

Introduction

Resistance to apoptosis is one of the hallmarks of human cancers and promotes cancer development and progression¹. Evasion from apoptosis represents one of the leading causes of treatment failure, since many anticancer treatments act by triggering apoptosis in cancer cells. Smac (second mitochondria-derived activator of caspase) has been identified as a protein released from mitochondria into the cytosol in response to apoptotic stimuli which efficiently suppress inhibition of the X-linked inhibitors of apoptosis (XIAP) and cellular-IAP1/2 (cIAP1/2) to the caspases. Debio 1143 (also named AT-406) is a potent and orally available monovalent Smac mimetic, a small molecule antagonist of IAPs, leading to the potentiation of apoptotic cell death in tumour cells. The objective of this study was to evaluate Debio 1143 pharmacokinetic (PK) data from two dose-escalating phase I studies investigating Debio 1143 as monotherapy and in combination with cytarabine and daunorubicin, respectively.

Materials & Methods

Data from the two following dose-escalating phase I studies were evaluated:
Study A
A phase I, open label, multicenter, dose escalation study of the safety, tolerability, pharmacodynamic and PK properties of orally administered AT-406 in patients with advanced solid tumours and lymphomas. Patients were administered Debio 1143 on days 1-5 and 15-19 in 28-day cycles (3 patients), or on days 1-5 in 21-day cycles.

Study A												Total
Debio 1143 dose (mg)	5	10	20	40	80	120	180	260	400	600	900	-
Patients (N)	1	1	1	1	3	3	6	3	3	3	6	31

Table 1 Debio 1143 doses received by the patients of study A included in the population PK analysis

Study B
A phase I dose escalation study of the safety, tolerability, PK, and pharmacodynamic properties of oral AT-406 in combination with daunorubicin and cytarabine in patients with poor-risk, acute myelogenous leukaemia (AML). Patients received an induction cycle of Debio 1143 per os on days 1-5, daunorubicin 90 mg/m² intravenous bolus on days 1-3, and cytarabine 100 mg/m² intravenously by continuous infusion on days 1 to 7.

Study B					Total
Debio 1143 dose (mg)	100	200	300	-	-
Patients (N)	8	12	4	-	24

Table 2 Debio 1143 doses received by the patients of study B included in the population PK analysis

A population PK model using NONMEM 7.2 (ICON Development Solutions) was developed to fit the plasma concentration-time data (n=961 from 48 evaluable patients) showing the following features:

- Debio 1143 displays variable PK, in particular the rate and extent of absorption.
- Absorption is characterised by one or two peaks at approximately 0-1 and 2-4 hours.
- Elimination appears to be bi- or tri-exponential.
- There is no obvious accumulation of Debio 1143 when given once daily.
- There is no clear deviation from dose-proportionality except for doses under 80 mg, which yield a lower exposure than expected. Because doses below 100 mg are not expected to be clinically relevant, concentration data from dose levels between 5 and 40 mg daily were excluded from the model.

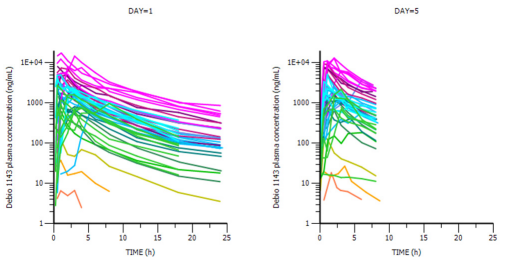


Figure 1 Individual Debio 1143 plasma concentration vs time curves (semi-log scale) at Day 1 (left panel) and Day 5 (right panel). Dose range: 5 mg; 10 mg; 20 mg; 40 mg; 80 mg; 100 mg; 120 mg; 180 mg; 200 mg; 260 mg; 400 mg; 600 mg; 900 mg

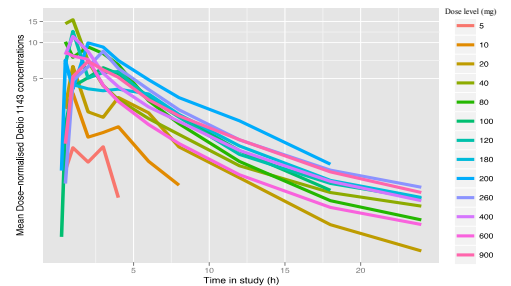


Figure 2 Mean dose-normalised Debio 1143 plasma concentration vs time curve (semi-log scale). Range of doses administered = 5 – 900 mg once daily.

