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Pharmacokinetic evaluation of vigabatrin dose for the treatment of refractory focal seizures in children using adult and pediatric data

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ABSTRACT

Vigabatrin is indicated as adjunctive therapy for refractory focal seizures. For children, European recommendations indicate maintenance doses varying from 30 to 100 mg/kg/day for this indication. Since cumulated dose was associated with retinal toxicity, it is essential to administrate the lowest effective dose to patients. This work was conducted with the purpose to determine the pediatric doses of vigabatrin that allow a similar exposure than effective doses in adults (2–3 g/day) through a pharmacokinetic (PK) study, using both pediatric and adult data. For this study, we focused on the active S(+) enantiomer of vigabatrin. First, the adult effective exposition range of vigabatrin-S was determined from an adult PK model. Then, this same model was scaled to the pediatric population using allometry and maturation principles to account for growth and development. The ability of the model to predict pediatric data was assessed by comparing population predictions with observed pediatric data. Finally, the extrapolated pediatric model was used to simulate pediatric expositions which were compared to the adult exposition range (36.5–77.9 mg.h/L). From those simulations, we determined that, for children aged between 3 months and 18 years, doses between 40 and 50 mg/kg/day allow vigabatrin-S expositions similar to those found in adults at the recommended posology. We proposed those doses as optimal maintenance doses that may be increased, if necessary, by slow titration.

1. Introduction

Seizures are fairly common in childhood especially in newborns, with an incidence slowly decreasing until reaching adulthood (Berg et al., 2013). Of those, focal seizures (FOS), are the most frequent type observed in children (Berg et al., 2013). Vigabatrin (VGB), which is indicated as monotherapy for infantile spasms (IS) (European Medicines Agency, 2002; Food and Drug Administration, 2015), is also licensed as adjunctive therapy for refractory FOS (rFOS) in children and adults, since 1989 in Europe and 2009 in the United States (US) (Kwan et al., 2011). VGB is a specific and irreversible inhibitor of the aminobutyric acid (GABA) transaminase and its activity is only due to its S-enantiomer (Meldrum and Murugaiah, 1983), even though VGB is orally administered as a racemic.

Regarding its pharmacokinetic (PK) properties, VGB is not metabolized to any significant degree (Durham et al., 1993), and its elimination is principally mediated by the kidney (Haegele et al., 1988). Furthermore, it was demonstrated that the R enantiomer did not affect the PK of VGB-S and no chiral inversion was observed (Haegele and Schechter, 1986).

VGB treatment is associated with retinal toxicity, resulting in permanent peripheral visual field loss (Eke et al., 1997; Hardus et al., 2001; Malmgren et al., 2001). This irreversible adverse effect is related to the cumulative dose and treatment duration (Maguire et al., 2010; Wild et al., 2009). The choice of the dose must therefore be carefully contemplated. On one hand, overdosage must be avoided to decrease the cumulated dose of VGB and the probability of retinal toxicity. On the other hand, underexposure and consequent uncontrolled of seizures may lead to cognitive and behavioral disorders (Auvin, 2011).

Because of this irreversible toxicity the development of VGB has

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Table 1
Summary of pediatric clinical trials.

