Publishable summary

Project context and objectives:

In rare diseases, **up to 90% of drug treatment is off-label**, due to lack of adequate clinical research data. This is particularly true for **the rare autoimmune rheumatic disease** systemic sclerosis (SSc). Due to the severity of SSc, several immunomodulating drugs such as cyclophosphamide, methotrexate, azathioprine etc. are used off-label in this disease but their use is mostly based on case reports or **small trials,** which do not meet the usual standards of controlled clinical trials, as is frequently the problem in rare diseases. Thus, it has only been possible to establish **preliminary guidelines** for the management of SSc so far. The DeSScipher projects aims at improving **clinical practice in the management of** SSc. The primary objective is to **compare the outcomes** of different **preventive measures** and **treatments** with respect to **efficacy and safety of currently used off-label drugs** from the early to the advanced phases of the SSc-associated organ system involvements. This approach is based on five **observational trials (OTs)**, which are designed to cover evolution phases of the disease and its related organ involvement from early functionally relevant manifestations such as digital ulcers (OT1) and hand arthritis (OT2) to the morbidity and mortality-driving manifestations such as interstitial lung disease (OT3), pulmonary hypertension (OT4) and severe heart disease (OT5). Based on the data of more than 4000 prospectively enrolled and well-characterised SSc patients, the DeSScipher project aims to evaluate currently used off-label treatment in real-life care and to compare the course of the disease under different therapeutic regimens with respect to their efficacy and safety in the **prevention** or **treatment** of the organ manifestations under investigation. In addition, DeSScipher will **define and validate appropriate outcome measures**.

Achievement of these objectives will be possible through utilization of the **unique pan-European EUSTAR** group (EULAR Scleroderma Trials And Research group, established and operating under the auspices of the European League Against Rheumatism (EULAR)), which in total comprises more than 190 expert centres from all European countries. In cooperation with the juvenile SSc Working Group (jSSc-WG) of the Pediatric Rheumatology European Society (PRES), not only adult but also juvenile SSc patients will be observed.

The specific objectives of the DeSScipher project are:

- To improve clinical practice in the management of SSc for both adult and juvenile patients
- To facilitate an earlier detection and prevention of SSc and its organ manifestations and subsequently initiate disease- or organ-specific treatment
- To improve both quality of life and morbidity/mortality in SSc by addressing functional impairments caused by digital ulcers and hand arthritis as well as life-threatening organ complications due to interstitial lung disease, pulmonary hypertension and severe heart disease
- To develop and validate a reliable algorithm for detecting organ manifestations of SSc at an early stage in adult and juvenile patients at risk using novel tools such as the VEDOSS tool
- To compare outcomes of prevention and treatment regimens in SSc to define appropriate outcome measures for SSc trials with an aim of defining at least 5 outcome measures
- To evaluate the efficacy and safety of off-label treatments currently used to target the main disabling and life-threatening organ manifestations of SSc
- To contribute actively to the development and rapid dissemination of national, European and international guidelines for the diagnosis and management of adult and juvenile SSc using the EUSTAR and PRES international network with an aim of disseminating to at least all European countries involved in the project

Work performed and main results:

The DeSScipher project started in December 2012. After completion of preparative tasks (obtaining ethics approvals, training of staff at recruting centers and set-up of the research database), the five observational trials started in April 2013. Within the first project period until May 2014, in total 1258 people with SSc have been screened and 1061 (84.3%) have been enrolled into at least one of the five observational trials. As one person can simultaneously participate in multiple observational trials, overall 2011 datasets of people with SSc are currently followed prospectively in OT1-5. This represents a baseline recruitment rate of around 50%, as overall 4077 datasets of people with SSc are planned to be enrolled into the five observational trials. Beyond the 10 initial DeSScipher partner centers, 11 additional EUSTAR centers from Croatia, France, Germany, Hungary, Italy, Romania, Russia, Switzerland and United Kingdom are currently contributing data to the five observational trials, as all five trials are still ongoing. Moreover, every SSc patient care center is invited and is welcome to contribute to the DeSScipher project.

In addition to the prospective observational trials, preliminary explorative analyses with the objective of comparing current patterns of drug treatment in SSc (in particular in people suffering from arthritis, interstitial lung disease, pulmonary hypertension and cardiac blocks) were carried out based on retrospective data of the EUSTAR database. At the end of the observational trials, the retrospective data of the EUSTAR cohort and the prospectively acquired data of the observational trials of DeSScipher will be merged to provide results about current patterns of drug treatment as well as to define specific outcome measures based on the currently largest available clinical database of SSc worldwide. Since the start of the observational trials of DeSScipher in April 2013 during the course of the last 12 months the total number of datasets from people with SSc recorded and followed in the EUSTAR cohort increased from 10507 to 11637 by June 2014.

Expected final results and potential impacts:

After completion, the DeSScipher project will not only be the largest multinational parallel prospective observational trial ever performed in systemic sclerosis and become a template how to manage such an approach including all predictable and unpredictable pitfalls prior to and during the trial, its main achievement will be to provide **scientific evidence** for key clincial questions and problems as outlined in this report in the respective sections in detail and will faciliate to advance from off-label use of treatments to their official approval for everyday clinical use. Moreover, based on the findings of DeSScipher, **novel clinical guidelines** will be developed and validated to **improve the management of SSc** and its related morbidity and mortality in both **adult** and **juvenile** patients.