Letter of support for Master Protocol for Type 1 diabetes prevention studies in INNODIA

On August 22nd 2019, the Applicant, the Innovative Medicines Initiative (IMI) -2 INNODIA Consortium (the Consortium), a partnership between academic researchers, industry and patients, requested initially qualification advice for the development of a Master Protocol (MP) for exploratory Phase 2 clinical trials in patients with newly diagnosed Type 1 Diabetes (T1D). The Consortium has established a Pan European infrastructure to evaluate prospectively clinical data from subjects with newly diagnosed Type 1 Diabetes (T1D) in the INNODIA 01 natural history study, with follow-up period of 2 years for patients with newly diagnosed T1D (n=1500) and 4 years for unaffected family members (n=4500). This observational study aims to inform ongoing and future Phase 2 studies designed to predict and/or prevent the variable decline in beta cell function which follows diagnosis of T1D. The backbone of the INNODIA 01 natural history study in terms of systematic sample collection and standardised collection of efficacy and safety outcomes is shared with the interventional phase 2 studies. Enriched by frequent measurement of existing and novel biomarkers, the MP has the potential to evaluate factors which could be used in future patient stratification.

Following regulatory assessment, this overall approach taken by INNODIA was supported by the Committee for Medicinal Products for Human Use (CHMP) (EMA/CHMP/SAWP/13547/2020). During those discussions the question of adapting the Master Protocol to the study of people with prediabetes (family members deemed to be at risk as they have diabetes related auto antibodies) was raised. For the second qualification advice in 2021, the Consortium has proposed to adapt the INNODIA Master Protocol to a new population of people with pre-diabetes. For planned Phase 2 exploratory safety, efficacy and mechanistic studies, again the existing network infrastructure and data collection backbone of the INNODIA natural history study is planned to be used. For example, the Consortium has kept the same central laboratories, same standard operating procedures, same data collection software and data warehouse etc., as for the Master Protocol in newly diagnosed type 1 diabetes. The Consortium is seeking CHMP qualification advice as to whether the plan to adapt the INNODIA Master Protocol in this high-risk group can be endorsed and the type of evidence that would be needed for a future qualification opinion.

Drug development need

The incidence of T1D is rising globally (Patterson 2019) and requires insulin therapy to replace that normally produced by the failing pancreatic beta cells. There is no direct therapy to reverse the immune destruction of the beta cells or predictive models to anticipate the subsequent rate of decline. The first steps may begin in early childhood with the appearance of islet cell specific auto-antibodies

but the subsequent development of symptomatic diabetes may be delayed for many years. Age, gender, BMI and number of auto-antibodies may influence the rate of progression. Development of therapeutics exhibited only very limited success yet. Once T1D has developed, rates of progression remain highly variable with older age being most predictive of slow declines in beta cell function, but BMI and gender remain significant factors. As in pre-diabetes, prediction of further disease progression is problematic. Without stratification for relevant factors it is difficult to assess predicted responses due to high variability in progression trajectories.

Background and rationale for model development

Model development has long been used to evaluate and design clinical trials. The aim of the proposed project is to identify factors which most reliably predict disease progression. In those subjects identified through population screening as being positive for auto-antibodies (anti-insulin (IAA), anti-glutamic acid decarboxylase 65 (GAD 65), anti-insulinoma antigen-2 (IA- 2) and zinc transporter 8 (ZnT8)), either through study of unaffected family members or general approaches, the risk for T1D increases and the number of auto-antibodies may be critical. Other factors such as gender, BMI and age at onset may also be critical and few studies have explored a sufficient set of the potential confounders.

In INNODIA the Consortium has screened over 3500 unaffected family members and around 7.7% have at least a single antibody and 2% have two or more antibodies. All antibody positive participants are followed prospectively with 6-monthly oral glucose tolerance tests, HbA1c, autoantibodies and continuous glucose monitoring (for dysglycaemic individuals), as well as a wide range of blood and stool samples. All of those who are antibody negative are re-tested every two years until the age of 18 years.

