Publishable Summary (Co-ordinator’s summary report)

The main objective of this proposal is to study the efficacy and safety of an orphan designated drug, nitisinone,

in order to obtain its marketing authorisation for the treatment of patients with Alkaptonuria (AKU), a rare and

debilitating Mendelian disease for which there is no licensed treatment. A second objective is to improve the

current knowledge of the natural history of AKU, especially in young people. Thanks to our existing successful

non-clinical and clinical research (cell and tissue models, animal models, natural history studies), we are now

in a position to complete the clinical development of nitisinone for AKU.

This has involved a dose-response study (SONIA 1), an efficacy study (SONIA 2) to demonstrate improved

clinical parameters, and a cross-sectional study (SOFIA) in children and young adults to provide information

on the age at which it might be most beneficial to begin treatment. The results of DevelopAKUre, if positive,

will allow us to make a European Marketing Authorisation Application for nitisinone for the treatment of AKU,

thereby contributing to the goal of the International Rare Disease Research Consortium of 200 new therapies

by 2020.

AKU, also known as Black Bone Disease, is caused by a deficient enzyme, homogentisate 1,2-dioxygenase

(HGD), leading to the accumulation of a substance called homogentisic acid (HGA). Some of this HGA is

oxidised into a black pigment polymer in a process called ochronosis. The black pigment polymer is deposited

in connective tissues, particularly cartilage, leading to early onset, severe arthritis, heart disease and disability.

Nitisinone is an enzyme inhibitor that reduces the accumulation of HGA and should prevent or slow the damage

from AKU.

The dose of nitisinone in SONIA 2 is 10 mg, the dose determined in SONIA 1. The efficacy of nitisinone will

be determined in the 4-year outcomes study (SONIA 2), a study which commenced in May 2015, the clinical

phase of which is expected to finish at the end of January 2019. Further progress in SONIA 2 is described in

this 66-month periodic report. In addition, a study (SOFIA) to determine the optimal time to begin nitisinone

has been amended even though it concluded a year ago and was the focus of the 54-month report.

The project is complex and required the co-operation of the large consortium that has come together to deliver

DevelopAKUre. They include the Royal Liverpool University Hospital as the Coordinator, the AKU Society

(UK) and ALCAP (France) patient groups for communications/dissemination and help with patient recruitment,

three SMEs (Nordic Biosciences (Denmark) for biomarker analysis, PSR (Netherlands) for clinical trial

coordination and Cudos (Netherlands) for medical monitoring), a mid-sized pharma company Sobi (Swedish

Orphan Biovitrum International) supplying the drug and regulatory advice, three universities (Liverpool, Siena

and the Biomedical Research Center of the Slovak Academy of Sciences) for the analysis and interpretation of

data and three clinical trial centres (Liverpool, Hôpital Necker (Paris), National Institute of Rheumatic Diseases

(Slovakia)) to recruit sufficient participants. It was only possible to execute this project through a Europe-wide

collaboration, allowing the recruitment of 138 patients for an adequately powered trial (SONIA 2) and

delivering access to elite AKU researchers.

The clinical phase of the SONIA 2 study has now just finished successfully with only a small number of patients

dropping out of the stud, with equal numbers in each arm of the study. The project has now begun the data

analysis phase which will be reported in the future.