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Executive Director

Letter of Support for PRE score

Chronic kidney disease (CKD) is an area of difficult drug development as, due to high reserve capacity of the organ, diseases are often detected late and at a point in time at which then in many instances dramatic deterioration cannot be reversed or delayed. In early stages, deteriorations are usually small and difficult to detect, or therapeutic interventions that may be developed may need to be studied for long time to demonstrate their efficacy.

Under these circumstances it is essential to develop tools / scores / biomarkers that may be used to

- select high risk patients for renal disease (even if such patient selection may come at the price of discussing generalization to the full population)
- select an optimal dose for an experimental drug in the context of a phase II clinical trial
- predict long-term renal protective drug effects (i.e., as a surrogate endpoint)

to support / enable drug development. The applicant is commended on investing into this research.

The idea of the so-called 'PRE-score' is to predict renal outcomes based on short-term (6 month) assessment of multiple markers to overcome current practice of investigating a limited number of parameters individually in an attempt to replace the current renal risk profiling and to replace a usually single drug target to estimate drug efficacy. This approach is innovative, and it is not considered a limitation that investigations are in a first step limited to diabetic kidney disease. Support for Go/No-Go decisions between phase II and phase III, dose selection and enrichment for clinical trials are valuable objectives to improve drug development.

In a first step the applicant is currently in the position to have access to the individual patient data from the (RENAAL (Losartan), IDNT (Amlodipine), Altitude (Aliskiren), and Sun-MACRO (sulodexide) studies. In total, more than 13.000 patients with Type 2 Diabetes Mellitus (T2DM) are available. It is agreed that this database will be a cornerstone in the project as the relatively large database with large variation in many biomarkers is ideal to developing a risk score and establishing surrogacy of a biomarker or (in the end) the composite PRE-Score.

Developing an expectedly complex model to describe "kidney health" with sensitivity to early changes introduced by experimental treatments is a challenging task., Obviously the validation of such an approach requires a considerable period of time, as such validation needs to include prospective steps as well, which then mandate long-term observation of patients. The EMA/CHMP support the

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development effort towards intermediate and final validation of the PRE-score as a tool for drug development in kidney diseases.

The letter of support is issued on the basis of qualification advice the applicant has received.

Yours sincerely,

Emer Cooke

Executive Director