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Proposition of a Minimal Effective Dose of Vigabatrin for the Treatment of Infantile Spasms Using Pediatric and Adult Pharmacokinetic Data

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Abstract

Vigabatrin is an antiepileptic drug indicated as monotherapy in infantile spasms. However, the pharmacokinetic profile of this compound in infants and young children is still poorly understood, as is the minimal effective dose, critical information given the risk of exposure-related retinal toxicity with vigabatrin. A reasonable approach to determining this minimal dose would be to identify the lowest dose providing a low risk of exposure overlap with the 36-mg/kg dose, which is the highest dose associated with an increased risk for treatment failure, based on randomized dose-ranging data. A population pharmacokinetic model was consequently developed from 28 children (aged 0.4-5.7 years) for the active S(+)-enantiomer, using Monolix software. In parallel, a population model was developed from published adult data and scaled to children using theoretical allometry and maturation of the renal function. A one-compartment model with zero-order absorption and first-order elimination described the pediatric data. Mean population estimates (percentage interindividual variability) for the apparent clearance, apparent distribution volume, and absorption duration were 2.36 L/h (24.5%), 17 L (38%), and 0.682 hours, respectively. Apparent clearance and apparent distribution volume were related to body weight by empirical allometric equations. Monte Carlo simulations evidenced that a daily dose of 80 mg/kg should minimize exposure overlap with the 36-mg/kg dose. Similar results were obtained for the adult model scaled to children. Consequently, a minimal effective dose of 80 mg/kg/day could be considered for patients with infantile spasms.

Keywords

vigabatrin enantiomers, West syndrome, infantile spasms, population pharmacokinetics, children, infants

Vigabatrin, (R, S)-γ-vinyl-gamma aminobutyric acid (GABA), is an irreversible inhibitor of GABA-transaminase, an enzyme responsible for the catabolism of GABA,[1] which results in an increase in the concentration of this neurotransmitter in the brain. Vigabatrin oral absorption is rapid, with maximum concentration reached within 2 hours.[2] Vigabatrin has a distribution volume of 0.8 L/kg,[3] does not interact with plasma proteins,[2,4] and is primarily excreted unchanged in the urine.[2] Vigabatrin is administered as a racemic (R and S), but only the S(+)-enantiomer is pharmacologically active.[5] Importantly, vigabatrin pharmacokinetics (PK) are stereospecific, with a higher exposure obtained for the R(-)-enantiomer, and no PK interaction or chiral conversion is expected between the 2 enantiomers.[2]

Currently, vigabatrin is mainly indicated as monotherapy for infantile spasms, a rare (incidence approximately 2-3.5/10,000 live births) but severe and pediatric-specific epilepsy syndrome with early onset (mainly in the first year of life) and age-related expression (mainly up to 4-6 years).[6]

Vigabatrin treatment is associated with a risk for retinal toxicity, consisting of an irreversible bilateral constriction of the visual field.[7–9] This severe adverse effect has been shown to be significantly related to cumulative doses of vigabatrin.[10,11] In order to avoid overexposure to vigabatrin, dose and treatment duration should therefore be minimized, but underdosage and premature withdrawal must also be avoided because they may induce treatment failure, leading to a highly pharmacoresistant form of infantile spasms with severe cognitive impact.[12,13]

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Therefore, it seems crucial to determine the minimal effective dose for vigabatrin, although a formal dose-ranging trial would be extremely difficult in infantile spasms. The risk for lower efficacy and for uncontrollable relapse if decreasing the dose after initial control[12,13] is considered ethically unacceptable because complete cessation of seizures is required in infantile spasms to avoid negative impact on cognitive development. As a result, the dose range of 36-100 mg/kg/d has not been formally evaluated in infants so far despite the current summary of product characteristics recommendation for the treatment of infantile spasms with an initial dose of 50 mg/kg/d, which can be gradually increased up to a maximum dose of 150 mg/kg/d.

The only available randomized dose study showed that a dose of 100-148 mg/kg/d was more efficient and carried a lower risk for relapse than a low dose of 18-36 mg/kg/d.[14,15] Pharmacokinetic modeling could be helpful to propose a minimal effective dose, but there are insufficient pediatric PK data currently available.

Indeed, few PK studies on the enantiomers have been conducted in children to date. The first one compared the PK of vigabatrin among 6 infants (aged 12.1 ± 5.9 months) and 6 children (aged 8.7 ± 3.8 years) after a dose of 50 mg/kg/d.[16] It showed that exposure to (S)-vigabatrin was lower than to (R)-vigabatrin, as observed for adults,[2] and that the area under the plasma drug concentration-time curve (AUC) and elimination half-life ($t_{1/2}$) of (S)-vigabatrin varied poorly or not at all with age, unlike the AUC and $t_{1/2}$ of (R)-vigabatrin, which both increased with age. This study proposed that a similar weight-normalized dose of vigabatrin racemate could theoretically be given from to children aged 1 month-15 years. A lower (S)-vigabatrin exposure (ie, approximately 50% of [R]-vigabatrin exposure) was also observed in neonates (aged 21.3 ± 4.2 days) with uncontrolled seizures.[17] However, the AUC of (S)-vigabatrin was higher than that observed in infants (+56%) and children (+21%), suggesting a possible age-related change of (S)-vigabatrin PK parameters during childhood.

Consequently, a population PK analysis could be of interest in order to assess the possible age- or weight-related changes in PK parameters of (S)-vigabatrin. The only population PK study previously performed for vigabatrin was based on racemic vigabatrin and included both children and adults,[18] so the evolution of the PK parameters of (S)-vigabatrin during childhood remains to be clarified. Such a study could be helpful for proposing a minimal effective dose. Due to the lack of PK/pharmacodynamic (PD) data, a reasonable endpoint would be to determine the lowest dose that provides a high proportion of children an exposure of (S)-vigabatrin greater than that obtained for the highest dose known to be suboptimal (36 mg/kg).

However, one issue regarding such a study is the low incidence and the narrow age range of infantile spasms. A small number of children would be expected to be enrolled, raising the question of the reliability of the results. To overcome this problem, it would be possible to scale the adult PK parameters of the drug to children using theoretical allometry and maturation, as has been previously described for several drugs.[19,20]

Consequently, the aim of the present study was to propose a minimal effective dose of vigabatrin for the treatment of infantile spasms using 2 different methods: i) a population PK model developed from pediatric data and ii) a population PK model developed from adult data and scaled to children, using theoretical allometry and maturation.

