

Pharmacokinetics and safety of Padsevonil in healthy Chinese subjects and comparison of two sampling methods for Padsevonil quantification

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Abstract. – OBJECTIVE: Padsevonil (PSL) is a novel antiepileptic drug candidate that inhibits seizure activity in both presynaptic and postsynaptic ways. The pharmacokinetic (PK) profiles and volumetric absorptive microsampling (VAMS) application of PSL in the Chinese population are limited. The objectives of this study were to evaluate the PK profile of PSL and its 2 metabolites, the safety of PSL, and compare the PK profile of PSL from samples collected using the VAMS technique with that of conventional venous samples in healthy Chinese subjects.

SUBJECTS AND METHODS: In this randomized, double-blind, placebo-controlled single-dose study, the participants received either 200 mg PSL or placebo. Blood samples for the PK variables were collected using both the traditional venous method and the VAMS Mitra® technique at the scheduled time points. The PK parameters of PSL and 2 metabolites were calculated, and the concentration agreement of VAMS and venous samples were also evaluated.

RESULTS: A total of 14 subjects were enrolled. The concentration-time profile of PSL showed rapid absorption with a median t_{max} of 1.25 h (range: 0.5 to 3.0), followed by an apparent biphasic disposition. For PSL, the geometric means of $AUC_{(0-t)}$, AUC , C_{max} , and $t_{1/2}$ were 6,573 h*ng/mL, 6,588 h*ng/mL, 1,387 ng/mL, and 5.275 h, respectively. The geometric mean body weight-normalized $AUC_{(0-t)}$, AUC , and C_{max} were 5,712 h*ng/mL, 5,725 h*ng/mL, and 1,205 ng/mL, respectively. The $AUC_{(0-t)}$, AUC , C_{max} of PSL and metabolites in VAMS-dried blood were all lower than those in plasma. The Passing-Bablok regression showed that the PSL and metabolite concentrations obtained by VAMS analysis were comparable to those obtained by plasma at some time points. The most frequently reported treatment-emergent adverse events (TEAEs) were somnolence and dizziness. There were no serious TEAEs, severe TEAEs, discontinuations due to TEAEs, or deaths reported during this study. No clinically significant laboratory, vital signs, electrocardiograph (ECG), or physical examination results were reported.

CONCLUSIONS: PSL has a favorable PK profile after single-dose oral administration and good safety properties in healthy Chinese volunteers. The regression analysis results of VAMS and plasma indicated that the application of VAMS for therapeutic drug monitoring in novel antiepileptic drug development is promising and needs further validation.

Key Words:

Padsevonil, Epilepsy, Pharmacokinetics, VAMS.

Introduction

Epilepsy is the second most common reported neurological disorder worldwide, characterized by a predisposition to generate epileptic seizures¹. The prevalence of epilepsy is six per 1,000 people and strikes people of all ages^{2,3}. Generally, antiepileptic drug (AED) therapy is effective in seizures control in most cases, studies⁴ have estimated that 60-70% of patients with epilepsy respond. However, there are still 30-40% of patients resistant to treatment with AEDs and the need to develop novel AEDs for better disease control and drug-resistant epilepsy is urgent.

Padsevonil (PSL) is a novel chemical entity, it was designed to interact with presynaptic and post synaptic targets: synaptic vesicle protein (SV) 2 and postsynaptic central benzodiazepine receptor (cBZR) sites on the gamma-aminobutyric acid A ($GABA_A$) receptor⁵⁻⁷. A broad range of rodent seizure and epilepsy models have demonstrated⁵ the superior efficacy of PSL. Furthermore, PSL was also confirmed the maintenance of seizure control in drugresistant patient population in a phase II proof-of-concept study⁸.

The initial PK characteristics of PSL were explored in two phase I ascending dose trials⁹ in healthy volunteers, in which PSL demonstrated high inter-subject variability and a median terminal half-life of ~6-7 hours. PSL was generally well tolerated at doses up to 400 mg b.i.d. The central nervous system adverse events (AEs) include fatigue, somnolence, dizziness, and disturbance in attention which are transient and self-limiting⁹. Although the PK characteristics of PSL have been investigated in several clinical trials⁹, no data in Chinese population was reported so far. Thus, we here firstly reported the data of this phase I study in Chinese population.