Results

A schematic representation of the base model is presented in Figure 3 and the model parameters are presented in Table 3.

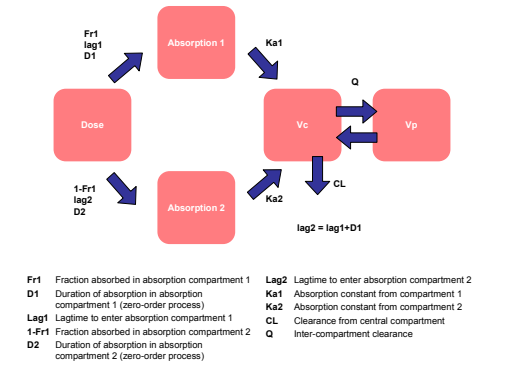


Figure 3 Schematic representation of the base model

Disposition model

Clearance

A two-compartment model proved sufficient to describe the distribution of Debio 1143. Adding a third distribution compartment did not improve the fit.

While there were indications that clearance (CL) decreased with increasing dose between 80 and 180 mg, no model exploring the relation between CL and dose proved significant improvement. A model with parallel linear and nonlinear clearance did not improve the fit. Consequently, no effect of dose on CL was included in the model.

Absorption model

Enterohepatic recirculation

A model with two absorption phases fitted the data best. Initially, after a 4 minute lagtime (lag1), a sequential zero-first order absorption took place. The zero-order absorption process lasted 31 minutes (D1). At the end of this zero-order phase, a second zero-first order absorption phase started with a lagtime of 4 + 31 minutes. D2 (zero-order process) lasted 52 minutes. Typically, the first absorption process corresponded to 12% of the fraction absorbed (Fr1), though this varied substantially between dosing occasions. The lagtime and the duration of the first and second zero-order processes were highly variable between individuals. Bioavailability was found to decrease with dosing occasion. This was best described by a reduction in F by 22% for doses after the second dose.

Although two peaks of absorption were observed in several patients, with the second peak at about 2 hours after dosing, the data could not be described by enterohepatic recirculation models. The first peak was sometimes smaller than the second peak, or even not present.

Variability

Residual error was modelled using a proportional model, with separate error terms for the two studies, as different bioanalytical assays had been used.

Parameter	Estimate	SE(%)	IVV(%)	IOV(%)
CL	13.2 L/h	10.4	30	
Vc	1.86 L	20.7		
Q	7.04 L/h	8.4		
Vp	167 L	7.4		
Ka ₁	1.145 h ⁻¹	12.7		
lag1	~ 4 min	26.8	137	
D1	31 min	17.6	80	
Ka ₂	0.2376 h ⁻¹	0.0	16	
D2	52 min	22.5	91	
Fr1	12.3 %	17.6		2.71*
F [Days 1-2]	100 %	Fixed	31	28
F [Days 3-5]	77.1 %	6.9	31	
Res Err [study A]	0.1815	3.3		
Res Err [study B]	0.2674	4.4		

* additive on log scale

Table 3 Model parameters				
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As shown in Figure 4 and 5, individual observations are adequately fitted by the model. As shown in Figure 6, the residual error model appeared adequate, with lack of trends in the absolute residuals. The distribution of CWRES was close to normal.

