PBPK modelling to derisk DDI: a case study

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Inspired by patients.
Driven by science.

Background

Setting the scene

Therapeutic area: epilepsy

Brivaracetam (Briviact®)

- Antiepileptic (AED) drug recently approved.
- Recommended doses: 100 & 200 mg/day
- Bioavailability ~ 100 %
- Linear pharmacokinetics
- *In vitro*, Brivaracetam had no effect on CYP1A2, 2A6, 2B6, 2C8, 2C9, 2D6 and 3A4 but inhibited 2C19 (competitive inhibition)
- No time dependant inhibition (TDI)

Phenytoin

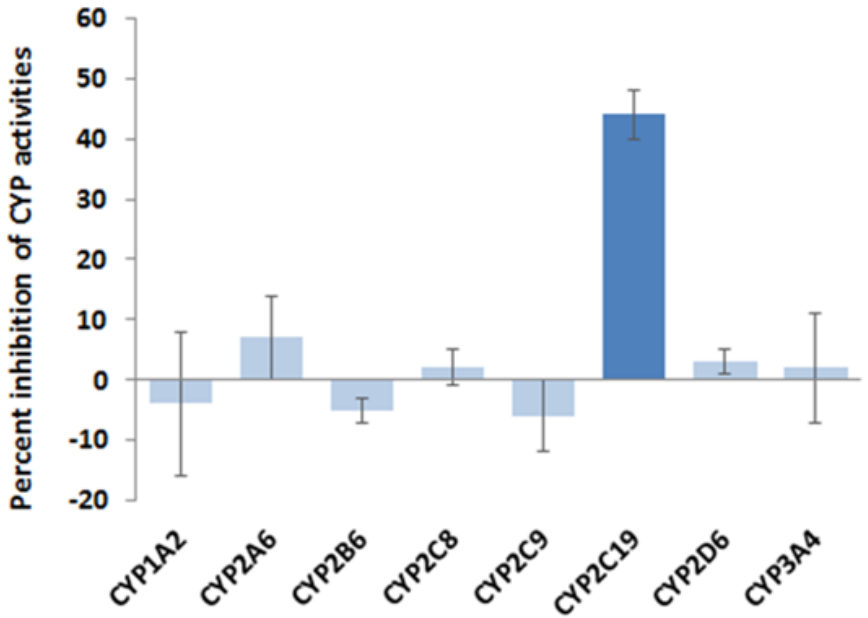
- Widely prescribed anticonvulsivant
- Small therapeutic index
- Potential severe adverse effects
- Elimination through CYP2C9 & CYP2C19
- Caution in CYP2C9/2C19 poor metabolizers and when coadministered with CYP2C9/2C19 inhibitors

Brivaracetam is likely to be co-administered with Phenytoin

Background

Brivaracetam is likely to be co-administered with Phenytoin

In vitro results



Concentration = 50 x $Cmax_u$ = 650 µM

Competitive inhibition – Ki = 314 µM

Background

Brivaracetam is likely to be co-administered with Phenytoin

In vivo study

- 19 epileptic patients stable on phenytoin monotherapy
- Repeated administrations of brivaracetam at 400 mg/day (200 mg bid)

	C_{max} (µg/mL)	AUC_{τ} (µg.h/mL)
PHE	**16.9** (37.5)	**252** (54.8)
PHE (with BRV)	**20.7** (38.1)	**306** (42.6)

On average, both Cmax and AUC of phenytoin were increased by 20 %

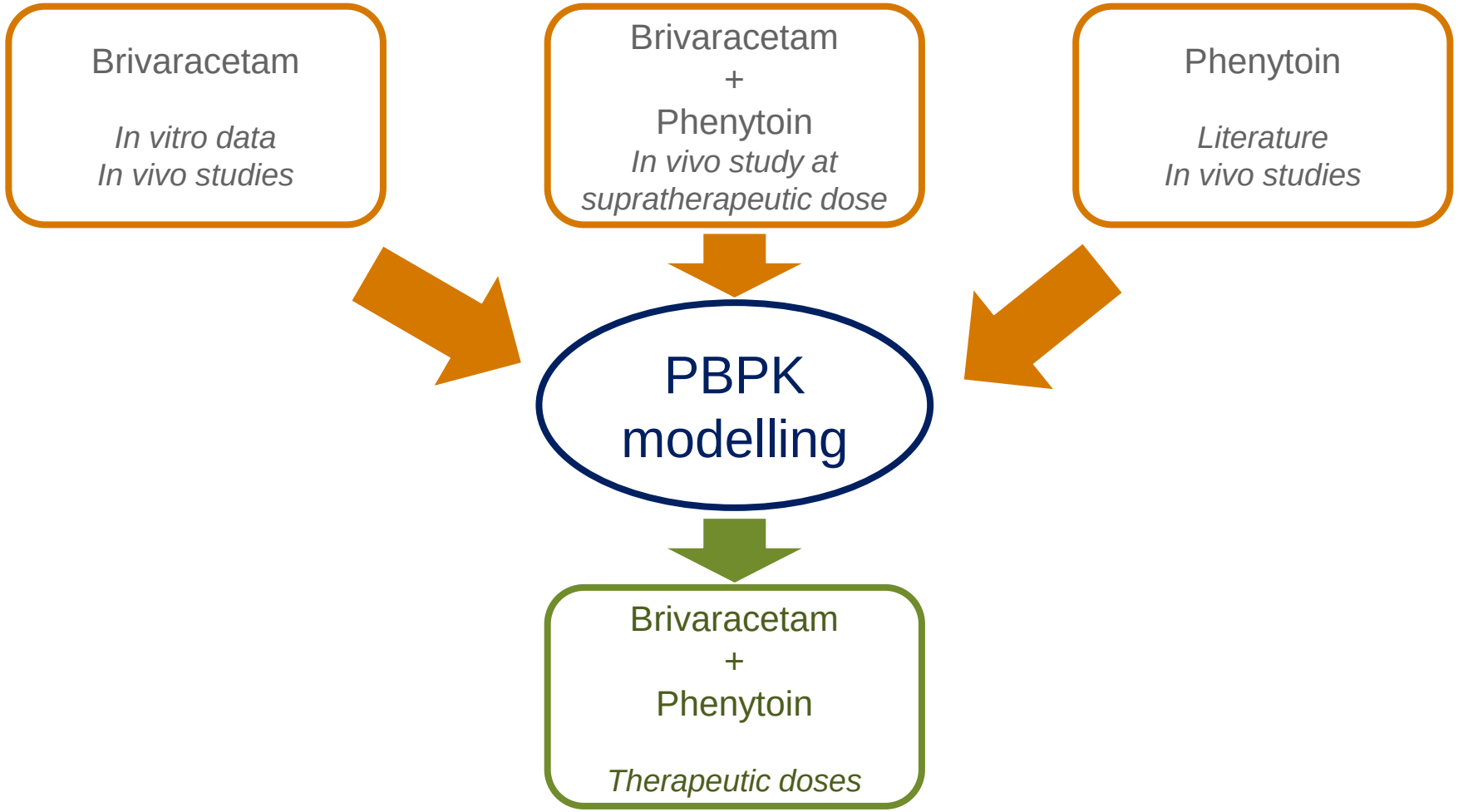
- modest amplitude
- non-approved dose
- difficult to distinguish from background variability