Due to various PK profiles, individual differences, and narrow therapeutic indices of AEDs, the clinical application of AEDs usually needs therapeutic drug monitoring (TDM). TDM can provide drug concentrations so as to offer an approach to improve epilepsy care. It is applied in clinical practice and is typically based on the analysis of plasma samples^{10,11}. However, the application of traditional TDM method was limited because of the technical problems and cost considerations, thus a convenient and minimal invasive method is necessary for those patients^{12,13}. The development of dried blood spot (DBS) method which require only easy-handled finger prick of a few drops of blood have been used in TDM of AEDs¹⁴⁻¹⁶. Volumetric absorptive microsampling (VAMS) is a novel approach which collect a dried blood sample for quantitative bioanalysis and was reported¹⁷ to overcome the area bias and homogeneity issues associated with conventional DBS. VAMS has been validated and proved^{18,19} to be a reliable extraction and analysis method in plenty of commonly used psychiatric drugs. Thus, in this phase I clinical trial, we detected the concentrations of PSL and metabolites with both VAMS finger prick sampling and conventional venous sampling.

The present study was designed to evaluate the PK and safety of PSL in healthy Chinese subjects and further to compare the PK data of PSL and metabolites between VAMS and conventional venous blood.

Subjects and Methods

Study Design

This was a phase I, single-center, randomized, double-blind, placebo-controlled, and single-dose study conducted in healthy Chinese volunteers. A

total of 14 subjects were planned to enroll and on Day 1, after randomization, they received either PSL 200 mg (12 subjects) or placebo (2 subjects) in the morning which required at least a 4-hour fast and followed by at least a 2-hour fast. The primary objective was to evaluate the PK profile of PSL and its 2 metabolites [desmethyl metabolite (UCB1431322-000) and carboxylic acid metabolite (UCB1447499-000)] following a single oral dose administration. The secondary objective was to evaluate the safety of PSL following a single oral dose administration. The exploratory objective of this study was to compare the PK profile of PSL and metabolite from samples collected using the VAMS technique with that of conventional venous sampling.

The study was conducted in compliance with the principles of Good Clinical Practice and the Declaration of Helsinki. The protocols and the informed consent documents were reviewed and approved by the Ethical Committee of West China Hospital of Sichuan University. All subjects signed informed consent form (ICF) before entering the study. This study was registered at <http://www.chictr.org.cn>, (ChiCTR2000041476).

Study Population

Healthy male and female Chinese subjects aged 18-45 years old and with a body mass index (BMI) within the range of 18 to 28.0 kg/m² were eligible to recruit. Subjects with a history or a current clinically significant psychiatric disorder requiring or having required hospitalization or medication within the previous 5 years were excluded. Other exclusion criteria included: subjects with any clinically significant disorders, a history of excessive alcohol consumption and smoking, or with abnormal heart rate, blood pressure, and electrocardiograph (ECG) abnormalities as described in the protocol or had used any medication treatment 14 days prior to screening or randomization.

Safety Evaluation

Safety was evaluated in terms of TEAEs and all the TEAEs were monitored and recorded during the entire study, including treatment and safety follow-up period. The baseline and changes in laboratory variables (haematology, clinical chemistry, and urinalysis), vital signs (pulse rate, respiratory rate, systolic and diastolic blood pressure), 12-lead ECG variables [RR interval, PR interval, QRS interval, QT, QT corrected by Bazett's formula, and QTc corrected by Fridericia's

formula (QTcF)], and physical examination were all recorded and evaluated according to protocol.

Physical examination was assessed at screening, D₋₁, and D₇. Vital signs were evaluated at screening, D₋₁, D₁, D₂, D₃, and D₇. Triplicate 12-lead ECG were performed at screening, D₋₁, D₁, D₃, and D₇. Clinical laboratory tests were evaluated at screening, D₋₁, D₃, and D₇.

All TEAEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA[®]) and characterized as pretreatment and treatment-emergent according to the intake of PSL. The occurrence and incidence of TEAEs were summarized by MedDRA system organ class and preferred term and by treatment. The occurrence and incidence of TEAEs were summarized by intensity and relationship to PSL. Immediate and permanent discontinuation of PSL is required for subjects with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $\geq 3\times$ upper limit of normal.

Volumetric Absorptive Microsampling

The VAMS samplers were supplied by Phenomenex (Torrance, CA, USA marketed as Mitra), blood samples were taken at the scheduled time points both by venous and VAMS Mitra samplers. The VAMS Mitra sampler absorbs a fixed volume of blood (10 μ L) in 2 to 4 seconds, and all the procedures were performed according to manufacturer's instruction¹⁷.

PK Assessment

Blood samples for the PK variables were collected using both the traditional venous method [for PSL and both metabolites (UCB1431322-000 and UCB1447499-000)] and the VAMS Mitra samplers [for PSL and its desmethyl metabolite (UCB1431322-000) only] at the scheduled time points (pre-dose and 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, and 48 hours post-dose).

