Implementation of volumetric absorptive microsampling technology in pediatric and adult clinical development programs

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Inspired by **patients.**
Driven by **science.**

Agenda

1. Introduction
2. Implementation of Patient Centric Sampling at UCB
3. Overall Strategy
4. Case studies
    1. Radiprodil
    2. Padsevonil
    3. Inhaled Alprazolam
5. Take-home messages

Introduction – Patient centric sampling approaches

Patient

- Less burden
- Patient centric (less painful, low volume
- Flexibility
- Potential increase equity for access to trial

Value proposition for Patient Centric Sampling

Sponsor – Scientific value

- Richer dataset/optimization of sampling time
- Potential increased access to more diverse population
- Potential sampling near the event of interest

Sponsor - Efficiency

- Decrease burden around PK samples handling
- Improved trial management
- Potential to recruit broader patient population

Implementation of Patient Centric Sampling in Clinical Programs At UCB

Three case studies

2016	2017	2018	2019	2020	2021	2022	2023

Radiprodil

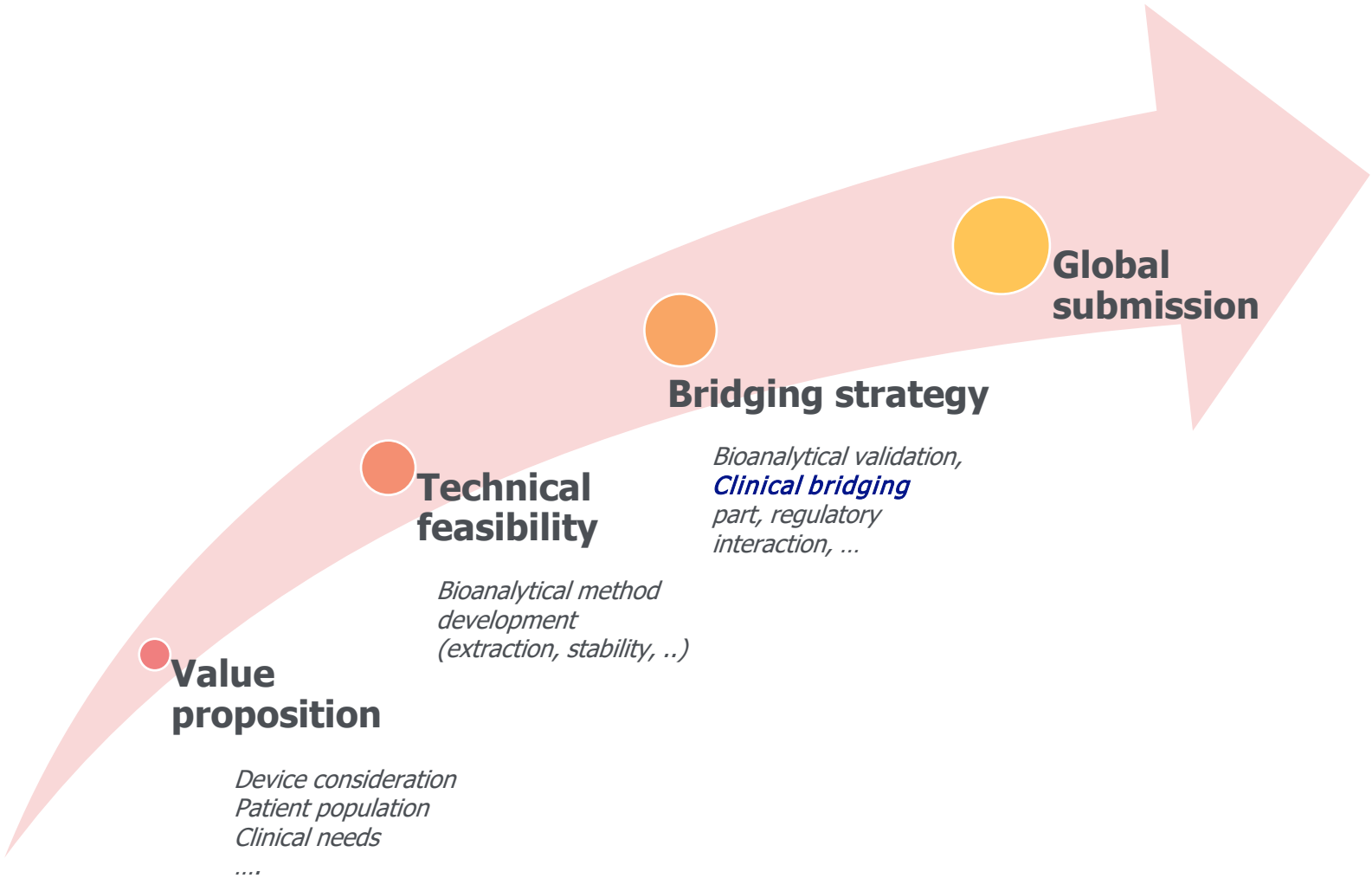
Padsevonil

Inhaled Alprazolam

Global UCB Initiative « Biosampling @ home »