BUT

notice in the US/EU labeling
+
phenytoin plasma monitoring (US)

And so what ?...

What could we expect at brivaracetam therapeutic doses ?

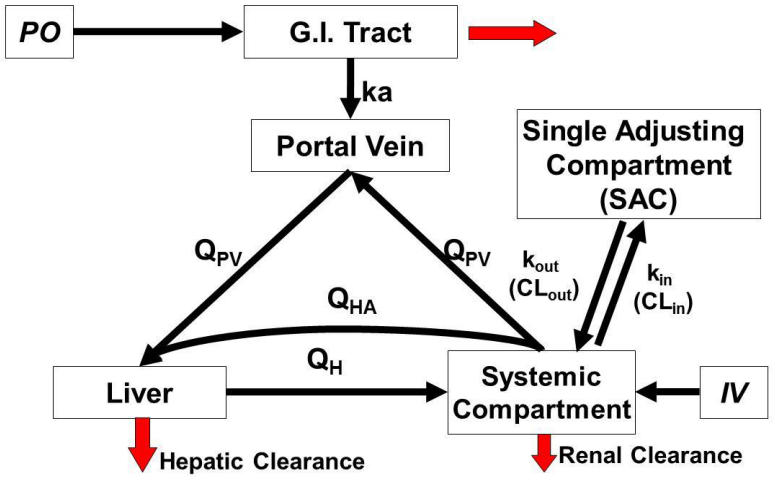


Modelling strategy

MODEL BUILDING

Brivaracetam
In house in vivo and in vitro data

Phenytoin
Simcyp compound file



POPULATION
Healthy volunteers
N = 250

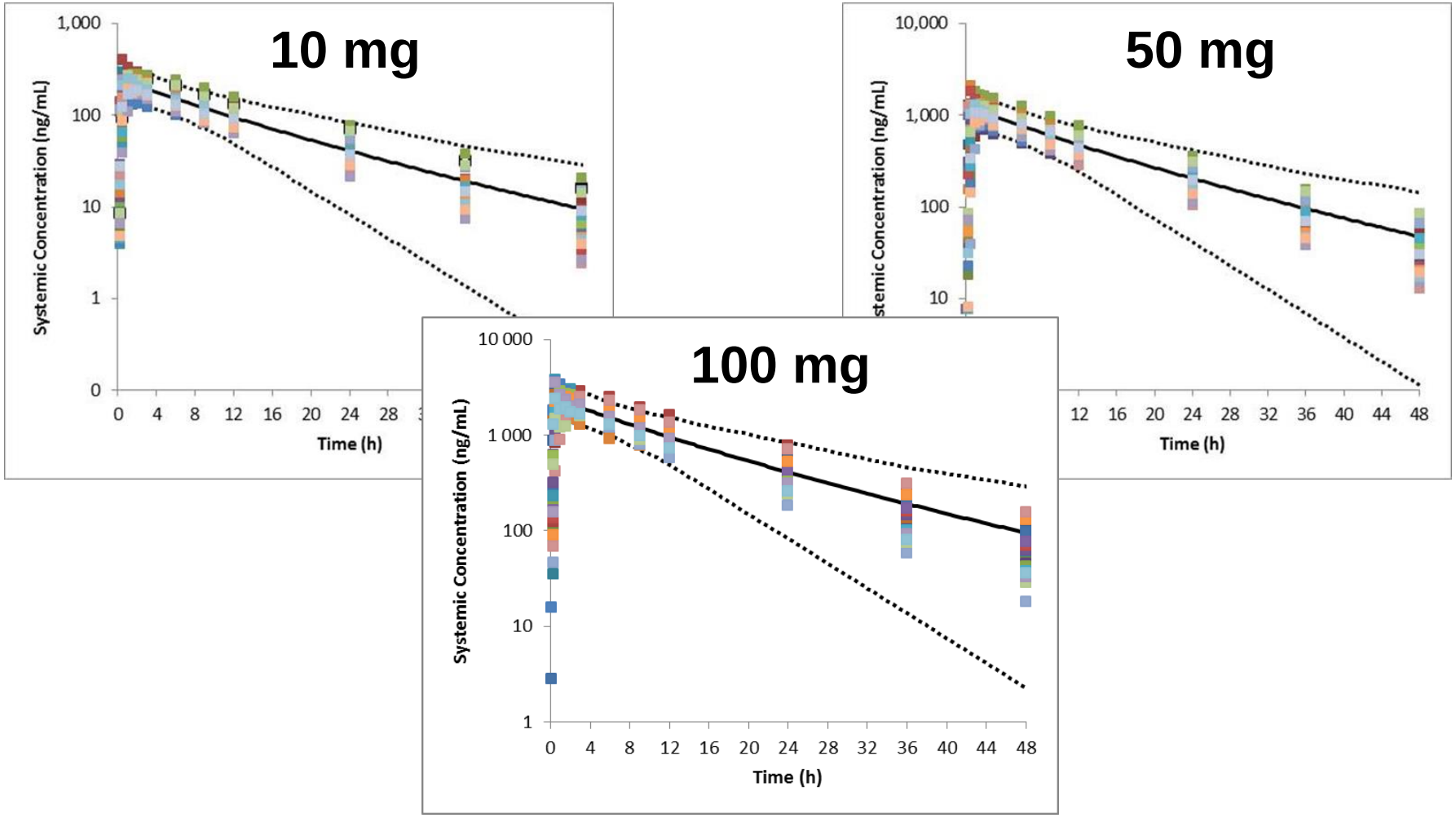
MODEL QUALIFICATION

Brivaracetam
FIM single PO doses + Repeated administration at therapeutic doses

Phenytoin
Dedicated publications

Modelling results / qualification

Brivaracetam – single oral administration



