Clinical Pharmacology Review

NDA/supplement #: 21,992/s042	**EDR Link:** \\CDSESUB1\evsprod\NDA021992\0330	
Submission Type: Pediatric Supplement	**Submission Date:** April 6, 2017	
Relevant IND: 64,552	**Indication:** Major Depressive Disorder (MDD)	
Brand Name: Pristiq	**Generic Name:** Desvenlafaxine	**Sponsor:** Wyeth/Pfizer
Formulation: Sustained-Release Tablet	**Strength (mg):** 25, 50, 100	
OCP Review Team: Huixia Zhang, Ray Baweja, Kevin Krudys, Hao Zhu		

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1. EXECUTIVE SUMMARY

Pristiq, desvenlafaxine succinate sustained release tablet (DVS SR), is approved for the treatment of major depressive disorder (MDD) in adults on February 29, 2008. A deferred post marketing program was required under PREA to assess safety and effectiveness of Pristiq as a treatment for MDD in pediatric patients aged 7 to 17 years old. In this application, the Sponsor is submitting study results to fulfill that requirement.

The pediatric clinical development program designed to fulfill PMR #1229-1 consisted of 6 studies:

- One single ascending dose study in children and adolescents (study B2061012), and its open label extension study (B2061013);
- Two pivotal short-term double-blind, placebo-controlled, randomized Phase 3 studies (B2061014 and B2061032), and their associated open-label extension studies (B2061031 and B2061030).

OCP's major findings are summarized as follows:

1. Efficacy of Pristiq was not demonstrated in children and adolescent patients with MDD (7 to 17 years old).
2. Population exposure-response analysis suggested no meaningful relationship between exposure to DVS and clinical response.
3. When compared to adult patients receiving the same dose of Pristiq, exposure to DVS (C_{max} and AUC_{inf}) in pediatric patients 7 to 11 years old is about 30% higher, while similar exposure is observed in adolescent patients 12 to 17 years old.

4. Approximate linear pharmacokinetics was demonstrated for Pristiq in children and adolescent patients.
5. Doses studied in the pediatric Phase 3 trials are considered reasonable.

1.1 Recommendation

From the Office of Clinical Pharmacology's perspective, PMR #1229-1 has been fulfilled.

1.2 Labeling Recommendation

Pending satisfactory agreement with the Sponsor, the following language is recommended for Section 8.4 Pediatric Use: "In clinical trials, compared to adults receiving the same dose, exposure to desvenlafaxine was similar in adolescent patients 12-17 years of age, and was about 30% higher in pediatric patients 7 to 11 years of age."

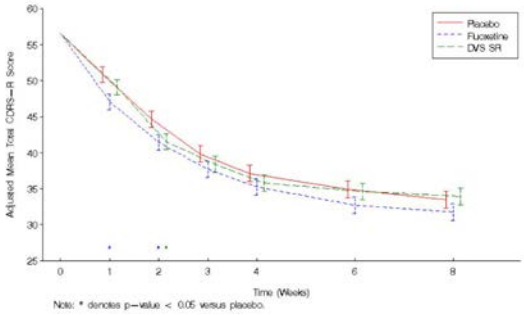
2. QUESTION BASED REVIEW

2.1 Is efficacy for Pristiq demonstrated in children and adolescent patients with MDD?

No. Clinical trials (B2061014 and B2061032) failed to demonstrate that Pristiq (DVS SR) was effective in treating pediatric patients with MDD (Figure 1 and Figure 2), and thus do not support a claim for use in pediatric MDD patients.

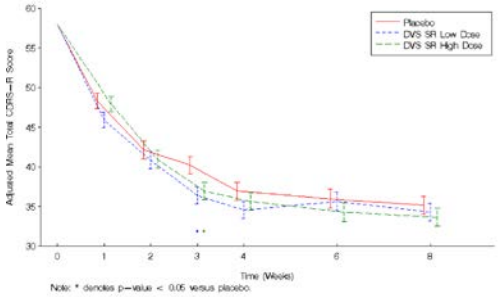
B2061014 was a Phase 3, multicenter, randomized, double-blind, placebo-controlled, fluoxetine-referenced, parallel-group study of DVS SR in the treatment of child (7 to 11 years of age) and adolescent (12 to 17 years of age) outpatients with MDD. Overall, the profile of change from baseline in Children's Depression Rating Scale-Revised (CDRS-R) during the course of the 8-week treatment phase was similar for all 3 treatment arms (placebo, fluoxetine, and DVS SR). Since fluoxetine (with established efficacy in children and adolescents with MDD) did not separate from placebo, it is not possible to draw a definitive conclusion on the efficacy of DVS SR in the treatment of pediatric MDD from this study.

Figure 1: CDRS-R total score over time (study B2061014)



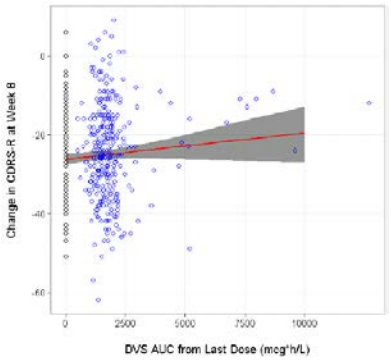
B2061032 was a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study of DVS SR in the treatment of child (7 to 11 years of age) and adolescent (12 to 17 years of age) outpatients with MDD. Both DVS SR low dose and high dose groups were not statistically significantly different from the placebo group for the primary endpoint of the study, the change from baseline in CDRS-R total score at Week 8. The CDRS-R total score in all 3 treatment groups improved to a similar degree during the study. As a result, this study did not show that DVS SR was more effective than placebo in the treatment of pediatric MDD. No apparent dose-response relationship can be identified either.

Figure 2: CDRS-R total score over time (study B2061032)



Additionally, in the tested exposure range from the two clinical trials, population exposure-response analysis using pediatric data indicated that there was no meaningful relationship between DVS AUC and the magnitude of change from baseline in the CDRS-R after 8 weeks of treatment (Figure 3). This finding is consistent with that from adult studies (Clinical Pharmacology Review checked in DARRTS on 10/26/2006).

Figure 3: Observed and Bootstrap Change in CDRS-R at Week 8 versus AUC from Last Dose of DVS SR



-Source: Figure 7 in Summary of Clinical Pharmacology Studies (Section 2.7.2)

2.2 Are the selected doses for the Phase 3 pediatric efficacy trials reasonable?

Yes, the selected doses for the Phase 3 pediatric efficacy trials are reasonable.

In both of the 8-week pediatric efficacy trials (B2061014 and B2061032), the studied DVS SR doses were body weight-based and were titrated in one week to the following high and low daily target exposures (Table 1). The high dose exposure group is to target an exposure similar to a 35 mg DVS SR dose in adults, although there would be significant overlap with the 50 mg of DVS SR dose. The low exposure group is to target an exposure in adults receiving 25 mg DVS SR.

