vectors derived from AAV and methods of production, to accelerate his research aiming to identify and characterize genomic safe harbors in humans and murine genomes for insertion of dystrophin expression cassettes. If successful, such technology may have important medical outputs in the field of gene therapy for a large spectrum of disorders.  
**University of Massachusetts Medical School, USA**
- [2] **€ 90'000** were awarded to Pr. Karim Wahbi to conduct an up-to-date study on the natural history of the cardiomyopathy prevalent in Duchenne patients. The results of this work will be essential on the one hand to ensure better cardiac monitoring of Duchenne boys during the evolution of their disease, and on the other hand to appraise the potential effects (beneficial or harmful) of the treatments currently being tested.  
**Institute Necker, Paris**
- [3] **€ 52'500** were awarded to Pr. Denis Duboc to study on the use of beta-blockers to preserve the cardiac muscle function in DMD patients.  
**Biologica Naturalia, Paris**
- [4] **€ 70'000** to support the Team of Dr. Aurélie Goyenvallé dedicated to understanding the entry mechanisms of antisense oligonucleotides into cells. Such outcome would allow the community to design more efficient antisense oligonucleotides, and therefore reduce the toxicity resulting from overdosages.  
**Université Versailles St-Quentin en Yvelines**
- [5] **€ 10'796** for a short-term postdoctoral fellowship to Dr. Jackub Malcher as part of a French-German (MyoGrad) research project entitled "Gene Transfer Efficiency of AAV vectors depending on Dysferlin Expression".  
**Charité Medical Faculty of Berlin and the Max Delbrück Center for Molecular Medicine**
- [5] **€ 4'961** for supplies for the 'Monégasque-French team LIA-BAHN' located at the Monaco Scientific Center (CSM). This partnership aims to create project synergies between the CSM and the teams of the University of Versailles in the field of biotherapies applied to neuromuscular disorders. LIA-BAHN is supported by the AMM since its creation in 2013.  
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### LOCAL PATIENT SUPPORT

**€ 7'000** to contribute mobility expenses of Philippe Ferreyrolles, an adult DMD patient living in Monaco.

## 2018

### FLAGSHIP PROJECT

*SQY-Therapeutics and Synthena are technological instruments in the hands of the AMM and allied parents for the development of a new class of drugs for the treatment of DMD.*

#### **SQY-Therapeutics / Synthena**

The 2016-2017-2018 period was devoted to bringing together the activities of the two companies to achieve a lead compound intended to be evaluated in DMD patients. Several compounds have been studied for targeting different exons of the dystrophin pre-mRNA (i.e., 51, 16, 44, 53).

SQY-Therapeutics focused on in silico design of the antisense sequences and ex vivo tests; Synthena ensuring on-demand synthesis of designated targets.

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### GRANTS and FELLOWSHIPS

- [1] **€ 150'000** were awarded to a novel research project of Pr. Christophe Marcelle aiming to setup an innovative strategy for repairing dystrophic muscles by using engineered blood born cells capable to fuse with regenerating muscle fibres. Preliminary results were very encouraging. If it worked it would be a remarkable conceptual and technological breakthrough useful for many neuromuscular diseases.  
**CNRS / NeuroMyoGene Institute (INMG), Lyon1 University Faculty of Medicine and Pharmacy**
- [2] **€ 50'000** were awarded to Dr. Cyrille Vaillend for a project entitled 'Gene Therapy to Correct Cognitive Deficits in Duchenne Muscular Dystrophy'.  
**CNRS / Université Paris-Sud, Orsay**
- [3] **€ 30'000** to support the Team of Pr. Markus Schuelke (50% of a technical assistant for one year) for developing a novel mdx transgenic mouse model of DMD allowing live-monitoring of dystrophin expression in vivo.  
**Charité Medical Faculty of Berlin and the Max Delbrück Center for Molecular Medicine**
- [4] **€ 11'750** for a short-term postdoctoral fellowship to Dr. Jackub Malcher as part of a French-German (MyoGrad) research project entitled "Gene Transfer Efficiency of AAV vectors depending on Dysferlin Expression".  
**Charité Medical Faculty of Berlin and the Max Delbrück Center for Molecular Medicine**
- [5] **€ 27'346** for supplies for the 'Monégasque-French team LIA-BAHN' located at the Monaco Scientific Center (CSM). This partnership aims to create project synergies between the CSM and the teams of the University of Versailles in the field of biotherapies applied to neuromuscular disorders. LIA-BAHN is supported by the AMM since its creation in 2013.  
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### LOCAL PATIENT SUPPORT

**€ 7'300** to contribute mobility expenses of Philippe Ferreyrolles, an adult DMD patient living in Monaco.