Dear friends and colleagues,

Thank you for the opportunity to update you on some of our research activities.

To begin, as you know the TreatWolfram trial has not yet given us a definite answer as to whether sodium valproate slows disease progression, as the people who took valproate were different to the people who took placebo. The people in the treatment arm were older, had worse vision, worse diabetes control, and optic atrophy for longer. This means that we could not truly compare their vision after treatment with valproate. To address this, we have combined forces with Prof Tammy Hershey's team in Washington University St Louis. They have kindly given us access to their data from their Wolfram natural history study. We now have a data sharing agreement in place. This means that our statistician, Tori Homer, can add the St Louis Data to the TREATWOLFRAM placebo data, to make a better match between groups. This should help us to detect if there is an effect of sodium valproate on progression of vision loss. We hope to have this information ready in time for the International Wolfram Research Conference in Windsor in the Summer.

Secondly, I am very grateful for the French Rare Disease Foundation, who have awarded our team some funds for research. As you know, to develop new medicines, researchers need to understand how the disease progresses and how to measure whether treatments are working. Usually, this means comparing patients receiving the medicine with a group receiving no treatment (a placebo). However, many patients do not want to be in a placebo group. To solve this, Dr Renuka Dias, Tori Homer, Prof Tammy Hershey and myself will combine information from two major studies (the TREATWOLFRAM trial and the Washington University Natural History study) to build a large, shared database. This will allow us to create a "historical control group," meaning we can compare new treatments to past data instead of using a placebo group. We have three main goals:1. Build a natural history database – Bring together existing study data to understand what information is most useful for trials. 2. Create an international registry – allow patients to self-register and share information safely, so we have a group of people ready for future trials. 3. Study genetics – Learn how changes in the *WFS1* gene affect symptoms like vision loss, and whether they can predict how fast the condition progresses. We think this will help patients and families to have clearer information about how Wolfram syndrome progresses; future treatment trials may not need placebo groups, making them easier for patients to join; and patients can sign up to hear about new trials and help shape what information is collected. We believe that the registry will bring together patients, doctors, and researchers worldwide to speed up the search for effective treatments.