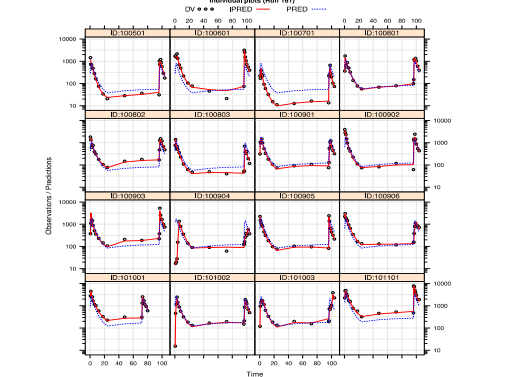


Figure 4 Individual fits for 16 subjects in study A. Full profile. Observed data (○); Population predictions (—); Individual predictions (---)

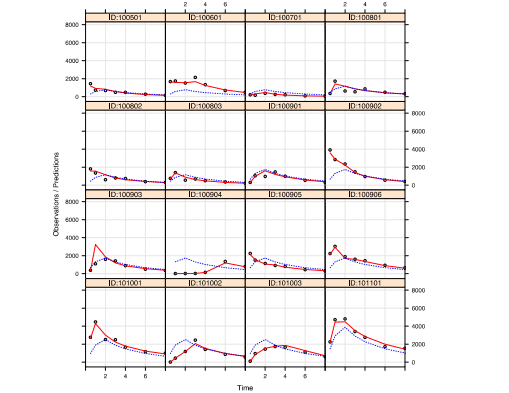
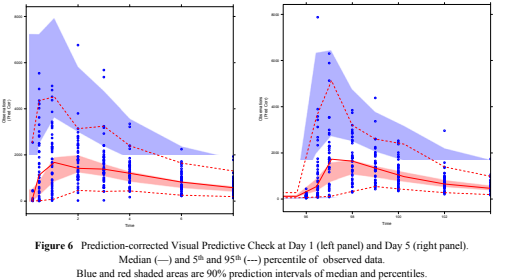
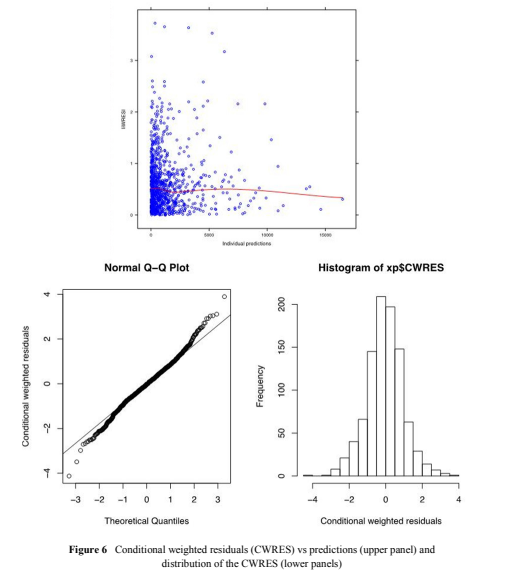


Figure 5 Individual fits for 16 subjects in study A. Absorption phase after Day 1. Observed data (○); Population predictions (—); Individual predictions (---)



Conclusions

The PK of Debio 1143 in studies A and B was well described by a two-compartment model with two absorption pathways.

Goodness of fit plots indicated a good fit. Some patterns were found in the residuals vs time, but were also found when fitting simulated data.

Predicted typical PK profiles in both studies a rather similar, indicating that the combination with daunorubicine and cytarabine does not influence the PK of Debio 1143.

The bioavailability appeared to decrease slightly with time, indicating a possible induction of metabolism.

In vitro studies showed that Debio 1143 is metabolised by CYP 450 together with other enzymes (final characterisation is ongoing) and may be implicated in significant inhibition and induction processes of such enzymes.

These observations have to be confirmed in vivo but genotype differences may explain the inter-individual variability in time-dependent bioavailability.

Pharmacogenetic covariate effect on the PK of Debio 1143 will be explored, together with the development of a PK/PD model with apoptosis biomarkers.

In addition, alternative schedules of administration are under exploration and will be uploaded in the model to help designing optimal trials in phase II.