Methods

Ethics

This PK analysis was part of the SoluWest study (EudraCT Number: 2014-000360-17). This study was approved by the Ethics Committee CPP Ile de France V. All procedures performed in studies involving human participants were in accordance with the ethical standards of local research committee and with the 1964 Helsinki declaration and its later amendments. Parents or legal guardian provided written informed consent for all children included in the study.

Patients and Treatment

This prospective study was planned to include children aged 1 month-6 years with epilepsy receiving vigabatrin or to be newly treated with vigabatrin.

Exclusion criteria were the use of more than 2 concomitant antiepileptic drugs; receipt of vigabatrin through a gastric tube; weight less than 4 kg; or any planned major surgery during the trial period.

The dosage form of vigabatrin used in the study was a novel pediatric form: scored soluble tablets of 100 and 500 mg, allowing an accurate measurement of the vigabatrin dose (Kigabeq).

Study Design

There were 2 consecutive protocols. Protocol 1 (patients with infantile spasms already stabilized under vigabatrin) included 13 patients and comprised 6 blood samples per patient. Two samples were collected 1.5 months after the first visit: one just before drug intake and the other 1 hour after. The 2 next samples were collected 2.5 months after the first visit: one 3-5 hours after drug intake and the other 6-9 hours after. The 2 last samples were collected 3 months after the first visit: one right before drug intake and the other 1 hour after. Protocol 2 (patients with new-onset infantile spasms) included 15 patients and, because of the difficulty of recruitment, comprised only 1 blood sample per patient, collected

just before the morning dose, approximately 3 months after the inclusion visit. All children received vigabatrin twice a day.

Blood samples (500 μL per sample) were collected in dry heparin tubes, immediately centrifuged, and the corresponding plasma was stored up to 2 years at –80°C until analysis (stability in plasma at –80°C was validated for a 2-year period).

Analytical Method

The plasma concentration of vigabatrin enantiomers was determined using a liquid chromatography mass spectrometry method, developed in our laboratory.[21] Briefly, 50 μL of internal standard (deuterated racemic vigabatrin) was added to 100 μL of plasma sample. Proteins were then precipitated with 600 μL of methanol. The supernatant was evaporated to dryness under a stream of nitrogen and the dry residue was reconstituted with 500 μL of ultrapure water (obtained from a Milli-Q water purification system, Millipore, Molsheim, France) and 100 μL of a mixture of O-phthaldialdehyde (0.1 mM) and N-acetyl-L-cysteine (0.1 mM) in borate buffer (0.1 M, pH = 9.5) for pre-column derivatization into diastereomeric isoindoles. The chromatographic separation was performed using a Phenomenex EVO C18 column (Phenomenex, Torrance, California), and a mobile phase consisting in a mixture of ammonium acetate 5 mM and methanol/acetonitrile (63/37 v/v), with a flow rate of 400 μL/min and a gradient elution mode. Detection was performed by heated electrospray ionization in positive mode using selected reaction monitoring. Intra- and interday precision and accuracy were lower than 15% over the calibration range (0.2-50 μg/mL for each enantiomer). The calibration curve was linear in the concentration range of 0.2-50 μg/mL for each enantiomer.

Population PK Model Development

Development of the Pediatric Model. The original data were split into 2 datasets. The first dataset included all patients from protocol 1 and was used to develop the model (modeling dataset). The second dataset included all patients from protocol 2 and was used to validate the model (validation dataset).

(R)- and (S)-vigabatrin concentration-time data were fitted independently because no PK interaction and no chiral conversion were expected.[2] Consequently, half of the racemic dose was used as the dose input. Monolix (version 4.3.2; Lixoft, Antony, France) was used to build the model using the stochastic approximation of expectation maximization algorithm.

One- and two-compartment models were investigated with first- or zero-order absorption, with and without lag time. Elimination was assumed to be ruled by a first-order process, according to previous results.[22,23] Interindividual and interoccasion variability were also investigated and assumed to correspond to a log-normal distribution of the PK parameters and were consequently described by exponential models. Additive, proportional, and combined residual error models were tested for both compounds.

Covariate Analysis

The effect of the covariates was assessed by the likelihood ratio test, that is, the chi-square test of the difference between the log-likelihood (LL) of the basic model (without covariate) and the LL of the model including the covariate. First, body weight (BW) was added on each parameter and was selected if its addition induced a significant drop of the LL. Because the reduction in LL follows a chi-square distribution, a decrease of 3.84 was considered significant ($P < .05$, one degree of freedom). Once BW was added, all the other covariates were tested. The significant ones were added to the model, obtaining the full model, and a backward elimination was performed. Covariates were retained if their deletion from the model resulted in an increase in the LL greater than 6.63 ($P < .01$, one degree of freedom). Finally, nonsignificant covariates were removed and the final model was obtained.

The effect of BW on clearance and distribution volume was included using an allometric model, as described below.

$$\theta_i = \theta_{TV} \times \left(\frac{BW}{BW_{median}}\right)^{\theta_{BW}} \quad (1)$$

BW is the body weight in kg, BW_{median} is its median in the modeling dataset, and θ_{BW} is the empirical allometric coefficient. Theory-based allometry was also tested (exponents of 0.75 for clearance and 1 for distribution volume).

The maturation function, in addition to theory-based allometry, was also investigated for clearance, as follows:

$$F_{mat} = \frac{AGE^{\gamma}}{AGE_{50}{}^{\gamma} + AGE^{\gamma}} \quad (2)$$

where γ is the sigmoidicity coefficient and AGE_{50} is the age at which clearance reaches 50% of its maximal value. Other continuous covariates were included in the model using a power function similar to equation 1, where BW was replaced by cov, the value of the covariate, and BW_{median} by cov_{median}, its median value in the population of the study, and θ_{cov} was the factor describing the relationship between the covariate and the parameter. Categorical covariates were

incorporated using a similar model (equation 3), as illustrated below:

$$\theta_i = \theta_{TV} \times e^{\theta_{cov} \times cov} \quad (3)$$

where cov is 1 or 0 in the presence or absence of the covariate.

Investigated covariates were age, height, estimated creatinine clearance, and sex.