Table 1: DVS SR Dosing Schedule for Pristiq Pediatric Trials

Baseline Visit Weight	Total Daily Dose DVS SR (mg) Week 1 Visit through Week 8 Visit
DVS SR Low Dose Exposure Group (Study B2061032)	
≥20 to <35 kg	20
≥35 to <70 kg	25
≥70 kg	35
DVS SR High Dose Exposure Group (Study B2061014 and Study B2061032)	
≥20 to <35 kg	25
≥35 to <70 kg	35
≥70 kg	50

The selected targeted exposures are reasonable. The recommended dose of DVS in adults is 50 mg. Per Pristiq label, "There was no evidence that doses greater than 50 mg per day confer any additional benefit" in adults. Thus, it seems logical to set the highest tested exposure in pediatric trials so that it provides some overlap, but does not exceed the 50 mg dose in adults. Also, in the adult program, the lowest dose tested in efficacy trials was 50 mg. It seems rational to test if lower exposures (i.e., the 20, 25, and 35 mg dose group) which were expected to allow for better tolerability and safety, would be effective in the pediatric population. The division agreed with the targeted exposures when the sponsor discussed the clinical trial design with the division (Refer to Dr.Burkhart's review checked in DARRTS on 4/29/2010).

Within each exposure group, different doses selected for patients with different body weight appear to be reasonable. The body-weight based dosing strategy is to reduce within group variability on clinical outcome due to variability in drug exposure.

The recommended dose of DVS SR in the treatment of adults with MDD is 50 mg per day, and the common dose studied in the efficacy trials for pediatric patients (≥70 kg) and adult patients is 50 mg. Because PK study results with 50 mg DVS SR in adults are not readily available, a PK comparison is performed for 100 mg (Table 2). Since approximate linear kinetics is demonstrated for DVS in the tested doses in all age groups, similar degree of difference in DVS exposure is expected for 50 mg in the different age groups. When compared to adults after 100 mg DVS SR administration, exposures to DVS (Cmax and AUCinf) in children is about 30% higher, while similar exposure is observed in adolescent group (Table 2).

Table 2: Mean Pharmacokinetic Parameters (Mean±SD) of DVS in Different Age Groups After single dose Administration of 100mg DVS SR

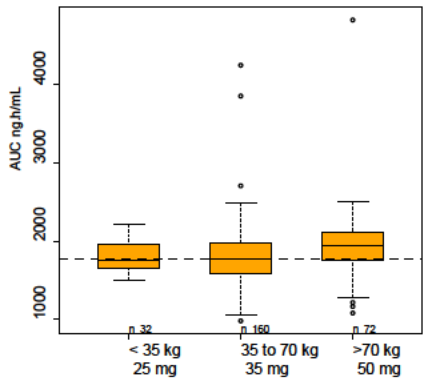
Age group	C_{max} (ng/mL)	AUC_{inf} (hr*ng/mL)	$T_{1/2}$ (hr)	CL/F (L/hr/kg)
Children (7-11 years old, n=7)[#]	263±66	6732±3031	9.0±2.0	0.44±0.20
Adolescents (12-17 years old, n=6)[#]	202±92	5290±2188	9.6±2.0	0.28±0.06
Adults (pooled, n≈397)*	204±61	5044±1601	10.6±3.1	0.31±0.15

[#]-source: Table11-1of Study CSR-81138
*-source: Table 9 of clinical pharmacology review checked in DARRTS on 10/26/2006 for NDA21,922

Further assessment was conducted based on population pharmacokinetic modeling and simulation. Based on population pharmacokinetic modeling, weight was found to be predictive for CL/F. The reviewer used post-hoc estimates of clearance in pediatric patients from Studies B2061014 and B2061032 to predict steady-state exposure (AUC) at the "high dose exposure

group" (i.e., 25 mg/day in subjects weighing < 35 kg, 35 mg/day in subjects weighing ≥ 35 kg and < 70 kg and 50 mg/day in subjects weighing ≥ 70 kg). These predicted exposure values were comparable to the AUC value in adults at the target adult dose of 35 mg/day (1773 ng.h/mL) (Figure 4). Exposure in the low dose group is expected to be similar to that in adults at the targeted adult dose level (i.e., 25 mg).. The results suggest that the doses studied in the pediatric clinical trials were adequate to provide desvenlafaxine exposure within the target range.

Figure 4. Comparison of Exposure in Pediatric Patients at High Dose Level to Adult Target (Dashed horizontal line represented adult target AUC of 1773 ng.h/mL)



Overall, the targeted exposures and body-weight based dosing strategy for pediatric patients appear to be reasonably selected.

2.3 What are the PK properties of DVS in children and adolescents?

Following a single dose administration of DVS SR in children and adolescent patients with MDD, DVS reached C_{max} in about 4-8 hours post dose (Table 3), with an estimated half life of about 8-12 hours.

Table 3: Mean Pharmacokinetic Parameters (Mean±SD) of Desvenlafaxine in Children and Adolescents

Dose (mg)	C_{max} (ng/mL)	T_{max} (hr)	AUC_{inf} (hr*ng/mL)	$T_{1/2}$ (hr)	CL/F (L/hr/kg)
Children (7 to 11 years old)					
10 (n=6)	33.9±12.1	4.7±2.1	628±346	7.8±1.4	0.505±0.135
25 (n=7)	98±60.5	4.3±1.4	1704±553	8.6±1.6	0.472±0.098
50 (n=9)	108±27	5.1±3	2414±924	9.4±2.7	0.540±0.244
100 (n=7)	263±66	5.0±2.0	6732±3031	9.0±2.0	0.441±0.200
Adolescents (12 to 17 years old)					
25 (n=7)	46.1±15.9	4.3±0.7	1123±361	12±3	0.306±0.079
50 (n=7)	93.9±15.5	8.7±7.1	2281±689	10.2±3.7	0.441±0.197
100 (n=6)	202±92	7.6±3.4	5290±2188	9.6±2.0	0.282±0.064
200 (n=8)	449±126	7.5±4.1	11730±3113	9.8±2.7	0.295±0.062

-Source: -Table11-1of CSR

3. INDIVIDUAL STUDY REVIEW

Analytical Methods: wherever it is mentioned throughout the document that the performance of the analytical method is acceptable, it implies that the method used met the following requirements:

• Quality control sample range is acceptable	☑ Yes ☐ No
• Internal standard was used	☑ Yes ☐ No
• Method was validated prior to use	☑ Yes ☐ No
• Sample chromatograms were provided	☑ Yes ☐ No
• Calibration range samples accuracy and precision are acceptable	☑ Yes ☐ No
• Quality control samples accuracy and precision are acceptable	☑ Yes ☐ No
• Method overall performance is acceptable	☑ Yes ☐ No

Acronym used for desvenlafaxine in the review: DVS

3.1 Safety, tolerability and PK/Study B2061012

Report # CSR-81138/3151A6-2000 **Study Period:** 2/18/2008-11/12/2009
Title: Multicenter, open-label, safety, tolerability, and pharmacokinetic study to evaluate single ascending doses and subsequent short-term administration of fixed doses of desvenlafaxine succinate sustained-release tablets in the treatment of child and adolescent outpatients with major depressive disorder.