Overall Strategy for implementation of PCS

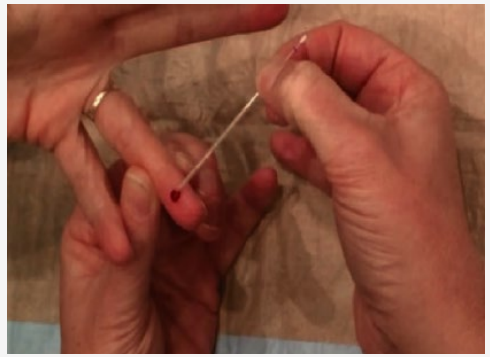
Based on implementation in ongoing clinical development



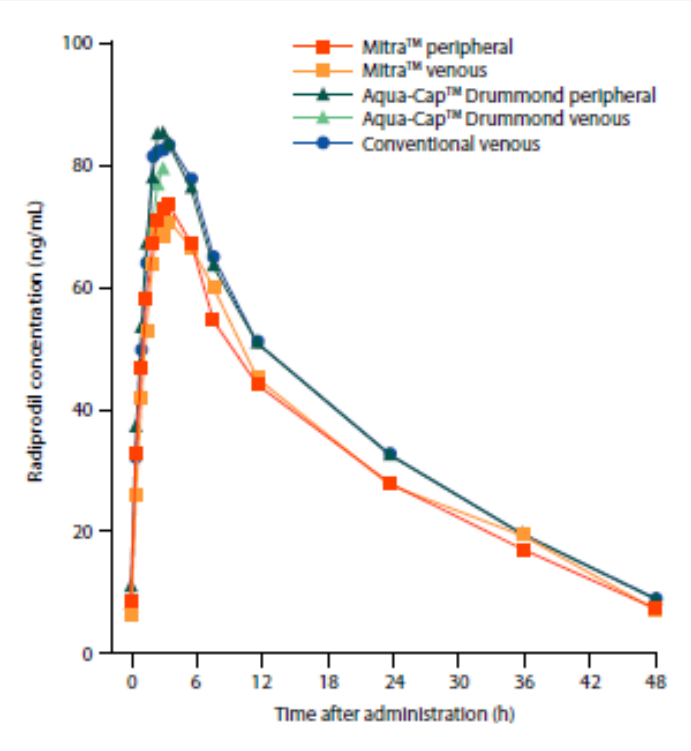
Radiprodil – Dose range finding in drug refractory pediatric patients (2-14 months) with Infantile Spasm

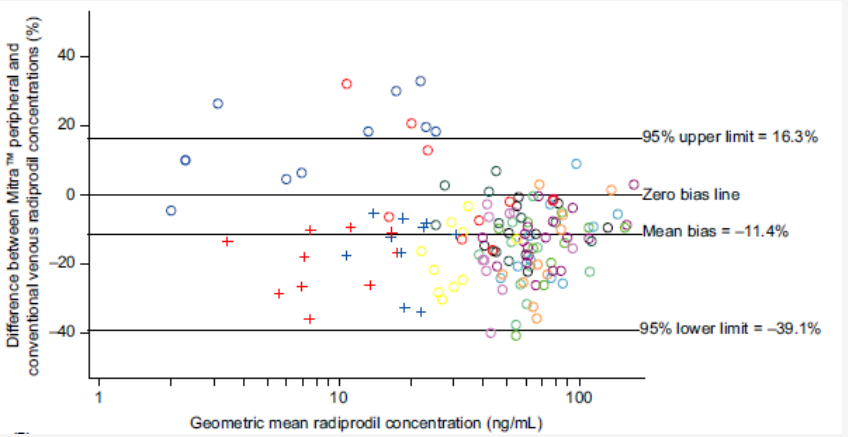
Mitra™

Aqua-cap™ Drummond



Bridging in adult healthy volunteers





PK parameters	Geometric LSMean Ratio* [95% CI]
AUC	0.86 [0.83, 0.89]
AUC(0-t)	0.86 [0.83, 0.90]
Cmax	0.89 [0.85, 0.94]

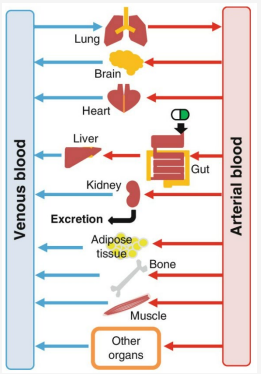
*Mitra over conventional venous sampling