Development of the Adult Model

Concentration-time data for (S)-vigabatrin obtained from 6 healthy volunteers were available in the publication of Haegele and Schechter.[2] The structural model was developed as described for children. However, no covariate was investigated. Instead, PK parameters were normalized by 70 kg and their size-related change was described by theoretical allometry. Because vigabatrin is eliminated unchanged by the kidneys, the maturation function of the glomerular filtration developed by Rhodin et al was applied to clearance.[24]

Internal Evaluation

Pediatric Model. Evaluation of the final model was performed via prediction corrected visual predictive checks (pcVPC) obtained from 1000 simulations of the original dataset (protocol 1) using the final model and by inspection of classical goodness-of-fit plots:

- Normalized prediction distribution errors (NPDE) versus time after dose and versus population predictions
- Individual weighted residuals (IWRES) versus time after dose and versus population predictions
- Observed versus predicted concentrations

Adult Model

Classic goodness-of-fit plots were also used to evaluate the model.

External Evaluation

Pediatric Model. The final models of (R)-vigabatrin and (S)-vigabatrin were applied to the validation dataset (protocol 2). The values obtained by population predictions were compared to the observed concentrations. Adequacy between actual and predicted concentrations was investigated by calculating precision and bias corresponding, respectively, to the root mean square error (RMSE) and the mean prediction error (MPE), using the following formulas:

$$RMSE = \sqrt{\frac{1}{n}\sum_{i=1}^{n}(C_{OBS} - C_{PRED})^2} \quad (4)$$

$$MPE\ (\%) = 100 \times \frac{1}{n}\sum_{i=1}^{n}\frac{C_{PRED} - C_{OBS}}{C_{OBS}} \quad (5)$$

where C_{OBS} is the observed concentration and C_{PRED} is the predicted concentration of the subject i and n is the total number of subjects. The correlation between actual and predicted concentrations was also investigated.

The external predictive ability of the model was tested with posterior predictive checks. For this, 1000 children, receiving 50 mg/kg of the racemate, were simulated based on the population characteristics of the group 1 included in the study by Rey et al (children aged 5 months-2 years), which was included in our population ages.[16]

Then the simulated area under the plasma drug concentration-time curve from 0 to 24 hours ($AUC_{0\text{-}24h}$) at steady state, $t_{1/2}$, and trough concentration (C_{trough}) at steady state were compared to the values obtained by Rey et al in their noncompartmental analysis.[16] In this study, $AUC_{0\text{-}24h}$ after the first 50-mg/kg dose was given, so $AUC_{0\text{-}24h}$ at steady state ($AUC_{0\text{-}24hSS}$) was calculated, using the following formula and the elimination half-lives given by Rey et al:

$$AUC_{0-24hSS} = AUC\ (0-24h) \times \frac{1}{1-e^{-k\tau}} \quad (6)$$

where $\frac{1}{1-e^{-k\tau}}$ corresponds to the accumulation factor (1.3 for the [S]-vigabatrin and 1.06 for the [R]-vigabatrin).

Adult Model. The ability of the adult model scaled to children to predict our pediatric data was evaluated by comparing the bias (MPE), and the dispersion (RMSE), of the population predictions versus the observations.

Simulation Study

Using both the pediatric and the adult models, Monte Carlo simulations were performed to evaluate the risk to obtain a (S)-vigabatrin AUC corresponding to the highest suboptimal dose of the racemate (36 mg/kg/d). One thousand children per investigated BW (mean BW = 9 kg for children <2 years and mean BW = 14.7 kg for children ≧2 years) were simulated for doses between 36 and 175 mg/kg/d of the racemate. This risk was calculated as the percentage of 95%CI of the simulated AUC at a determined dose that was within the 95%CI of the AUC simulated for the 36-mg/kg/d dose. Interindividual variabilities of 25% were applied to all the PK parameters of the adult model in order to perform the simulations.

Simulations were also used to assess the relevance of the currently accepted reference range for racemic vigabatrin C_{trough} of 0.8-36 μg/mL[25,26] by calculating for each simulated dose the percentage of racemic vigabatrin C_{trough} within this range.

Table 1. Patient Characteristics

Characteristic	Statistic	Study Population		Total
		Protocol 1	Protocol 2	
Patients	N	13	15	28
PK samples	N	144	30	174
Sex				
Boys	N (%)	7 (53.9)	7 (46.7)	14 (50)
Girls	N (%)	6 (46.2)	8 (53.3)	14 (50)
Epilepsy type				
Infantile spasms	N (%)	13 (100)	11 (73.3)	24 (85.7)
Pharmacoresistant focal epilepsy	N (%)	0 (0)	4 (26.7)	4 (14.3)
Age (years)	Mean (± SD)	2.23 (0.9)	1.39 (0.9)	1.78 (0.98)
	Median (range)	2.03 (0.8-4.1)	0.86 (0.4-5.7)	1.42 (0.4-5.7)
Body weight (kg)	Mean (± SD)	12.54 (2.3)	9.72 (2.7)	11.03 (2.9)
	Median (range)	12.16 (9.3-19.6)	8.68 (6.5-22.8)	9.55 (6.5-22.8)
Creatinine clearance (mL/min)	Mean (± SD)	156.95 (54.4)	173.16 (45.6)	164.96 (43.2)
	Median (range)	167.25 (99.7-248.2)	167.29 (100.1-264.6)	165.98 (99.7-264.6)
Vigabatrin daily dose (mg/kg)	Mean (± SD)	81.58 (24.6)	84.19 (27.6)	82.98 (26.2)
	Median (range)	82.27 (40.7-138.7)	91.80 (38.8-140.5)	84.92 (38.8-140.5)
Vigabatrin Trough Concentration (μg/mL)				
(R)-Vigabatrin	Mean (± SD)	2.57 (1.8)	5.26 (8.2)	3.60 (5.4)
	Median (range)	1.72 (0.7-8.01)	1.52 (0.4-31.8)	1.69 (0.4-31.8)
(S)-Vigabatrin	Mean (± SD)	3.08 (1.6)	4.80 (6.1)	3.78 (4.0)
	Median (range)	2.63 (1.2-7.2)	1.97 (0.7-23.8)	2.63 (0.7-23.8)

N, number; SD, standard deviation.