Modelling results / qualification

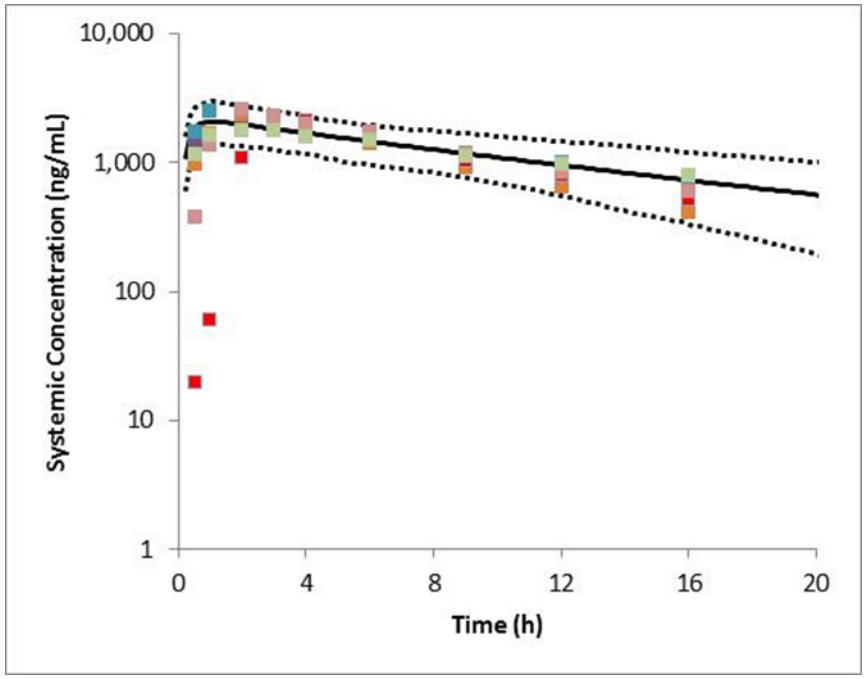
Brivaracetam – single oral administration

	PREDICTED		OBSERVED	
	Cmax (ng/ml)	AUC (ng.h/ml)	Cmax (ng/ml)	AUC (ng.h/ml)
10 mg	217 (*29.4*)	3059 (*36.4*)	240 (*21.4*)	3123 (*25.6*)
50 mg	1084 (*29.4*)	15297 (*36.4*)	1236 (*27.8*)	15712 (*25.7*)
75 mg	1626 (*29.4*)	22946 (*36.4*)	1941 (*23.9*)	23791 (*24.9*)
100 mg	2168 (*29.4*)	30594 (*36.4*)	2570 (*22.4*)	31491 (*25.0*)

- simulated profiles comparable to the clinical data for all doses
- predicted geometric mean Cmax and AUC within 1.25-fold of the observed data

