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RESEARCH PAPER

Development of a Level A *in Vitro-in Vivo* Correlation for Veliparib (ABT-888) Extended Release Tablet Formulation

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ABSTRACT

Purpose The aim of the current manuscript is to develop and validate a level A *in vitro-in vivo* correlation (IVIVC) for veliparib extended-release (ER) tablet formulations.

Methods The *in vitro* release profiles of veliparib formulations were determined using USP Dissolution Apparatus 2 with 900 mL of 0.1 N HCl at 75 rpm. In a clinical study, 24 subjects with solid tumors received one of the ER formulations (200 mg): fast (Formulation A), intermediate (Formulation B), and slow (Formulation C), and two 100 mg immediate release capsules (Formulation D). Blood samples were collected over a period of 48 h and analyzed using LCMS/MS. A linear correlation model was developed using fraction absorbed and fraction dissolved data from formulations A and B. Besides assessing internal predictability, external predictability was evaluated using formation C. Prediction errors were estimated for maximum observed plasma concentration (C_{max}) and area under the plasma-concentration time curve from zero to last measured time point (AUC_t) to determine the predictive ability of the correlation.

Results There was a significant linear relationship ($r^2 = 0.944$) between the fraction of drug absorbed and the fraction of drug dissolved. The prediction error using the internal validation for C_{max} and AUC_t were below 15% for the individual formulations and below 10% for the average. The prediction error in AUC_t and C_{max} for formulation C was 5% and 11%, respectively.

Conclusions A level A IVIVC for the veliparib ER tablet formulation was established. The IVIVC may allow the associated dissolution data to be used as a surrogate for bioavailability.

KEY WORDS dissolution · extended-release formulation · *in vitro/in vivo* correlations (IVIVC) · pharmacokinetics · veliparib

ABBREVIATIONS

AUC_{inf}	Area under the plasma-concentration time curve from zero to infinity
AUC_t	Area under the plasma-concentration time curve from zero to last measured time point
C_{max}	Maximum observed plasma concentration
ER	Extended-release
IVIVC	*In vitro in vivo* correlation
PARP	Poly (ADP-ribose) polymerase
PE	Prediction error
T_{max}	Time to maximum observed plasma concentration
$T_{1/2}$	Terminal half-life

INTRODUCTION

Veliparib is a potent orally bioavailable inhibitor of Poly (ADP-ribose) polymerase (PARP) 1 and 2 [1, 2]. PARP-1 and 2 are nuclear enzymes that play key roles in the modulation of deoxyribonucleic acid (DNA) repair [3]. Veliparib has demonstrated anti-tumor activity in patients with ovarian and breast cancers as a monotherapy treatment [1]. Veliparib was shown to potentiate the effects of DNA-damaging agents including, temozolomide, platinum compounds, cyclophosphamide, and ionizing radiation in preclinical models [2]. Veliparib is currently being evaluated in several Phase 3 clinical trials in various

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solid tumors including non-small cell lung cancer, breast cancer, ovarian cancer, and glioblastoma multiforme [1].

Veliparib is a weak BCS class I base. Veliparib is supplied as conventional immediate-release (IR) capsules and administered twice daily to patients in clinical studies. The pharmacokinetic data from cancer patients showed that veliparib is rapidly absorbed with peak concentrations occurring at approximately 1 to 2 h after oral dosing, follows linear pharmacokinetics with a half-life of approximately 6 h, and is eliminated primarily in the urine as unchanged parent drug [1, 4]. In clinical studies with veliparib in cancer patients, nausea and vomiting were the commonly observed adverse events related to study [5]. It was hypothesized that veliparib maximum observed plasma concentration (C_{max}) may play a major role in causing nausea and vomiting. Thus, developing an ER formulation that exhibits decreased veliparib C_{max} while maintaining the area under the plasma concentration-time curve (AUC) may mitigate the gastrointestinal adverse events. Furthermore, given the relatively short half-life of veliparib, an ER formulation could also decrease the dosing frequency.