Study	Study design	Participants enrolled [completed]	Age range	Dose	Responders*	Comments about dosage
Livingston et al. (1989)	Open, add-on, preliminary screening	135 [112] (FOS = 42%)	2m-2y	Initial dose: 40 – 80 mg/kg/day Mean maintenance dose: 87 mg/kg/day (27 – 100)	38%ǂ (49%ᵖ)	High doses (> 100 mg/kg/day) were not associated with greater efficacy
Luna et al. (1989)	Single-blind *vs* placebo, add-on	61 [45] (FOS = 47.5%)	1y-19y	Initial dose: 50 mg/kg/day Maintenance dose: up to 150 mg/kg/day	38% ǂ	Doses over 100 mg/kg does not seem useful
Dulac et al. (1991)	Single blind *vs* placebo, add-on	66 [58] (FOS = 48.5%)	2y-15y	Initial dose: 25 – 75 mg/kg/day Maintenance dose: 25 – 125 mg/kg/day Titration of the dose up to 50-150 mg/kg/d	50 %ǂ	Recommendation to initiate therapy at 40 mg/kg/day and to increase up to 80 mg/kg/day if necessary, since higher doses did not result in a better response.
Herranz et al. (1991)	Open dose-ranging, add-on	20 [20] (FOS = 95%)	2m-18y	From 1 – 2 g/day (± 60 mg/kg/day), up to 2 – 4 g/day (± 80-100 mg/kg/day) Fixed doses depending on BW	60 – 80 % ǂ	Doses above 60 mg/kg/day produced no additional beneficial effect
Uldall et al. (1991)	Open dose-ranging, add-on	33 (FOS = 82%)	10.5y[a]	> 8y : 2 g/day < 8y : 40-80 mg/kg/day	54 % ǂ (at 6 months)	Optimum doses between 2-3 g/day. Doses of 4-6 g/day produce no improvement and could even increase seizure rates
Gibbs et al. (1992)	Retrospective, add-on	43 [43] (FOS = 46.5%)	1y-16y	From 55-85 mg/kg/day up to 100 mg/kg/day	42% ǂ (60%ᵖ)	The dose was increased in only 10 patients
Bernardina et al. (1995)	Single blind *vs* placebo, add-on, fixed-sequence	46 [39] (FOS = 100%)	7m-12y	40 mg/kg/day (single dose), increasing up to 80 mg/kg/day	76 %	Doses > 80 mg/kg/day produce no additional benefit in children (except those with IS)
Gherpelli et al. (1997)	Open, add-on	47 [47] (FOS = 79%)	1y-18y	From 20 – 30 mg/kg/day up to 80 – 100 mg/kg/day	58.1 %ᵖ	Mean effective dose = 63.6 mg/kg/day (range: 19.3-110.5 mg/kg/day)
Nabbout et al. (1997)	Open, add-on	178 (FOS = 100%, IS = 25%)	1w-19y	> 2y : 50-100 mg/kg/j < 2y : 100-200 mg/kg/j	70% ǂ	–
Gobbi et al. (1999)	Open, Monotherapy vs CBZ	40 [37] (FOS = 100%)	1y-17y	Initial dose : 20 – 80 mg/kg/day Maintenance dose: 20 – 90 mg/kg/day	73-82%	–
Zamponi and Cardinali (1999)	Open, Monotherapy vs CBZ	38 [38] (FOS = 100%)	6m-10y	Initial dose: 10 – 15 mg/kg/day Maintenance dose: 50 – 60 mg/kg/day	76.3 %	–
Nielson et al. (2014)	Pop PK Data from 3 non reported RCT *vs* placebo (interrupted)	175 (FOS = 93%)	3y-16y	Initial dose: 20 mg/kg/j Maintenance dose: 60-100 mg/kg/j weight-based**	–	** 10-15 kg : 0.5-1 g/j 16-30 kg : 0.5-2 g/j 31-50 kg : 1-3 g/j > 50 kg : 1-4 g/j

ǂfor all seizure types.
ᵖfor partial onset seizures only.
FOS = focal seizures.
Pop PK = Population pharmacokinetics.
RCT = randomized controlled trial.
[a] Only the mean age was indicated.
* Responders = patients with a ≥50% reduction in seizure frequency.