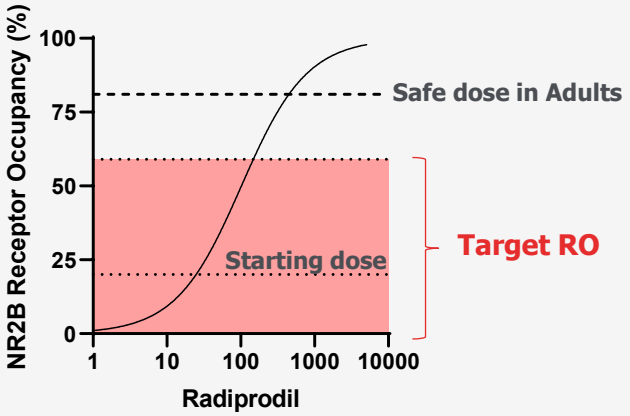
Sciberras et al (2019) *Pharmacol Res Perspect* (DOI: 10.1002/prp2.459)
Johnson et al (2020) *Br J Clin Pharmacol* (DOI: 10.1111/bcp.14528)

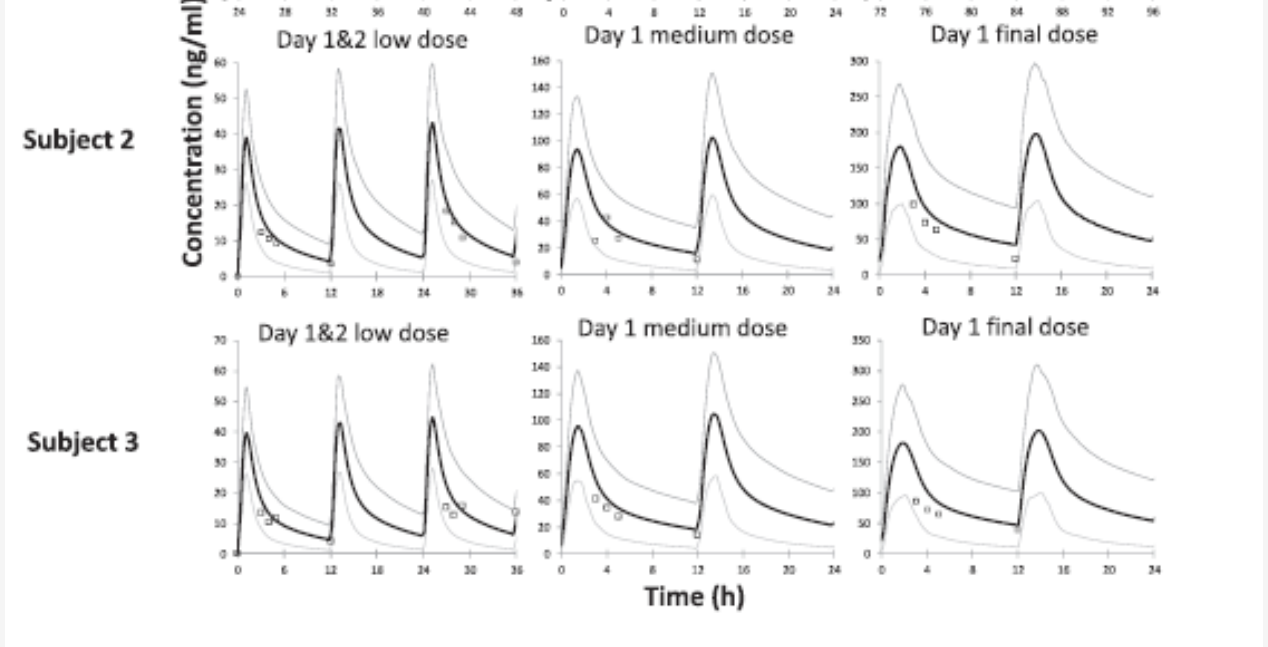
Radiprodil – Dose range finding in drug refractory pediatric patients (2-14 months) with Infantile Spasm

Use of Mitra, as PK sampling approach in infants to confirm exposure

PBPK







Black lines are the simulated mean concentration time profile and grey lines 5th and 95th percentile. Open squares are clinical data.