The plasma concentrations of PSL and both metabolites (UCB1431322-000 and UCB1447499-000) were determined by a valid Liquid Chromatography-tandem Mass Spectrometry method (LC-MS/MS) developed by Frontage Laboratories Co., Ltd (Shanghai, China).

The concentrations of PSL and UCB1431322-000 in VAMS Mitra samplers were also determined by LC-MS/MS developed by Frontage Laboratories Co., Ltd. (Shanghai, China), using UCB1702046 and UCB1434684-000 as internal standards with calibration ranges of 2.0-120.0 ng/mL for PSL and UCB1431322-000.

The primary PK variables include the following: AUC (area under the plasma concentration-time curve from time zero to infinity, calculated as $AUC = AUC_{(0-t)} \pm C_{last}/\lambda_z$, where C_{last} is the last observed quantifiable plasma concentration and λ_z is the apparent terminal elimination rate constant), $AUC_{(0-t)}$ (area under the plasma concentration-time curve from time zero to the time of last detectable concentration, as determined using the linear trapezoidal rule), C_{max} (maximum observed plasma concentration), t_{max} (time of maximum concentration), CL/F [apparent total body clearance, calculated as dose/AUC (assessed for PSL only)], $t_{1/2}$ [apparent terminal half-life, reported in hours, as determined *via* simple linear regression (slope= $-\lambda_z$) of natural log (ln) concentration *vs.* time for data points in the terminal phase of the concentration-time curve; $t_{1/2}$ is calculated as $\ln 2/\lambda_z$], and VZ/F [apparent volume of distribution (assessed for PSL only)]. The other PK variables include the following: $AUC_{(0-t)}$ normalized by body weight (BW) ($AUC_{(0-t)}/BW$), AUC/BW , C_{max}/BW . PK assay of PSL and metabolites were performed using both conventional plasma as well as VAMS Mitra techniques to compare the difference.

Statistical Analysis

All analyses were performed using SAS Version 9.3 (SAS Institute, Cary, NC, USA). For continuous variables, summary statistics include number of subjects, mean, median, standard deviation, minimum, and maximum. Categorical endpoints are summarized using number of subjects, frequency, and percentages.

The PK noncompartmental analysis was performed using Phoenix WinNonlin version 8.2 (Certara Inc., Princeton, NJ, USA). The linear trapezoidal method was used to calculate the AUC parameters. Conventional venous and VAMS Mitra analysis was performed by non-compartmental analysis in Phoenix WinNonlin 8.2 on the PK-PPS. Passing-Bablok regression analysis was performed to investigate linear relationship between the VAMS and venous plasma sampling. A Bland-Altman comparison analysis was used to calculate the agreement between concentrations of these two methods^{20,21}.

The concentrations and PK parameters of PSL and metabolites were summarized with descriptive tables. Individual concentration-time profiles were displayed graphically on a linear-linear and semi-logarithmic scale. Geometric mean plasma concentrations-time curves including 95% confidence intervals were also displayed.

Laboratory variables and changes from baseline (at screening), vital sign variables, 12-lead ECG, and physical examination abnormalities were summarized by descriptive statistics.

Results

Study Population

A total of 14 (9 male and 5 female) subjects were enrolled in this study. The mean and median ages at screening were 26.3 years and 25.0 years, respectively, with a range of 20 to 36 years. The mean BW, height, and BMI of all study participants were 60.11 kg, 165.82 cm, and 21.76 kg/m², respectively. All 14 subjects (100%) were from China and of Asian ethnicity.

PK Characteristics of Venous Blood

Single-dose administration of PSL at 200 mg was rapidly absorbed with a median t_{\max} of 1.25 h (range: 0.5 to 3), followed by an apparent biphasic disposition. Overall, t_{\max} was shorter for the metabolites UCB1431322-000 and UCB1447499-000 than for PSL, with medians of 1.75 h and 3.0 h, respectively. The geometric mean C_{\max} values for

PSL, metabolite UCB1431322-000, and metabolite UCB1447499-000 were 1,387 ng/mL, 529.5 ng/mL, and 151.4 ng/mL, respectively, and the geometric mean $AUC_{(0-t)}$ values were 6,573 h*ng/mL, 4,023 h*ng/mL, and 1,234 h*ng/mL, respectively.

Exposure ($AUC_{(0-t)}$) was generally lower than PSL by approximately 40% for UCB1431322-000 and approximately 80% for UCB1447499-000 over the sampling period of 48 h. The geometric mean $t_{1/2}$ values for PSL and metabolite UCB1447499-000 were 5.275 h and 9.08 h, respectively; a geometric mean $t_{1/2}$ was not calculated for metabolite UCB1431322-000 since the data were available for at least two-thirds of study participants. All PK data are summarized and presented in Table I.