been interrupted so that there are neither dose-ranging studies nor randomized-controlled trial available in children with FOS, but only observational studies. Since clinical responses were observed with doses between 40 and 80 mg/kg/day, Dulac et al. (1991) recommended to initiate treatment at 40 mg/kg/day and to increase, if necessary, up to 80 mg/kg/day. Consistently, different studies evidenced that high doses (> 60–100 mg/kg/day) were not associated with greater efficacy (Bernardina et al., 1995; Dulac et al., 1991; Herranz et al., 1991; Livingston et al., 1989; Luna et al., 1989; Uldall et al., 1991). A brief review of these studies is available on Table 1. However, current dose recommendations are not consistent with these results. The current European Summary of Products Characteristics (SPC) recommends in 10–50 kg children a starting dose of 40 mg/kg followed by a wider maintenance dose range: 30 to 100 mg/kg/day (European Medicines Agency, 2002). For children > 50 kg, a maintenance dose of 2000 to 3000 mg/day is recommended. On the other hand, US recommendations propose, for children with rFOS between 10 and 16 years and weighing 25 to 60 kg, a starting dose of 250 mg BID, corresponding to dose/kg decreasing from 20 to 8 mg/kg/day, followed by a fixed maintenance dose of 1000 mg BID corresponding to a weight-normalized dose decreasing from 80 mg/kg to 33 mg/kg during this period. For children > 16 years or 60 kg, the maintenance dose can be increased to 3000 mg/day. There are no US approval or dose recommendations for rFOS in children < 10 years (Food and Drug Administration, 2015).

Considering the efficacy of an antiepileptic drug observed in adults for rFOs can be extrapolated at least to children > 2–4 years (Barrett et al., 2018; European Medicines Agency, 2010; Food and Drug Administration, 2016; Pellock et al., 2017), a reasonable assumption would be that the exposure/efficacy relationship of a drug may be similar between adults and children. Thus, a possible approach to determine a relevant pediatric dose could be to determine the dose providing in children an exposure of VGB-S similar to the one obtained with the effective adult dose.

However, current knowledge about VGB pharmacokinetics in children, especially about the active enantiomer, is not sufficient to attain this objective. To our knowledge, only two studies evaluated VGB-S PK in the pediatric population: a study enrolling 6 neonates (15 to 26 days old) (Vauzelle-Kervroëdan et al., 1996) and another one including 12 infants and children aged 5 months to 14 years (Rey et al., 1990). The first study focused in a reduced age range while the other compared the PK properties of both enantiomers in two age groups (5 months^{-2} years versus 4–14 years). No study really investigated the evolution of VGB-S pharmacokinetics over time, probably because of the small number of children receiving VGB. The time course of racemic VGB was previously studied in children and adults (Nielsen et al., 2014), with data obtained from interrupted randomized clinical trials (due to retinal toxicity), but no information about the enantiomers was available.

To deal with this situation, one of the methods used to investigate pediatric dosing schemes without a significant amount of PK data in children is to scale an adult PK model to children. The principle of scaling is to extrapolate pediatric parameters from adult parameters taking into account the size- and maturation-related changes (Anderson and Holford, 2008).

So, the aim of this work was to determine whether the wide maintenance dose range indicated in the SPC is reasonable, and to determine the optimal starting pediatric dose for rFOS according to age, using PK extrapolation from adult to children for VGB-S.

2. Material and methods

A complete description of the methods used in this work is presented in Appendix A. An overview is presented in Fig. 1. Briefly, the adult data presented by Haegele and Schechter (1986) were used to build an adult PK model for the active enantiomer of vigabatrin (VGB-S). Monte Carlo simulations were performed with this model in order to determine the expositions (area under the curve, AUC) obtained with

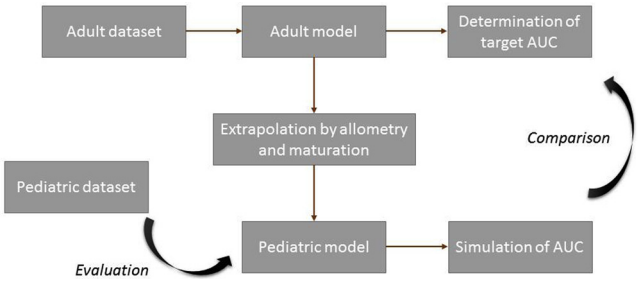

Fig. 1. Overview of the extrapolation method used in this analysis.