Results

Patient Characteristics

The database included 28 children (14 boys/14 girls), 13 for protocol 1 (7 boys/6 girls; 9 children had 6 samples, 2 had 5 samples, and 2 had 4 samples) and 15 for protocol 2 (7 boys/8 girls), who provided 174 concentrations (87 concentrations of [R]-vigabatrin and 87 concentrations of [S]-vigabatrin). The median vigabatrin dose was 84.92 (range, 38.8-140.5) mg/kg/d. There was no concentration below the lower limit of quantification of the method (0.2 μg/mL) for either enantiomer. Estimated creatinine clearance was calculated from creatinemia and height by the Schwartz formula.[27] Characteristics of this population are described in Table 1.

Population PK Modeling

Pediatric Model. The best base model was a one-compartment model with zero-order absorption and no lag time for either enantiomer. The residual error model was proportional for both enantiomers. Interindividual variability could not be estimated for absorption duration (Tk0) in either model, but interoccasion variability could be estimated on this parameter. In contrast, interindividual variability, but not interoccasion variability, could be estimated for apparent clearance (Cl/F) and apparent distribution volume (V/F). Interoccasion variability consequently had to be fixed to a negligible value for V/F and Cl/F in order to allow the minimization process.

Body weight was the only covariate explaining the interindividual variability of V/F and Cl/F. Once BW was added to the model, other covariates such as height, age, or estimated creatinine clearance could not be included successfully. The use of theory-based allometry combined with a maturation function did not provide satisfying results, as the parameters could not be correctly estimated.

The final models, thus, were:

(R)-vigabatrin:

$$\text{Tk0 (h)} = 0.521$$

$$\text{V/F (L)} = 9.54 \times (\text{BW}/12.1)^{1.01}$$

$$\text{Cl/F (L/h)} = 1.9 \times (\text{BW}/12.1)^{0.771}$$

(S)-vigabatrin:

$$\text{Tk0 (h)} = 0.682$$

$$\text{V/F (L)} = 17 \times (\text{BW}/12.1)^{1}$$

$$\text{Cl/F (L/h)} = 2.36 \times (\text{BW}/12.1)^{1.04}$$

Table 2 displays the estimated values and their corresponding precision for the base and final model for both enantiomers.

Table 2. Mean Estimates and Precision of the Parameters for the Base and Final Pediatric Model for Each Enantiomer

	(R)-Vigabatrin				(S)-Vigabatrin			
	Base Model		Final Model		Base Model		Final Model	
Parameters	Estimate	RSE %	Estimate	RSE %	Estimate	RSE %	Estimate	RSE %
Tk0	0.33	63	0.521	49	0.895	28	0.682	37
V/F	9.72	13	9.54	11	17	16	17	13
$\Theta_{BW\_V/F}$	–	–	1.01	50	–	–	1	59
Cl/F	1.89	10	1.9	8	2.38	11	2.36	8
$\Theta_{BW\_Cl/F}$	–	–	0.771	46	–	–	1.04	34
ωV	0.397	28	0.255	36	0.533	24	0.38	27
ωCl	0.322	24	0.205	28	0.387	21	0.245	24
γTk0	1.44	34	1.01	38	0.879	27	1.02	31
γV	0.001 (fixed)	–	0.001 (fixed)	–	0.001 (fixed)	–	0.001 (fixed)	–
γCl	0.001 (fixed)	–	0.001 (fixed)	–	0.001 (fixed)	–	0.001 (fixed)	–
ηTK0	–		79		–		74	
ηV	–		39		–		28	
ηCl	–		22		–		21	
B (exponential error)	0.314	12	0.325	11	0.221	13	0.229	12

γ, interoccasion variability; η, shrinkage value; Θ, allometric coefficient; ω, interindividual variability; BW, body weight (kg); Cl/F, apparent clearance; F, bioavailability; RSE, relative standard error; Tk0, absorption duration; V/F, apparent distribution volume.

Adult Model

The best model was a two-compartment model with zero-order input, a lag time, and first-order elimination. The residual error model was proportional. Interindividual variability was estimated for all parameters. No covariates significantly improved the model.

The final model, thus, was:

(S)-vigabatrin:

$$\text{Tlag (h)} = 0.241$$

$$\text{Tk0 (h)} = 0.111$$

$$\text{Cl/F (L/h)} = 11.5$$

$$\text{V1/F (L)} = 54.6$$

$$\text{Q/F (L/h)} = 6.85$$

$$\text{V2/F (L)} = 41.8$$

where Tlag corresponds to the lag time, Tk0 to the zero-order absorption constant, Cl/F to the elimination clearance (F being the bioavailability), V1/F to the central volume of distribution, Q/F to the distribution clearance, and V2/F to the peripheral volume of distribution.

Scaling the Adult Model to Children

First, allometric scaling was added to the adult model to describe the size-related changes of the PK parameters during growth. Those size differences on PK parameters were described using the following equation:

$$F_{size} = \left(\frac{BW_{child}}{BW_{adult}}\right)^{\alpha} \quad (7)$$

where BW_{child} is the body weight of the child i, BW_{adult} is the standard adult body weight (ie, 70 kg), and α is the allometric exponent describing the relationship between BW and the parameter. This exponent was fixed to the theoretical values of 1 for the volumes and 0.75 for the clearances.[28]

Then maturation of the glomerular filtration described by Rhodin et al[24] was applied to Cl/F, as follows:

$$Cl_{Child}/F = Cl_{adult}/F \times \left(\frac{BW_{child}}{70}\right)^{0.75} \times \frac{PMA^{3.40}}{47.7^{3.40} + PMA^{3.40}} \quad (8)$$

where PMA is the postmenstrual age (in weeks).

Final Model Evaluation

Pediatric Model. No significant bias was observed on the graphs representing the IWRES (Figure S1) and the NPDE versus population-predicted concentrations or time after dose (Figure 1), nor on the graphs representing the observed versus predicted concentrations (Figure 2). No bias was observed on the pcVPC for either enantiomer (Figure 3).