Following single-dose administration of PSL, the overall exposure using BW normalized PK parameters was higher for PSL than the metabolites assessed. The geometric mean BW normalized C_{\max} values for PSL, metabolite UCB1431322-000, and metabolite UCB1447499-000 were 1,205 ng/mL, 460.1 ng/mL, and 131.6 ng/mL, respectively, and the geometric mean BW normalized $AUC_{(0-t)}$ values were 5,712 h*ng/mL, 3,496 h*ng/mL, and 1,072 h*ng/mL, respectively (Table II).

Table I. Venous plasma PK parameters of PSL and metabolites UCB1431322-000 and UCB1447499 000.

Parameter	Statistic	PSL N=12	Metabolite UCB1431322-000 N=12	Metabolite UCB1447499-000 N=12
C_{\max} (ng/mL)	GeoMean (GeoCV%) (95% CI)	1387 (33.7) (1,126, 1,708)	529.5 (39.7) (415.2, 675.2)	151.4 (53.6) (110.0, 208.4)
$AUC_{(0-t)}$ (h*ng/mL)	GeoMean (GeoCV%) (95% CI)	6,573 (34.2) (5,322, 8,118)	4,023 (22.4) (3,495, 4,632)	1,234 (45.4) (937.2, 1,625)
AUC (h*ng/mL)	GeoMean (GeoCV%) (95% CI)	6,588 (34.3) (5,330, 8,142)	NC (NC, NC)	1,222 (51.9) (812.1, 1,838)
$AUC_{(0-12)}$ (h*ng/mL)	GeoMean (GeoCV%) (95% CI)	5,643 (29.2) (4,706, 6,768)	2,437 (21.9) (2,125, 2,796)	848.7 (41.9) (657.2, 1,096)
t_{\max} (h)	Median (min, max)	1.25 (0.5, 3.0)	1.75 (0.5, 3.0)	3.0 (1.25, 6.0)
$t_{1/2}$ (h)	GeoMean (GeoCV%) (95% CI)	5.275 (14.6) (4.809, 5.786)	NC (NC, NC)	9.080 (20.2) (7.681, 10.74)
CL/F (L/h)	GeoMean (GeoCV%) (95% CI)	30.36 (34.3) (24.56, 37.52)	--	--
V_z/F (L)	GeoMean (GeoCV%) (95% CI)	231.0 (33.9) (187.4, 284.9)	--	--

CV=coefficient of variation; Geo=geometric; max=maximum; min=minimum; NC=not calculated.

Table II. Body-weight-normalized venous plasma PK parameters of PSL and metabolites UCB1431322-000 and UCB1447499-000.

Parameter	Statistic	PSL N=12	Metabolite UCB1431322-000 N=12	Metabolite UCB1447499-000 N=12
C_{\max} /BW (ng/mL)	GeoMean (GeoCV%) (95% CI)	1,205 (36.1) (964.7, 1,506)	460.1 (35.6) (369.4, 573.1)	131.6 (48.3) (98.37, 176.0)
$AUC_{(0-t)}$ /BW (h*ng/mL)	GeoMean (GeoCV%) (95% CI)	5,712 (39.8) (4,476, 7,290)	3,496 (18.7) (3,108, 3,934)	1,072 (39.7) (841.3, 1,367)
AUC/BW (h*ng/mL)	GeoMean (GeoCV%) (95% CI)	5,725 (40.0) (4,482, 7,312)	NC (NC, NC)	1,016 (41.5) (728.4, 1418)

AUC/BW=body-weight-normalized AUC; $AUC_{(0-t)}$ /BW=body-weight-normalized $AUC_{(0-t)}$; C_{\max} /BW=body weight normalized C_{\max} ; CV=coefficient of variation; Geo=geometric; max=maximum; min=minimum; NC=not calculated; PK parameters were normalized by body weight as a value multiplied by body weight (kg)/70. Body weight was measured pre-dose on Day 1.

Comparison of PSL Concentration Via VAMS and Plasma

VAMS dried blood concentrations of PSL and metabolite UCB1431322-000 were compared with samples of venous blood from the same subjects and same timepoints. Generally, the concentrations of PSL and metabolite UCB1431322-000 were lower in VAMS dried blood. Linear regression plots of the VAMS dried blood and venous plasma concentrations for PSL and metabolite UCB1431322-000 are provided in Figure 1.