Three (fast-, intermediate-, and slow-releasing) veliparib ER formulations were developed using hydroxypropyl methyl cellulose (HPMC) as a release controlling polymer. The pharmacokinetics and relative bioavailability of veliparib ER formulations were evaluated in a clinical study in subjects with advanced solid tumors (NCT01853306). Establishing a correlation between *in vivo* plasma concentration-time profiles and the *in vitro* dissolution profiles of ER formulations is of great interest to pharmaceutical industry to decrease the time and cost during drug development [6]. An *in vitro in vivo* correlation (IVIVC) model establishes a meaningful relationship between the *in vitro* release and *in vivo* performance of the dosage form. A level A correlation represents a point-to-point relationship between *in vitro* dissolution and *in vivo* absorption and is considered as the most useful [7]. A validated IVIVC may serve as a surrogate for human bioequivalence studies, justify the dissolution specifications, and select appropriate formulations [7]. The current manuscript describes the development and validation of a level A IVIVC for veliparib ER formulations.

MATERIALS AND METHODS

Formulations

Extended release formulations of veliparib were developed using varying levels and viscosities of the release controlling polymer, hydroxypropyl methyl cellulose (HPMC). The formulations were designed to release veliparib at three different rates which were referred to as "Fast (Formulation A)", "Intermediate (Formulation B)", and "Slow (Formulation C)". All the formulations contained 200 mg veliparib and had same total tablet weight.

In Vitro Dissolution Data Analysis

The dissolution profiles of 6 individual dosage units from each ER tablet were determined using USP Dissolution Apparatus 2 with 900 mL of 0.1 N HCl at a paddle speed of 75 rpm using automatic sampling. The samples were collected at different time points up to 16 h and were analyzed using HPLC. The dissolution profiles for each formulation were determined by plotting cumulative fraction of veliparib released over several time points up to 16 h.

In Vivo Study

An open-label 3-period crossover study was conducted to evaluate the relative oral bioavailability and food effect of the three ER tablet formulations of veliparib. The study was conducted in accordance with Good Clinical Practice guidelines and ethical principles that have their origin in the Declaration of Helsinki. Informed consent was obtained from all individual subjects included in the study. The detailed study schematic is shown in **supplemental Table I**. The reference formulation used was a 100 mg strength IR veliparib capsule. Each ER formulation was studied in a group of eight subjects with solid tumors. Subjects received a single veliparib ER tablet (200 mg) orally in Periods 1 and 2 under fasting (after a 10-h fast) and fed (after a high-fat breakfast) conditions,