- **Objectives:** 1) To investigate the safety and tolerability of single ascending doses of desvenlafaxine succinate monohydrate (DVS) sustained release (SR) in children and adolescents with major depressive disorder (MDD); 2) to characterize the pharmacokinetic profile of single ascending doses of DVS SR in children and adolescents with MDD.
- **Study Design:** This was a phase 2a, multicenter, open-label, safety, tolerability, and PK study in children (7-11 years old at baseline) and adolescent (12-17 years old at baseline) patients with MDD. The study included an 8-week treatment period comprising a 3.5-day inpatient period and a 7.5-week outpatient period, followed by a taper period of 0 to 2 weeks.
  - Inpatient phase: Subjects were to be admitted to inpatient units on study day -1, to receive single doses of DVS SR under fasting conditions on study day 1, and to have blood and urine samples collected over a 72-hour period for PK analysis. There were a total of 8 active dose cohorts of DVS SR in child (10 mg, 25 mg, 50 mg, and 100 mg) and adolescent (25 mg, 50 mg, 100 mg, and 200 mg) outpatients with MDD. There was no dose titration for higher dose groups.
  - Outpatient phase: Following the inpatient phase, there was an outpatient phase to evaluate short-term, daily administration of fixed doses of DVS SR. On study day 4, after completion of the 72-hour PK sample collection, subjects began taking DVS SR once daily in an open-label manner through week 8 (study day 56). Subjects were assigned to receive the same fixed dose of DVS SR to which they were assigned in the inpatient period. Depending on the dose cohort to which subjects were assigned, subjects titrated to their maintenance dose across 0 to 12 days. Blood samples for population PK analysis were collected on study days 28 and 56 or at the time of early withdrawal.
- **PK Blood Sampling Times (PK):** Day 1predose, 0.5, 1, 1.5, 2, 4, 5, 6, 8, 12, 24, 36, 48, and 72 hours post dose in the inpatient phase. Blood samples for population PK analysis were collected on study days 28 and 56 or at the time of early withdrawal.
- **Urine Sample Collection:** urine samples for PK analysis were collected at the following time-points during the inpatient period: pre-dose and at 0 to 4, 4 to 8, 8 to 12, 12 to 24, 24 to 48, and 48 to 72 hours after Day 1 test article administration.
- **Analytical Methods:**

Analyte	Desvenlafaxine	Desvenlafaxine
Method	LC/MS/MS	LC/MS/MS
Matrix	plasma	urine
Linear range (ng/mL)	2.0-500.0	100-50000
Performance	acceptable	acceptable

- **Results:**

Formulations

Table 1: Products used in Study		
Dosage (mg)	**Formulation #**	**Batch #**
10	0932578C	2007B0221
25	0932477C	2006B3087/2066B0388
50	0932353C	2007B0090
100	0932355C	2007B0091
Placebo	0	
a. Placebo tablets of equal size to the 50-mg and 100-mg DVS SR tablets were supplied. A placebo-swallow test was administered at the screening visit to ensure that subjects were able to swallow a tablet or tablets of size equal to the largest-sized DVS SR tablet studied in the subject's respective age stratum.		

Study Population

Table 2: Demographic Characteristics of Study Subjects (# subjects): Safety Population		
	Children	Adolescents
Treated/Completed/Withdrawn Due To AE/Other Reasons	29/27/0/2	30/25/4/2
Age (mean±SD)	9.6±1.2	14.1±1.7
Male/Female	15/14	15/15
Height (cm, mean±SD)	141.7±9.1	163.5±8.9
Weight (kg, mean±SD)	40.3±10.6	69.7±23.0
Race (White /African American/Other)	15/14/0	13/15/2/0

Plasma Pharmacokinetics

Table 3: Mean Pharmacokinetic Parameters (Mean±SD) of DVS in Children and Adolescents					
Dose (mg)	C_{max} (ng/mL)	T_{max} (hr)	AUC_{inf} (hr*ng/mL)	$T_{1/2}$ (hr)	CL/F (L/hr/kg)
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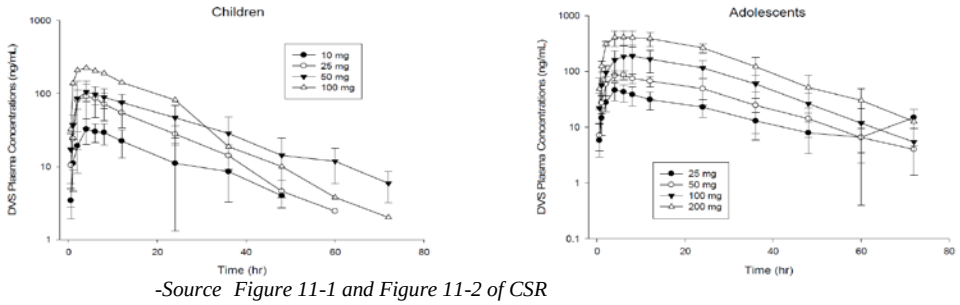
200 (n=8)	449±126	7.5±4.1	11730±3113	9.8±2.7	0.295±0.062
-Source: -Table11-1of CSR					

Figure 1: Mean (SD) Desvenlafaxine Plasma Concentrations vs. Time Profiles in children and adolescents



-Source Figure 11-1 and Figure 11-2 of CSR

Urine Pharmacokinetics

Table 4: Descriptive Statistics (Mean±SD) for Urinary Recovery (0-72 hours) as Percent of Dose for Total Desvenlafaxine and Total NODV in Children and Adolescents

	Children			
	DVS SR Treatment			
	10 mg	25 mg	50 mg	100 mg
n	6	7	7	7
Ae% (%)	39.78 ± 20.01	56.58 ± 16.27	60.54 ± 25.61	61.31 ± 25.27
	Adolescents			
	DVS SR Treatment			
	25 mg	50 mg	100 mg	200 mg
n	7	7	6	6
Ae% (%)	54.81± 17.18	69.24± 12.67	67.99 ± 13.29	58.12 ± 14.45

Ae% = percentage of total desvenlafaxine and NODV in relation to administered dose excreted unchanged in urine; NODV = N,O-didesmethylvenlafaxine.
- Source Talbe 11-5 of CSR

- **Safety:** Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA
- **Sponsor's Summary & Conclusions:**
  - Dose related increases in C_{max} and AUC were observed for increasing doses in children and adolescents.
  - Oral clearance appeared higher in children than in adolescents with considerable overlap in values.
  - Total urinary elimination of DVS over 72 hours was similar in children and adolescent patients.
- **Reviewer's Comments:**

1) Study design:
- *Subjects: There were about 6 to 9 subjects completed in each dose cohort, and about same number of male and female subjects in both children and adolescent groups. This is consistent with Agency recommendation for pediatric PK studies.*
- *Dose administration: There was no up titration for higher doses. This is consistent with label recommendation (though tapering is recommended when therapy is discontinued).*
- *PK sampling schedule: blood samples were collected 72 hours post dose and the sampling frequency was considered reasonable. It is adequate to capture the PK profiles of DVS, and for accurate PK parameter estimation, considering the half-life is about 7-10 hrs.*