effective doses, i.e., 2–3 g/day (Gram et al., 1985; Grünewald et al., 1994; Loiseau et al., 1986; McKee et al., 1993; Rimmer and Richens, 1984; Tartara et al., 1986; Tassinari et al., 1987) currently recommended in the drug SPC (European Medicines Agency, 2002; Food and Drug Administration, 2015) for rFOS. These AUC associated with efficacy became the target AUC for children. The adult model was then extrapolated to children with the following steps: (i) theoretical allometry, i.e., the effect of size, was applied to the volumes and clearances paremeters (M_{allo}), (ii) a maturation function, i.e., the effect of age, for the glomerular filtration rate (GFR) was added to the elimination clearance. Two different maturation functions were tested, one developed by Hayton (2002) (M_{Hayton}) and the other developed by Rhodin et al. (2009) (M_{Rhodin}).

Pediatric data were available for children with IS and/or FOS, aged 5 months to 5.7 years. This dataset was used to evaluate the three models (M_{allo}, M_{Hayton} and M_{Rhodin}). The model that gave the less biased and more precise predictions was kept as the final extrapolated model. From this model and using Monte Carlo simulations, the pediatric doses needed to obtain AUC similar to the effective AUC in adults were determined.

3. Results

The median [95% confidence interval] simulated adult AUCs were 43.5 [36.5–51.6] mg.h/L and 64.8 [55.3–77.9] mg.h/L for doses of 2 g/day and 3 g/day respectively. Using those values, we determined an AUC target comprised between 36.5 and 77.9 mg.h/L (Fig. 2).

Concerning the Monte Carlo simulations, a boxplot of the simulated pediatric AUC_S with respect to daily weight-normalized dose and age is provided on Fig. 3. A dose of 40 mg/kg/day provided the highest probability to be within the target AUC_S range for children aged 10–18 years (Table 2). For children aged between 6 months and 5 years, a dose of 50 mg/kg/day provided the highest probabilities to be within the 36.5–77.9 mg.h/L range (Table 2 and Fig. 3).

4. Discussion

Neonates, infants and children greatly differ from adults, not only in terms of size but also in body composition, organ maturation and development, enzyme capacity, growth, etc… There are many anatomical, physiological and biochemical child-specific characteristics that affect exposure and response in this population (Fernandez et al., 2011; Kearns et al., 2003). As a result, appropriate PK studies are mandatory in children in order to develop rational pediatric dosing regimens. However, those studies may be challenging in pediatric epilepsy, not only because of the ethical issues at this age range, but also due to the limited number of subjects available for inclusion (De Cock et al. (2011)). Scaling an adult PK model to children may be an alternative. With this approach, body weight (BW) and age are usually considered to reflect these size- and maturation- related changes respectively. Allometry, which originally aimed to extrapolate parameters between species, is now accepted as the most accurate model to describe the influence of size on parameters (Anderson and Holford, 2008). The

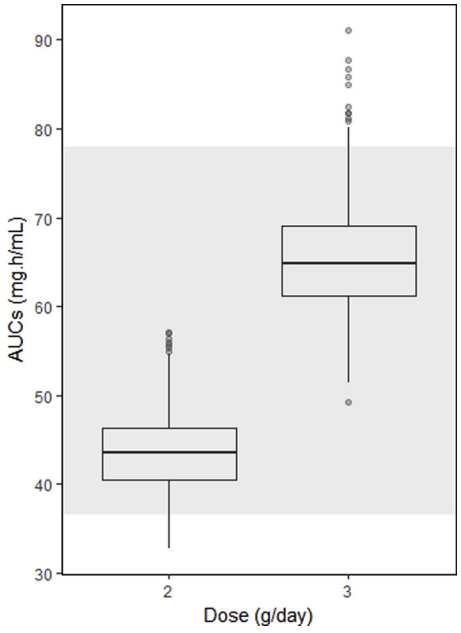

Fig. 2. Boxplot of adult vigabatrin-S areas under the curve (AUC_S) with respect to the daily dose. The grey area represents the calculated target range.