A satisfying consistency was found between the observed and calculated concentrations for the

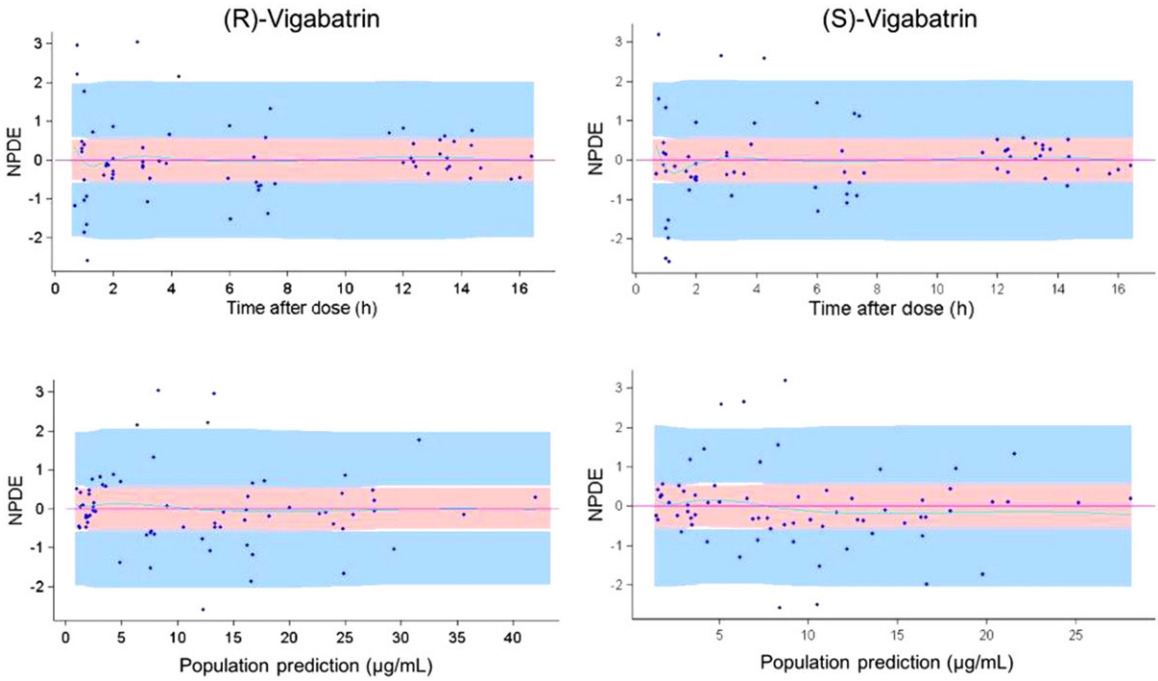

Figure 1. Normalized prediction distribution errors (NPDE) versus population prediction and time after dose for (R)-vigabatrin (left) and (S)-vigabatrin (right). The lower and upper blue areas are the 90%CI of the fifth and 95th simulated percentiles. The red area is the 95%CI of the 50th simulated percentile. Blue line = spline.

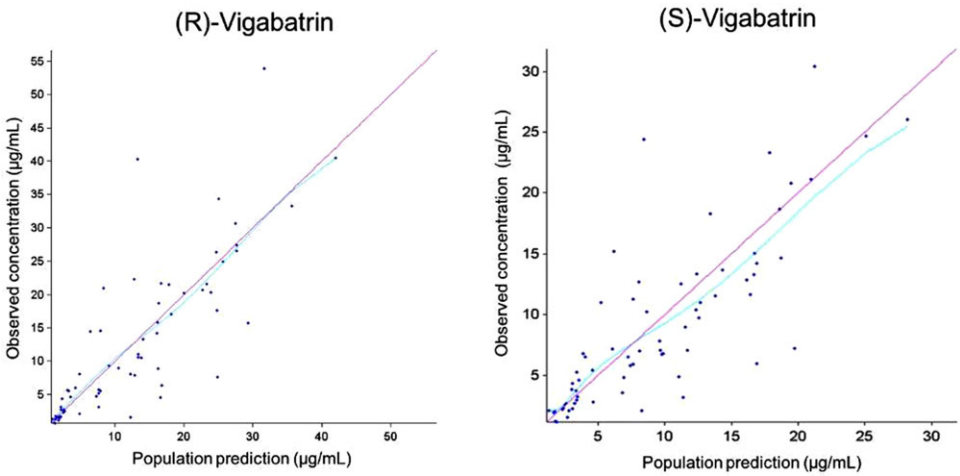

Figure 2. Observed concentrations versus population-predicted concentrations of (R)-vigabatrin (left) and (S)-vigabatrin (right). Pink line = identity (Y = X) line and blue = spline.

validation dataset with MPE <16% and RMSE <6 for both molecules (Figure S2). The correlation coefficient (r) was 0.81 for (R)-vigabatrin and 0.85 for (S)-vigabatrin.

Posterior predictive checks also supported the satisfying predictive ability of the model for both enantiomers, as the AUC, C_{trough}, and elimination $t_{1/2}$ derived from the paper by Rey et al[16] were within the 95% prediction interval determined by Monte Carlo simulations (Figure 4).

Adult Model

No bias was observed on the classic goodness-of-fit plots (Figure S3, S4).

The prediction of the pediatric data with this adult model scaled to children provided MPE and RMSE of 23.2% and 5, respectively.

Simulation Study

The AUC of (S)-vigabatrin increased with the dose but was constant between BW for the same weight-based