Sciberras et al (2019) *Pharmacol Res Perspect* (DOI: 10.1002/prp2.459)
Auvin et al (2020) *Ann Clin Transl Neurol* (DOI: 10.1002/acn3.50998)
Johnson et al (2020) *Br J Clin Pharmacol* (DOI: 10.1111/bcp.14528)

Padsevonil (PSL) – A drug candidate for refractory epilepsy

Implementation of Mitra during clinical development (after positive POC)

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To support pediatric program (from neonates)

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Opportunity of the clinical pharmacology program to bridge between the 2 sampling approaches (Mitra and conventional venous blood)

Robust and extensive bridging in adult participants

Study Number	Study Type	Study population	Ethnicity	Dose regimen	Paired samples	Purpose
UP0039	Phase 1 ethno-bridging PK	HV	Japanese	50-200mg SD	240	**Model development**
UP0057	Phase 1 PK DDI	HV	White	100mg SD & BID	2033	
UP0070	Phase 1 PK DDI	Epilepsy patients	White	400mg BID	307	
UP0075	Phase 1 Chinese PK	HV	Chinese	200mg SD	119	
UP0039	Phase 1 ethno-bridging PK	HV	White	200mg SD	80	**Model Validation**
EP0091	Phase 2b	Epilepsy Patients	Multiple	50-400 mg BID	269	

Padsevonil (PSL) – A drug candidate for refractory epilepsy

Graphical Analysis

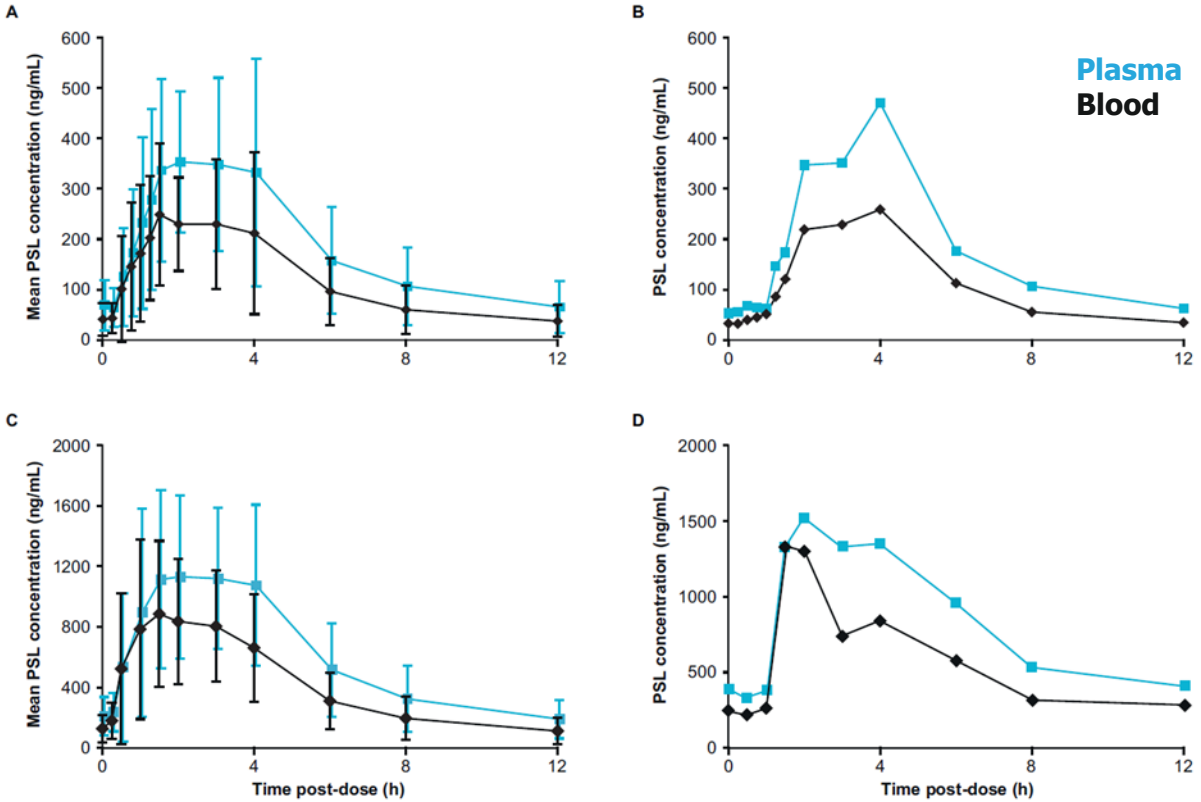
- Plasma and blood (Mitra) concentration-time profile

Mean Profile

Representative individual profile

100mg BID (Healthy Volunteers [HV], n= 28)

400mg BID (Epilepsy patients, n=28)