2) Study conduct: No protocol violations were reported for patients during the inpatient period, except for three subjects in adolescent 100 mg cohort. Subject 121 consumed chocolate on multiple occasions during the inpatient period, and it is not considered a major violation. For Subject 272 and Subject 273, no plasma concentrations were available

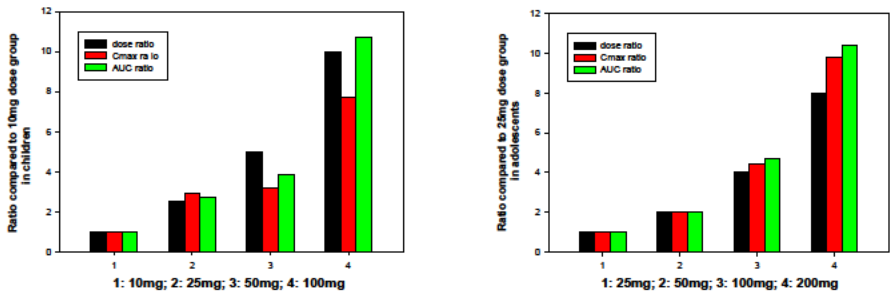
due to unknown reasons (per Sponsor, possible dispensing error).

3) *PK data analysis: All the treated subjects in the children group were included in the PK analysis, while in the adolescent group, Subject 272 and Subject 273 in the 100mg cohort, no plasma concentrations were available due to unknown reasons (possible dispensing error). They were not included in the PK analysis. In addition, Subject 121 consumed chocolate on multiple occasions during the inpatient period, which is reported as a protocol violation. This is not considered to bear significant effect, and it is acceptable to include the subject in PK analysis.*
4) *PK results:*
   - *Approximate PK linearity was demonstrated for DVS in the tested dose range for both children and adolescent patients (Table 5, Figure 2).*

Table 5: Dose Proportionality Analysis for DVX Based on Mean Values

Children	Dose (mg)	10	25	50	100
	Dose Ratio	**1**	**2.5**	**5**	**10**
	Cmax Ratio	1	2.9	3.2	7.7
	AUC Ratio	1	2.7	3.8	10.7
Adolescents	Dose (mg)	25	50	100	200
	Dose Ratio	**1**	**2**	**4**	**8**
	Cmax Ratio	1	2	4.4	9.8
	AUC Ratio	1	2	4.7	10.4

Figure 2: Exposure ratio across dose groups in children (left) and adolescents (right)



   - *The sponsor also measured urinary excretion of DVS. Except in the child 10 mg cohort, urinary recovery of total (conjugated and unconjugated) DVS and NODV (N,O-didesmethylvenlafaxine) was about 55% to 69% in most study cohorts, generally similar to what is reported in Pristiq label (< 69% of the dose after oral administration in adults). For the child 10 mg cohort, ~40 % of the dose in urine was DVS and NODV. Urine collection variation could be one of the possible reasons of the low excretion ratio.*

- **Overall Comments:** *Similar PK properties of DVS across age groups were observed after DVS SR administration, and approximate PK linearity was demonstrated in the tested dose range. Study results are considered acceptable.*

3.2 Pharmacometrics Review

OFFICE OF CLINICAL PHARMACOLOGY
PHARMACOMETRIC REVIEW

1. SUMMARY OF FINDINGS

1.1 Key Review Questions

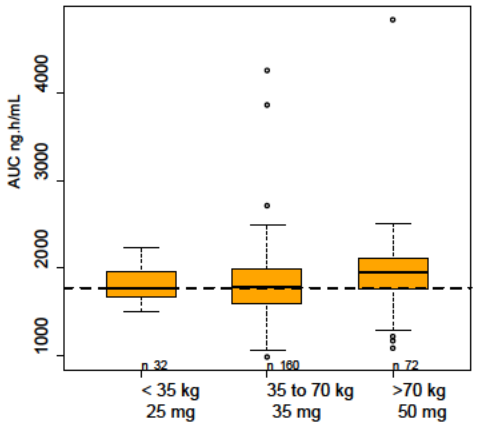
1.1.1 What patient factors characterize the variability in the pharmacokinetics (PK) of DVS SR?

Weight was found to be predictive for CL/F. Weight and age were found to be predictive of V/F and superior to other metrics of body size (e.g., BMI, BSA).

No other covariates were identified as being predictive of DVS SR PK, including the effect of food, administered dose, study, race, patient sex, and blood urea nitrogen (BUN). Neither renal function [(estimated glomerular filtration rate (eGFR) or creatinine clearance (CrCL)] nor liver function (ALT, AST, ALKP, or BILI) contributed to the model in estimating oral clearance.

The reviewer used post-hoc estimates of clearance in pediatric patients from Studies B2061014 and B2061032 to predict steady-state exposure (AUC) at the "high dose exposure group" (i.e., 25 mg/day in subjects weighing < 35 kg, 35 mg/day in subjects weighing ≥ 35 kg and < 70 kg and 50 mg/day in subjects weighing ≥ 70 kg). These predicted exposure values were compared to the AUC value in adults at the target adult dose of 35 mg/day (1773 ng.h/mL) (Figure 1). See Dr. Burkhart's review (04/29/2010) for discussion regarding agreement of the adult target dose. The results suggest that the doses studied in the pediatric clinical trials were adequate to provide desvenlafaxine exposure within the target range.

Figure 1. Comparison of Exposure in Pediatric Patients at High Dose Level to Adult Target (Dashed horizontal line represented adult target AUC of 1773 ng.h/mL)



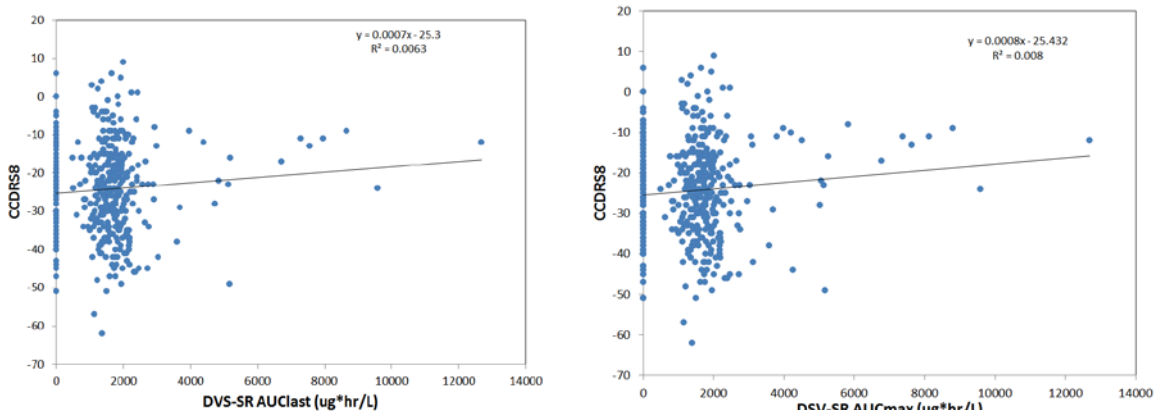
Even though weight appears to be a predictor of clearance and also both weight and age predictors of volume of distribution, we do not recommend to include pharmacokinetic information in the label because two placebo-controlled studies in pediatric patients with MDD did not demonstrate efficacy and thus are not sufficient to support a claim for use in pediatric MDD patients.