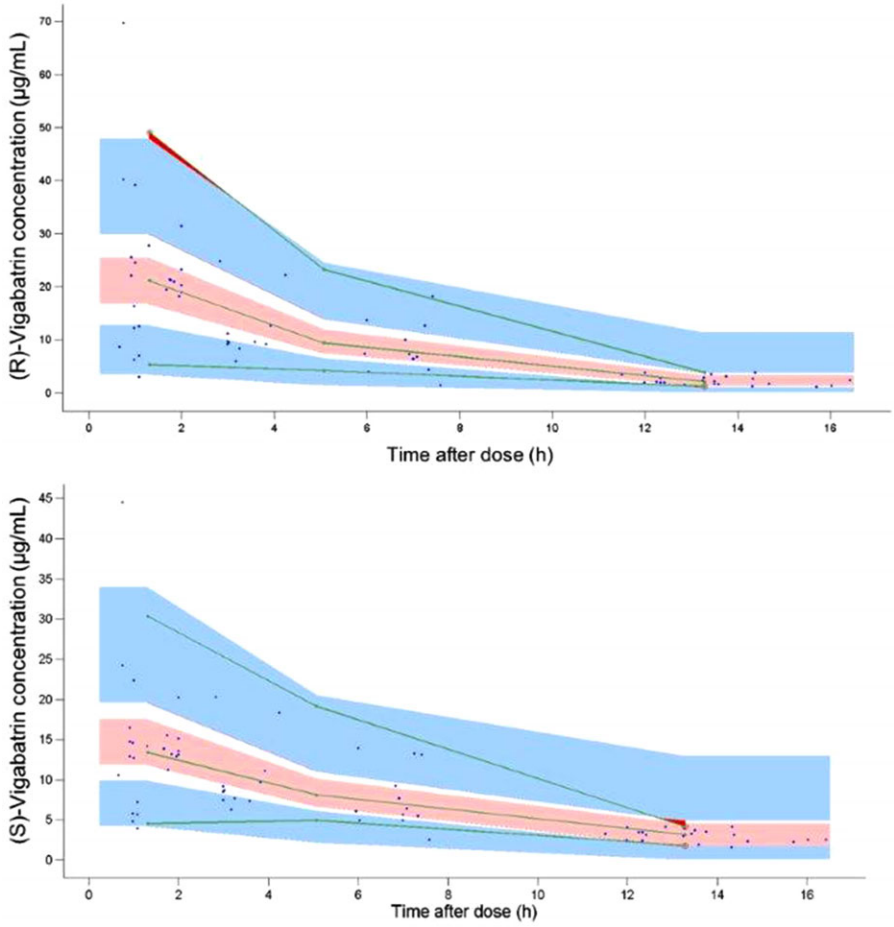

Figure 3. Prediction corrected visual predictive checks (pcVPC) for (R)-vigabatrin (top) and (S)-vigabatrin (bottom). Blue dots represent the observed concentrations; green lines correspond to the fifth, 50th, and 95th percentiles of the observed concentrations. The pink area corresponds to the 95%CI of the 50th percentile based on simulated concentrations. The upper and lower blue areas correspond to the 95%CI of the 95th and fifth percentiles, respectively, based on simulated concentrations. The red area and circles represent the outliers (empirical percentiles outside the prediction intervals).

dose. Conversely, for the same dose, AUC of racemic vigabatrin increased with BW, due to the increase in the AUC of (R)-vigabatrin (Figure 5).

The risk to achieve an AUC potentially obtained with the highest suboptimal dose of 36 mg/kg was investigated: it was equal to 70%, 11%, and 6% for doses of 50, 75 and 80 mg/kg/d, respectively (Table 3). This risk progressively decreased with higher doses and became null for a dose of 95 mg/kg/d. The simulations performed with the adult model scaled to children provided similar results (Table 3).

The probability of simulated C_{trough} of racemic vigabatrin to be included in the reference range of 0.8-36 μg/mL was also investigated: the probability was higher than 91% for each simulated dose (Table 3).

Discussion

The present study characterizes the PK of the S and R enantiomers of vigabatrin in infants and young children with epilepsy. A one-compartment model with zero-order absorption and first-order elimination appropriately described the data for each enantiomer.

For (R)-vigabatrin, a mean post-Bayesian estimate of weight-normalized clearance of 0.16 L/h/kg was obtained, corresponding to a mean $t_{1/2}$ of 3.5 ± 0.4 hours. Based on our model, the $t_{1/2}$ is expected to increase from 2.9 to 4.1 hours for BW increasing from 9 to 20 kg. This is in accordance with the finding of Rey et al[16] who found a $t_{1/2}$ of 2.87 ± 1.03 hours for children aged 1 month-2 years and 5.68 ± 2.86 hours in children aged 2-15 years. We obtained a mean weight-normalized volume of 0.8 L/kg, which is the lower limit of the range of values reported in the literature for racemic vigabatrin (0.8-1.1 L/kg).[3,29] Lastly, the present empirical allometric coefficients (0.771 for Cl/F and 1.01 for V/F) were similar to the theoretical values of 0.75 for clearance and 1 for volume.[30]

Regarding the active enantiomer, (S)-vigabatrin, the mean Bayesian estimate of weight-normalized clearance of 0.19 L/h/kg corresponded to a $t_{1/2}$ of 5.0 ± 0.8 hours. According to our model, there is no trend

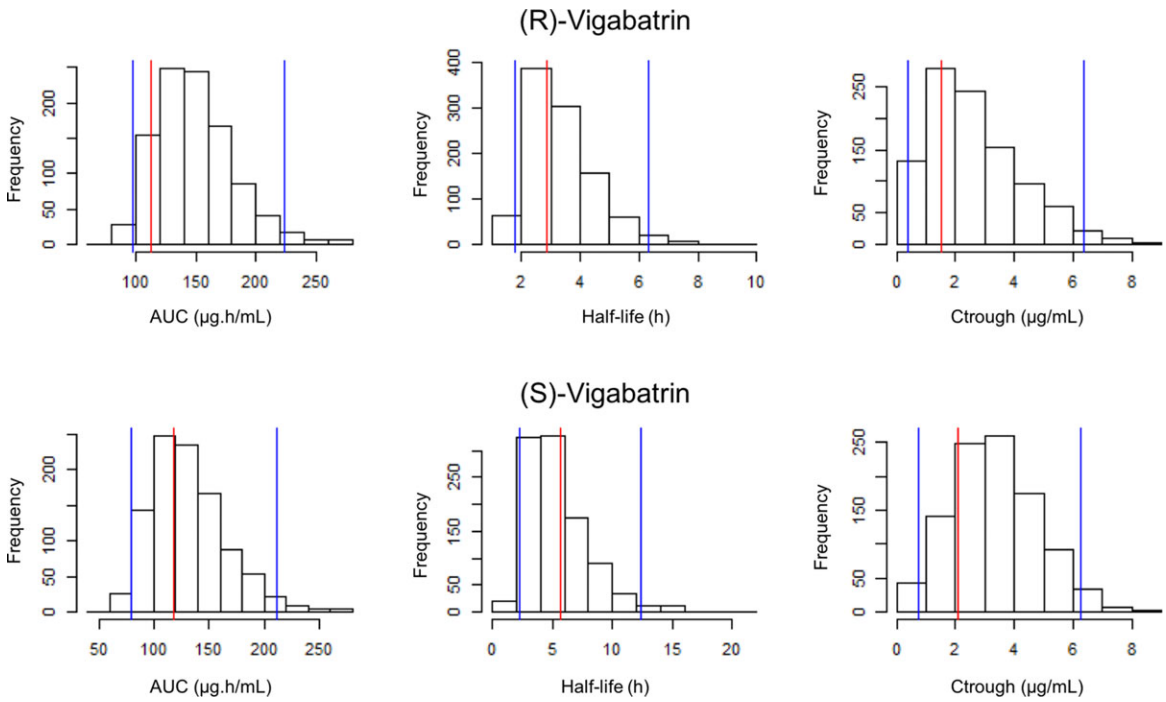

Figure 4. Posterior predictive checks for area under the curve (AUC), $t_{1/2}$, and C_{trough} for each enantiomer. The blue lines represent the bounds of the 95%CIs. The red line corresponds to the value obtained for $AUC_{0-\infty}$, $t_{1/2}$, and C_{trough} in the study of Rey et al.[16]