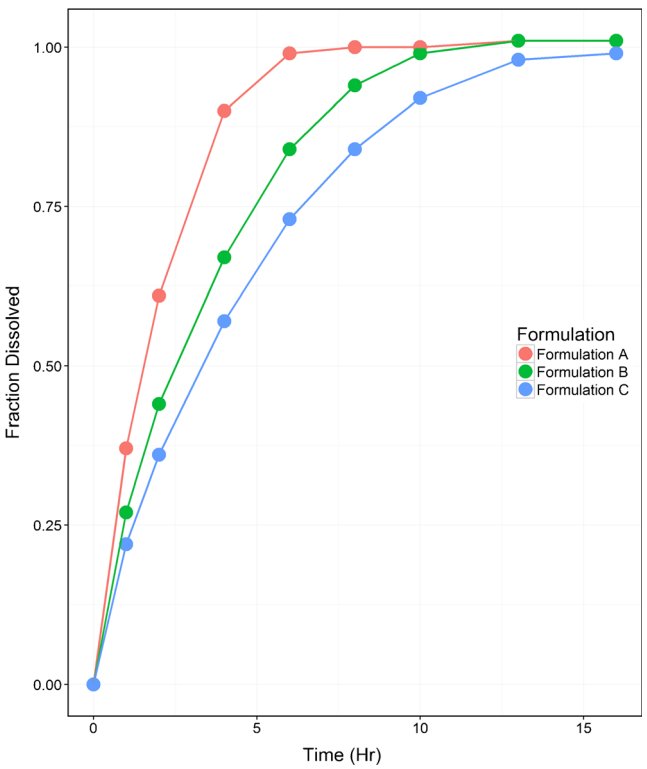

Fig. 1 Cumulative fraction dissolved *versus* time profiles for fast- (formulation A), intermediate- (Formulation B), and slow-release (Formulation C) veliparib extended release tablet formulations.

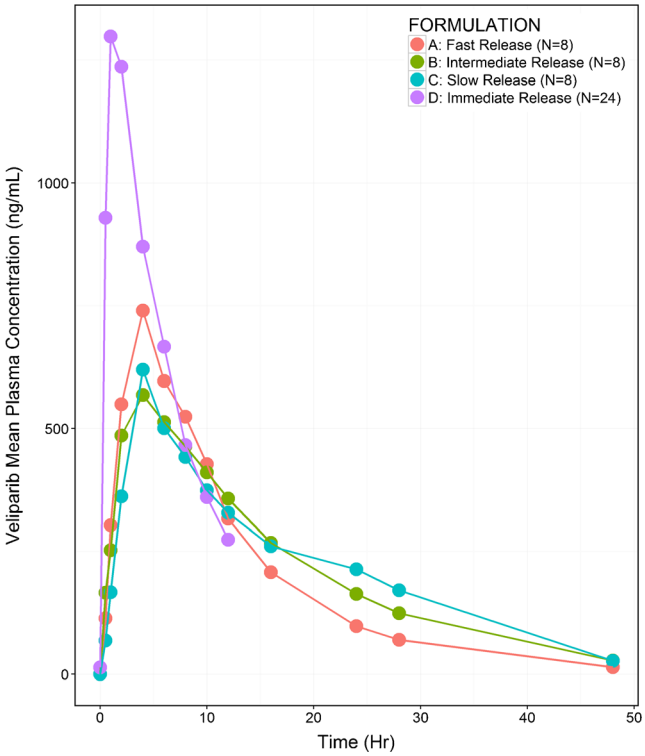

Fig. 2 Mean veliparib plasma concentration-time profiles for veliparib extended release tablets and immediate release capsule formulations. (Formulation A: Fast release; Formulation B: Intermediate release; Formulation C: Slow release).

respectively. Subjects then received two 100 mg IR capsules in Period 3 under fasting condition. A washout interval of approximately 48 h separated the doses in the three study periods. Blood samples for the determination of veliparib concentrations were obtained at multiple time points from predose (0-h) to 48 h post dosing. The plasma veliparib concentrations were determined using liquid chromatography with tandem mass spectrometry. The lower limit of quantification (LLOQ) was 1 ng/mL. The assay was linear over a range of 1 ng/mL to 543 ng/mL. The accuracy and precision was <15% for quality controls and ≤20% for the LLOQ.

Pharmacokinetic Parameters

The concentration-time data were analyzed using a non-compartmental approach. The maximum observed plasma veliparib concentration (C_{max}) and time to C_{max} (t_{max}) values were directly determined from plasma concentration-time data of each subject. The apparent terminal phase elimination rate constant was estimated from the slope of the least squares linear regression of the logarithms of the plasma concentration *versus* time data from the terminal log-linear phase of the profile. The area under the plasma concentration-time curve from zero to last measured time point (AUC_t) and area under the plasma concentration-time curve from zero to infinity (AUC_{inf}) was calculated using linear trapezoidal/linear interpolation algorithm.

