



Introduction

Background

As part of the EU funded AIDA project a multicenter, open-label, randomized 360 patient clinical trial (180 patients in each arm) has been initiated with the aim to compare colistin alone vs. colistin plus meropenem against severe infections caused by carbapenem-resistant bacteria [1]. This work describes the design and interim evaluation of a sparse PK study for colistin exposure determination.

Objective

- Propose a sparse sampling pharmacokinetic (PK) schedule for colistin and its prodrug CMS with focus on the individual CL, by application of optimal design (OD) methodology.
- Perform an interim analysis on the study PK data to evaluate the PK design.

Methods

Sampling schedule design

The intended CMS dosing schedule was a 9 MU loading dose, and a 4.5 MU twice daily maintenance dose given as 30 min infusions. The sampling points were optimized for individual exposure determination of colistin in PopED [2] using the MAP_{occ} [3] method to handle inter occasion variability (IOV) present in the PK model [4] (Figure 1) using the following conditions:

- 2 samples in the interval 45min to 12h
- Occasion duration set to 24h

The performance of the optimized design was evaluated by simulations and MAP – re-estimations of the Empirical Bayes Estimates (EBEs) in NONMEM7 [5] using MCETA=1000. The gain in precision over the population prior variance ω was evaluated in terms of decrease in individual parameter uncertainty (dSD) and shrinkage (SH) calculated as:

$$dSD = 1 - \frac{SE_{EBE}}{\omega}$$
$$SH = 1 - \frac{SD(EBEs)}{\omega}$$

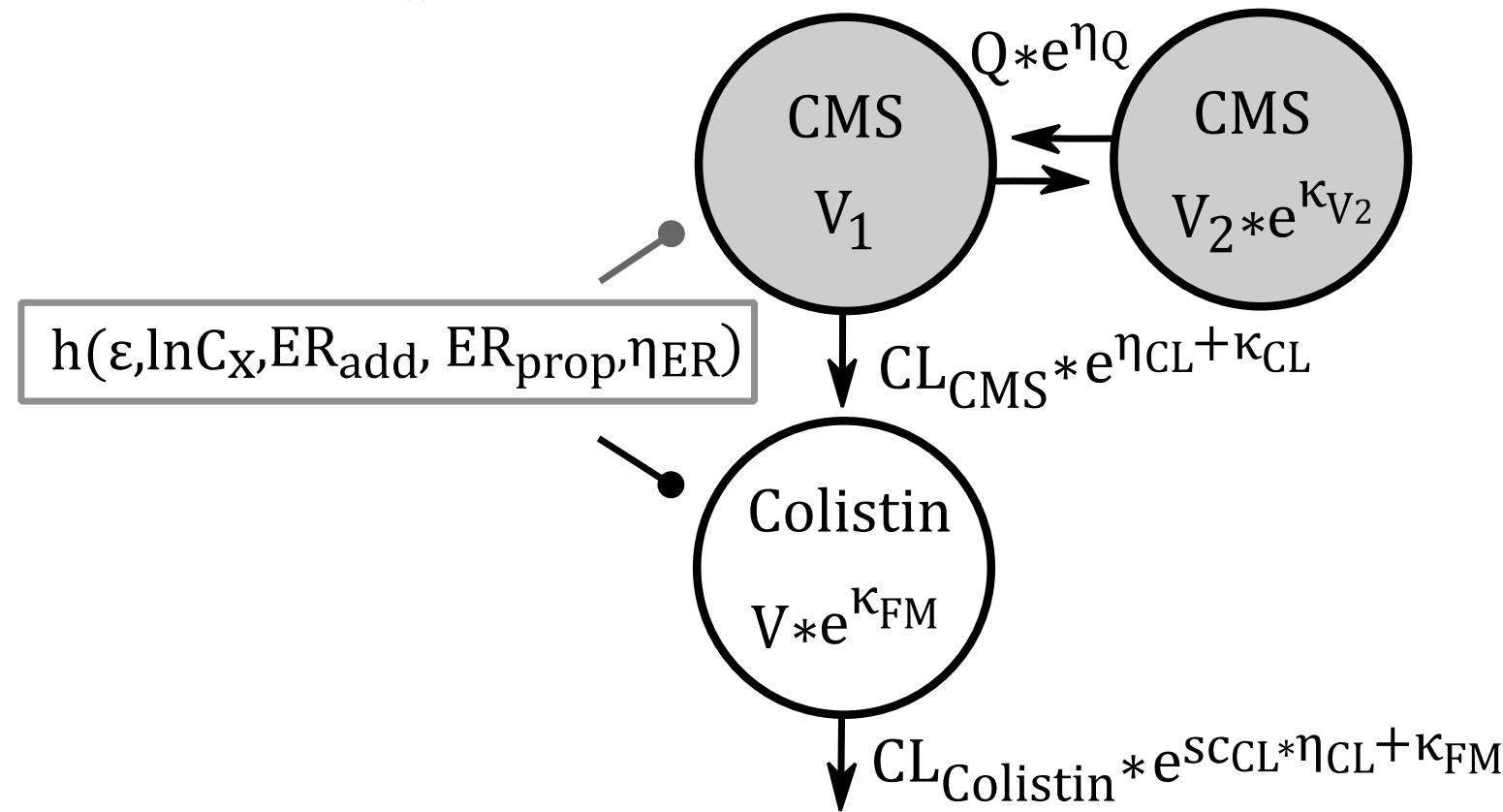


Figure 1. The colistin PK model [4] with two compartments for the prodrug CMS and one compartment for formed colistin. Individual effect are denoted η and occasion effects κ , while ϵ represents the residual error. Both CMS and colistin is measured from each sample and enters the model through the error function $h(\cdot)$.

Plasma concentration samples

Plasma samples from six hospitals in Israel, Greece, and Italy have been included and were assayed for CMS and colistin. The limit of quantification (LOQ) was 0.026 μ M (corresponding to 45 and 30 mg/L for CMS and colistin respectively).

Since CMS is sensitive to *ex vivo* hydrolysis to colistin, the following exclusion criteria were used to ensure sufficient data quality:

- $C_{col} (M) > C_{CMS} (M)$ AND time after dose < 3h
- ≥ 1 observation >LOQ per ID

Modelling and design evaluation

The fit of the new data to the colistin PK model was evaluated by prediction corrected visual predictive checks (pcVPCs). The fixed effect parameters were re-estimated in NONMEM guided by the pcVPC and accepted if the decrease in OFV was >10.84 (corresponding to $p < 0.001$). The random effect parameters were not re-estimated based on the new data. The M3 method was used to handle data below the LOQ.

The dSD and SH of the EBEs of the observed data was calculated as for the simulated.

References

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Results

Design

The optimal sampling times were at 45 min after start of first CMS infusion and at 22h, 10h after start of second infusion (Figure 2a). The sampling schedule is expected to result in satisfactory precision and SH in the individual CL estimates but is too sparse to estimate the individual intercompartmental clearance (Q) or error magnitude (ER). (Table 1)