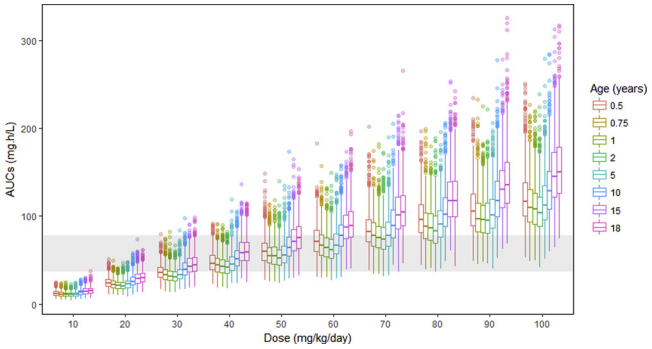

Fig. 3. Evolution of vigabatrin-S areas under the curve (AUC_S) with age and dose. The grey area represents the target range determined in adults.

Table 2
Vigabatrin-S expositions obtained with daily doses of 40 and 50 mg/kg and their probability to be within the 36.5 and 77.9 mg.h/L adult range.

Age (years)	Dose (mg/kg/day)	AUC_S (mg.h/L)		Probability (%)
		Median	[IC95]	
0.5	40	46.3	[28 - 76]	81.7
	50	59.5	[35.9 - 97.8]	84.7
0.75	40	44.3	[27.4 - 69]	75.9
	50	54.6	[34 - 88.4]	87.7
1	40	42.5	[26.4 - 73]	73.2
	50	54.6	[33.7 - 86.9]	85.4
2	40	41.7	[26.5 - 68.4]	70.5
	50	52.4	[31.2 - 85.7]	86.4
5	40	45.3	[26.9 - 73]	78.2
	50	55.7	[33.5 - 92.4]	85
10	40	51.5	[31.2 - 82.7]	86.3
	50	64.5	[40.1 - 105]	77
15	40	58.2	[36.3 - 95.3]	83.5
	50	70.9	[43.3 - 116.7]	63.9
18	40	58.8	[35.7 - 99.6]	82.4
	50	75.1	[47.8 - 117.7]	56

AUC_S – Vigabatrin-S area under the curve.
IC95 – 95% confidence interval.

maturation function is a sigmoid function that adjusts elimination clearance to age and tends towards 1 with increasing age (Tod et al., 2008).

For compounds solely eliminated via glomerular filtration as VGB is, weight-normalized clearance (CL) increases rapidly in neonates, along with the GFR. By the end of the first year of age, GFR reaches adult values and, during preschool years, it exceeds those values, until pre-pubertal age. This is probably due to a relative larger kidney size in children and/or an increase in kidney function per unit of kidney weight (Chen et al., 2006; Kearns et al., 2003; Rodieux et al., 2015). This developmental evolution was taken into account in our extrapolated model with the addition of Rhodin's et al. (2009) GFR maturation function on VGB-S clearance.

However, to our knowledge, no study has been conducted so far to evaluate the contribution of the different pathways involved in VGB renal elimination. It is possible that tubular reabsorption may be involved since VGB renal clearance was found to be about 20% lower than true or expected creatinine clearance in adults (Haegele et al., 1988) and children (Rey et al., 1990), respectively. Unlike glomerular filtration and active secretion, there is no maturation model developed for tubular reabsorption. It is indeed a pathway difficult to study and its development is under-investigated (Strolin Benedetti et al., 2005). However, it seems that maturity is reached between 1 and 3 years after birth (Hua et al., 1997), the age range for which a validation of our model was performed with external data and gave good results (Table A1 of the Appendix A).