1.1.2 Is there a relationship between DVS SR exposure values and the key efficacy endpoint, CCDRS8?
PD effects were described using a linear function relating AUC from the last dose of DVS SR (AUClast) to the change from baseline in CDRS-R at week 8 (CCDRS8). However, the slope of this linear function was 0, suggesting no relationship between AUC and CCDRS8.

Plots of **C**CDRS8 versus AUClast and AUCmax are provided in Figure 2. The black line in these plots is a linear regression.

The correlation coefficient, 'r', is 0.08 essentially showing that there is no correlation between the PD (response markers) and exposure. In all plots there is no visual relationship between the PD marker and drug exposure metrics.

Figure 2. CCDRS8 vs AUC



DVS-SR – Desvenlafaxine succinate sustained release, AUC – area under the curve, CDRS8 - Children Depression Rating Scale- Revised Value at Week 8 Assessment, ug – microgram, hr – hour, L - liter

Source: ccdrs8 vs auclast.png, ccdrs8 vs aucmax.png

In summary, there was no clear effect of DVS SR in the pediatric population as measured by the change from baseline in CDRS-R at week 8 (CCDRS8). The sponsor also performed some modeling analysis but found no relationship between PK and PD. These results are consistent with the results of two placebo-controlled studies in pediatric patients with MDD that did not demonstrate efficacy.

2. PERTINENT REGULATORY BACKGROUND

Desvenlafaxine succinate (DVS) sustained release formulation (SR) is approved for the treatment of major depressive disorder (MDD) in adults. The recommended dose for treatment of MDD in adults is 50 mg once daily, with or without food. DVS SR is the extended release formulation of the succinate salt of DVS, the major metabolite of the antidepressant venlafaxine.

2.1 Desvenlafaxine SR Pediatric Supplement (S-042)

Desvenlafaxine SR was approved in February 2008 for the treatment of MDD in adults. The approval letter mentioned the deferred Pediatric Research Equity (PREA) commitment for the sponsor to conduct pediatric studies to assess the safety and effectiveness of desvenlafaxine as a treatment for major depressive disorder in pediatric patients ages 7 to 17 years. This supplement (S-042) dated 6 April 2017 provides data in the pediatric population.

The population pharmacokinetic analysis is an integrated population approach which utilized pharmacokinetic (PK) and pharmacodynamic (PD) data collected in pediatric patients (Studies B2061012, B2061014, and B2061032) with MDD.

2.2. Labeling

(b) (4)

3. RESULTS OF SPONSOR'S ANALYSIS

Objectives

The objectives of the Sponsor's integrated analysis were to characterize the PPK of DVS SR in children and adolescents with MDD, and to relate the efficacy based on the key efficacy endpoint which is the change from baseline in the CDRS-R total score at the week 8 (CCDRS8) to the plasma concentrations of desvenlafaxine by conducting pharmacokinetic pharmacodynamicanalysis.

Data

The population PK (PPK) and population PD (PPD) analysis utilized PK data collected in Studies B2061012, B2061014 and B2061032. For the PK database, all available observed concentration data from all three studies were pooled into a single NONMEM database. The final PK database contained 342 evaluable subjects with 1165 PK records. The final PPD database contained 411 subjects (97 had received placebo) with evaluable CDRS-R records [i.e., they had both baseline (CDRS-R) and week 8 measurements (CDRS8) of the CDRS-R].

Study B2061012 was a Phase 2, multicenter, open-label study with single ascending dose and multiple dose (approximately 7.5 weeks) treatment periods in children and adolescents with MDD. A total of 59 subjects received DVS SR (29 children aged 7 to 11 years, and 30 adolescents aged 12 to 17 years). The single dose in children was 10 mg, 25 mg, 50 mg and 100 mg, and in adolescents it was 25 mg, 50 mg, 100 mg and 200 mg. For multiple dosing subjects went on to receive fixed doses of once daily dosing of DVS SR.

Studies B2061014 and B2061032 were Phase 3, multicenter, randomized, double-blind, placebo controlled, parallel group studies of DVS SR in the treatment of children (7 to 11 years of age) and adolescents (12 to 17 years of age) outpatients with MDD. In these two Phase 3 parallel-group studies subjects were randomized to receive once daily dosing of 20 mg to 50 mg DVS SR depending on body weight.

The dependent variable for PD analysis was CCDRS8 (i.e., the difference between the CDRS-R at baseline and at week 8 (CDRS8 – CDRS-R) and was log transformed.

Method

The structural PPK and PPD models were developed first with a base model being developed without consideration of covariate effects. Once a base model was established, covariates were evaluated and a full model was constructed. Then the final model was evaluated using unstratified, nonparametric bootstrapping, visual predictive checks (VPC) and other approaches. The FO method was used to evaluate DVS SR PK and the FOCE method was used to estimate DVS SR PD parameters. A Visual Predictive Check (VPC) was conducted first for the PPK model, then for the PPD model using all data. In addition, a Posterior Predictive Check (PPC) was conducted for the PPK model.

Software

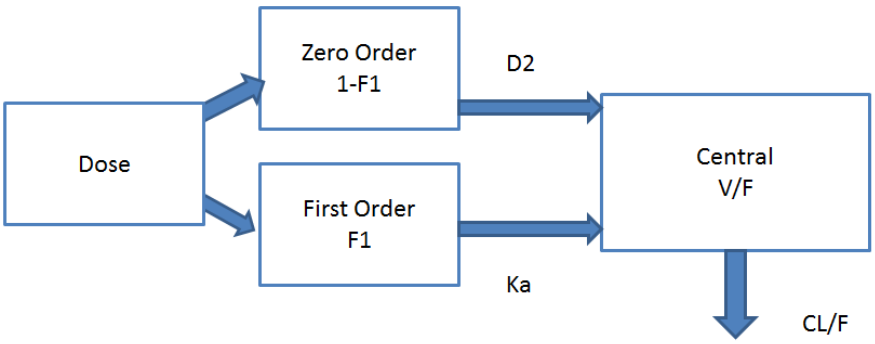
All model fitting was performed by the sponsor using either the FO (for PPK) or FOCE (for PPD) as implemented in the NONMEM version 7 level 3 software and compiled using Intel Fortran Parallel Studio 2011, installed on a grid server system running Windows Server 2008 x64-bit. Diagnostic graphics, exploratory analyses, and post-processing of NONMEM output were performed using R version 3.2.0. Microsoft Excel 2007 was used for viewing data (which was stored as a comma separated variable, CSV, format).

A. Base Model

The base PPK model of DVS SR in the pediatric population was characterized by a 1-compartment disposition model with first order elimination and parallel zero and first order input (Figure 3). Parameters for the absorption component of the model (Ka, F1 and D2) were fixed along with the associated IIV. The base model included terms describing IIV on CL/F, V/F, F1, Ka, D2 and lag time, with IIV on Ka, F1, D2 and Lag being fixed.