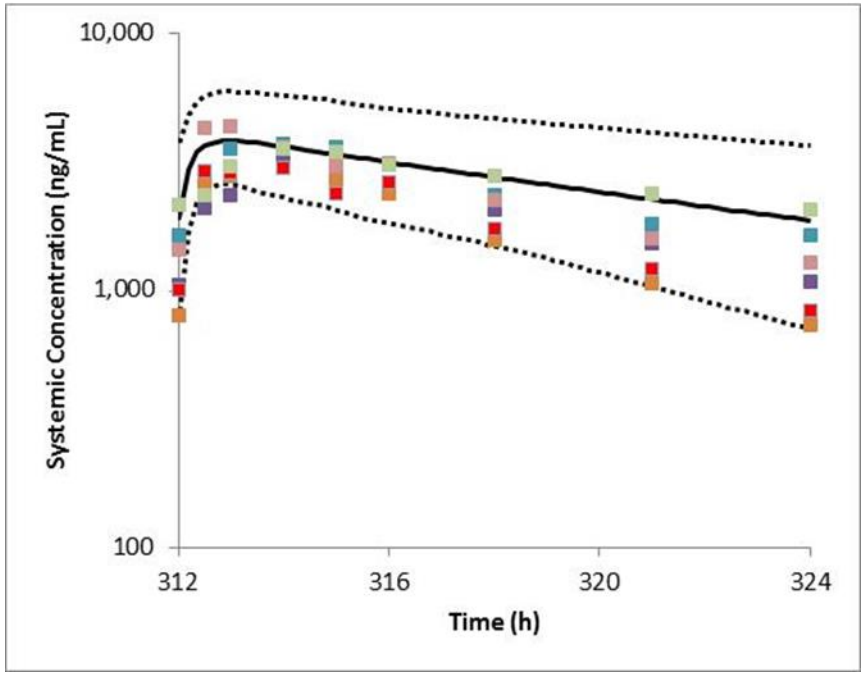
Modelling results / qualification

Brivaracetam – repeated oral administration



100 mg – day 1

100 mg bid – day 14



Modelling results / qualification

Brivaracetam – repeated oral administration

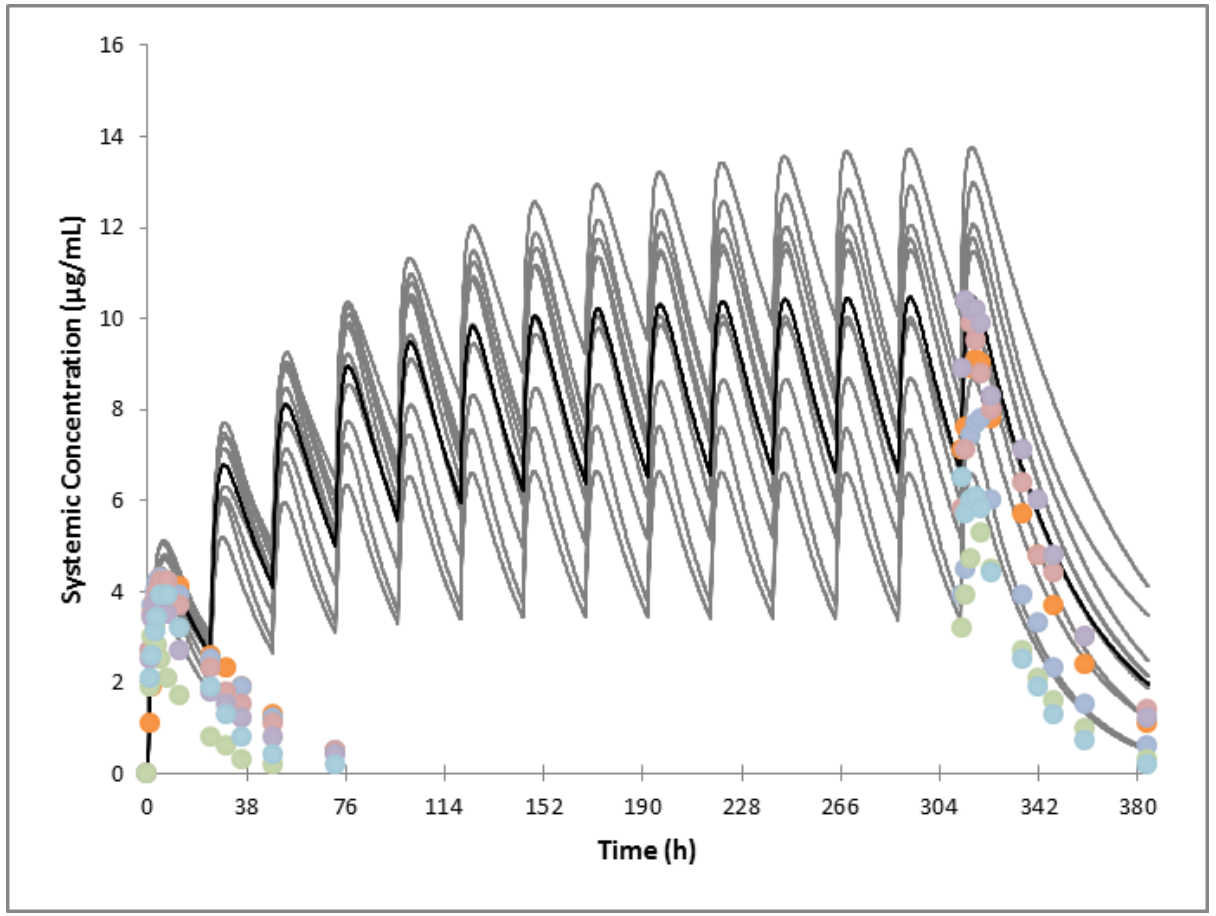
	PREDICTED		OBSERVED	
	Cmax (ng/ml)	AUC (ng.h/ml)	Cmax (ng/ml)	AUC (ng.h/ml)
Day 1	2170 (*27.0*)	24725 (*24.8*)	2200 (*14.0*)	27500 (*23.0*)
Day 14	3726 (*25.9*)	31898 (*34.7*)	3500 (*27.8*)	28000 (*25.7*)

