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Switchability of Gabapentin Formulations: A Randomized Trial to Assess Bioequivalence Between Neurontin and Gabasandoz on the Individual Subject Level

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Generic substitution of antiepileptic drugs is generally not advised by neurologists. The present study investigated the switchability of gabapentin 800 mg tablets (Neurontin and Gabasandoz) using an individual bioequivalence (IBE) study design with two batches of each product and assessed whether between-batch and between-formulation variability in exposure play a significant role in the within-subject variability. The trial was analyzed according to the US Food and Drug Administration (FDA) framework to establish IBE. The IBE was shown between both products with the 95% upper confidence bound of the IBE criterion being −2.01 and −2.31 for area under the concentration-time curve from zero to infinity (AUC_{0-inf}) and peak plasma concentration (C_{max}), respectively. Subject-by-formulation variability (1.35%) was negligible compared with the within-subject variability of AUC_{0-inf} with Neurontin (19.0%) and Gabasandoz (23.6%). Inclusion of an additional batch did not significantly change this within-subject variability (20.2% and 23.6%, respectively). This study shows that substitution of gabapentin 800 mg tablets of Neurontin and Gabasandoz should be possible without affecting clinical outcomes.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Neurontin and gabapentin generics are bioequivalent on the average population level. Notwithstanding average bioequivalence, problems associated with switching from reference listed drug to and between generic antiepileptic drugs (AEDs) have been reported. For AEDs, the within-subject variability is important.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ Are Neurontin and Gabasandoz bioequivalent on the individual subject level, and may between-batch and between-formulation variability play a significant role in the within-subject variability?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ Neurontin and Gabasandoz 800 mg tablets are bioequivalent on an individual subject level. Provided correct medication use and adherence, switching between the brand and the generic formulation of 800 mg gabapentin tablets, and probably also lower doses, should be possible without affecting clinical outcomes in patients with epilepsy.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ The replicate pharmacokinetic (PK) data of this study may help to refine the population PK model for gabapentin described by Pieter Glerum and colleagues. This study shows that no-switch-lists are longer than needed from a PK viewpoint and supports the position taken by the British Medicines and Healthcare products Regulatory Agency for gabapentin.

Regulatory authorities, such as the US Food and Drug Administration (FDA) and the European Medicines Agency require population-based average bioequivalence (ABE) with the reference listed drug (RLD) formulation before a marketing authorization for a generic can be granted.[1,2] In general, a bioequivalent generic product is considered interchangeable with the

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Table 1 Study design

Allocation number	Period 1	Period 2	Period 3	Period 4	Period 5	Period 6
1	R2	T2	R1	T1	R1	T1
2	R2	R1	T1	R1	T1	T2
3	R1	T1	R1	T1	T2	R2
4	T2	T1	R1	T1	R1	R2
5	T2	R1	T1	R1	T1	R2
6	T2	R2	T1	R1	T1	R1
7	T1	R1	T1	R1	R2	T2
8	T1	R1	T1	R1	T2	R2
9	R2	T2	T1	R1	T1	R1
10	T2	R2	R1	T1	R1	T1
11	R2	T1	R1	T1	R1	T2
12	R1	T1	R1	T1	R2	T2
…			…			

Study design with the two-sequence fixed design (R1/T1/R1/T1 or T1/R1/T1/R1) and the additional batches of reference (R2) and test (T2) drug before and/or after the fixed design. Subjects were randomized to the 12 possible sequences. The randomization list showed each sequence at least twice and no more than three times. Shaded area indicates the fixed sequence as recommended by the US Food and Drug Administration (R1/T1/R1/T1 or T1/R1/T1/R1). R1, Neurontin 800 mg batch 1 (1269012); R2, Neurontin 800 mg batch 2 (1091082); T1, Gabasandoz 800 mg batch 1 (CJ7435); T2, Gabasandoz 800 mg batch 2 (CT9850).