This work evidenced that, for children aged between 3 months and 18 years, doses between 40 and 50 mg/kg/day should provide VGB-S exposures similar to those found in adults at the recommended posology for rFOS (2–3 g/day) (Fig. 3). These results are in accordance with the European recommendations and Dulac et al. (1991) results, i.e. to start the therapy at 40 mg/kg/day with further change based of clinical responsiveness. Oppositely, our results do not support the current US recommendations consisting in a lower starting dose (8–20 mg/kg) and to an important decrease in the weight-normalized dose between 10 and 16 years (Food and Drug Administration, 2015). Indeed, according to Table 2, the mean increase in the AUC of VGB-S for the same dose/kg within this age range will be around 15%, which seems negligible. The current French SPC recommends doses ranging from 30 to 100 mg/kg/day (European Medicines Agency, 2002). According to our simulations (Fig. 2), doses > 80 mg/kg will provide an exposure in VGB-S much higher than the one observed in adults, more particularly for children > 6 years. That supports the previous lack of evidence for a greater efficacy with high VGB doses (Bernardina et al., 1995; Dulac et al., 1991; Herranz et al., 1991; Livingston et al., 1989; Luna et al., 1989; Uldall et al., 1991).

The consistency between our results and the results of the clinical studies cited above supports the relevance of our hypothesis about a similar exposure/effect relationship between adults and children. This hypothesis was based on the fact that the efficacy of antiepileptic drugs observed in adults for rFOS can be extrapolated to children > 2–4 years (Barrett et al., 2018; European Medicines Agency, 2010; Food and Drug Administration, 2016; Pellock et al., 2017). However, extrapolation of drug efficacy from adults to children < 2–4 years has not been validated to date, so efficacy trials are mandatory in these young children. Consequently, the doses we determined could be used as a basis for such trials.

The main limitation of this work is that the predictive ability of the extrapolated model could not be validated for children > 5 years because of the lack of pediatric PK data. However, it was demonstrated that the use of theoretical allometry is accurate for all drugs undergoing glomerular filtration after the age of 5 years (Calvier et al., 2017). This allows us to conclude that our extrapolated model should be valid from 6 months to 18 years. Another limitation is the small number of adult subjects used to build the model. However, the model described well the data and was in accordance with Haegele and Schechter's (1986)

results. Furthermore, to our knowledge, there is not further PK data of the enantiomers available in the literature. The racemic VGB was indeed previously studied (Nielsen et al., 2014) but, since the PK profiles of the enantiomers are not parallel, a deduction of VGB-S PK parameters was not possible. Lastly, the pediatric dataset used to validate the model included children with IS and FOS. There is, however, no reason to believe that the type of seizures influences the pharmacokinetics of the drug.

In conclusion, a pediatric model for VGB was developed from adult data, taking into account growth and the maturation of the glomerular filtration. It evidenced that doses between 40 and 50 mg/kg/day, divided in two intakes, are necessary to obtain an exposition similar to the one obtained in adults for the recommended adult doses for rFOS. Such a precise measure of the dose is now possible thanks to a new pediatric form consisting in scored soluble tablets of 100 and 500 mg (Kigabeq®). We propose those doses as optimal maintenance doses in rFOS that may be increased, if necessary, by slow titration. It is noteworthy that these doses are not adequate for the main indication of vigabatrin, that is infantile spasms, and for which doses of 100–150 mg/kg/day are recommended (European Medicines Agency, 2002; Food and Drug Administration, 2015).

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Conflict of interest

C.R., M.O., O.D. and R.N. had nothing to disclose. C.C. reports personal fees and non-financial support from ADVICENNE, outside the submitted work. V.J. reports grant from the French National Research Agency, during the conduct of the pediatric study (collection of the data), and a research grant from BIOCODEX.

Appendix A

Development of the adult PK models

In their publication, Haegele and Schechter (1986) provided the plasma concentrations of both enantiomers and the demographic characteristics of the six healthy volunteers included in their study. This information was used to create a dataset for the enantiomer S, for which two sets of concentrations were available for each volunteer: one posterior to the racemic drug administration (1500 mg) and one after VGB-S administration (750 mg). The model was built on Monolix (version 4.3.2; Lixoft, Antony, France) with the Stochastic Approximation of Expectation Maximization (SAEM) algorithm.

Structural models composed by one or two compartments were evaluated, and the absorption phases were evaluated with first- or zero-order models, with or without lag time. Due to the linearity of VGB pharmacokinetics (Hoke et al., 1993), elimination was assumed to be ruled by a first-order process.