For PSL, the C_{\max} of VAMS dried blood was approximately 61.5% of that of venous blood (90% CI, 49.67, 83.19), and the $AUC_{(0-t)}$ of VAMS dried blood was approximately 56.8% (90% CI, 45.26, 73.01). The $AUC_{(0-12)}$ of VAMS-dried blood was approximately 60.5% of that of venous blood (90% CI, 45.66, 73.59), the AUC of VAMS dried blood is approximately 57.3% of venous blood (90% CI, 48.44, 73.08), (Table III). Phoenix WinNonlin analysis results showed that for UCB1431322-000, the C_{\max} of VAMS dried blood was approximately 83.3% of venous blood (90% CI, 61.17, 109.75), the $AUC_{(0-t)}$ of VAMS dried blood was approximately 76% of venous blood (90% CI, 63.09, 86.8), and the AUC of VAMS dried blood was approximately 77.1% of venous blood (90% CI, 62.73, 89.35) (Table III).

Passing-Bablok regression analysis was performed for both PSL and metabolite UCB1431322-000 concentrations to evaluate the agreement of these two sampling methods^{18,21}. For PSL, the intercept is -10.74 (95% CI, -20.6, -3.06) and the slope is 0.65 (95% CI, 0.62, 0.69). For metabolite UCB1431322-000, the intercept is -2.13 (95% CI, -3.82, -0.47) and the slope is 0.80 (95%

CI, 0.77, 0.82). According to the previous study²², if one is included in the 95% CI of the slope and zero is included in the intercept, respectively, this indicates the good agreement of these two methods. According to the Passing-Bablok regression analysis performed at each single time point, there are good agreement at some timepoints of these two methods (Figure 2 and [Supplementary Table I](#)).

According to the results of Bland-Altman analysis, most of the points are within the range of 95% upper and lower limits of PSL and metabolite UCB1431322-000. The mean bias of PSL is 232.05, with 95% upper and lower limits of agreement are 618.932 and -154.832 respectively. For metabolite UCB1431322-000, the mean bias is 40.065, with 95% upper and lower limits of agreement are 154.73 and -76.602, respectively. (Figure 3).

Safety

During the treatment period, 1 study participant (50%) in the placebo group and all 12 study participants (100%) in the PSL group reported at least one TEAE. All reported TEAEs in both the placebo and PSL groups were considered drug related by the investigator. None of these TEAEs were serious, severe, led to study participant discontinuation, or led to death.

The most frequently reported TEAEs were nervous system disorders, including somnolence (1 study participant in the placebo group and 9 study participants in the PSL group) and dizziness (no study participants in the placebo group and 9 study participants in the PSL group). The AE reported by ≥ 2 study participants during the