- simulated profiles comparable to the clinical data for all doses
- predicted geometric mean Cmax and AUC within 1.25-fold of the observed data

Modelling results / qualification

Phenytoin – repeated oral administration

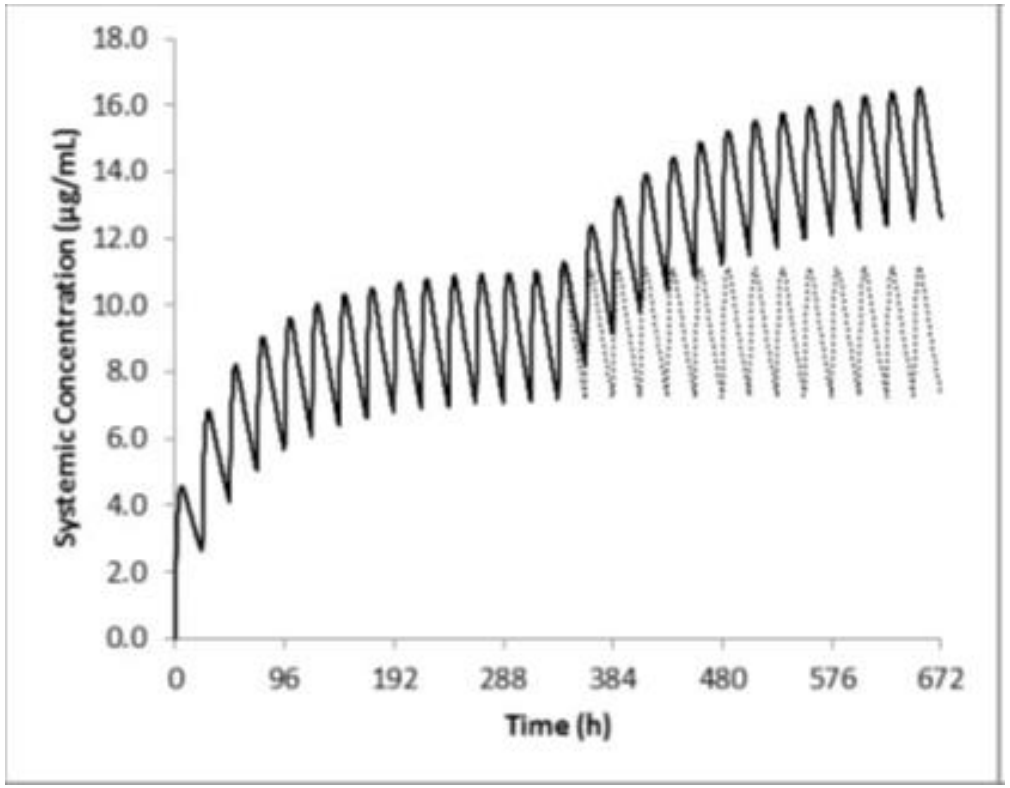
300 mg once a day



Modelling results / qualification

Phenytoin – CYP2C19 contribution

300 mg once a day and ticlopidine (250 mg bid)