corresponding RLD. Notwithstanding ABE, problems associated with switching from RLDs to generics and between generics have been reported for some drugs, among which antiepileptic drugs (AEDs).[3–6] This has led to no-switch advices for these drugs.[7,8] Although, from a statistical perspective the probability to get significant differences in exposure is very small when ABE has been established,[9] neurologists do not advise switching between AEDs because establishment of ABE cannot exclude the possibility of important differences in within-subject variances between a generic formulation and the RLD.[6,10] For this information, replicated data are needed, which can be obtained with a study design like that proposed to investigate bioequivalence on an individual level.[1,11] Gabapentin is an AED for which interchangeability is still being discussed. A recent study found interchangeability on a population basis (ABE) of different gabapentin formulations.[12] However, authors concluded that issues with generic interchangeability may still exist on an individual basis and that further research into the individual bioequivalence (IBE) level is warranted. In addition, generic substitution of gabapentin is differently advised by national competent authorities. Countries like Belgium have all AEDs on the no-switch list.[8] On the other hand, the Medicines and Healthcare products Regulatory Agency of the United Kingdom judged it unnecessary that patients are maintained on a specific manufacturer's gabapentin product unless there are specific reasons, such as patient anxiety and risk of confusion or dosing errors.[7]

The overall goal of the present study was to contribute to the discussion of the interchangeability of gabapentin products from different manufacturers. The study investigated the within-subject variability in exposure with Neurontin (originator; Pfizer, New York, NY) and Gabasandoz (generic; Sandoz, Holzkirchen, Germany) tablets, related to between-batch variability and between-formulation variability, using an IBE study design with two batches of each product. Based on literature data,[13] the highest dose (800 mg) of gabapentin showed the broadest confidence intervals (CIs) for area under the serum concentration time curve (AUC) and peak concentration (C_{max}). In line with the regulatory requirement, this 800 mg dose was chosen in the present study.

RESULTS

The study was a two-part, single-blind, randomized six-way crossover study with 12 possible sequences (**Table 1**). Study medication, consisting of two different batches of RLD (Neurontin 800 mg tablets; R1 and R2, respectively) and its generic counterpart (Gabasandoz 800 mg tablets; T1 and T2, respectively), were given as a single oral dose on six occasions. Part I of this study was performed between March and May 2013 on 12 subjects and was used for sample size calculation. Part II was performed on 18 subjects between August and October 2013 (more details in the **Methods** section). The clinical study was accompanied with *in vitro* dissolution tests on all four gabapentin batches. The potencies of R1, R2, T1, and T2 were, respectively, 99.6%, 99.0%, 97.8%, and 106.1% of the theoretical active pharmaceutical ingredient content. The *in vitro* dissolution profiles were similar between T1 and T2, T1 and R1, and T1 and R2. The *in vitro* dissolution differed between T2 and R1 and T2 and R2, whereas similarity was doubtful between R1 and R2.

Subjects and data

Thirty healthy volunteers were enrolled and 29 completed the study (subject 22 was withdrawn from the study after the fourth dose of gabapentin). Their demographic characteristics are shown in **Table 2**. The subjects were nonsmokers, aged between 20 and 55 years, and had a body mass index between 18.3 and 29.9 kg/m^2. All subjects were in good physical and mental health at the time of inclusion.

Blood samples were taken prior to gabapentin administration and up to 36 hours after dosing. A total of 2,876 serum concentrations were measured, of which all predose and 36 postdose samples

Table 2 Subject characteristics (n = 30)

Characteristic	Mean (SD)	Range
Age (years)	35.1 (12.4)	20–55
Weight (kg)	71.0 (13.0)	49.8–95.8
Height (cm)	169.9 (9.6)	1.54–1.92
BMI (kg/m²)	24.5 (3.5)	18.3–29.9
Sex (n males/n females)	10/20	
$eGFR_{CKD\text{-}EPI}$ (mL/min/1.73 m²)	101.9 (15.8)	74–130

Data are presented as mean (SD); for sex numbers are given.
BMI, body mass index; $eGFR_{CKD\text{-}EPI}$, estimated glomerular filtration rate (using the Chronic Kidney Disease Epidemiology Collaboration equation).

were below the lower limit of quantification (BLOQ; 0.03 mg/L). All postdose BLOQ values were reported from blood samples taken 24 or 36 hours postdosing. **Figure 1** shows a spaghetti plot of the concentration-time profiles for the two gabapentin formulations. BLOQ values were omitted in this Figure.

Some blood samples were missing for subject 22 (withdrawn) and subjects 13 and 14 (problems during blood sampling). Due to missing serum levels, the calculation of bioavailability (BA) measures (area under the concentration-time curve from zero to infinity (AUC_{0-inf}) and C_{max}) was based on 29 subjects for the second administration of R1 and for T2 and based on 27 subjects for the second administration of T1.

