T-064

A Model-Based Approach to Bridging Plasma and Dried Blood Spot Concentration Data for Phase 3 Verubecestat Trials

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BACKGROUND AND OBJECTIVES

- Dried blood spot (DBS) pharmacokinetic (PK) sampling was investigated as a potential alternative to plasma sampling for Phase 3 verubecestat (MK-8931) trials due to several potential advantages (ie, reduced cost, reduced clinical site burden, and lower blood volume requirements)
- Following initial evaluations from simultaneously sampled DBS and plasma concentrations in the verubecestat EPOCH trial (P017), prespecified criteria to proceed with DBS as the PK matrix were met. Plasma sampling was discontinued, and DBS was intended as the sole PK matrix for the remainder of the trial[1]
- Subsequently, a stability issue with DBS emerged, necessitating re-examination of the planned DBS-plasma bridging approach (**Figures 1** and **2**)
- A conversion algorithm for calculating plasma-equivalent concentrations from DBS concentrations, accounting for sample stability, was developed to enable verubecestat population PK (pop PK) analysis from pooled plasma and DBS samples

Figure 1. Linear Regression Analysis for Observed Verubecestat DBS vs Plasma Concentrations Indicates Potential DBS Stability Issue

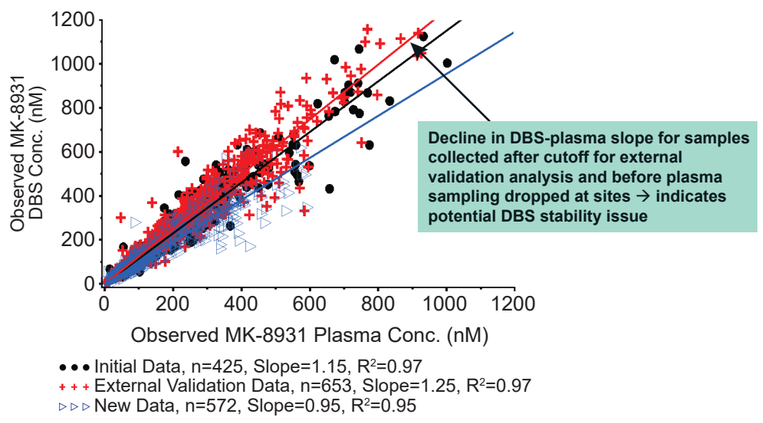
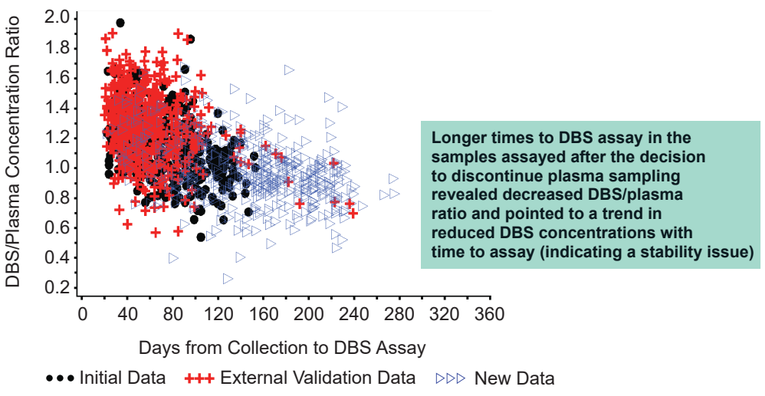


Figure 2. Decreasing Verubecestat DBS/Plasma Concentration Ratio With Time to DBS Assay Indicates Potential DBS Stability Issue



