Optimal Design for First In Human Studies to Investigate the Pharmacokinetic/Pharmacodynamic Behaviour of TGF-beta RI Kinase Inhibitor

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ABSTRACT

To suggest optimal sampling times for a prospective study to characterize pharmacokinetics and pharmacodynamics in cancer patients following administration of TGF-beta RI kinase inhibitor.

Data from tumor growth kinetics Xenograft model in mice and from in vivo target inhibition (IVTI) in rats and in mice were incorporated in our PK/PD analysis. The PK/PD model in mice integrated the plasma time course of the compound, the inhibition of SMAD phosphorylation (biomarker) and tumor growth data, which were our pharmacodynamic measures. An indirect response model was used to describe plasma concentrations and observed pSMAD data. The model integrated factors within the tumor cell responsible for the synthesis and degradation of pSMAD. The tumor growth curve was described by a Gompertz model, which was extended to further understand the relationship between the time course of the tumor growth and the time course of TGF-beta RI kinase inhibitor. Additionally a PK/PD model, incorporating plasma concentrations and inhibition of pSMAD from the IVTI studies was fit to available rat data. The model used TGF-beta RI kinase inhibitor concentrations, relating those to the inhibition of the SMAD phosphorylation. The developed PK/PD models in the two species, mice and rat, were extrapolated to human. This enabled prediction in human of the targeted inhibition of SMAD phosphorylation under different dosing regimens. Using the extrapolated model we calculated the optimal sampling scheme for both concentration and effect measurements, to be used in patients. We used D-optimal design criterion, which minimises the volume of the joint confidence region by maximising the determinant of the Fisher information matrix (FIM) (inverse of variance-covariance matrix). It was further assumed that measurements made at distinct times are independent, but measurements made of each concentration are correlated with a constant variance-covariance matrix. Optimal sampling times were suggested for both individual and population designs. To determine the D-optimal design the determinant of the FIM has

to be maximised over the whole design space using a number of optimisation methods (downhill simplex, simulated annealing, modified Fedorov). Potentially, the relationship between time course of TGF-beta RI kinase inhibitor concentrations and clinical tumor response was defined. Following analysis of Phase I data we will update the PK/PD model and use optimal design as a guidance tool in designing future studies.

References:

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