In Vitro – in Vivo Correlation

The phoenix WinNonlin® IVIVC Tool kit, version 6.4 (Pharsight, CA, USA) was used to perform the analyses. Due to the similar C_{max} and AUC between Formulations B and C (both <10% difference), only Formulations A and B were used to develop a point-to-point relationship between *in vitro* dissolution and *in vivo* input rate (a level A correlation). Mean *in vitro* dissolution and individual concentration-time data from *in vivo* study Periods 1 and 3 (fasting condition) were used to build a correlation. The IVIVC model development consisted of the following steps: calculation of cumulative *in vitro* dissolution rate, calculation of cumulative *in vivo* absorption rate from the concentration-time data by numerical deconvolution using

Table I Geometric Mean (%CV) Veliparib Pharmacokinetic Parameters Following Oral Administration of Veliparib Extended Release Tablet and Immediate Release Capsule Formulations

PK parameter[a]	Formulation A ($N = 8$)	Formulation B ($N = 8$)	Formulation C ($N = 8$)	Formulation D ($N = 24$)
T_{max} (h)[b]	4.0 (4.0–6.0)	4.0 (2.0–10.0)	4.0 (2.0–4.0)	1.5 (0.5–4.0)
C_{max} (ng/mL)	705 (42)	623 (25)	615 (23)	1380 (27)
$T_{1/2}$ (h)[c]	7.4 ± 1.8	8.6 ± 1.7	8.2 ± 2.9	4.6 ± 1.5
AUC_t (μg*hr./mL)	9.00 (34)	9.99 (27)	10.1 (30)	8.05 (22)
AUC_{inf} (μg*hr./mL)	9.20 (33)	10.3 (29)	11.1 (28)	10.1 (29)

[a] Values represent Geometric mean (% CV)

[b] Median (range)

[c] Harmonic mean and pseudo-standard deviation

Formulation A: Fast release ER tablet;

Formulation B: Intermediate release ER tablet;

Formulation C: Slow release ER tablet;

Formulation D: Immediate release capsule

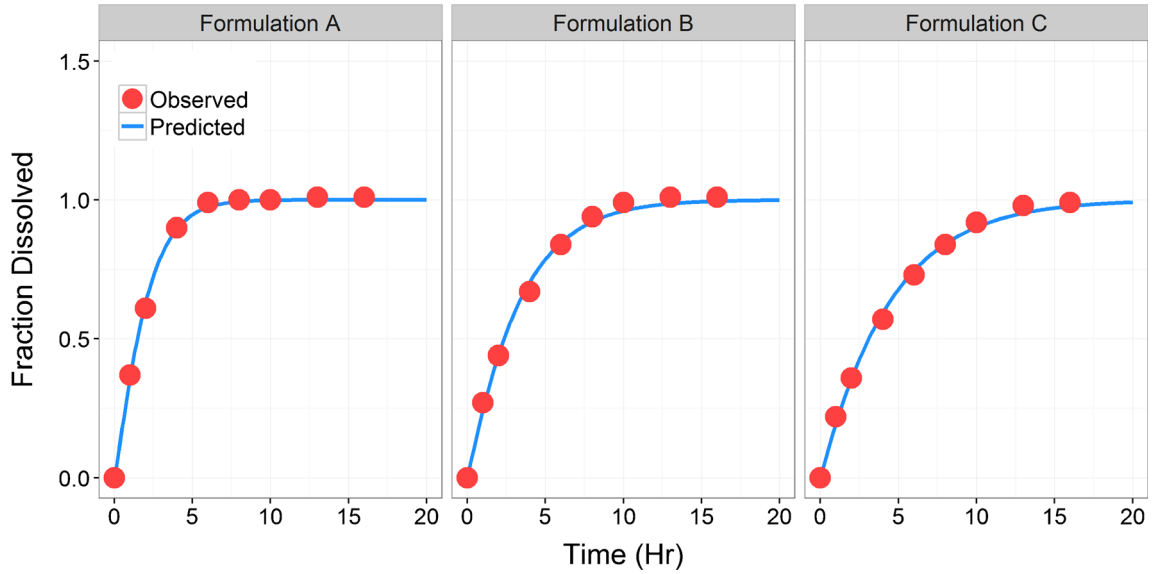

Fig. 3 Comparison of observed *versus* model predicted fraction dissolved for veliparib extended release formulations A (Fast), B (Intermediate), and C (Slow).

the reference IR formulation, and building the relationship between *in vivo* absorption and *in vitro* dissolution.

