Saint-Quentin-en-Yvelines, October 6th, 2023

Letter from Luis Garcia (CNRS Research Director, Director of the ENDICAP Laboratory UMR 1179 Inserm-UVSQ, UFR santé Simone Veil, Scientific Advisor SQY Therapeutics) to the Only Watch Community.

"Understanding the parents-researchers-doctors united coalition strategy to find a therapy to the Duchenne muscular dystrophy."

1. Thirty-five years after the discovery of the Duchenne gene, there is still no effective and/or satisfactory treatment for Duchenne muscular dystrophy, despite the numerous therapeutic strategies tested over the last twenty years (e.g. cell therapy, gene therapy, exon skipping, growth factors etc.).

2. Some twenty years ago, faced with this lack of treatment, a handful of parents, founders of associations fighting against Duchenne muscular dystrophy (Association Monégasque contre les Myopathies, Duchenne Parent Project France), decided to join forces and federate their actions to support research into this disease, in the hope of contributing to effective treatments for their children.

3. From the outset, **this alliance of parents has included researchers, each working in their own area of expertise.**

   3.1. Parents, through their Associations, have focused on obtaining and making available the financial resources essential for innovative research and its translation into clinical practice.

   3.2. This constant support has enabled many researchers and doctors to facilitate their work and venture into new fields of investigation previously inaccessible due to the level of funding required.

   3.3. The **strategic choices of this coalition (i.e., in their form and outcome) have always been discussed collegially (e.g., Parents-Researchers-Doctors)** in line with scientific advances and presumed opportunities for effective treatments.

4. By general agreement, the first actions consisted in identifying and regularly bringing together the best research teams working on different therapeutic approaches for Duchenne muscular dystrophy; cycle of the 'Tables Rondes de Monaco' and the multidisciplinary 'ICE (international Collaborative Effort) for DMD' project (2003-2012).

5. At the end of the multi-year 'ICE for DMD' project, in which a dozen university laboratories had taken part, a real opportunity had arisen in the form of a highly promising new class of antisense oligonucleotides (i.e. tricyclo-DNA), for which everything remained to be done.

6. Two options were open to this group:
   6.1. Sprinkle funds over as many projects as possible.
   6.2. Concentrate the bulk of our resources on a lead project aiming at reaching clinical application.

7. Considering that “Who grasps all, might lose all”, we decided to concentrate on the new tricyclo-DNA chemistry, in the hope of creating a molecular toolbox that would go beyond Duchenne muscular dystrophy and provide therapeutic prospects for a multitude of pathological conditions for which the treatment offering still remains unsatisfactory or even unsatisfied.

8. To this end, while continuing to support certain research projects (e.g. doctoral fellowships, post-doctorates, research teams, etc.), **we have unanimously subscribed to the need to capitalize on sufficient funds to achieve our R&D objectives for a new class of drug through to clinical evaluation** (i.e. Phases 1 and 2 in Duchenne boys).

9. In this adventure, this parent-researcher coalition has surrounded itself with the necessary talents and indispensable skills, most often animated by a spirit of solidarity and philanthropy in line with **our objective, which is and always will be, to offer the patient community a well-rounded instrument designed to open up therapeutic avenues for causes supposedly lost.**

10. Together, parents and researchers decided to set up two companies as a sine qua non condition for the development of a drug (NB. this role cannot be carried out directly by parents' Associations nor academic laboratories).

- Synthena in Switzerland (Berne – created in 2012) for the development of the chemistry of tricyclo-DNA.
- SQY Therapeutics in France (Saint-Quentin-en-Yvelines – created in 2015) for the development and evaluation of the antisense molecules generated by Synthena.

11. In order to guarantee control of the project, we did not want investors to take a stake in the capital of these two companies, which must remain under the control of parents and Associations of parents. **In fact, these two sister companies operate in a way similar to that of a social and solidarity foundation, for which no dividends are expected.**

12. The financial resources required for current clinical developments are considerable, amount to millions of euros. **The rigorous management of funds generated by Only Watch since its creation enables us to now have the resources required to achieve our objectives.**

13. The actors in this adventure have always combined a strong, potentially impactful action for patients with a discreet, unheralded narrative. The reasons are twofold:
    13.1. On one hand, no need for outside investors.
    13.2. On the other hand, the need for caution and confidentiality when developing a promising molecule.
    Today, the results are tangible, and the first clinical trial for Duchenne resulting from our work is underway in France. This is AVANCE 1, the first 'First in Human' clinical trial with a molecule from the tricyclo-DNA class (SQY51) in twelve DMD patients (pediatric and adult).

14. AVANCE 1 received ANSM-EMA authorization in November 2022 (EUCT N° 2022-500703-49-01; clinicaltrials.gov NCT05753462). Phase 1 of the trial began in the spring of 2023: the first five patients will have completed Phase 1 (NB. intra-patient SQY51 dose escalation) this autumn - to date, with no notable drug-related adverse events; subsequent patients will be enrolled sequentially before the end of the year, and Phase 2 is likely to begin in early 2024 following the green light from ANSM-EMA on the basis of the final Phase 1 safety report.

15. This project would not have been possible without the resources provided by Only Watch and AMM. **Developing a drug goes far beyond the discovery of an active ingredient and proof of principle of its potential interest.** It also underpins pre-industrial development, with scale-up for drug production, GMP (Good Manufacturing Practice) production in sufficient quantities for human use, all the requisite quality controls, regulatory toxicology studies and drug packaging, preparation of files including the clinical protocol, costs related to patient hospitalization, medical staff mobilized for the trial and all dosages guaranteeing the safety of participating patients, as well as their clinical evaluation, travel from their residence to the trial's investigating hospital (NB. Over forty visits per patient over the duration of the trial).

16. **All this is obviously extremely costly, and has required precise management of cost control and, above all, of the timing of expenditure. Without this rigor and a successful strategy, the SQY-Synthena tool for patients and their families would never have seen the light of day.**

17. We have done things differently from the usual practice in the pharmaceutical world (with whom we have good contacts and relationships), but our modus operandi has enabled us to achieve our goals, and our R&D tools open up the prospect of other drug candidates for Duchenne muscular dystrophy and at least two other neuromuscular diseases, as well as a very debilitating skin disease. Each of these new projects will benefit from our way of doing things and the know-how acquired since the first 'Monaco Roundtable', and will require new Only Watch funds to come to fruition.

18. We, the researchers and clinicians, due to the exceptional results of Only Watch, from one edition to the next, thanks to enthusiastic watchmakers, donors and partners, urged the AMM and its President to **keep a substantial part of the donations received in reserve, so that when the time came, we would have the means to fulfill our ambitions in an independence unhampered by a possible lack of cash as the clinical trials ramped up**. And we were heard. This gave us time for research, and the opportunity to go through all the stages of the project without depending on anything other than the generosity of this OW community.

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