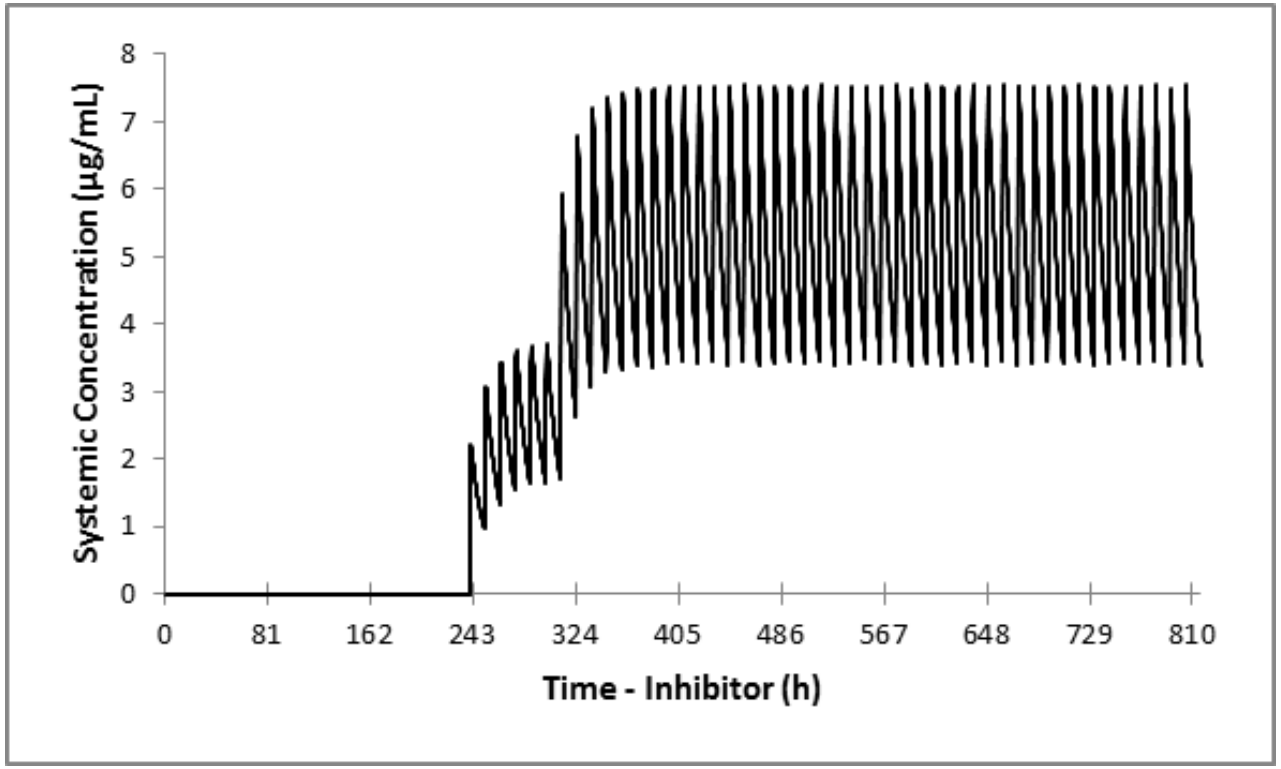


- **Simulations**:
  - phenytoin Cmin increase by 74 %
- **Observations**:
  - 2 individuals showing Cmin increasing by 70 – 80 %
  - 6 individuals with a dose adjustment corresponding to a 80% decrease

Modelling results / qualification

Brivaracetam (400 mg) & Phenytoin

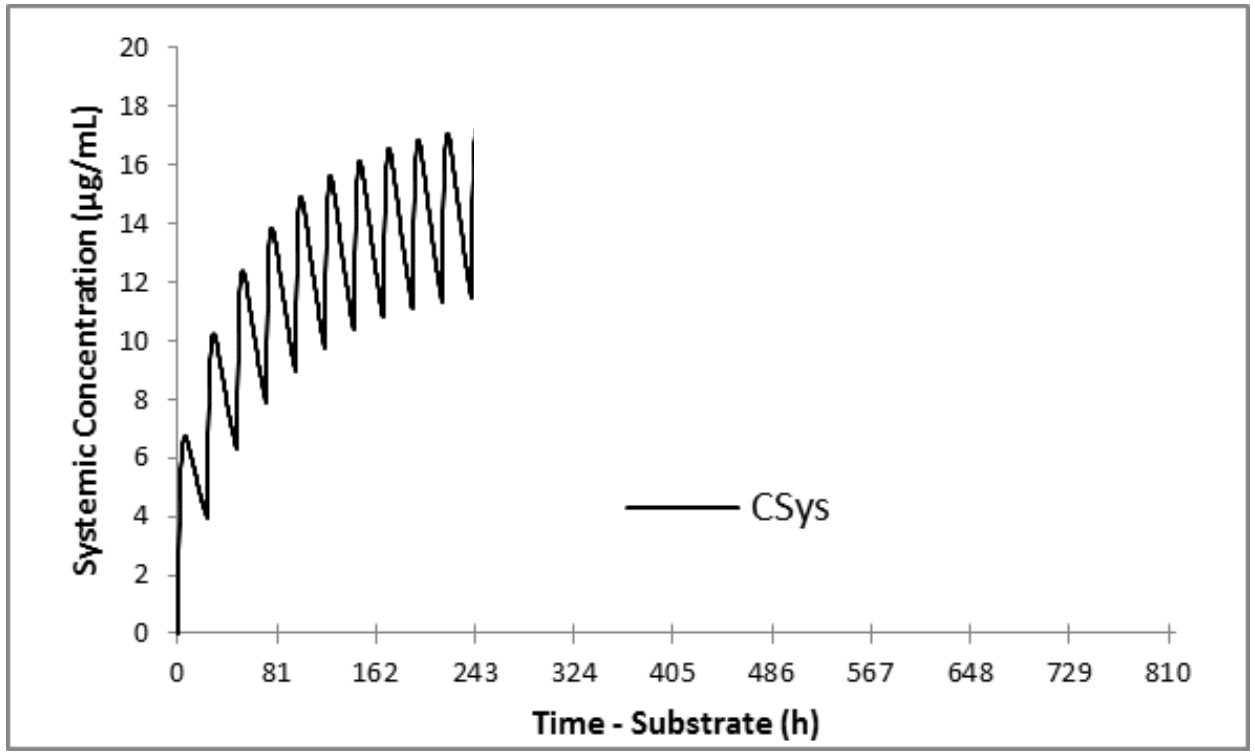
- Brivaracetam: 100 mg BID for 3 days followed by 200 mg BID for 3 weeks



Modelling results / qualification

Brivaracetam (400 mg) & Phenytoin

- Brivaracetam: 100 mg BID for 3 days followed by 200 mg BID for 3 weeks
- Mean concentration of Phenytoin (alone) in the target range of 7-23 µg/mL