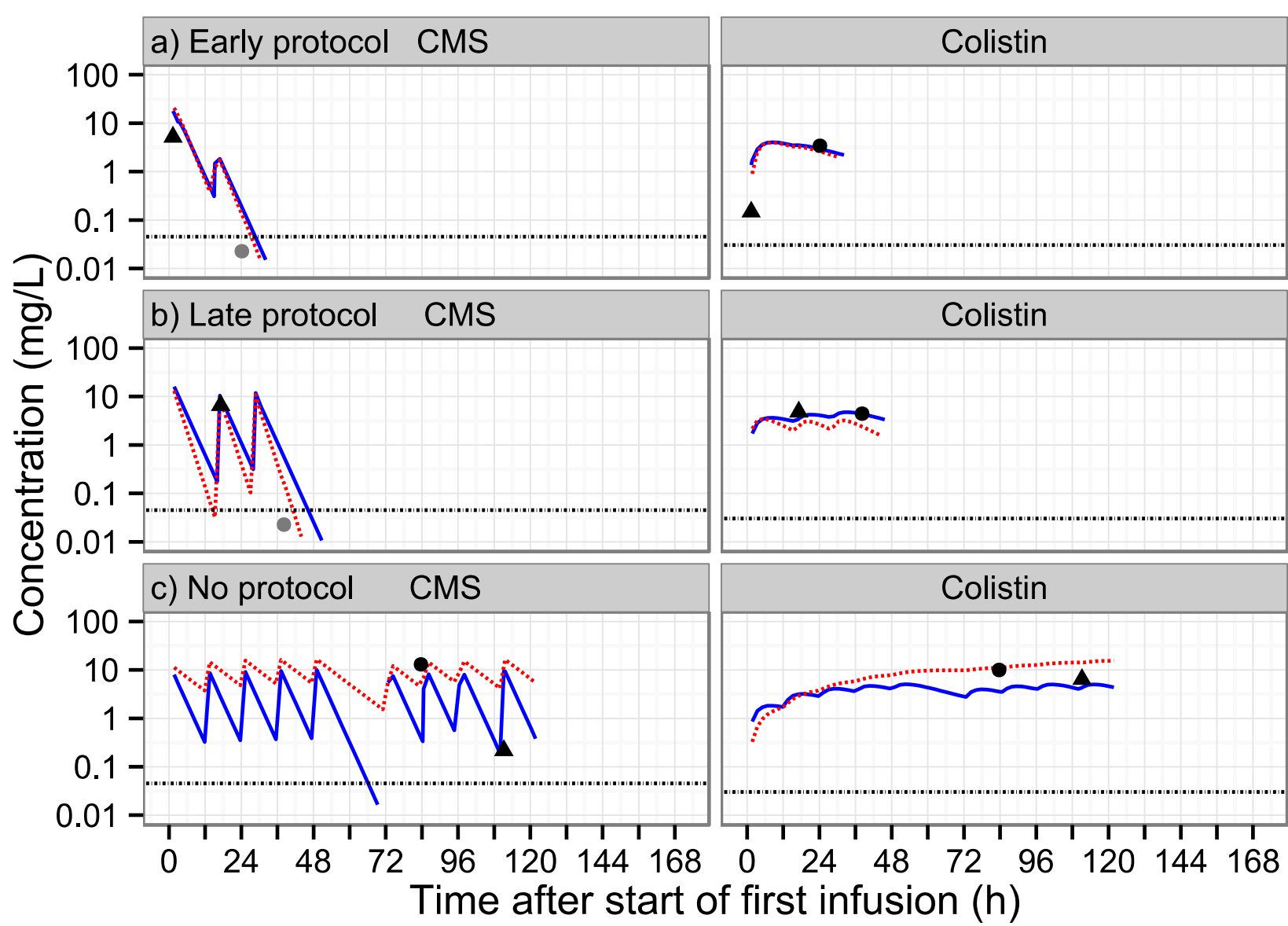


Figure 2 Representative concentration time profiles of CMS and colistin for a) patients conforming to the optimized sampling protocol b) patients recruited after initiation of therapy but conforming to the optimal sampling times, and c) patients not conforming to the optimal sampling times. Triangles - nominal 45 min sample observation, dots– nominal 22h (10h after start of 2nd infusion) observation, solid line – population prediction, dashed line – individual prediction (excluding occasion variance), dot-dash line – LOQ

Data

A total of 124 patients and 442 (5% <LOQ) observations entered the data set for interim analyses. Patients with samples taken within 0-30 minutes and 8.5-10.5h after the infusion were defined as on protocol. 45 patients adhered to the optimal sampling times (Early protocol, Figure 2a), 34 patients had at least one observation at later times (post 24h) but still within the defined intervals (Late protocol, Figure 2b) and the remaining 45 patients had only one sample, or samples outside the defined intervals (No protocol, Figure 2c).

The mean colistin trough concentration (nominal 10h sample) was 3.8 (SD 2.2) mg/L in the Early group (samples taken less than 24h after first dose) and 4.2 (SD 2.8) mg/L in the Late group (samples taken post 24h), both which are higher than expected [4,6].

Model re-estimation

Similarly to a recent study by Karaiskos *et al.* [6] the available fraction CMS A + B was estimated to be increased (+114%) compared to the prior study [4]. Additionally, the colistin volume of distribution (V) was estimated to be increased (from 218 to 278 L) and the CL of CMS decreased (from 13.1 to 12.4 L/h). Re-estimation of CL_{Colistin} did not improve the model fit significantly ($p > 0.001$).

The model fit to the data is presented in Figure 3. The median observation is generally well predicted except for the nominal 45min colistin sample which is over predicted for the Early group. The variability is over all well predicted based on the prior model for the Late group, but is under predicted for the nominal 45min sample in the early group.