A novel aspect of the INNODIA protocols is the use of home collected filter paper c-peptide data (Willemsen 2018) which increases the number of measurements and better allows subsequent trends to be analysed. The primary questions relate to determining rates of progression in terms of beta cell function and glycaemic control over the study period.

In participants identified as being auto-antibody positive, progression in those with a single auto-antibody is likely to be slow except the ones who develop additional antibodies over time. Age at onset of auto-antibody positivity is only known in those followed from birth and selection bias is an issue in that population. Age, gender, HLA and non-HLA genotypes as well as family history and as yet unknown factors may play a part in disease progression.

Context of use and Modelling strategy

INNODIA provides an opportunity to study the transition from auto-antibody positivity to diagnosis of T1D. To investigate this disease trajectory, moving from the state of auto-antibody positivity via the state of dysglycaemia to the state of T1D can be modelled using a multistate Markov model (Jackson 2011 and Smith et al. 2021). Rates of transition from state to state can be estimated that vary over time and depend on fixed (e.g. gender) or time-varying covariates (such as the regular DBS C-peptide measurements). The model can be set up to be flexible enough to allow subgroups of individuals who remain in their current state, e.g., individuals that are auto-antibody positive who never progress to later stages of T1D. Transition intensities can be estimated separately in different height, age, BMI and puberty strata, if there are sufficient data and evidence to support this.

For designing future intervention studies the desire of the Consortium is to have primary endpoints such as DBS C-peptide or the OGTT/MMTT C-peptide results established as proven surrogates of the usual clinical endpoints (such as for Hba1c or number of hypoglycaemic events). To achieve this, the relationship between (bio-)markers and clinical endpoints, potentially for regulatory decision-making

would have to be established. The general approach will be to follow guidance provided by MJ Daniels and MD Hughes (Daniels MJ & Hughes MD, 1997) who used a meta-analysis approach for the validation of a potential surrogate marker. The Consortium would consider the association between both the difference in treatment effects on the clinical outcome and the potential marker over a range of trials within INNODIA. Inclusion of additional external studies could be helpful if their data are suitable for this. A meta-analysis approach would be used for the i-th randomized treatment comparison using a model where $\theta_i = \alpha + \beta \gamma_i + \varepsilon_i$, where γ_i = true difference for surrogate and θ_i = true difference for clinical endpoint. In case of $\beta = 0$ the marker has no predictive value (i.e. is not useful as a surrogate), while for the case of $\beta \neq 0$ for a surrogate marker to allow outcome prediction the aim would be to achieve low variability indicated by small ε_is. Ideally in this model the offset would be zero ($\alpha = 0$), as then no difference in surrogate means no difference in clinical endpoint.

Conclusion

EMA supports the approach by the INNODIA Consortium to set up a master protocol for Phase 2 exploratory studies within the INNODIA clinical network. The approach taken by the Consortium using standardised recruitment, centralised data collection and standardised data evaluation provides a very valuable opportunity to track T1D from the appearance of auto-antibodies, through dysglycaemia and to the full presentation with symptomatic disease. Although the number of individuals moving from pre-diabetes to T1D may be small, these data will be highly relevant for studying that transition. Once T1D has developed, there may be the opportunity to observe distinct trajectories of c-peptide (e.g. a transient rise in c-peptide followed by a variable decline). Factors such as age, gender and BMI standard deviation score explain a limited amount of about 17% of variability in fasting c-peptide and the goal and approach of the Consortium to identify early predictors of disease progression are supported.

References:

Daniels & Hughes; Statistics in Medicine. 1997; 16(17):1965-82.

Jackson. Journal of Statistical Software. 2011 Jan, 38(8):1-28

Patterson et al.; Diabetologia. 2019 Mar 28; 62(3):408–17.

Smith et al., Statistics in Medicine, 2021, 40:1960–1971

Willemsen et al., The Journal of Clinical Endocrinology & Metabolism, 2018 Sep; 103(9): 3350–3358