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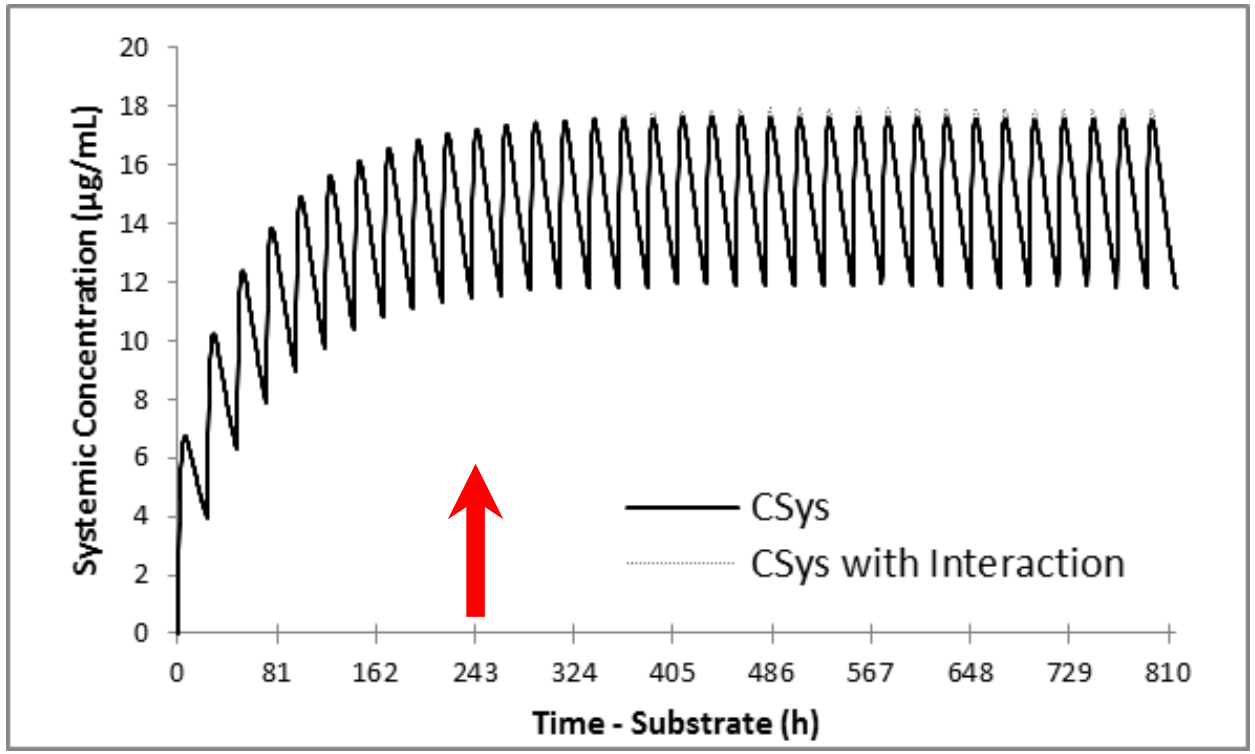

Ki = 314 µM → simulations did not show any effect on the phenytoin pharmacokinetics

Modelling results / qualification

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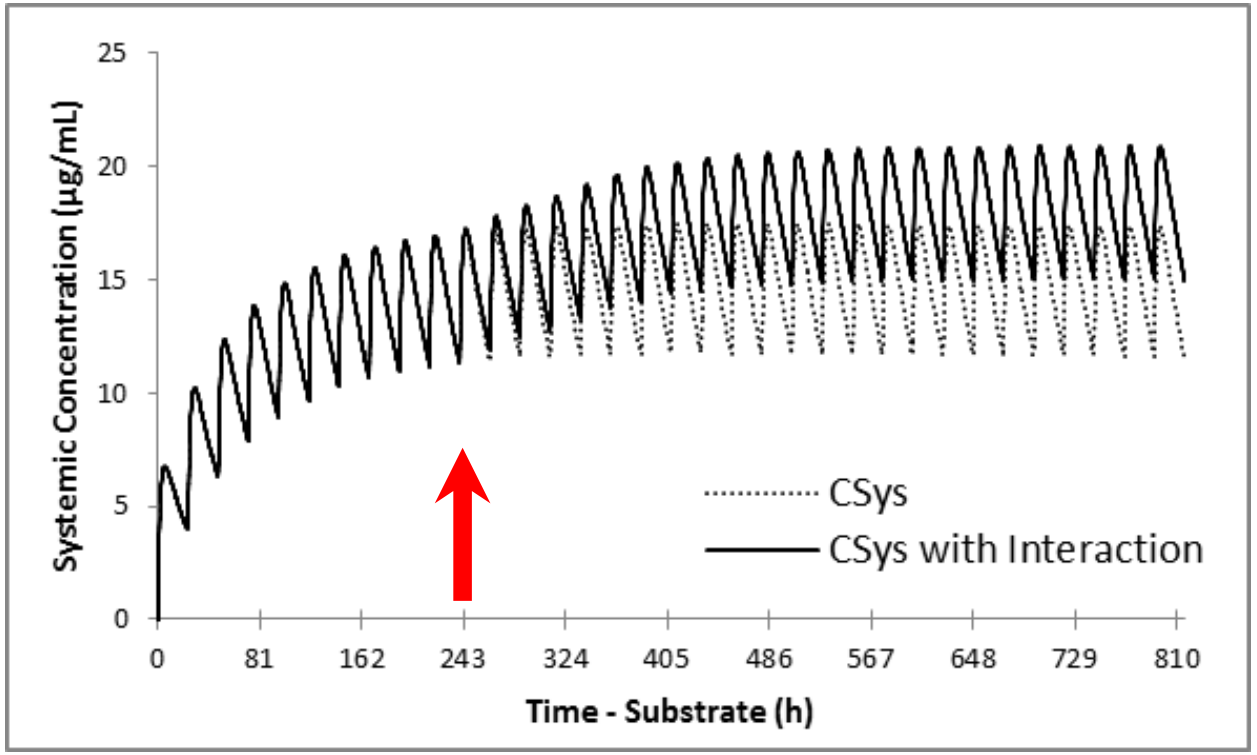


Ki = 22 µM → simulations did show an effect on the phenytoin pharmacokinetics

Modelling results / qualification

Brivaracetam (400 mg) & Phenytoin

- Brivaracetam: 100 mg BID for 3 days followed by 200 mg BID for 3 weeks
- Mean concentration of Phenytoin (alone) in the target range of 7-23 µg/mL