Figure 3 provides a schematic for the PK structural model in NONMEM.

Figure 3 Schematic for Structural PK Model



F1 – fraction of dose absorbed via first order process, D2- duration of zero order absorption, Ka – first order absorption rate constant, V/F –apparent volume of distribution, CL/F – apparent clearance

According to the sponsor the basis for fixing the absorption parameters was because attempts to estimate absorption parameters were not successful possibly attributed to the fact that two clinical studies, namely -014 and -032, had sparse data, especially during the early portion of the PK profile.

The parameters for the base model are provided in Table 1. Goodness of fit plots are shown in Figure 4.

Table 1 Base PPK Model Parameters

Parameter (Units)	Population Mean	SE (%)
CL/F (L/hr)	20	2.9
V/F (L)	329	8.2
Ka (1/hr)	0.486	Fixed
F1 (%)	0.727	Fixed
D2 (hr)	25.6	Fixed
LAG (hr)	0.273	6.1
Residual Error (CV%)	57.9	5.9
IIV CL (CV%)	32.6	2.9
IIV V (CV%)	55.3	30.04
IIV Ka (CV%)	70.7	
Fixed	Fixed IIV F1 (CV%)	179
Fixed IIV D2 (CV%)		10
Fixed	Fixed IIV Lag (CV%)	10
Fixed	Fixed Corr (CL,V)	0.55

NE	Corr (Ka, F1)	-0.712
NE		

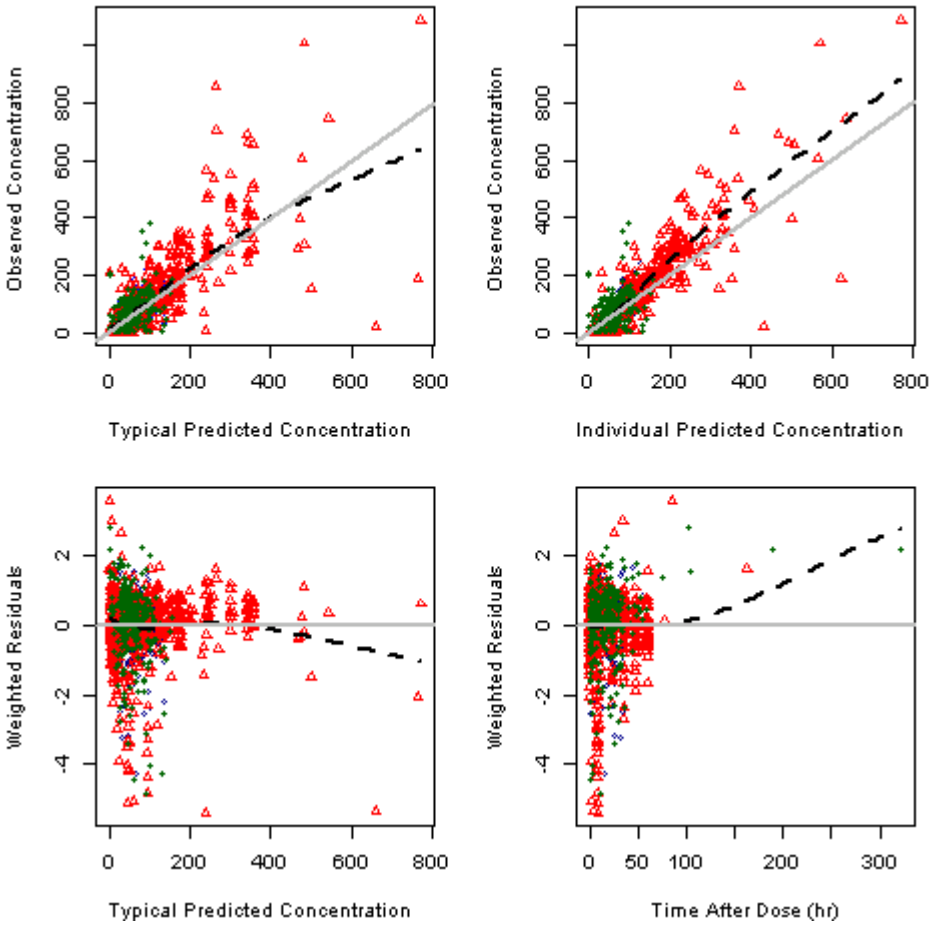
CL/F – clearance, L – liters, hr – hour, CV – coefficient of variation, V /F– volume of distribution, Ka - absorption rate constant,

F1 – bioavailable fraction undergoing first order absorption, D2 – zero order input duration, Lag – lag time, IIV – interindividual variability, Corr – correlation, NE – not estimated, SE – standard error, PPK – population pharmacokinetics

Source: PK model table xls, 16Apr_Best_base.smr

Figure 4 demonstrates an acceptable and comparable level of correspondence of observed and predicted DVS concentrations.

Figure 4 Base PPK Model Goodness of Fit Plots



hr – hour, PPK – population pharmacokinetics

Source: GOF_Plots_pk_Base.R; GOF.Basic.AllData.Base.png

Note: Concentrations are in micrograms per liter, the solid grey line is the line of unity or null as appropriate, the dashed black line is a loess smooth. Study B2061012 is represented with open red triangles, Study B2061014 is represented with open blue circles, Study B2061032 is represented with filled green circles

Reviewer's Comment:
In Figure 4 above the plot of weighted residuals versus predicted concentration shows that at a concentration of 100 ng/ml (mcg/L) some of the weighted residual values were at or greater than negative 4, (i.e., -4). This could possibly be due to the choice of the sponsor to 'fix' the absorption parameters of Ka, F1 and D2 (ascending phase). Thus these weighted residual values at or greater than negative 4 (-4) indicate a certain degree of overprediction.

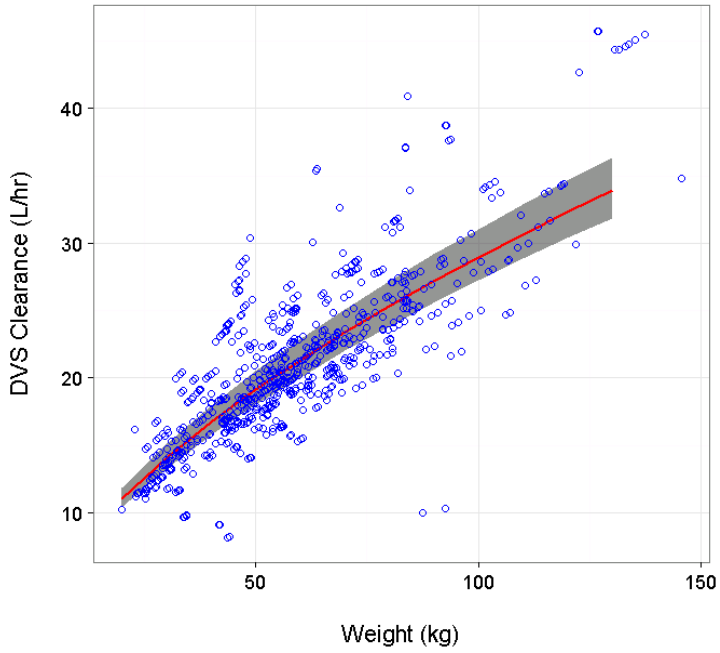
Overall the goodness of fit plots in Figure 4 above suggest that the base model (one compartment, linear elimination) provides the starting point for the subsequent assessment of covariate parameters.