Noncompartmental analysis and mixed-effects modeling

The estimated secondary pharmacokinetic (PK) parameters are shown in **Table 3**. After log-transformation of the BA measures, the linear mixed-effects model was fitted to the data to estimate all relevant model parameters. These model parameters with their associated 90% bootstrap CIs are shown in **Table 4**.

Figure 2 shows the individual differences and the population average (dashed line) in AUC_{0-inf} between Neurontin and Gabasandoz. The degree of variability in the "slopes" of the full lines is described by the subject-by-formulation-interaction (σ_D; calculated from the final parameter estimates according to Eq. 1) and was estimated to be 1.35% (90% CI: 0.33–9.06). Compared with a recent retrospective study of Yu *et al.*,[14] comparing intrasubject variation in drug exposure between generic and brand-name drugs, the subject-by-formulation interaction estimated in the present study is small, indicating that the differences between Neurontin and Gabasandoz are similar across individuals and close to the population average difference ($(\mu_T - \mu_R) = -3.2\%$; **Table 4**). When compared with the magnitude of the within-subject variability, estimated to be 19.0% and 23.6% for Neurontin ($\sigma_{B,R}$) and Gabasandoz ($\sigma_{B,T}$), respectively, the differences between Neurontin and Gabasandoz on an individual level are negligible.

Estimation of the ABE/IBE criterion

ABE and IBE were estimated on 27 subjects with complete BA measures on replicated data.

The ABE criteria ($\Delta\mu$) and their associated 95% upper confidence bounds (UCBs) were −0.032 and 0.034 and −0.025 and 0.038 for AUC_{0-inf} and C_{max}, respectively. In both cases, the 95% UCB was lower than the limit of 0.22 (i.e., ln(1.25)). In addition, in a *post hoc* analysis, we compared the BA measures for Neurontin batch 1, first administration with Gabasandoz batch 1, first administration, thereby mimicking the classical ABE approach with nonreplicated data. The geometric mean of the ratios of AUC_{0-inf} and C_{max} were 96.2% (90% CI: 85.5–108.0%) and 98.0% (90% CI: 87.8–109.0%), respectively. Both the ABE criteria based on the full dataset with replicated data and the *post hoc* pairwise comparison of the first administration of batch 1 for both products demonstrate that no differences exist between the RLD and the generic in terms of ABE.

The IBE criteria (η) with their associated 95% UCBs were −2.01 and −1.35 and −2.31 and −1.86 for AUC_{0-inf} and C_{max}, respectively. In both cases, the 95% UCB is lower than zero, thereby demonstrating that no differences exist between both products in terms of IBE.

Finally, in an attempt to broaden the IBE assessment using a study design closer resembling the real-life situation, the analysis was repeated on the entire dataset (i.e., using the additional batches R2 and T2 and, hence, the full six-period crossover trial data). The ABE as well as the IBE criteria and their associated 95% UCBs did not differ substantially from the results from the four-period, single-batch ABE and IBE data (**Table 4**). As a consequence, the conclusions drawn with respect to the ABE and IBE were identical (i.e., the RLD and its generic counterpart were bioequivalent on an average as well as on individual scale).

In a separate analysis, we expanded the linear mixed-effects model with an additional fixed-effect parameter to account for the difference in BA between batches of the same formulation. The estimate we obtained from the data for AUC_{0-inf} was −0.031 (90% CI: −0.145 to 0.078). The 90% CI for this parameter contains zero, thereby showing that on average there is no difference in BA between batches of the same formulation. On the same account, our analysis of the entire dataset using the FDA-proposed linear mixed-effects model showed that the within-subject variabilities $\sigma_{W,R}$ and $\sigma_{W,T}$ (20.2% and 23.6%, respectively) were not significantly different from the estimates obtained in the primary analysis (19.0% and 23.6%; **Table 4**). This again indicates that there is no significant contribution of the batch-to-batch differences to the overall within-subject variability (as shown in **Table 4**, similar results were obtained for C_{max}).

Figure 3 shows the magnitude of within-subject variability, between-batch variability, and between-formulation variability in AUC_{0-inf} in our study population (similar results were obtained for C_{max}).