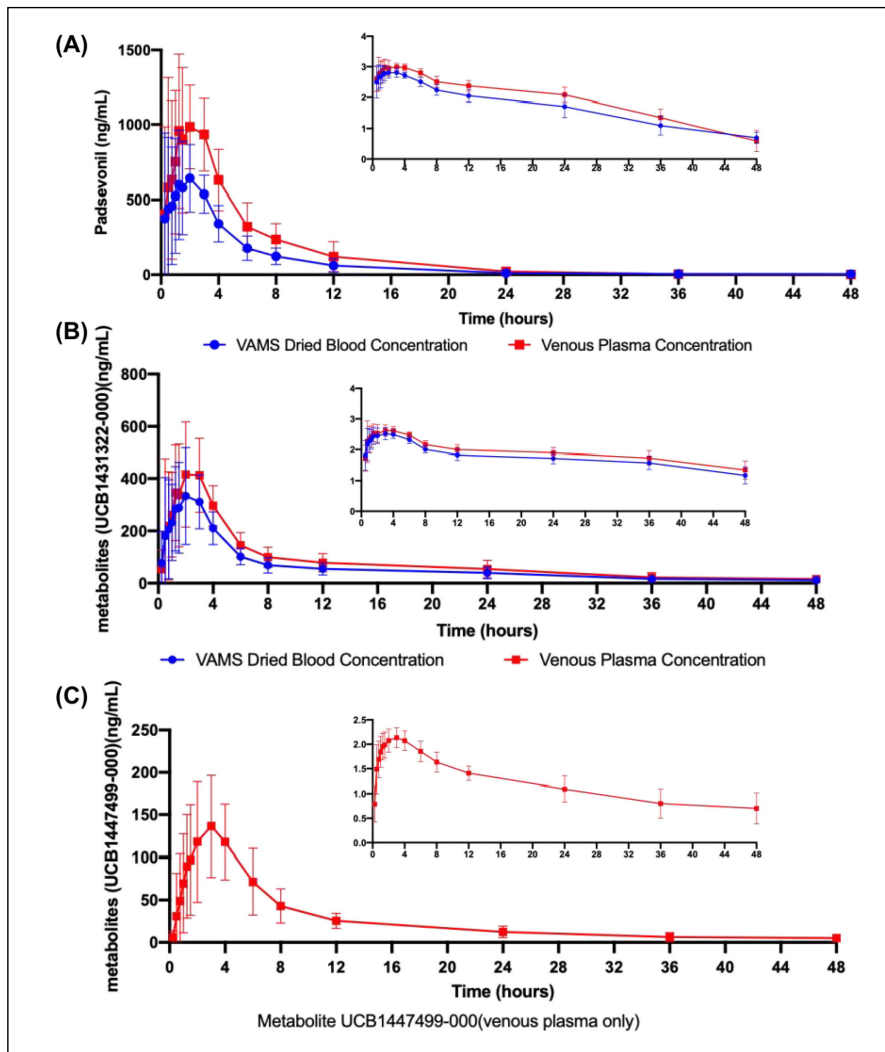


Figure 1. Geometric mean and semilogarithmic scales of plasma and VAMS sample concentration profiles. **A**, PSL. **B**, metabolite UCB1431322-000. **C**, metabolite UCB1447499-000.

treatment period was nausea (no study participants in the placebo group and 2 study participants in the PSL group); all other AEs during the treatment period were reported by ≤ 1 study participant each (Table IV).

All TEAEs were mild or moderate and resolved spontaneously without medical intervention. There was no clinically significant abnormality of clinical laboratory tests, vital signs, or physical examination in subjects who received PSL and placebo.

Table III. Comparison of PK data of VAMS mitra and venous blood sampling.

Parameter	PSL N=12		Metabolite UCB1431322-000 N=12	
	Ratio (VAMS/venous)	90% CI	Ratio (VAMS/venous)	90% CI
C_{max} (ng/mL)	61.50%	(49.67, 83.19)	83.30%	(61.17, 109.75)
$AUC_{(0-t)}$ (h*ng/mL)	56.80%	(45.26, 73.01)	76%	(63.09, 86.80)
AUC (h*ng/mL)	57.30%	(48.44, 73.08)	NC	(64.72, 89.35)
$AUC_{(0-12)}$ (h*ng/mL)	60.50%	(45.66, 73.59)	77.10%	(62.73, 89.98)

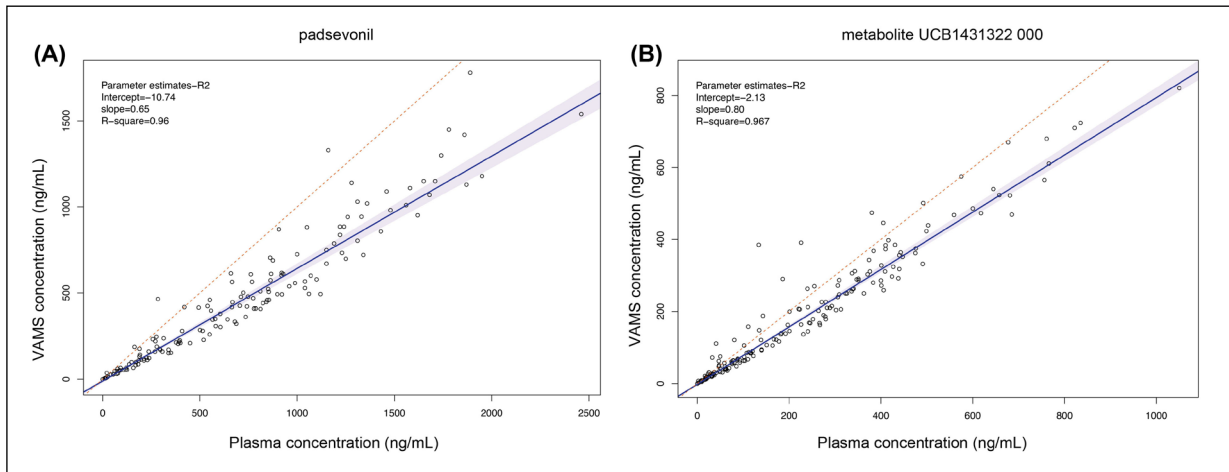


Figure 2. Passing-Bablok regression analysis plotting of PSL (A) and metabolite UCB1431322-000 (B) concentrations obtained from VAMS and conventional venous sampling. Light grey area represents 95% confidence interval (CI) of the slope.