	Observed			Predicted		
	Cmax (µg/ml)	Tmax (h)	AUC (µg.h/ml)	Cmax (µg/ml)	Tmax (h)	AUC (µg.h/ml)
Without BRV	16.9	4.6	252	17.4	4.6	355
With BRV 200 mg BID	20.7	4.7	305	20.92	4.7	440
ratio	1.22		1.21	1.19		1.24

Ki = 22 µM → simulations did show an effect on the phenytoin pharmacokinetics

Modelling results / qualification

Brivaracetam (400 mg) & Phenytoin

- Brivaracetam: 100 mg BID for 3 days followed by 200 mg BID for 3 weeks
- Mean concentration of Phenytoin (alone) in the target range of 7-23 µg/mL

- Ki from 314 to 22 µM to accurately predict the DDI…

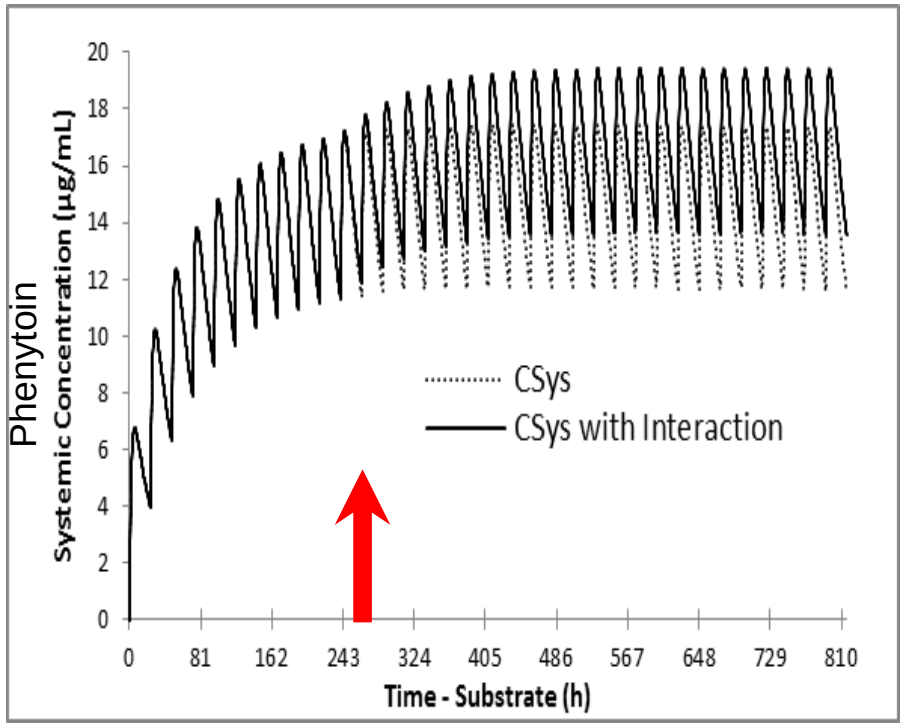
- This finding is not unique: fluvoxamine, topiramate, imipramine, …
- Ticlopidine and felbamate: very few examples with good IVIVE for DDI prediction with phenytoin

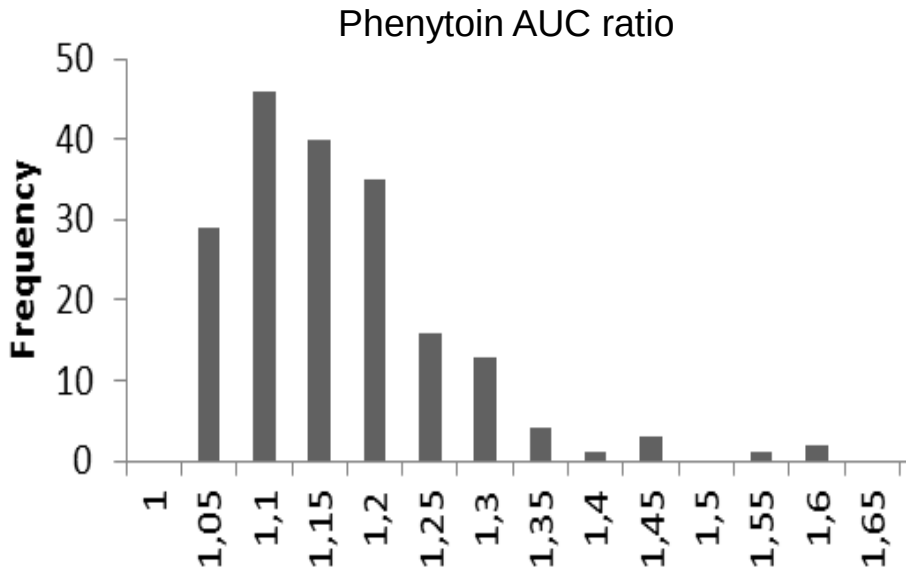
Modelling application

Brivaracetam (200 mg) & Phenytoin

- Brivaracetam: 100 mg BID starting on day 11 for 3 weeks
- Mean concentration of Phenytoin (alone) in the target range of 7-23 µg/mL

- Ki of Brivaracetam on CYP2C19 → 22 µM





Conclusions

- PBPK modelling allowed both model building and model qualification
- In vivo data allowed the calculation of an in vivo Ki
- Sensitivity analysis
- The simulations illustrate that the highest recommended brivaracetam dosage of 100mg BID is expected to be devoid of significant risks of interaction with phenytoin

Thanks!

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