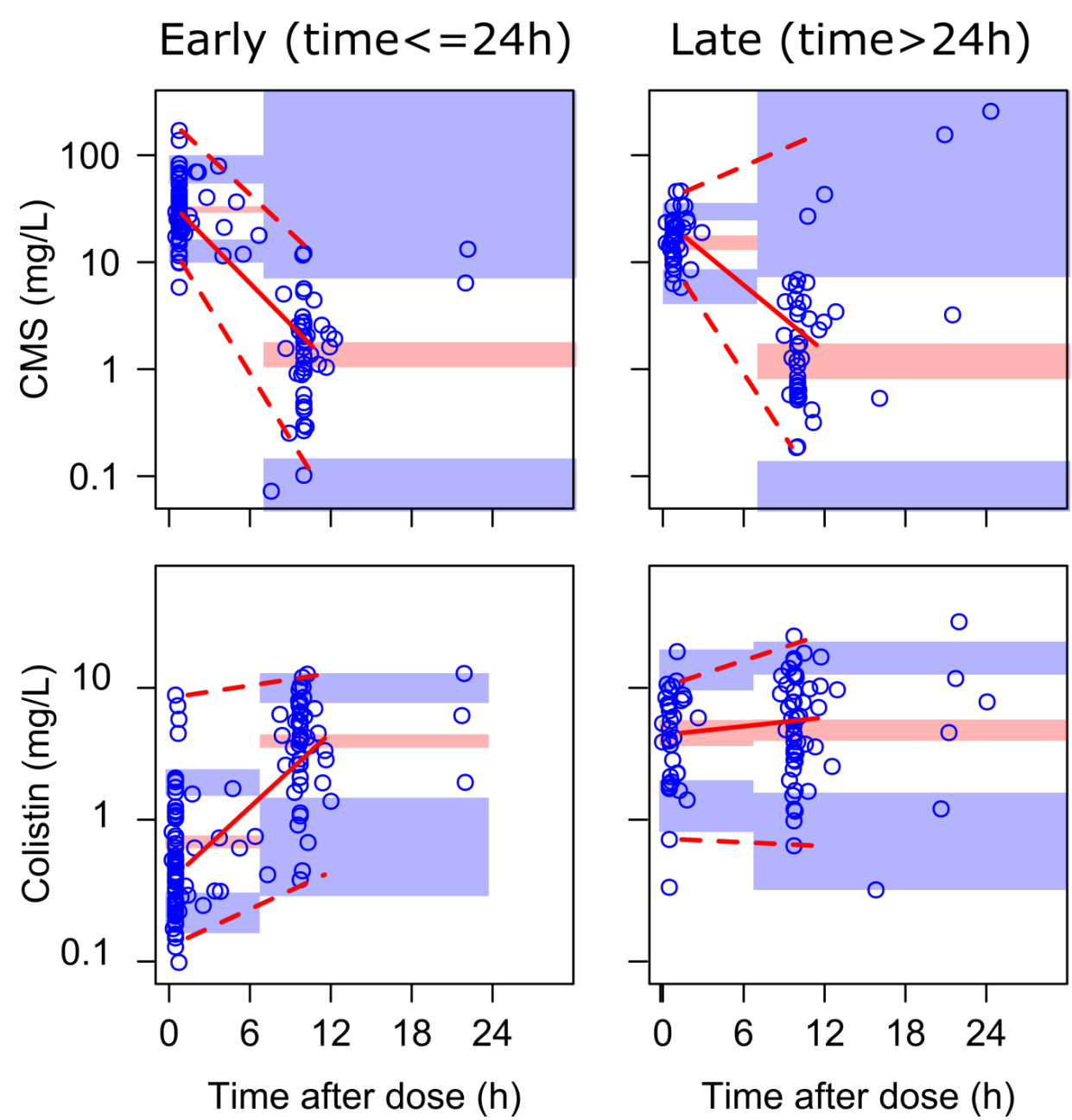


Figure 3 Prediction-corrected visual predictive check (pcVPC) of CMS (top) and colistin (bottom) at early (pre 24h) and late (post 24h) time points. Observations – circles, solid line – median (50th percentile) of observations, dashed lines 5th and 95th percentiles of observations, shaded areas – 95% confidence interval of the 2.5th, 50th and 97.5th percentiles based on 300 simulations of the sample.

Precision of the individual parameters (EBEs)

	CL dSD	SH	Q dSD	SH	ER dSD	SH
Expected	63%	12%	19%	45%	30%	72%
Early	54%	0%	20%	0%	7%	-16%
Late	60%	-8%	1%	59%	10%	8%
No	54%	6%	65%	59%	15%	-20%

Table 1 The dSD (high better) and SH (low better) for the simulated (Expected) and for the groups of observed data (Early, Late, and No protocol).

The dSD and SH in the individual CL was close to expected for all groups but was best for the Late protocol group. As expected, the sampling was too sparse to estimate the individual Q and ER parameters. Due to the large contribution of one site to the early protocol group (29/45 patients), it is not possible to directly compare the parameter precision across the protocol groups at this point.

Conclusions

- The proposed sparse sampling schedule yielded individual CL estimates with low SH and close to expected precision.
- The observed colistin trough concentrations are higher than expected.
- The result brings confidence for the ability to evaluate covariates that may affect CL as well the relationship between colistin exposure and microbiological and clinical outcomes.
- A full analysis is intended to be completed by the end of this year.