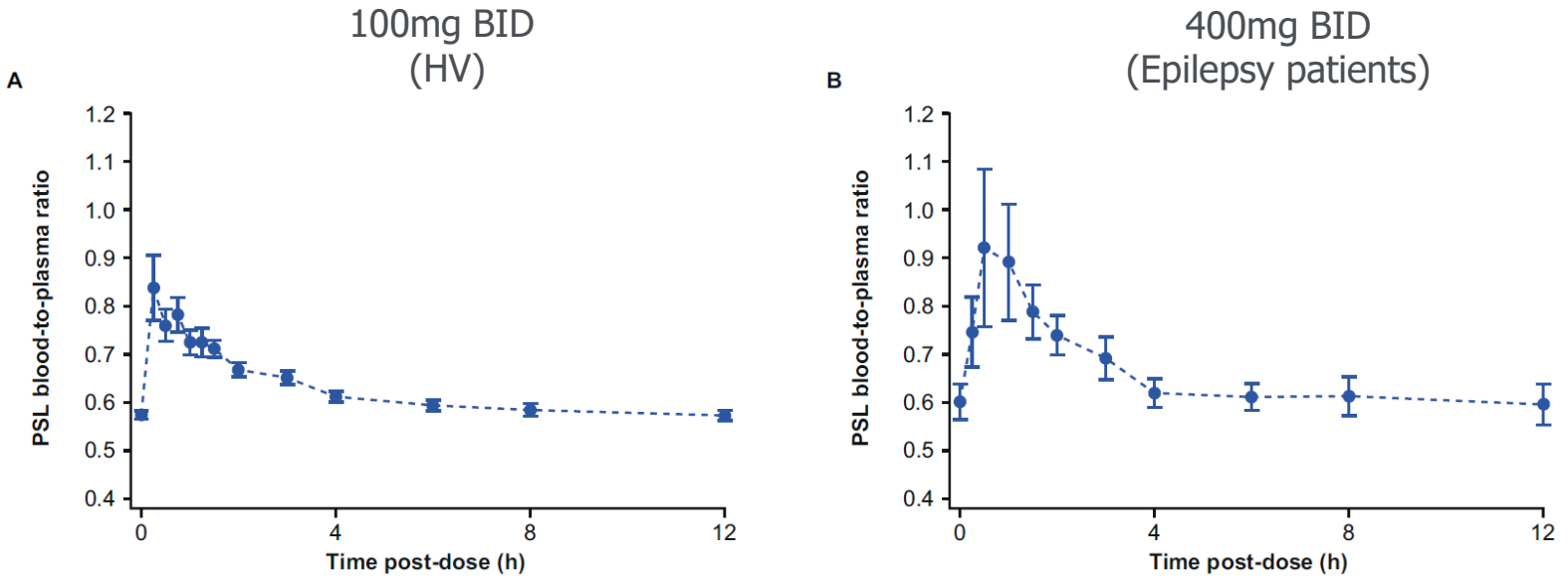
UP0057 (Top) and UP0070 (Bottom)

Kramer et al, submitted

Padsevonil (PSL) – A drug candidate for refractory epilepsy

Graphical Analysis

- Mean Blood-to-plasma ratio profile over time



In vitro B/P : 0.6-0.7

B/P showed « time effect » with values increasing from ~0.6 to 0.9 directly after dosing and then declining back to ~ 0.6-0.7
Similar pattern observed across all bridging studies

UP0057 (Left) and UP0070 (Right)

Kramer et al, submitted

Why is blood-to-plasma ratio changing over time ?

Sampling site | Type of blood | Arterio-venous difference

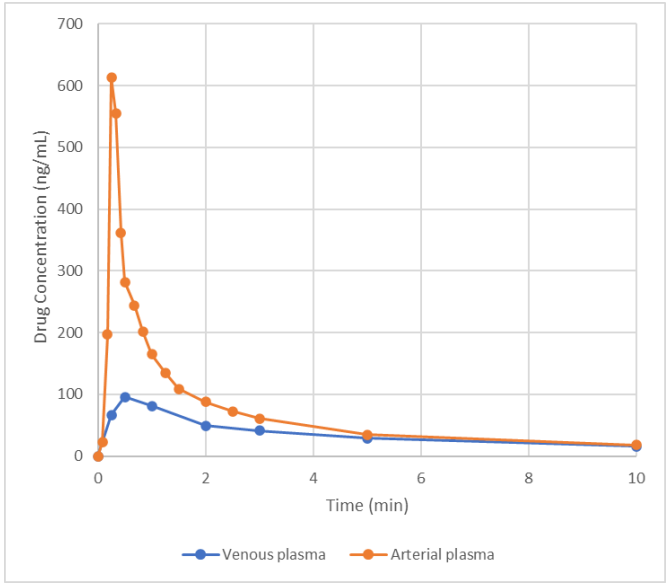
Finger-prick

Arteriolar, venous and capillary blood

Venous sampling

Venous blood

Example from dog PK (iv dosing)