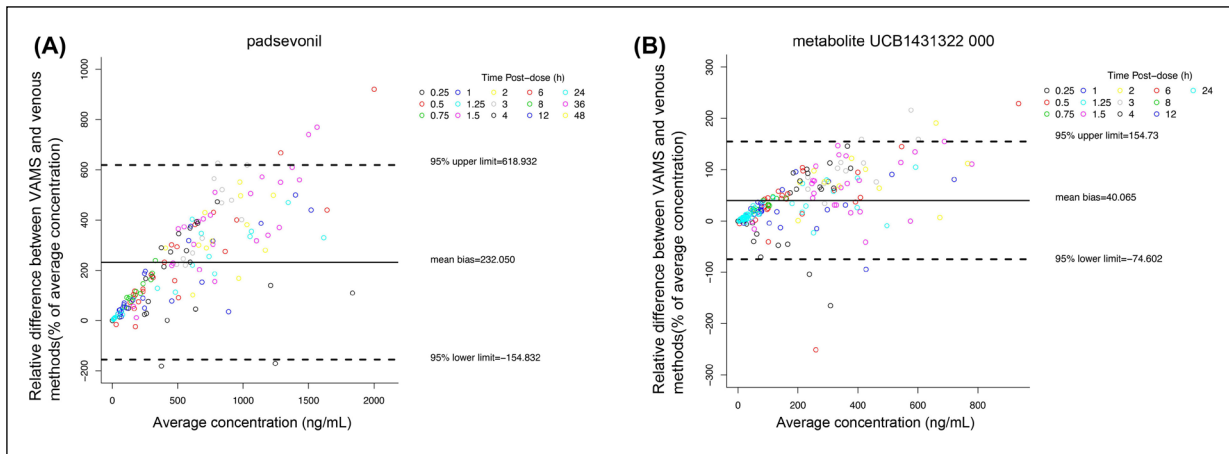


Figure 3. Bland-Altman analysis plotting the differences of PSL (A) and metabolite UCB1431322-000 (B) concentrations obtained from VAMS and conventional venous sampling. The solid line represents the mean bias. The dotted lines indicate the 95% CI of upper and lower limits.

Table IV. Most common TEAEs during the treatment or the safety follow up period.

AEs	Placebo (N=2)		PSL (N=12)	
	Treatment Period n (%) [#]	SFU Period n (%) [#]	Treatment Period n (%) [#]	SFU Period n (%) [#]
Nausea	0	0	2 (16.7) [2]	0
Blood triglycerides increased	0	0	0	2 (16.7) [2]
Somnolence	1 (50.0) [1]	0	9 (75.0) [9]	0
Dizziness	0	0	9 (75.0) [9]	0

SFU=Safety Follow up; TEAE=treatment-emergent adverse event.
 Treatment period=starting from Day -1 to Day 6. SFU Period=starting at Day 7.
 n=number of study participants who reported at least 1 TEAE.
 [#] is the number of individual occurrences of the TEAE in that category.

Discussion

PSL is a novel anti epilepsy chemical with selective affinity for both SV2 and cBZR sites on the GABA_A receptor both *in vitro* and *in vivo*⁵⁻⁷. The phase I and phase II clinical trials^{8,9} have been conducted in healthy volunteers and patients to evaluate the initial PK properties and treatment efficacy of PSL. However, the PK data and the application of VAMS in PSL were limited in Chinese population. This trial was the first study conducted in healthy Chinese volunteers to evaluate the PK and safety of this novel AED candidate. The PK parameters comparison between venous blood and VAMS was also performed in this study.

In this study, we evaluated the PK parameters of PSL and its main metabolites. Single dose administration of PSL at 200 mg was rapidly absorbed with a median t_{\max} of 1.25 h. Overall, t_{\max} was later for the metabolites UCB1431322-000 and UCB1447499-000 than for PSL with medians of 1.75 h and 3.0 h, respectively. Exposure ($AUC_{(0-t)}$) was generally lower than PSL by approximately 40% for UCB1431322-000 and approximately 80% for UCB1447499-000 over the sampling period of 48 h. The PK properties were compared with previous studies⁹, for PSL, the geometric mean $t_{1/2}$ was 5.275 h, which was close to the reported median terminal half-life of PSL ~ 6-7 hours in dose-escalation studies. Furthermore, both our and earlier studies⁹ demonstrated rapid absorption and an apparent biphasic disposition of PSL. This study also showed that the geometric mean plasma concentration-time profiles of metabolites followed a similar pattern with a rapid formation and then elimination following a biphasic disposition.