The following Weibull equation was used to fit the *in vitro* dissolution data.

$$y(t) = F_{inf}\left(1-\exp\left[-\left(\frac{t}{MDT}\right)^{b}\right]\right)$$

where, F_{inf} is the fraction released at time infinity, MDT is the mean dissolution time, and b is a slope factor.

The unit impulse rate was estimated using the reference IR formulation and the input rate for ER formulations was assessed using the numerical deconvolution. A level A correlation was established using the following linear correlation model:

$$F_{abs} = AbsScale \times Diss\,(T_{scale} \times T_{vivo})$$

where, F_{abs} is fraction absorbed, AbsScale is a correlation parameter, Diss is *in vitro* dissolution, T_{scale} is time scaling factor, and T_{vivo} is *in vivo* time.

The predictability of the IVIVIC model was evaluated by internal validation using formulations A and B, and by external validation using formulation C. Further, a model with all the three ER formulations was also evaluated separately. The *in vivo* concentration-time profiles and pharmacokinetic parameters (C_{max} and AUC_t) were predicted using *in vitro* dissolution data based on the correlation model. The predicted pharmacokinetic parameters (pred) were compared with observed values (obs) and prediction errors (% PE) were estimated using the following formula:

$$\%PE = \left[\frac{(obs-\text{pred})}{obs}\right] \times 100$$

Per FDA guidance, a % PE of 15% or less for individual formulation and 10% or less for the average establishes the internal predictability of the IVIVC. A % PE of 10% or less for C_{max} and AUC establishes the external predictability of an IVIVC [7].

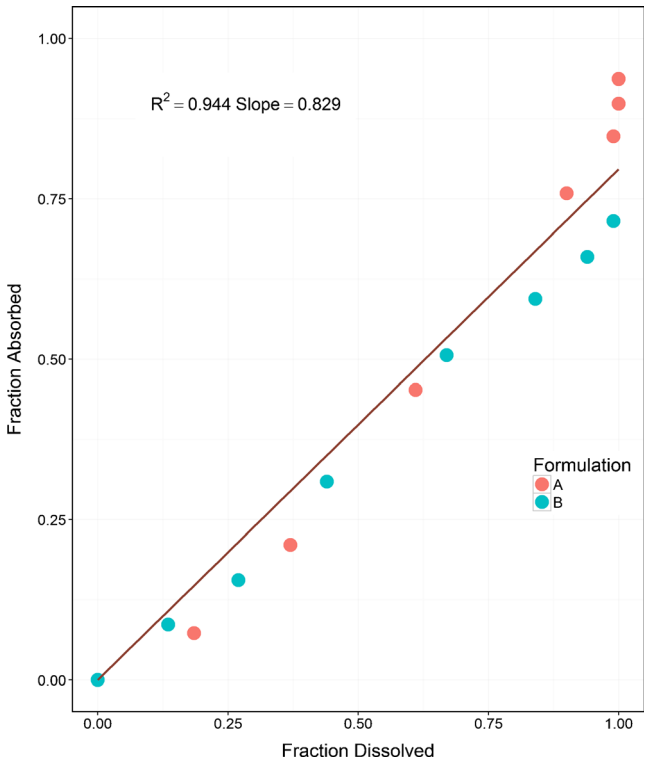

Fig. 4 Correlation between the observed fraction absorbed and the fraction dissolved for veliparib extended release formulations B (Intermediate) and C (Slow).

