Accelerating clinical trials in Wolfram syndrome: development of efficacy biomarkers and patient relevant outcome measures

1st teleconference meeting report

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Report validated by: Prof. Timothy Barrett, project coordinator

The first update teleconference meeting on Biomarker project led by Professor Tim Barrett took place on Tuesday 24 April, six months after the official beginning of the project. Representatives of the three funding organizations were present: Stephanie Gebel (The Snow Foundation), Nolwen Le Floch & Virginie Picard (Association du syndrome de Wolfram) and Lode Carnel (Eye Hope Foundation).

The project coordinator, Professor Timothy Barrett, presented the progress of the project, with the kind assistance of two members of his consortium: Dr. Dewi Astuti and Dr. Anita Slade (University of Birmingham).

As an introduction, Professor Barrett recalled that the project is aimed at validating biomarkers relevant to underlying Wolfram syndrome mechanisms and at developing Patient-Reported Outcomes (PROs) to capture the broader experience of the patient and to define patient-relevant clinical trial endpoints for future clinical trials. The ultimate goal of the project is to hasten delivery of treatments to the patient in the clinic and to develop tools allowing to predict within the first 6 months /1 year of a clinical trial whether a candidate medicine has a chance to succeed or not.

The progress of three work packages was then presented:

Dr. Anita Slade presented the work she is doing on the development of PROs. She has achieved initial consultations with British patients (adults or adolescents) and parents in order to define what the expected outcomes of a candidate medicine on the patient life and health can be. She has based her research on patients experience as well as on various existing clinical Quality of Life questionnaires that are relevant to Wolfram syndrome and vision loss. She has been able to establish a list

of potential PROs that now need to be evaluated for their clinical meaningfulness and usefulness.

Dr. Dewi Astuti next presented her current work on the identification of biomarkers that can be used to evaluate the progress of Wolfram syndrome and more especially the neurodegenerative component of the disease. She has searched for biomarkers that can be preferentially measured in small amounts of blood and that are time and cost-effective. For this, she has made an extensive literature search, looking for candidate biomarkers already used for neurodegenerative diseases. Thanks to this, she has been able to identify 4 new candidate biomarkers that are now being tested for their relevance and sensitivity in cultures of cells depleted of WFS1 gene and in sera of patients with Wolfram syndrome. One of the biomarkers selected seems to be consistently increased in sera of Wolfram patients. Additional assays are ongoing.

Professor Barrett then presented progress being achieved with Euro-WABB, the patient registry for rare diabetes (including Wolfram syndrome). In May 2018, new European standards on data protection will be published, as well as a set of common data elements for all rare disease registries. Moreover, a common consent form for European Reference Networks is now available. The aim of all these new measures is to make all registries interoperable and linked to an EU platform for rare diseases registration. Euro-WABB is currently being modified by Richard Sinnott to comply with these new regulations and requirements. Data from past registry will be transferred to a new, user-friendly database. Hopefully, work will be completed during the summer.

Another project work package has not started yet. This work package is aimed at validating the first candidate efficacy biomarker $p21^{cip}$ within the frame of the European Phase II clinical trial on candidate drug Valproate. For this, bio samples need to be collected from patients treated and non-treated with the drug. The organization of the clinical trial has faced some delays, but it is now expected to start in Autumn 2018.

This work will be extensively presented at next international workshop organized by the Association du syndrome de Wolfram that will take place in June in Paris, France. The second update teleconference meeting is due in September 2018.