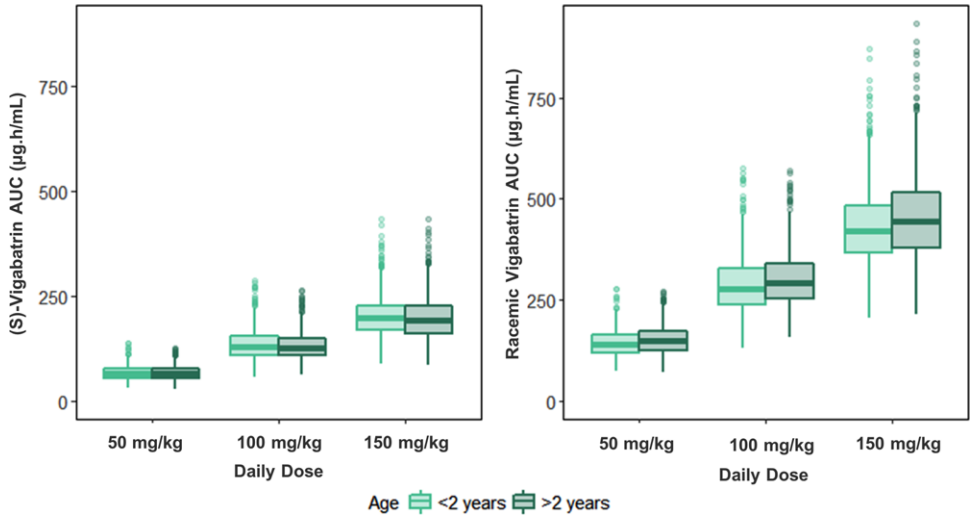

Figure 5. Area under the curve (AUC) simulations for (S)-vigabatrin (left) and racemic vigabatrin (right) for BW of 9 kg (<2 years) and 14.7 kg (≧2 years).

between age and elimination $t_{1/2}$, which was consistent with the results of Rey et al (5.65 ± 1.52 hours for children aged 1 month-2 years and 5.47 ± 1.93 hours for children aged 2-15 years).[31] Apparent weight-normalized volume was 1.4 L/kg, which is slightly greater than the reported value for racemic vigabatrin (0.8-1.1 L/kg).[3,29] Of note, the mean of the distribution volume of the 2 enantiomers obtained by the present model (1.08 L/kg) is similar to the value reported for racemic vigabatrin. Thus, our results support a different value of distribution volume between the 2 enantiomers, with the value for the S(+)-enantiomer being higher. This difference could be explained by lower bioavailability or wider tissue distribution of the S(+)-enantiomer, as proposed by Challier et al.[32] In fact, there could be a stereoselectivity in the fixation or the transport of vigabatrin, indicating a possible involvement of proton-coupled amino acid transporter.[33] This stereoselectivity has been described in neurons by Schousboe et al.[34]

The empirical allometric coefficient obtained for the distribution volume of (S)-vigabatrin corresponded to

Table 3. Median and 95%CI of Simulated Steady-State AUC for (S)-Vigabatrin, According to Different Daily Doses of the Racemate, and Probability of 95%CI AUC Overlap With 95%CI of the 36-mg/kg/d Dose Median and 95%CI of Simulated Steady-State C_{trough} for Racemic Vigabatrin, for the Same Daily Doses of the Racemate, and Probability of C_{trough} for Racemic Vigabatrin Within the Reference Range of 0.8-36 μg/mL

	AUC (S)-Vigabatrin				C_{trough} Racemic Vigabatrin		
Dose (mg/kg/day)	Median (μg.h/mL)	95%CI	Risk (%) From Pediatric Model	Risk (%) From Adult Model	Median (μg/mL)	95%CI	Probability (%)
36	46.4	30-73.4	100	100	2.48	0.33-6.8	91.8
50	65.1	39.4-105.5	69.6	67.8	3.61	0.54-9.97	94.6
55	71.5	45-114.3	55.4	56.3	4.82	0.96-12.2	98.1
60	78.7	48.7-127.3	36.3	42.2	5.35	0.99-13.8	98.5
65	84.9	53.3-137.5	24.9	30.1	5.87	0.8-14.6	97.4
70	90.8	57.2-144.4	17.2	20.9	6.22	1.01-15.5	98.4
75	97.7	61.3-156.1	11.4	12.0	5.43	0.93-14.4	98.1
80	103.9	64.7-164.6	6.1	7.7	6.86	0.87-18.1	98
85	108.5	68.1-177.6	2.7	4.3	7.26	1.21-19.3	98.6
90	117.2	72.3-188.8	0.4	1.9	7.79	1.28-20.1	98.9
95	122.1	73.5-197.5	0	0.5	8.26	1.33-21.1	98.2
100	129.4	80.1-211.5	0	0	7.25	1.04-19.5	98.3
150	196.7	121-316.2	0	0	11.11	1.94-28.9	99.2
175	225.8	140-361.6	0	0	12.5	1.49-33.87	96.9

AUC, area under the curve; C_{trough}, trough concentration.
Risk is the percentage of 95%CIs of simulated AUCs overlapping with the 95%CI of the AUC obtained with the 36-mg/kg/d dose; probability is the percentage of simulated C_{trough} for racemic vigabatrin included within the 0.8-36 μg/mL reference range.