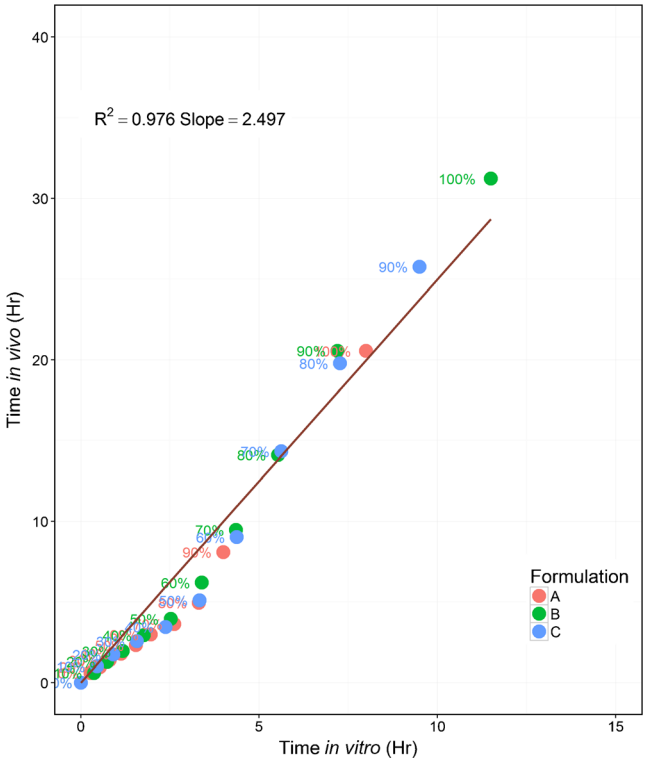

Fig. 5 Levy plot showing *in vitro* dissolution time and *in vivo* absorption time for a given percentage for the three extended release formulations of veliparib.

RESULTS

In Vitro Dissolution Study

The mean *in vitro* release profiles for the three veliparib ER formulations are shown in Fig. 1. The coefficient of variation at each time point for each dissolution profile was less than 10%. Eighty percent of drug was released at approximately 4, 6, and 8 h for formulations A, B, and C, respectively. A Weibull function with uniform weighting well described each *in vitro* dissolution profile.

In Vivo Study

The mean plasma concentration-time profiles from the *in vivo* study for the ER formulations A, B, C, and the IR formulation D are presented in Fig. 2**.** The pharmacokinetic parameters are shown in Table I. The terminal half-life of veliparib with ER formulation was approximately 2-fold higher as compared to that of IR formulation. The median T_{max} was 4.0 h for all ER formulations A, B, and C as compared to 1.5 h for formulation D. The C_{max} was reduced by approximately 50% with the ER formulations compared to the IR formulation D. Among the ER formulations, C_{max} was the highest for Formulation A and the lowest for Formulation C indicating that the *in vivo* profiles follow the rank order of the *in vitro* dissolution profiles in terms of drug release pattern. The AUC_{inf} was similar across the ER release formulations and was comparable to that of the IR formulation.

Final IVIVC Model

The IVIVC model developed using formulation A and B is described below.

$$F_{abs} = 0.990 \times Diss\,(0.537 \times T_{vivo})$$

The observed and the Weibull predicted fraction dissolved are presented in Fig. 3.There was a good correlation between fraction of drug absorbed *in vivo* and the fraction of drug dissolved *in vitro* ($r^2 = 0.944$) and between the *in vitro* dissolution time and *in vivo* absorption time ($r^2 = 0.98$) for the ER formulations (Figs. 4 and 5).