METHODS

- Verubecestat concentrations from available time-paired DBS and plasma samples were graphically explored, including assessing relationships with potential influencing factors:
  - **Time Factors:** Total time to DBS assay, time from collection at site to receipt at central lab, time stored at central lab, time from central lab shipment to assay
  - **Desiccant Factors:** Shipped with no desiccant, shipped with small desiccant, shipped with large desiccant included (with or without small desiccant)
  - **Procedure Factors:** Early shipping/handling procedures prior to identification of stability issue, interim procedures, final procedures
  - **Location Factors:** Central lab location (4 locations in use)
  - **Other Factors:** Patient hematocrit, dose, period, cohort
- Regression analyses were performed in NONMEM to establish the DBS/plasma-equivalent concentration algorithm
- Forward selection, along with standard goodness-of-fit criteria, were used to select the most appropriate factors for inclusion in the algorithm
- Population PK models were developed from both (1) plasma and plasma-equivalent concentrations from acceptable DBS samples and (2) plasma-only data and compared to help inform the sufficiency of the conversion algorithm

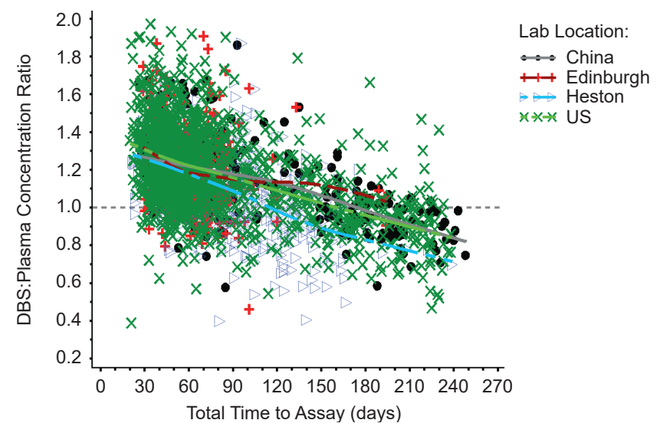
RESULTS

Graphical Analyses

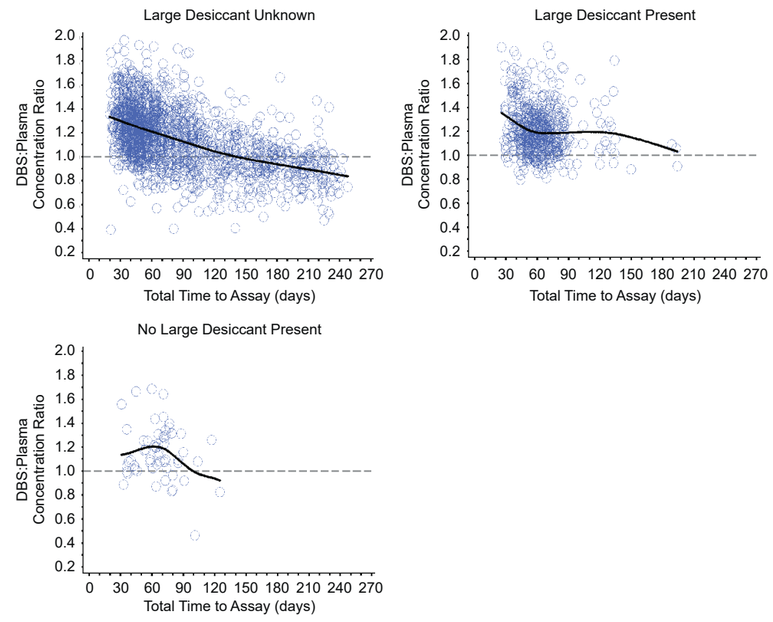
Graphical analyses indicated that time to DBS assay **(Figure 1)**, central lab location **(Figure 3a)**, presence of a central large desiccant **(Figure 3b)**, and hematocrit **(Figure 3c)** were potential influencing factors in the DBS-plasma relationship

Figure 3. Graphical Analysis of Potential Influencing Factors on Verubecestat DBS/Plasma Concentration Ratios