the theoretical value of 1.[30] The value of 1.04 obtained for the allometric exponent for Cl/F was different from the theory and explains why our simulations suggest no change in (S)-vigabatrin AUC for a given dose in our population (Figure 5). This is nevertheless in accordance with the conclusion by Rey et al that a similar dose/kg could be given for children aged >1 month.[16] However, the small number of subjects in our study (due to the very low incidence of infantile spasms) combined with the narrow age range of the included children (which reflects the age range of infantile spasms) may have penalized the estimation of this allometric exponent. The adult model scaled to children allowed to investigate the evolution of the weight-normalized clearance of (S)-vigabatrin according to age (Figure S5). According to this evolution, the maximum change in weight-normalized clearance within our investigated age range was very low (ie, 0.19-0.22 L/h/kg) and would probably be difficult to estimate from sparse data. Another interesting point is the comparison between the results of the study by Rey et al[16] and this theoretical evolution in the weight-normalized clearance of (S)-vigabatrin. Indeed, according to this theoretical evolution, the mean ages and weights of the 2 groups included in the Rey et al study (12.1 months/8.9 kg and 8.7 years/31 kg) corresponded to mean weight-based clearances of 0.23 and 0.19 L/h/kg, respectively. This small difference would probably be hardly identified from clinical data and it is possible that the age-categorization chosen in this study did not allow an appropriate evaluation of the age-related changes in the PK of (S)-vigabatrin. Our approach using adult data considered glomerular filtration as the sole elimination pathway of vigabatrin, which is likely a simplification of reality. In fact, the renal clearance of vigabatrin was found to be 20% lower than glomerular filtration rate in healthy volunteers,[35] suggesting the implication of tubular reabsorption. To our knowledge, these transporters, as their maturation function, have not been identified to date. Differential affinity between the 2 enantiomers of vigabatrin for these renal transporters, as also suggested above for proton-coupled amino acid transporter, may explain the different allometric exponent empirically found for the clearances of (R)- and (S)-vigabatrin.

Taken together, these elements suggest that our pediatric model should not be applied to children with ages or body weights outside the values observed in the present study.

A major issue regarding vigabatrin is the determination of the minimal effective dose. Indeed, because of the high severity of infantile spasms and the risk of pharmacoresistant relapse after initial spasm control, combined with the exposure-related retinal toxicity of vigabatrin, no classic dose-ranging study has been undertaken for vigabatrin in infantile spasms to date. In their clinical trial, Elterman et al compared 2 groups of young children with infantile spasms, treated randomly with low (18-36 mg/kg/d) or high (100-148 mg/kg/d) doses of vigabatrin. They found that the group receiving low doses demonstrated lower efficacy. With high doses, the rate of spasms was higher and the relapse rate was lower. It was then concluded that doses lower than 36 mg/kg/d were ineffective.[14,15] The current

summary of product characteristics recommends an initial dosage of 50 mg/kg/d, with a maximum dose of 150 mg/kg/d. For the vigabatrin trials performed in infants with infantile spasms, this initial dosage was increased to 100 mg/kg/d over no more than 3 days.[36–39] In addition, prompter control of spasms is associated with better cognitive outcome.[40,41] As a result, the dose interval between 50 and 100 mg/kg/day has never been tested from the efficacy point of view, but it may be a potential margin for choosing a lower dose expected to reduce the incidence of retinal toxicity within this dose range. According to our simulations, doses lower than 80 mg/kg/d should be avoided to initiate the treatment, as they are associated with an important risk of exposure overlap with the 36-mg/kg/d dose (Table 3). We believe this result is supported by the published clinical trials because, as explained above, all the children who started vigabatrin at a 50-mg/kg/d regimen had their dose very quickly increased to 100 mg/kg.[36–39] The daily dose of 80 mg/kg seems to be the lowest dose with a negligible risk (ie, <10%) to provide an exposure observed with the suboptimal 36-mg/kg/d dose and could consequently be considered as the minimal effective dose in infantile spasms.

Besides this major indication, vigabatrin is also approved as adjunctive therapy in pharmacoresistant focal epilepsy from infancy to adulthood. However, there has been no randomized controlled trial or dose trial performed in pediatric subjects. In the present study, the proportion of patients with focal epilepsy was very low compared to patients with infantile spasms (Table 1).

Therapeutic drug monitoring is helpful for individualizing the dose for several antiepileptic drugs. However, no PK/PD data for vigabatrin in infantile spasms are available to date. Patsalos et al and Gram et al reported that the expected vigabatrin concentration in adults weas 0.8-36 μg/mL for a vigabatrin dose of 1000-3000 mg/d, but this range of expected concentration did not correlate with clinical outcome.[25,26] C_{trough} was simulated in the present study for racemic vigabatrin: almost all simulated C_{trough} values were within this reference range, even using the 36-mg/kg/d dose that was proven suboptimal. This indicates that the reference range of vigabatrin should be re-evaluated for children treated for infantile spasms. Until specific PK/PD data are available in this context, physicians could use the range of C_{trough} provided in Table 3 as the basis for the interpretation of the measured concentrations of vigabatrin.

In conclusion, we present here a PK model for the 2 enantiomers of vigabatrin in infants and young children. Although this remains a pilot study, given the small number of included patients, results were supported by an adult PK model scaled to children. These 2 approaches confirmed that the weight-normalized dose should be equivalent for patients aged 6 months-5.7 years with epilepsy. Based on our simulations, a minimal dose of 80 mg/kg/d could be sufficient to control infantile spasms, compared with the 100 mg/kg/d used in clinical practice. Nevertheless, until a relationship between plasma concentration and effect is available, dose adjustment should remain based on clinical effectiveness.

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Author Contributions

R.N., C.C., G.P., H.B., and V.J. designed the study. M.O., C.R., and V.J. performed the PK analysis. M.O. and P.D. analyzed the blood samples. C.C. and R.N. conducted the clinical trial (R.N.: principal investigator). M.O., C.R., and V.J. wrote the manuscript.

Disclosures

M.O., C.R, P.D., G.P., O.D., and R.N. have nothing to disclose. H.B. reports other from ORPHELIA Pharma, during the conduct of the study, a patent WO2017153800: solid dosage forms of vigabatrin pending. C.C. reports personal fees and nonfinancial support from BIOCODEX, personal fees from UCB-Pharma, personal fees and non-financial support from BIAL, non-financial support from DESITIN, personal fees and nonfinancial support from ADVICENNE, outside the submitted work. V.J. reports grants from the French National Research Agency, during the conduct of the study; and research grants by BIOCODEX.

Data Accessibility

Study data are accessible on demand by contacting the corresponding author: vincent.jullien@aphp.fr.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.