Adverse events

Single doses of 800 mg gabapentin were moderately well tolerated. Thirty individuals (100%) reported 370 adverse events (AEs), of which 291 were considered drug related. All AEs were mild or moderate in intensity, except for one episode of somnolence, which was rated as severe. All drug-related AEs had resolved by the end of the trial. The most common AEs were somnolence/fatigue (reported by 27 subjects), dizziness (reported by 22 subjects), and headache (reported by 21 subjects). Subject 22 was hospitalized due to a substance-induced (cannabis and mephedrone)

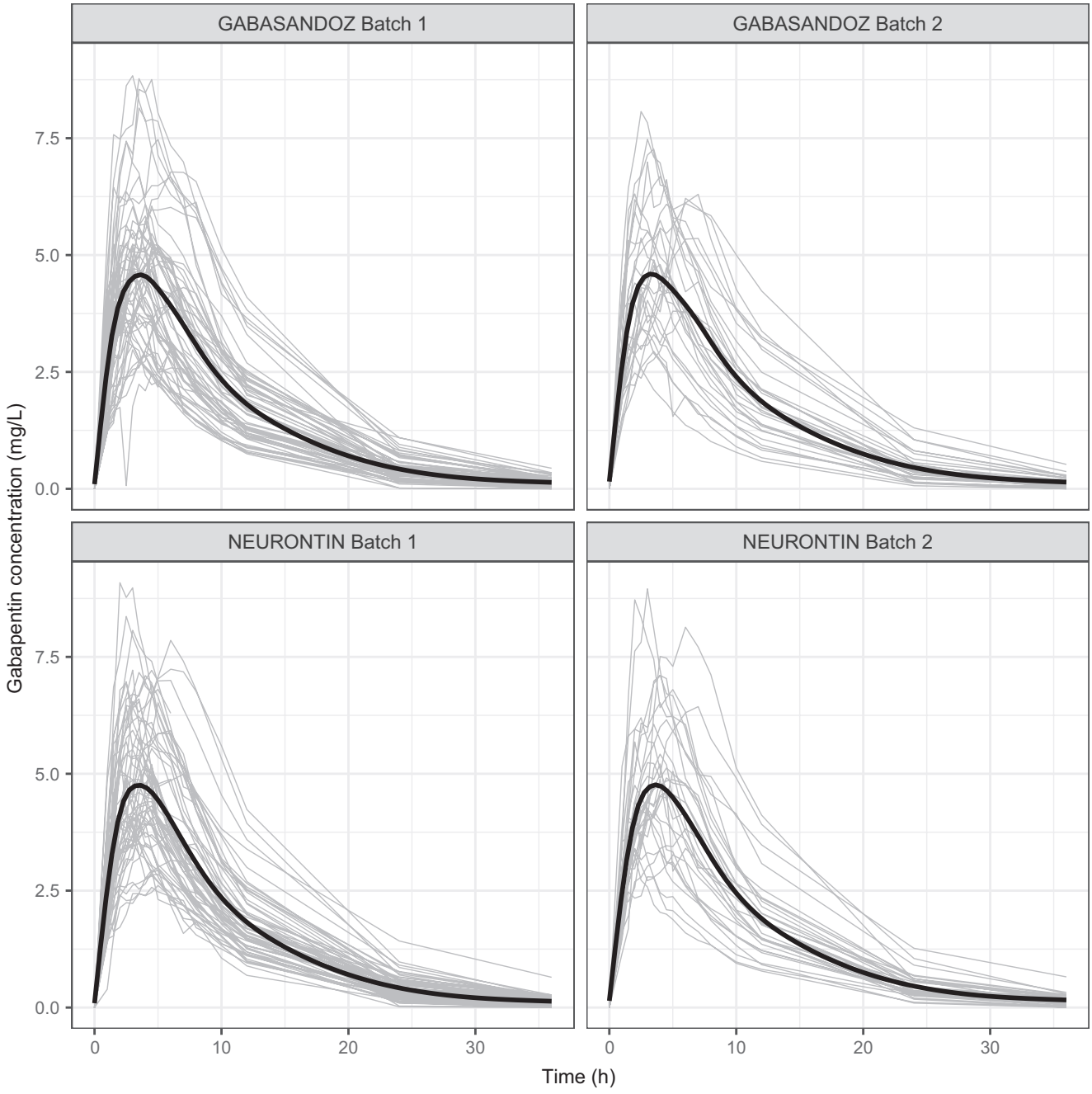

Figure 1 Spaghetti plot of the measured serum concentration-time profiles per drug formulation and batch. Gray lines represent individual serum concentration-time profiles. The black solid line represents the median concentration-time profile obtained by nonparametric smooth of the individual profiles. AUC_{0-inf}, area under the concentration-time curve from zero to infinity.

