Clinical Pharmacokinetic (PK) / Pharmacodynamic (PD) Model for Debio 1143, a Novel Antagonist of IAPs in Cancer Treatment

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Inhibitors of apoptosis proteins (IAPs) modulate multiple processes, including caspase activation and NF-κB signaling. Overexpression of IAPs in a variety of tumor types has been correlated with tumor growth and chemotherapeutic resistance to apoptosis. Debio 1143, an orally-active IAP antagonist is able to promote apoptosis in tumor cells. Based on the clinical PK and PD of Debio 1143 in cancer patients, we created a PK/PD model to support treatment optimization with Debio 1143.

PK/PD modelling approach
• For visual inspection of PD change from baseline relative to PK, predicted plasma concentrations by time and cumulative plasma exposures were both considered.
• The onset of Debio 1143-induced degradation of cIAP in PBCMs is rapid (full effect at 1-12 h post dosing) (Fig. 1). In addition, there may be a relationship with concentration at the 1st time point.

Plotting the plasma caspase-cleared cytokeratin-18 fragment M30 showed a baseline change at day 5 vs the cumulative Debio 1143 AUC indicating an exposure response (Fig. 2). Patients with a cumulative AUC = 60,000 ng/mL showed increase in M30.

Simulations
An alternative dosing regimen, where Debio 1143 is administered once daily during 14 days, every 21 days (q14d21) is currently under clinical evaluation. Simulation of such regimen was performed to anticipate exposure/response relationship.

PK/PD Model: Graphically, markers of target engagement (cIAP1 levels in PBCMs) and apoptosis (caspase-3 generated cytokeratin-18 fragments plasma levels (M30)) showed change with Debio 1143 PK. The indirect response model, where Debio1143 stimulated the elimination of cIAP1 fitted the data best to describe the time-course of effect on cIAP1. In this model, Debio1143 had a direct stimulating effect on the elimination rate of cIAP1, working through an Emax model.

Results
Simulation of 14-day treatment effect on M30 predicted different outcomes according to the slow (Fig 6A – overall 75%) or the fast (Fig. 6B – increase 20-35%) onset model.

Conclusions
• For 80-900 mg doses the PK of monotherapy Debio 1143 was linear. Debio 1143 PK is compatible with oral administration q5d1 and steady-state conditions are reached after the first dose.
• A clear relationship between PK and markers of target engagement (cIAP1) as well as target modulation (M30) was confirmed: the indirect response model reflected adequately the action of IAP inhibitors on cIAPs where the binding induces a conformational change in cIAPs that promotes autoubiquitination and leads to rapid protein degradation [2]. The transit compartment model enabled to characterize the specific kinetic of M30.
• The q42d1 simulations also indicated a promising PK/PD relationship for this schedule which is currently clinically evaluated. Exploration of relationship between PK/PD and safety and efficacy in the ongoing studies are promising and will help the model to support Debio 1143 treatment optimization.

References

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