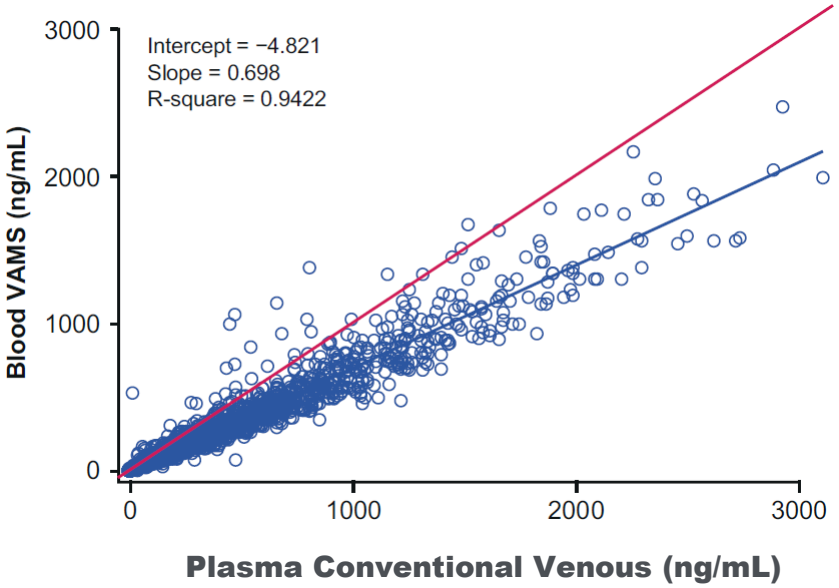


Arterial-to-venous concentration ratio is changing during the distribution phase of drugs (extraction in tissue)

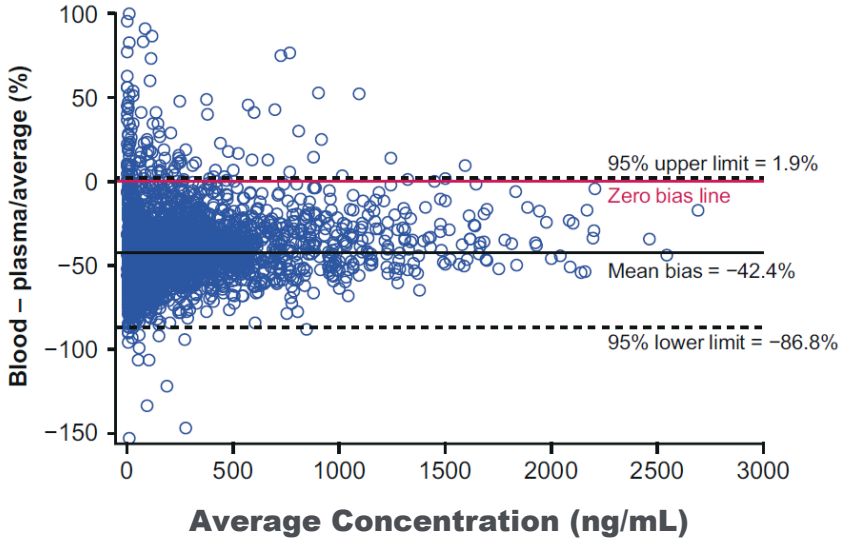
Unpublished data (UCB data on file)

Padsevonil – A drug candidate for refractory epilepsy

Statistical Analysis – Pooled dataset



Bland-Altman



Time-matched blood and plasma concentration data (from 0 to 12h post-dose) pairs were fitted to a **linear mixed effects model**

Covariate analysis (race, ethnicity, gender, …) performed and only timepoint and dosing found as significant covariate

→ Validation of the model with 2 independent datasets

log_Plasma (ng/mL) = 1.01577***log_Blood** (ng/mL) + 0.01042* **Timepoint** (hour) + 0.07560***Dosing#**