The reviewer was able to replicate the results of the Sponsor.

B. PPK Covariate Evaluations

The effects of the identified covariates were examined from the bootstrap output. Vectors of bootstrapped parameters were used to compute the effects of identified covariates on CL/F and V/F and the computed trends with 95% confidence interval along with the observed individual parameters were plotted. The results are presented in Figure 5 through Figure 7 below.

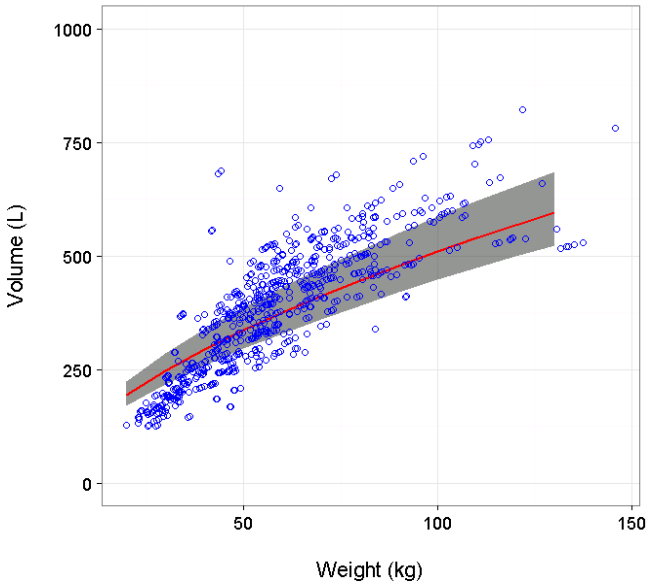
Figure 5 Bootstrap Results – Effect of Weight on Clearance



DVS – desvenlafaxine, L/hr – liters per hour, kg – kilogram; Source: plot
WT effect on CL bootstrap rev.R; final Model CL bootstrap WT.png
Note: Blue open circles are the individual estimates of CL/F, the red line is the median of the bootstrap function of the covariate effect, the gray area is the 95% CI of the bootstrap covariate effect.

It is clear from Figure 5 that as weight increases the clearance of desvenlafaxine also increases in the pediatric population.

Figure 6 Bootstrap Results – Effect of Weight on Volume



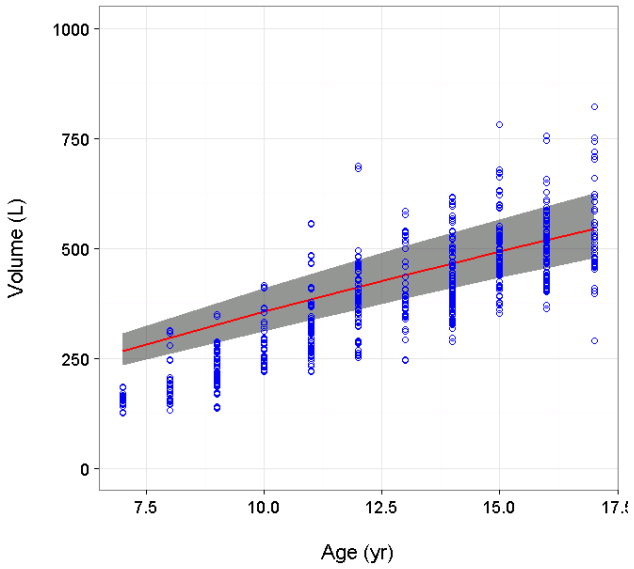
L – liters, kg - kilograms

Source: plot WT effect on V bootstrap rev.R ; final Model V bootstrap T.png

Note: Blue open circles are the individual estimates of V/F, the red line is the median of the bootstrap function of the covariate effect, the gray area is the 95% CI of the bootstrap covariate effect.

Figure 6 shows that there is a clear trend that as weight increases the volume of distribution of desvenlafaxine also increases in the pediatric population.

Figure 7 Bootstrap Results – Effect of Age on Volume



L – liters, yr - year

Source: plot AGE effect on V bootstrap.R, final Model V bootstrap Age.png

Note: Blue open circles are the individual estimates of V/F, the red line is the median of the bootstrap function of the covariate effect, the gray area is the 95% CI of the bootstrap covariate effect.

Figure 7 shows that as the pediatric population ages, the volume of distribution of desvenlafaxine also increases in this population.

Weight was seen to increase with age which is to be expected in the pediatric population. However, a linear regression of age against weight yielded r^2 of 0.33 (i.e., correlation coefficient, r = 0.57). Similarly, when weight or age were removed from the final PK model, the quality of the model deteriorated. Thus, both of these correlated covariates were retained in the final PPK model.

In summary, the effects of body weight were important predictors of DVS SR PK for CL/F and V/F. Age entered the model as a covariate on V/F.

No other covariates were identified as being predictive of DVS SR PK, including the effect of food, administered dose, study, race, patient sex, and blood urea nitrogen (BUN). Neither renal function [(estimated glomerular filtration rate (eGFR) or creatinine clearance (CrCL)] nor liver function (ALT, AST, ALKP, or BILI) contributed to the model in estimating oral clearance.

C. Final Model

A final model was constructed by testing physiological covariate effects. The parameter estimates are shown in Table 2.

The final model has the following characteristics:

