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

#2585

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Background

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 chemo- and radiation therapy induced 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.

Patients

Study & Patient Characteristics	**28 Patients with advanced cancer**
Drug administration characteristics	**Oral drug**
	Once daily day 1-5 every 3 weeks (q5d21)
	Dose range = 80-900 mg
Blood sampling	**Rich PK sampling at days 1 and 5** • **Debio 1143**
	PD measurements at days 1 and 5 • **cIAP, XIAP** • **Apoptosis markers (CK18-M30/M65)** • **Inflammation markers (MCP-1, IL-8,TNFα)**

Methods

PK Model and PK/PD Modelling Approach

- A population PK model was built within NONMEM 7.2 to describe Debio 1143 PK disposition.
- Plots of change from baseline in PD *vs.* time and vs. summary PK parameters were inspected.
- Population PK/PD models were explored based on relevant graphs.

A population PK model was used to develop the PK/PD model [1].

- *Disposition*: A two compartment model described the distribution of Debio 1143.
- *Absorption*: A model with two absorption phases was used. The first absorption process corresponded to 12% of the absorption (Fr1), although this varied substantially between dosing occasions. Bioavailability (F) was found to decrease with dosing occasion. It was best described by a reduction in F by 33% for doses after the first dose.
- *Elimination*: A linear elimination process fitted Debio 1143 data.

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 cIAP1 in PBMCs is rapid (full effect at 1-12 h after dosing) (Fig. 1). In addition, there may be a relationship with concentration at the 1 h time point.

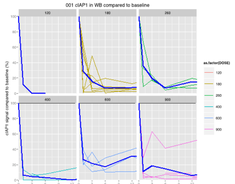

Fig. 1. Individual change in cIAP1 signal compared to baseline as a function of time, per Debio 1143 dose level [range = 120 – 900 mg] (thick blue line = mean).

Plotting the plasma caspase-cleaved 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*h/mL showed increase in M30.

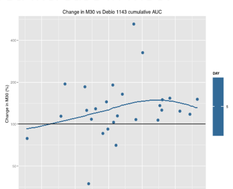

Fig. 2. Change in M30 vs cumulative AUC over 5 days. High AUCs appeared to be correlated with increases in M30 from baseline to day 5.

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.

Results

PK/PD Model: Graphically, markers of target engagement (cIAP1 levels in PBMCs) and apoptosis (caspase-3 generated cytokeratin-18 fragments plasma levels (M30)) showed change with Debio 1143 PK.

cIAP1: 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 E_{max} model.

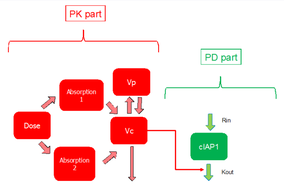

Fig. 3. PK/PD indirect response model correlating Debio 1143 PK to modification of cIAP1 in PBMCs. PK model (red); PD model (green).

Parameter	Typical Value	Inter-Individual Variability [95% CI]
E_0 (baseline cIAP1 signal)	12,660	8,031-17,300
IC_{50} (ng/mL)	26.0	5.17-131
I_{max}	15.4	9.2-25.8

Table 2. Main PD Parameters obtained from the PK/PD model for cIAP1.

M30: M30 showed a possible early decrease followed by an increase at day 5 from the baseline. Several models were explored to describe the possible early negative effect. However, a transit compartment model suggesting a delayed effect (unchanged M30 during the first 24 h) gave a significantly better fit although discrimination between 2 different models with 2 different rates of onset (fast or slow) was difficult.

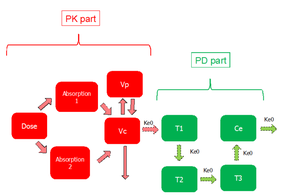

Fig. 4. PK/PD indirect response model correlating Debio 1143 PK to modification of M30. PK model (red); PD model (green).

Parameter	Typical Value [95% CI] (Slow onset model)	Typical Value [95% CI] (Fast onset model)
$M30_0$ (baseline signal)	167 [121-213]	167 [121-213]
EC_{50} (ng/mL)	0.00265 [0.00023-0.031]	633 [47-8600]
$E_{max,M30}$	87.5% [30-260]	10.5% [25-440]
Ke_0	0.0001 [fixed]	0.0415 [fixed]

Table 3. Main PD Parameters obtained from the PK/PD model for M30.

Simulations

Both PK/PD models of target engagement (cIAP1) & apoptosis (M30) were used to simulate the PK and outcomes in a different regimen (q14d21). Simulation of 14 day-treatment data predicted a clear decrease in **cIAP1** in all subjects with a nearly maximal effect at 100 mg and 200 mg doses also suggesting limited effect of doses > 200 mg (Fig. 5).

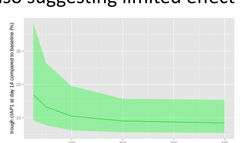

Fig. 5. Comparison of simulated cIAP1 change from baseline to Debio 1143 dose. 95%CI (shaded green); median (thick green line).

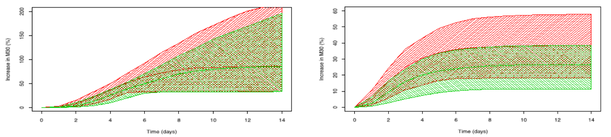

Fig. 6. Simulated increase in M30 after 14 days of treatment with 100 mg (green) or 200 mg (red) of Debio 1143 according to the slow (A) or fast (B) onset of effect model.

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 q5d21 and steady-state conditions are reached after the first dose.
- A clear relationship between PK and markers of target engagement (cIAP) 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 q14d21 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 feed the model to support Debio 1143 treatment optimization.

References

[1]. Rouits et al. 2013. Population Pharmacokinetic model for Debio 1143, a novel antagonist of IAPs in cancer treatment, Abstr. I-06 PAGE Meeting 2013, Glasgow

[2]. Dueber et al. 2011. *Science* **334**: 376-80.

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