Exponential models were used to describe inter-individual variability, as illustrated bellow (Eq. (1)):

$$\theta_i = \theta_{TV} \times \exp(\eta_i) \quad (1)$$

Where θ_i is the estimated value of a parameter in an individual i, θ_{TV} is the typical value of this parameter in the population and η_i is the individual deviation from this typical value, i.e., the inter-individual variability that is assumed to be normally distributed with a mean of 0 and a variance of ω^2.

Additive, proportional and mixed residual error models were tested.

Available demographic variables (age, height and body weight) were tested as potential covariates. These continuous covariates were included in the model using a power function equation (Eq. (2)):

$$\theta_i = \theta_{TV} \times \left(\frac{cov}{cov_{median}}\right)^{\theta_{cov}} \quad (2)$$

where cov is the value of the covariate, cov_{median} is its median and θ_{cov} is the factor describing the relationship between the covariate and the parameter.

A two-compartment model with zero-order absorption following an absorption lag-time, and first-order elimination, best described the adult data of VGB-S. The parameters of the model were: lag-time (Tlag), zero-order absorption constant (Tk0), central volume of distribution (V1/F, where F means bioavailability), peripheral volume of distribution (V2/F), distribution clearance (Q/F) and elimination clearance (CL/F). No covariates significantly improved the model, perhaps due to the lack of statistical power. IIV was estimated for all parameters, and the residual error model was set as proportional.

The final model for VGB-S was then:

$Tlag = 0.241\,h$

$Tk0 = 0.111\,h$

$CL/F = 11.5L/h$

$V1/F = 54.6\,L$

$Q/F = 6.85\,L/h$

$V2/F = 41.8\,L$

Determination of the exposition target in adults

Monte Carlo simulations were performed with the final adult model in order to obtain the areas under the curve of VGB-S (AUC_S) expected with the recommended doses of 2 and 3 g/day. For this, 1000 adults were simulated for each posology (1 g and 1.5 g twice daily). AUC_S was calculated using the equation below (Eq. (3)):

$$AUC_S\,(mg.\,h/L) = \frac{Dose_S\,(mg)}{CL_S/F\,(L/h)} \quad (3)$$

The target range of AUC_S was determined to be between the 2.5th percentile of the lowest dose (1 g bid) and the 97.5th percentile of the highest dose (1.5 g bid), including this way 95% of the AUC_S that adults could obtain with doses comprised between 2 and 3 g/day.

Development of a pediatric model from the adult model

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 Eq. (4):

$$F_{size} = \left(\frac{BW_{child}}{BW_{adult}}\right)^{\alpha} \quad (4)$$

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 (Anderson and Holford, 2008). This was the first model tested, M_{allo}.

For drugs only eliminated through glomerular filtration, the pediatric renal clearance (CL_R) can be scaled from the adult CL_R with the following equation (Edginton et al., 2006):

$$CL_{Rchild} = \frac{GFR_{child}}{GFR_{adult}} \times \frac{f_{uchild}}{f_{uadult}} \times CL_{Radult} \quad (5)$$

where, GFR means glomerular filtration rate and f_u means unbound fraction. Since VGB does not bind to plasma proteins (Mumford, 1988), the correction for the unbound fraction was not considered.

Two models were developed to describe the glomerular filtration rate in children (Hayton, 2002; Rhodin et al., 2009). According to Rhodin et al. (2009), the GFR_{child} depends on the body weight (F_{size}) and the age (F_{mat}) of the child in the following manner:

$$GFR_{child} = F_{mat} \times F_{size} \times GFR_{adult} \quad (6)$$

Indeed, for young children, maturation of organ function and enzyme expression also influences the elimination clearance. The Hill model is a sigmoid function (Eq. (7)) that describes the gradual maturation of clearance in early life until reaching maturity. It takes values between 0 and 1, and represents the fraction of the adult CL (Tod et al., 2008).

$$F_{mat} = \frac{PMA^{HILL}}{PMA_{50}^{HILL} + PMA^{HILL}} \quad (7)$$

HILL is the sigmoïdicity coefficient that defines the shape of the curve, PMA is the post-menstrual age (in weeks) and PMA_{50} is the PMA at which clearance reaches 50% of its maximal value, *ie* its mature value. PMA was estimated by adding 40 weeks to the postnatal age.