AEDs are characterized by relatively great individual differences and narrow therapeutic indices, thus TDM is appealed and necessary for those patients to guide dosage adjustment to achieve greater efficacy and better safety^{12,13}. However, professional operation like venous blood collection was inconvenient and not suitable for some patients on AEDs. VAMS is a novel approach to obtain a dried blood sample for quantitative bioanalysis and has been explored in the use of AEDs and other psychiatric drugs^{18,19}. It has the advantage of a very small sample, useful for individuals who cannot easily provide a blood sample by injection, easy to store, no need for centrifugation and plasma extraction to analyze drug concentrations^{12,22,23}. Actually, the VAMS method for blood sampling in PSL clinical studies of healthy

subjects and epilepsy patients have been presented²⁴ by investigators previously, including bioanalytical validation, comparison of results between VAMS and conventional venous sampling methods. However, there is no PK study data and the application of VAMS of PSL in Chinese population was limited. Thus, we adopted venous plasma and VAMS for PK analysis and comparison of PSL and its metabolites in this study. Generally, the concentrations and PK parameters of PSL and metabolite from VAMS were lower than venous blood. This difference is very similar to the *in vitro* measured blood-to-plasma ratio and consistent with the previous description²⁴.

Several studies^{22,25,26} compared the VAMS technique drug levels with plasma by venipuncture through validated quantitative methods and demonstrated a good correlation. Dubois et al²⁵ reported that there was no concentration difference in cannabidiol levels in epilepsy patients between VAMS technique and plasma (n = 5). Patteet et al²² proved that the concentrations of multiple antipsychotics in serum, whole blood and DBS were highly identical in a proof-of-concept study (sensitivity 91.6-97.6%). Most of these studies^{22,25,26} compared the VAMS with venous blood in single or limited timepoints from patients, but it is hard to know the concentrations difference of the whole metabolism process. The data of this study show that the concentrations of all timepoints are not in good agreement, the small sample size of this study might be one of the reasons. This result indicated that the choice of timepoint in clinical drug monitoring is very important and that a single timepoint may not reveal the correlation dynamically. As the variation of different timepoints, pooled analysis of data may could not accurately reflect the possible differences or consistency in this process. Compared with the previous data, not only we evaluated the PK characteristics of PSL, but also metabolite UCB1431322-000. The correlation difference of the PSL and metabolite shows that in drug monitoring, above the prototype drug, we should also pay attention to the metabolite.

The most frequently reported TEAEs were somnolence and dizziness in this study. In two phase I clinical trials⁹ of PSL conducted in healthy volunteers, the transient, self-limiting central nervous system TEAEs including fatigue, somnolence, dizziness, and disturbance in attention. The reported serious TEAE was delirium, and one healthy volunteer withdrew due to fatigue. At the highest doses (≥ 400 mg/d), transient reduc-

tions were seen in memory, alertness, psychomotor performance, and vigilance that lessened with repeated dosing⁹. In a phase II study⁸, the most common AEs of patients with PSL were somnolence, headache, and fatigue. In the present study, no new safety signals were identified and there was no serious TEAEs, discontinuations due to TEAEs, or deaths reported during this study. No clinically significant laboratory, vital sign, ECG, or physical examination results were reported during this study. Overall, the safety profile of PSL was as expected based on the pharmacology of the antiepileptic drug and was consistent with previous studies^{8,9}.

Limitations

There are several limitations of this study, first, the relatively small sample size may lead to the absence of some data, for example, the $t_{1/2}$ of metabolite UCB1431322-000. The limited sample size may also have effect on the results of the Passing-Bablok regression and Bland-Altman comparison analysis. The second limitation is that the subjects in this study only took a single dose.

Conclusions

PSL showed a favorable PK profile after oral administration and good safety properties in healthy Chinese volunteers. The correlation results of VAMS and plasma indicated that the application of VAMS for therapeutic drug monitoring in novel antiepileptic drug development is promising and needs further validation.

Conflict of Interest

All authors declare no conflicts of interest in relation to this work.

Informed Consent

Each subject prior to screening provided written informed consent.

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Authors' Contributions

Zhu Luo: conceptualization. Xiaoyu Li: original draft preparation. All authors: supervision and editing the original paper.

Ethics Approval

The study was conducted in compliance with the principles of Good Clinical Practice and the Declaration of Helsinki. The protocols and the informed consent documents were reviewed and approved by the Ethical Committee of West China Hospital of Sichuan University. All subjects signed informed consent form (ICF) before entering the study. This study was registered at <http://www.chictr.org.cn>, (ChiCTR2000041476).

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