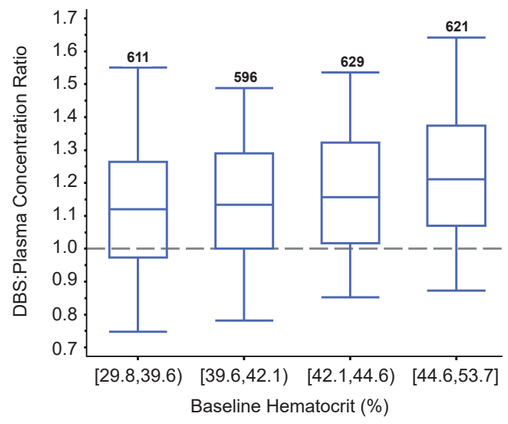
a) Central Lab Location



b) Presence of Large Desiccant During Shipment to Central Lab



c) Baseline Patient Hematocrit



DBS/Plasma-Equivalent Concentration Conversion Algorithm

- A conversion algorithm **(Equation 1)** was developed from 2,457 matched pairs of plasma and DBS concentrations in 1,028 patients

Equation 1. DBS/Plasma-Equivalent Verubecestat Concentration Conversion Algorithm

$$C_{plasma\text{-}equiv,ij} = (SC_{INT,ij} + SLP_i \times TIME_{TOT,i}) \times C_{DBS,ij}$$

$$SC_{INT,j} = 0.733 - 0.00799x(Hct_j - 42.25)$$

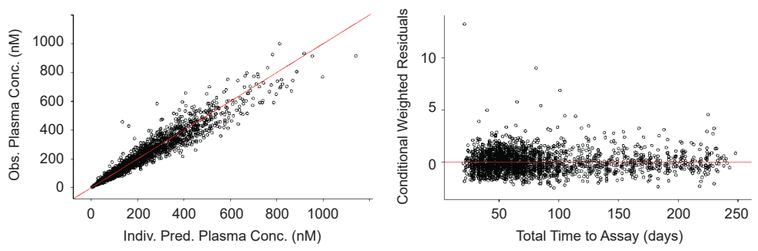
$$SLP_i = 0.00195 - (0.000382 \times LAB_{Ch,i}) + (0.000806 \times LAB_{HoE,i}) - 0.000722 \times DESICC_{LRG,i}$$

where, for the i^{th} DBS sample from the j^{th} patient:

- $C_{plasma\text{-}equiv,ij}$ = plasma-equivalent MK-8931 concentration (nM)
- $SC_{INT,j}$ = intercept representing the value of SC when $TIME_{TOT,i}$ = 0 days
- Hct_j = baseline hematocrit (%)
- SLP_i = slope (day^{-1})
- $LAB_{Ch,i}$ and LAB_{HoE} = indicator flags for central laboratory location of DBS sample storage
- $DESICC_{LRG,i}$ = indicator flag for presence of a large desiccant upon receipt at the central lab
- $TIME_{TOT,i}$ = total time from collection to assay (days)
- $C_{DBS,ij}$ = measured DBS MK-8931 concentration (nM)

- The conversion algorithm described decreasing DBS/plasma ratios with increasing time to assay, with varying rates of decline associated with sample handling/storage factors identified as significant predictors of DBS degradation (central lab location and presence of a large desiccant)
- Baseline hematocrit was also included as a predictor of the DBS-plasma relationship
- A 250-day time-to-assay limit was established for inclusion of DBS-derived concentrations in the population PK analysis based on available data range
- All model parameters were estimated with very good precision (%SEM values ranging from 1.55% to 33.5%)
- Goodness-of-fit plots showed a reasonable fit to the data **(Figure 4)**. Predicted plasma concentrations for 88% of samples were within 25% of observed plasma values

Figure 4. Goodness-of-Fit Plots



- The model predictions indicated no bias and reasonable precision. The mean % prediction error (%PE) and mean absolute value of % prediction error (|%PE|) were -0.1% and 13.5%, respectively

Population PK Models

- Parameter estimates from population PK models developed using (1) plasma and plasma-equivalent concentrations from acceptable DBS samples vs (2) plasma-only data were very similar, supporting sufficiency of the applied conversion algorithm (**Table 1**)