Table 2. Final PPK Model Parameter Estimates

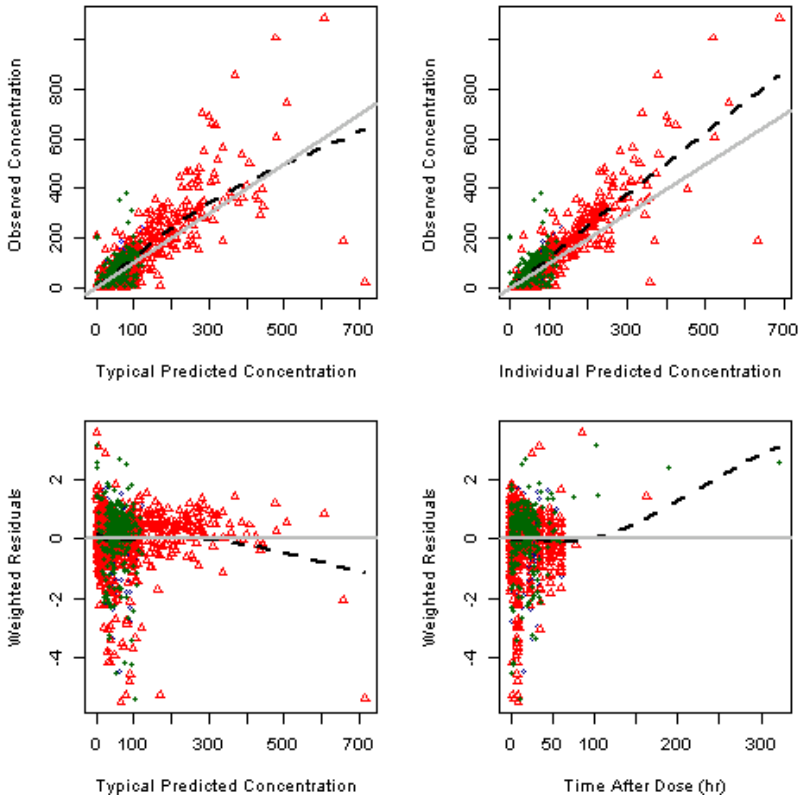
Parameter (Units)	Model Parameter	Population Mean	SE (%)	Bootstrap Lower 95% CI	Bootstrap Median	Bootstrap Upper 95% CI
CL/F (L/hr)	θ1	23.4	3.1	22	23.4	25.1
V/F (L)	θ2	415	6.2	361	412	473
KA (1/hr)	θ3	0.486	FIXED			
F1	θ4	0.727	FIXED			
D2 (hr)	θ5	25.6	FIXED			
LAG (hr)	θ6	0.276	5.6	0.233	0.276	0.31
Residual Error (CV%)	θ7	0.582	5.5	0.506	0.575	0.637
Weight on CL/F, V/F	θ8	0.599	11.2	0.459	0.603	0.745
Age on V/F	θ14	0.804	27.5	0.376	0.808	1.24
Emesis on F1	θ26	1.32	6.0	1.22	1.33	1.38
IIV CL (%)	η1	24	13.5	17.8	24.7	36.6
IIV V (%)	η2	27.4	55.2	5.5	26.3	59.7
IIV Ka (%)	η3	70.7	FIXED			
IIV F1 (%)	η4	1.79	FIXED			
IIV D2 (%)	η5	0.1	FIXED			
IIV Lag (%)	η5	0.1	FIXED			
Corr (CL,V)	--	-0.2		-1	-0.208	0.656
Corr (Ka, F1)	--	-0.712	FIXED			
Condition Number	8.5					

CL/F – clearance, L – liters, hr – hour, CV – coefficient of variation, V /F – volume of distribution, Ka = absorption rate constant, F1 – bioavailable fraction undergoing first order absorption, D2 – zero order input duration, Lag – lag time, IIV – interindividual variability, Corr – correlation, SE – standard error, CI – confidence interval

Source: PK model table for report.xls, best_final.smr

Basic goodness of fit plots for all data are provided in Figure 8 below.

Figure 8 Goodness of Fit of Final PPK Model



hr –hour, PPK – population pharmacokinetics

Source: GOF_Plots_pk_Final.R; GOF.Basic.AllData.Final.png

Note: Concentrations are in micrograms per liter, the solid grey line is the line of unity or identity as appropriate, the dashed black line is a loess smooth. Study B2061012 is represented with open red triangles, Study B2061014 is represented with open blue circles, Study B2061032 is represented with filled green circles.

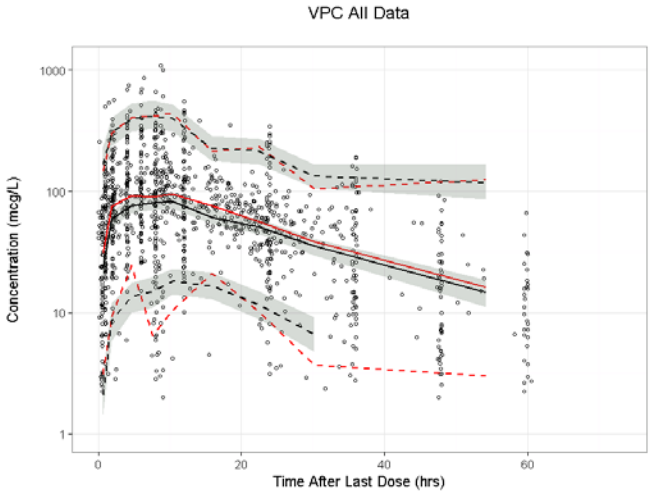
Reviewer's Comment:

The reviewer was able to replicate the findings of the Sponsor for the final PPK model.

In Figure 8 above the plot of weighted residuals versus predicted concentration shows that at a concentration of 100 ng/ml (mcg/L) some of the weighted residual values were at or greater than negative 4, (i.e., -4). This could possibly be due to the choice of the sponsor to 'fix' the absorption parameters of Ka, F1 and D2 (ascending phase). Thus these weighted residual values at or greater than negative 4 (-4) indicate a certain degree of overprediction.

A VPC was performed using the final PPK model. Figure 9 shows the results of the VPC for all data. As can be seen in Figure 9 below, most of the observed data points (i.e., the black closed circles) are within the prediction intervals. Furthermore, the data that is not within these intervals seems to be equally spread above and below the intervals. The solid *red* line which is the median of the observed data provides a reasonable match to the solid *black* line which is the median of the simulated data. Similarly, the upper and lower percentiles of the observed data indicated by the dashed red lines correspond closely with their respective percentiles of simulated data which is shown by the dashed black lines.

Figure 9 **VPC Results for Final Model – Observed and Simulated Concentrations versus Time After Dose – All Data**



VPC – visual predictive checks, mcg/L – microgram per liter, hrs - hours

Source: VPC_pk_95percentPI_best.R; vpcall_95percentci final.png

Note: Black closed circles are the observed data; solid red line is the median of the observed data; red dashed lines are the upper and lower 95th percentiles of the observed data, black solid line is the median of the simulated data; black dashed lines are the upper and lower 95th percentiles of the simulated data, grey shaded area is the 95 percent confidence intervals associated with the simulated data.

D. PKPD: Ascertaining the Relationship between DVS SR Exposure Values and the Key Efficacy Endpoint, CCDRS8

For the PD model building database metrics of exposure (Dose and AUC) and PD markers (CCDRS8) were pooled into a single NONMEM database.

The dependent variable is CCDRS8 which is the change in CDRS-R from baseline to week 8. DVS AUC was calculated by dividing the last recorded dose of DVS SR by the oral CL/F, yielding the AUC(0-τ) for that dose and individual. The AUC (AUClast) was the primary covariate of response. The DVS AUCmax was calculated in a similar manner from the highest administered DVS SR dose and included in the PPD analysis as an exploratory covariate.

The PD database initially contained 447 subjects. Only 411 (including 97 in placebo group) of these subjects had **both** baseline (CDRS-R) and week 8 measurements (CDRS8) of the CDRS-R, and, could be evaluated in the PD assessment [**C**CDRS8: the difference between the CDRS-R at baseline and at week 8 (CDRS8 – CDRS-R)]. The evaluable PD subjects were 314 excluding the 97 in the placebo group. No relationship between desvenlafaxine exposure and CCDRS8 was observed. For results of the PD analysis, please see the answer to Key Review Question 2 (see section 1.1.2).

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/s/

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01/11/2018

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