Red line is the identity line

#1=single dose, 2=Repeated dose

Kramer et al, submitted

Padsevonil – A drug candidate for refractory epilepsy

Statistical Model Validation using 2 different datasets

Caucasian, HV, 200mg SD

Plasma concentration predicted from blood (Mitra) concentration

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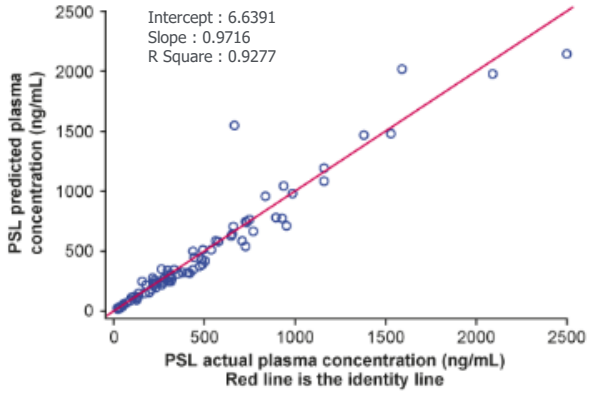
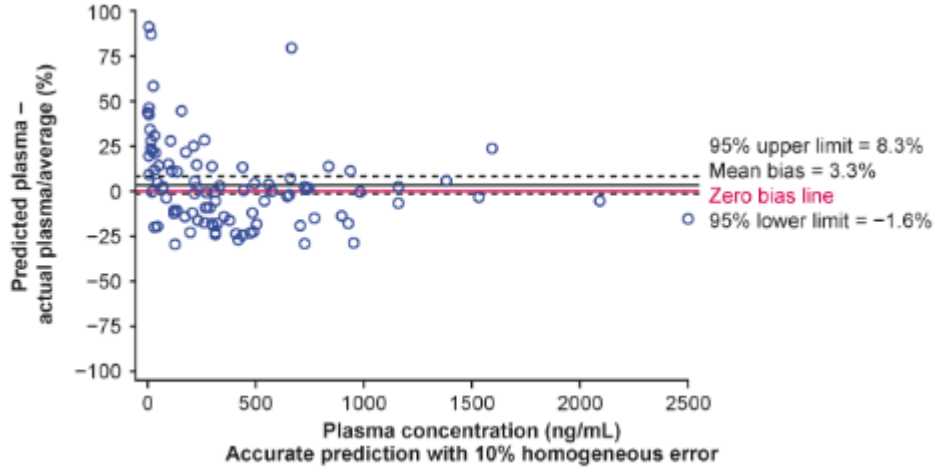
Compared with actual Plasma concentration

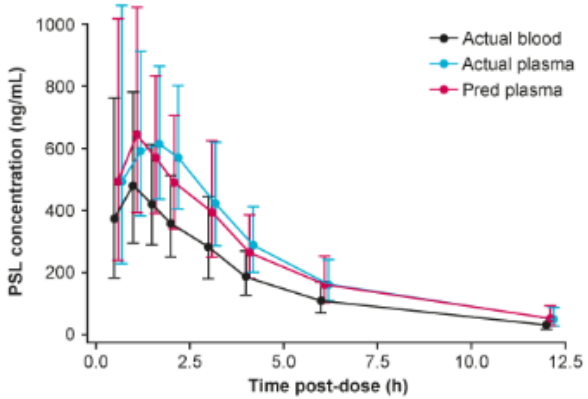
Linear regression (Predicted vs Observed)



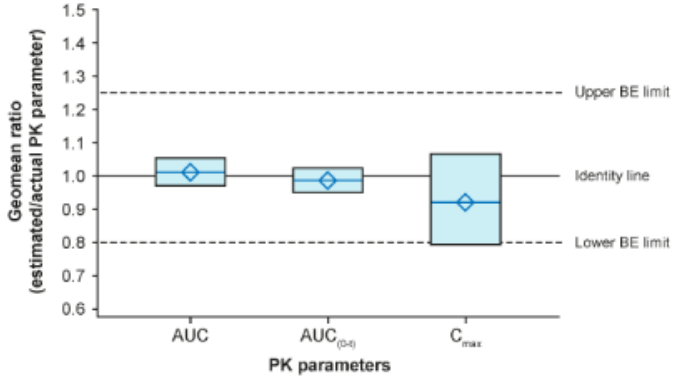
Bland-Altman (Predicted vs Observed)



PK Profiles



Plasma PK Parameters (Predicted vs Observed)



Kramer et al, submitted

Padsevonil – A drug candidate for refractory epilepsy

Statistical Model Validation using 2 different datasets

All ethnicities, Patients, 50 to 400 mg BID (Phase 2b)

Plasma concentration predicted from blood (Mitra) concentration (Sparse sampling)