Internal and External Validation:

The developed correlation model was used to predict the plasma concentrations for formulations A and B (internal validation) and formulation C (external validation). The prediction error for both C_{max} and AUC_t was less than 15% for the individual formulations and less than 10% for the average using the internal validation (Table II). The prediction error for AUC_t using the external validation for formulation C was less than 10% meeting the FDA criteria; however, for C_{max} the prediction error was 11% which was slightly above the criteria of 10% (Table II). As a separate analysis, a model with all three formulations was also evaluated and the prediction error for both C_{max} and AUC_t was less than 15% for the

Table II Summary of Internal and External Validation Parameters for Veliparib Extended Release Formulations

Model description	Formulation	% Prediction Error			
		Internal validation		External validation	
		AUC_t	C_{max}	AUC_t	C_{max}
A, B internal and C as external	A	0.175	9.14		
	B	4.36	1.94		
	C			4.94	11.4
	Average	2.27	5.54		

individual formulations and less than 10% for the average using the internal validation (**supplemental Table II**).

DISCUSSION

Veliparib is an orally bioavailable small molecule inhibitor of PARP-1 and PARP-2 enzymes. Veliparib is currently being evaluated in various Phase II and Phase III clinical trials in cancer patients [1]. The recommended Phase 2 dose of veliparib as monotherapy is 400 mg BID [8]. In veliparib clinical trials with cancer patients, nausea and vomiting were most commonly observed [5] and it was hypothesized that veliparib C_{max} may play a role in it. An ER formulation may decrease the C_{max} while maintaining the AUC which in turn may help mitigate nausea and vomiting. A series of ER formulations of veliparib were developed and the PK and bioavailability were evaluated as a part of clinical study in cancer patients (NCT01853306). The purpose of the current manuscript was to develop an IVIVC for veliparib ER formulations. The analyses suggested that a level A IVIVC is feasible with the available *in vitro* dissolution data and *in vivo* pharmacokinetic data as the prediction errors from the developed model were within the acceptable regulatory limits [7].

Veliparib is a BCS Class 1 compound with high solubility and high permeability. These properties, along with a relatively short plasma half-life, make veliparib a suitable candidate for developing an ER formulation and possibly a good candidate for the establishment of IVIVC given that the release from ER formulations is maintained [9]. Three veliparib ER formulations with fast, intermediate, and slow release were developed. Veliparib is the first PARP inhibitor with an ER formulation being tested in clinical trials. The *in vivo* profiles showed that C_{max} was highest for formulation A and lowest for formulation C, which confirmed the *in vivo* absorption of veliparib from the ER formulation in the GI tract is controlled by its release from the formulation. The ER formulations had prolonged half-life, lower C_{max}, and maintained a similar AUC compared to those of the IR formulation.

The *in vitro* dissolution data were fitted using the Hill, Weibull, Double Weibull, and Makoid-Banakar models with uniform weighting. Double Weibull failed to fit the model. Based on the parameters for model selection (goodness of fit, AIC) the Weibull model appeared to best describe the *in vitro* dissolution data (Fig. 3). Several correlation models were explored to describe the relationship between the fraction of drug absorbed *in vivo* and the *in vitro* fraction of drug dissolved and the model with time scale described the data well. Introduction of other models, which include parameters such as a time shifting factor or an absorption baseline correction factor, did not improve the correlation.

The predictive ability of the developed IVIVC was assessed by comparing the % PE for C_{max} and AUC_t both by internal and external validation. The individual % PE was less than 15% and the average was less than 10% for both C_{max} and AUC_t establishing the internal predictability. The prediction error for AUC_t using the external validation for formulation C was less than 10% meeting the FDA criteria; however, for C_{max} the prediction error was 11% which was slightly above the criteria of 10%.

In conclusion, ER formulations of veliparib showed prolonged half-life, lower C_{max}, and a similar AUC compared to the current IR formulation. A level A IVIVC was developed for veliparib ER tablets and validated using the internal and external prediction. The established IVIVC will facilitate future development of the veliparib ER formulations.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of Interest This study was sponsored by AbbVie Inc. AbbVie Inc. contributed to the study design; research; data interpretation; and writing, review and approval of the manuscript for publication. Rajendar K Mittapalli, Silpa Nuthalapati, Alyssa Delke DeBord and Hao Xiong are employees of AbbVie Inc. and may hold AbbVie stocks or options.

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