SUMMIT
surrogate markers for micro- and macro-vascular hard endpoints for innovative diabetes tools

1. Executive summary Reporting Period 4

1.1. Project rationale and overall objectives of the project

Diabetes mellitus is a lifelong, incapacitating disease affecting multiple organs, which at present cannot be cured but only symptomatically treated or, at best, partially prevented in the case of type 2 diabetes (T2D). The disease is associated with devastating chronic complications including coronary heart disease, stroke and peripheral vascular disease (macrovascular disease) as well as micro-vascular disorders leading to damage of kidneys (nephropathy or DN), eyes (retinopathy or DR) and feet (Lower Extremity Arterial Disease or LEAD). These complications impose an immense burden on the quality of life of the patients and account for more than 10% of health care costs in Europe. Novel means to prevent and/or treat these devastating diabetic complications are urgently needed.

1.2. Overall deliverables of the project

SUMMIT develops innovative approaches to make clinical trial testing of novel medications in diabetic vascular complications faster and more efficient. To do so SUMMIT aims to develop novel **genetic markers** and **soluble biomarkers**, which can be used i) to identify patients at high risk (antecedent biomarkers), ii) differentiate between fast-progressors and slow-progressors and iii) monitor progression, reduction or prevention of diabetic vascular complications. In addition, SUMMIT aspires to develop novel and improve existing **imaging techniques** for monitoring progression in atherosclerosis and retinopathy, novel **animal models** for micro- and macrovascular complications to better replicate disease as seen in men and novel ***in silico* methods** for modelling and predicting diabetic complications. The ultimate goal is to make these markers and tools accepted by regulatory authorities and to disseminate the findings not only to the scientific community but also to lay people and patient organizations.

1.3. Summary of progress versus plan since last period

SUMMIT achieved in its 4th period a new level of integration, complementing the methodologically organized Work Package structure by collecting its expertise for each complication in workshops and discussion groups for a multi-disciplinary, holistic approach of pathway analysis. This integration ensures an optimized exploitation of the various results acquired from the different parts of the project.

With respect to SUMMIT's comprehensive GWAS studies, all primary GWAS are now complete, and have been imputed to 1000G. Replication of these findings for which we also have contacted external studies to get access to a larger set of replication samples, is now underway. Bioinformatic approaches will be used in to seek evidence of pathway enrichment in these data.

The first ever exome sequencing in diabetic nephropathy including 1000 subjects has been completed and primary analyses finalized.

Results from the SUMMIT genetic studies are being integrated and jointly analysed with data from the soluble biomarkers, imaging and animal model approaches undertaken in SUMMIT.

SUMMIT's extensive soluble biomarker measurements - encompassing lipidomics, metabolomics and proteomics discovery experiments - have in period 4 been completed. A joined team has analysed all data for CVD, DR and LEAD and are nearing completion of the analysis of the DN data. Evidence for novel serum biomarkers and pathways has been shown and best combinations of predictive serum biomarkers been defined. We can now select those biomarkers to be moved forward to validation based both on our discovery studies but also our findings from genetic and animal model studies.

The development and validation of the novel ultrasound/radiofrequency-based virtual histology for characterization of atherosclerotic plaque structure, Ultrasound Plaque Structure Analyses (UPSA), was a major feat in SUMMIT imaging research. The platform, for which a patent application has been filed, provides a non-invasive, safe and rapid way to identify high risk atherosclerotic plaques with a similar sensitivity and specificity as intra-coronary ultrasound and MRI. UPSA should also be a useful tool to monitor response to interventions by providing a surrogate endpoint (change in atherosclerotic plaque vulnerability) for hard cardiovascular endpoints.

The largest ever macro- and microvascular complication multi-centre studies have completed their baseline investigation into CVD and DR and re-examinations of the first patients for the 3-year follow-up have started. Analysis of genetic and soluble biomarkers in participants in these studies will be completed early 2014.

The SUMMIT pulse wave velocity (PWV) clinical study has investigated whether pulse wave velocity differs between postprandial hyperglycemia and nearly normal postprandial glycaemia and whether albuminuria but normal kidney function influences the outcome of this comparison. The investigation should answer the question whether PWV can serve as a surrogate marker for macro vascular risk in this test setting. The study has been completed and analysed. A manuscript is being prepared and will be submitted in the next months.

SUMMIT achieved to generate new animal models for CVD and diabetes that more closely than current models mimic the disease and its complications as seen in humans.

Continued characterisation of the previously chosen models for CVD, DN and DR, and generation (and characterization) of new ones based on SUMMIT discoveries, has refined our knowledge of the complication phenotypes they represent.

A patent application for a unique rat strain for CVD and DN has been submitted. Animal models have been further evaluated for vascular inflammation, cardiac function and cardiac metabolism using state-of-the-art non-invasive imaging techniques. Steps have been taken to ensure future availability of these valuable animal models to the scientific community.

The *in silico* team in SUMMIT has had a strong focus on setting up all tools and pipelines for the multivariate analysis of SUMMIT data. Several published software tools were refined and a new tool for multivariate selection of genetic markers was implemented and published. The team improved the *in silico* model of diabetes complications, based on the Dynamic Bayesian Networks formalism, starting from the DCCT - EDIC dataset, as well as refined the previously developed model of platelets generation and Aspirin action in T1D.

With 62 written or oral publications and 24 more on its way, plus the organisation of the IMI Diabetes Platform symposium in Barcelona, SUMMIT has stepped up its dissemination effort substantially.

1.4. Significant achievements since last report

Cardiovascular complications

Independent genetic and soluble markers for cardiovascular complications were identified and are now taken to the replication phase.

The Ultrasound Plaque Structure Analyses (UPSA) platform for a non-invasive, safe and rapid way to identify high-risk atherosclerotic plaques has been validated and a patent is pending.

A new mouse model for CVD was generated and a patent was filed for the SUMMIT rat model for diabetic vascular complications.

Diabetic nephropathy

The largest ever genetics discovery effort on diabetic nephropathy, including GWAS and exome sequencing, was completed and identified at least one genome-wide significant signal for DN. Numerous promising markers are taken to replication.

Analysis of the soluble biomarker discovery phase provided multiple factors independently associating with kidney functioning.

Prediction models for both CVD and DN were improved.

Diabetic retinopathy

Four soluble biomarkers showed association with the presence of diabetic retinopathy.

The SUMMIT clinical studies for CVD and DR have completed and analysed their baseline investigations. Biomarker analyses on these studies are close to completion.

SUMMIT as a whole made a successful change to a more phenotype-focused approach.

The consortium markedly increased its visibility and dissemination and organised its first IMI Diabetes Platform symposium.