Table 1. Population PK Model Parameter Estimates

Parameter	Parameter Description	Plasma + DBS Model				Plasma-Only Model			
		Final Parameter Estimate		IIV or RV		Final Parameter Estimate		IIV or RV	
		Typical Value	% SEM	Magnitude	% SEM	Typical Value	% SEM	Magnitude	% SEM
Ka (hr^{-1})	First-order absorption rate constant	0.545	4.78	88.4% CV	14.2	0.518	5.48	78.9% CV	12
CL/F (L/hr)	Apparent clearance	19.3	2.14	22.5% CV	7.56	19.6	2.36	22.4% CV	10.9
CLAGE[1]	Effect of age on CL/F	0.0075	9.21			0.0068	11.2		
CLETH[2]	Effect of Japanese ethnicity on CL/F	1.04	2.28			1.09	3.17		
CLRENL[2]	Effect of severe renal impairment on CL/F	0.877	4.54			0.832	4.91		
CLSEX[2]	Effect of gender on CL/F	0.883	1.77			0.877	2.24		
CLWTKG[3]	Effect of body weight on CL/F	0.258	16.4			0.303	17.1		
CLAD[2]	Effect of Alzheimer's disease on CL/F	1.11	2.2			1.03	2.49		
Vc/F (L)	Apparent volume of the central compartment	385	3.53	33.1% CV	19.3	388	3.60	29.4% CV	18.5
VcAD[2]	Effect of Alzheimer's disease on Vc/F	1.54	3.62			1.42	4.20		
VcSEX[2]	Effect of gender on Vc/F	0.897	3.48			0.874	3.68		
VcWTKG[3]	Efect of body weight on Vc/F	0.763	10.4			0.715	11.1		
Vp/F (L)	Apparent volume of the peripheral compartment	151	8.40	NE	NA	148	8.87	NE	NA
Q/F (L/hr)	Apparent inter-compartmental clearance	9.90	18.4	NE	NA	9.46	19.6	NE	NA
Covariance (IIV in Ka, IIV in Vc/F)	—	0.1670	26.5	NA	NA	0.121	26.3	NA	NA
Covariance (IIV in CL/F, IIV in Vc/F)	—	0.0352	16.6			0.0333	17.4		
RV (Log Scale) for Phase 1 Data	Additive RV	0.137	6.91	0.370 SD	NA	0.137	6.91	0.370 SD	NA
RV (Log Scale) for P017 Data	Additive RV	0.169	5.16	0.411 SD		0.166	8.21	0.407 SD	

Plasma + DBS model based on data from 2,597 plasma and 3,558 plasma-equivalent concentrations from 1,465 P017 patients and 8,475 plasma concentrations from Ph 1/1b in 245 Ph 1 subjects and 25 Ph 1b patients.

[1]Covariate incorporated as a linear function; [2]covariate incorporated as a proportional shift; [3]covariate incorporated as a power function

Abbreviations: %CV, % coefficient of variation; %SEM, % standard error of the mean; IIV, interindividual variability; NA, not applicable; NE, not estimated; RV, residual variability; SD, standard deviation.

CONCLUSIONS

- This work describes the approach that was taken to adapt to DBS stability issues that emerged during the course of the EPOCH trial
- The developed conversion algorithm sufficiently described the DBS-plasma relationship, enabling DBS samples without corresponding plasma samples to be included in the pop PK model. Without these "rescued" samples, the # of samples available for analysis would have been decreased by 3,558 samples (58% of EPOCH samples) and the # of patients included would have been decreased by 404 patients (representing 28% of total EPOCH patients in the pop PK analysis)
- Novel sampling approaches such as DBS have the potential to decrease patient burden and provide augmented clinical trial datasets. They are a key component to enabling more patient-centric trials. However, unanticipated challenges can occur in moving from well-controlled early-phase to late-stage trials. It is imperative that we learn from these experiences and adapt as necessary to enable successful implementation of these approaches

Reference

1. Kothare PA, et al. *AAPS* J. 2016;18(2):519-527.

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