Replacing this in Eq. (5) and using the maturation function they estimated, we obtain the second model, M_{Rhodin}:

$$CL_{Rchild} = CL_{Radult} \times \left(\frac{BW_{child}}{70}\right)^{0.75} \times \frac{PMA^{3.40}}{47.7^{3.40} + PMA^{3.40}} \quad (8)$$

According to Hayton (2002), GFR_{child} is also a function of BW and age, described in Eq. (9).

$$GFR_{child} = 2.6 \times BW_{child}^{0.662} \times e^{-0.0822 \times age_m} + 8.14 \times BW_{child}^{0.662} \times (1 - e^{-0.0822 \times age_m}) \quad (9)$$

where age_m is the age in months. This formula can be used to estimate the GFR_{child} on Eq. (5), using a GFR_{adult} of 136 ml/min (value determined by this formula on a 20 years old adult weighting 70 kg), which was the third model, M_{Hayton}.

Validation of the pediatric model

A pediatric dataset was used for the validation of the models. This dataset included 28 pediatric patients, aged 5 months to 5.7 years, with a median (range) BW of 9.55 (6.47–22.8) kg, with IS and/or FOS. Those children provided 174 samples (1–6 per patient).

The ability of the 3 models (M_{allo}, M_{Rhodin} and M_{Hayton}) to predict the observed pediatric data was assessed by comparing the bias (mean prediction error (MPE), Eq. (10)) and the dispersion (root mean square error (RMSE), Eq. (11)) of the population predictions versus the observations.

$$RMSE = \sqrt{\frac{1}{n}\sum_{i=1}^{n}(C_{OBS} - C_{PRED})^2} \quad (10)$$

$$MPE(\%) = 100 \times \frac{1}{n}\sum_{i=1}^{n}\frac{C_{PRED} - C_{OBS}}{C_{OBS}} \quad (11)$$

The model with the lowest values of MPE and RMSE was selected as the final model.

Of the three models tested, M_{Rodhin} was the less biased, and more precise (Table 1 of the Appendix A) and was considered the final model.

Determination of the pediatric doses allowing to obtain VGB-S exposition within the target range

The final extrapolated VGB-S model was used to determine the pediatric doses necessary to obtain AUC_S within the target range determined in adults. Monte Carlo simulations were performed to investigate this matter. To do so, a population of children was simulated at different ages (from 0.5–18 years). The BW was predicted for each age using the model developed by Sumpter and Holford (2011). For this, the mean predicted BW of 1000 children per age was used for the simulation dataset. These mean predicted BWs were 7.9, 9.8, 11.4, 14.1, 20.6, 36.6, 57.4 and 65.7 kg, for 0.5, 0.75, 1, 2, 5, 10, 15 and 18 years respectively. Investigated doses were 10, 20, 30, 40, 50, 60, 70, 80, 90 and 100 mg/kg/day, administered as a bid regimen.

Clearance inter-individual variability (IIV) was fixed to 25%, which corresponds to the mean IIV found on this parameter, after adding BW as a covariate in several pediatric studies (Ding et al., 2015; Jullien et al., 2015; Peigné et al., 2018; Rodrigues et al., 2017; Sallas et al., 2003).

One thousand children per combination age/dose were simulated with the final model, and AUC was calculated for each child. The probability to be within the target range determined in 2 was calculated for each age/dose combination.

Table A1
Bias and precision of extrapolated models.

Model	MPE	RMSE
M_{allo}	−8.7	5.3
M_{Rhodin}	−2.7	5.1
M_{Hayton}	−8.1	5.1

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