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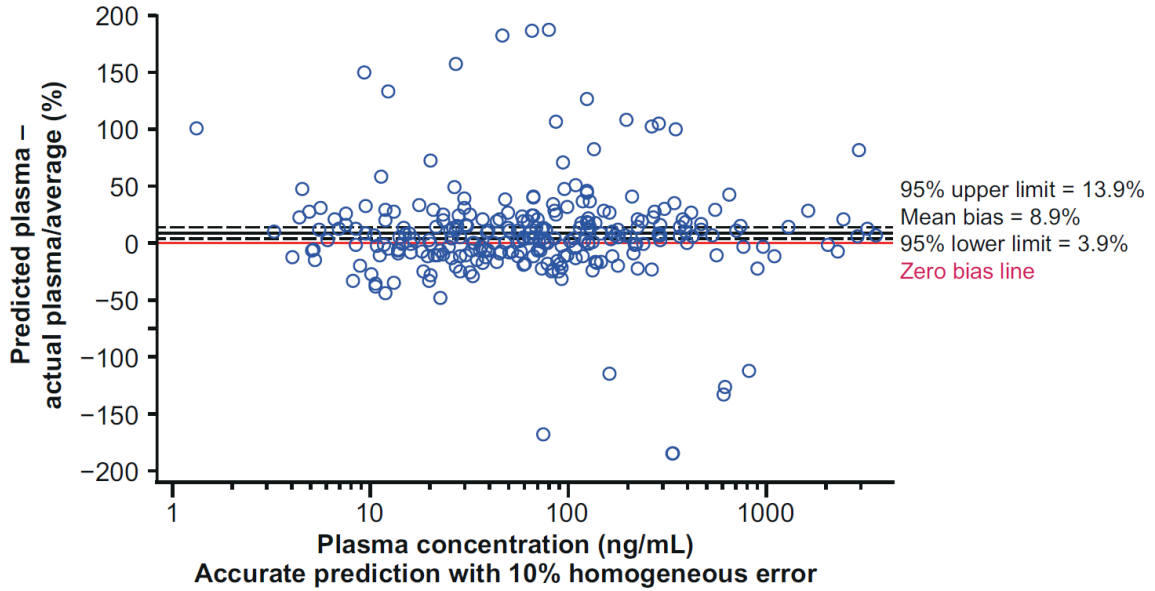
Compared with actual Plasma concentration

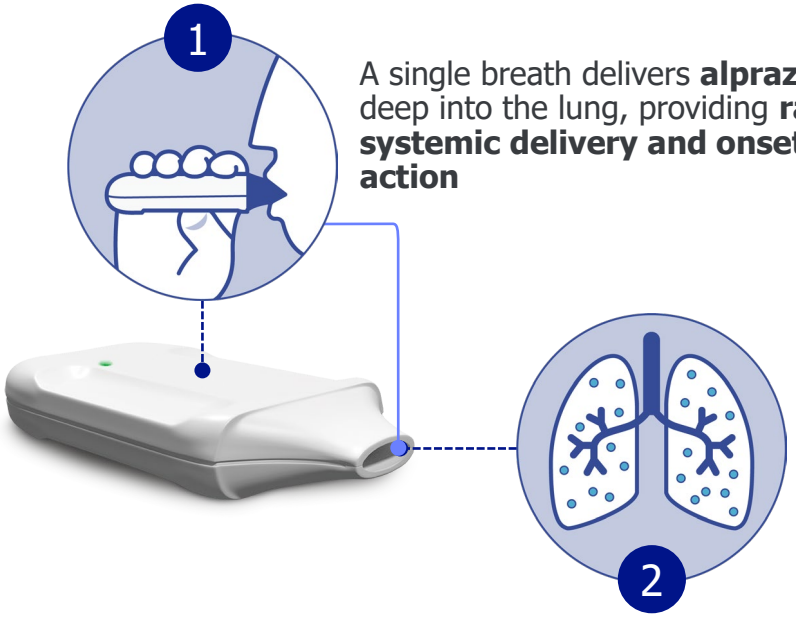
Bland-Altman
(Predicted vs Observed)



Overall, the model was found to be adequate to describe the data and to link plasma concentration with blood concentration (Mitra)

Kramer et al, submitted

Inhaled Alprazolam for rapid termination of stereotypical prolonged seizures



A single breath delivers **alprazolam** deep into the lung, providing **rapid systemic delivery and onset of action**

Inhaled Alprazolam is developed for the **rapid termination (<90s) of prolonged seizures**

Clinical bridging between conventional venous sampling and TassoM20 in 2 Phase 1 studies

Global Phase 3 study

- Single dose for acute treatment of a prolonged seizure
- Fully outpatient setting with study caregiver
- **PK sampling at home** by caregiver (Tasso M20) after seizure treatment

Take-home messages for implementation of PCS in clinical development

- Bridging is key to establish a correlation between the conventional venous blood sampling and the selected PCS method
  - Ideally, paired samples collected at the same timepoint in Phase 1 studies
  - No specific critieria for successful bridging, you need to demonstrate that the relationship between 2 methods is well characterized
- There is no « one fits for all » strategy. Bridging should be tailored to program needs and specificities
- Considerable cross-functional team effort to implement PCS in global pivotal Phase 3 studies – Key to identify the right subject matter experts and get them involved as soon as possible because process for implementation is tedious !
- Interactions with Health Authorities on the adequacy of the bridging strategy to support the use of PCS as sole source of PK sampling in global Phase 3 studies

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Miguel Hernandez
Elizabeth Webster
Tony Daniels

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