psychotic disorder in period 4. This serious AE was considered not study-drug–related and the subject was withdrawn from the study. All other subjects completed the study per protocol. There were no clinically meaningful changes in laboratory tests, blood pressures, heart rates, or electrocardiograms.

DISCUSSION

To the best of our knowledge, this study is the first to investigate IBE between a brand and generic formulation of gabapentin 800 mg, including two different batches of each product.

The end-of-study analysis showed that Gabasandoz 800 mg tablets (batch 1) are bioequivalent to Neurontin 800 mg tablets (batch 1) on both the average and individual levels. The results of the present study on ABE are in accordance with previous nonreplicated studies showing ABE between Neurontin 800 mg and its generics.[12,13] Gabapentin IBE results are in line with ABE results. In this study, despite different *in vitro* dissolution between some batches of originator and generic products, ABE and IBE were also proven in a more real-life situation, when data on two different batches of each product (R2 and T2) were included. Nevertheless,

Table 3 Pharmacokinetic parameters from the noncompartmental analysis

Treatment	Repl.	*N*	AUC_{0-t} (mg•hour)/L	AUC_{0-inf} (mg•hour)/L	C_{max} (mg/L)	T_{max} (hour)	$T_{1/2}$ (hour)
R1	1	30	55.0 [32.7; 106.4]	56.5 [32.7; 108.2]	5.1 [2.6; 9.1]	4.0 [2.0; 6.0]	6.7 [4.7; 10.5]
	2	29	52.4 [31.5; 98.2]	53.5 [31.6; 99.8]	4.9 [2.8; 8.4]	4.0 [2.0; 7.0]	6.5 [4.4; 8.7]
R2	1	30	54.8 [27.8; 98.2]	56.5 [27.8; 107.4]	5.1 [3.3; 9.0]	4.0 [1.5; 7.0]	6.9 [4.6; 10.1]
T1	1	30	52.9 [30.0; 99.3]	54.5 [33.0; 102.1]	4.9 [2.8; 8.8]	4.0 [1.5; 7.0]	6.8 [4.8; 9.9]
	2	27	52.3 [28.1; 107.7]	53.5 [28.7; 111.2]	5.0 [3.0; 8.8]	3.5 [1.5; 6.0]	6.4 [4.1; 8.8]
T2	1	29	53.2 [22.2; 97.7]	54.5 [22.2; 101.4]	5.1 [2.9; 8.1]	3.5 [1.5; 7.0]	6.6 [4.5; 9.4]

AUC_{0-inf}, area under the serum concentration-time curve from predose to infinity; AUC_{0-t}, area under the serum concentration-time curve from predose to last available blood sample; C_{max}, maximal concentration; Repl., replicate; T_{max}, time to maximal concentration; $T_{1/2}$, plasma elimination half-life.
R1, Neurontin 800 mg batch 1 (1269012); R2, Neurontin 800 mg batch 2 (1091082); T1, Gabasandoz 800 mg batch 1 (CJ7435); T2, Gabasandoz 800 mg batch 2 (CT9850). Data are presented as the geometric mean and the range. For T_{max}, the median and range is given.

Table 4 Final model parameters and associated 90% bootstrap CIs derived from the linear mixed-effects model

	Four-period two-sequence crossover		Six-period two-sequence crossover	
Parameter	Final estimate	90% CI	Final estimate	90% CI
AUC_{0-inf}				
$\mu_T - \mu_R$ (%)	−3.2	[−9.4; 3. 4]	−2.5	[−10; 2.5]
$\sigma_{B,R}$ (%)[a]	24.0	[15.3; 28.5]	26.0	[16.3; 30.9]
$\sigma_{B,T}$ (%)[a]	22.6	[13.6; 27.6]	25.0	[20.3; 34.3]
ρ	1.00	[0.93; 1.00]	0.98	[0.81; 1.00]
$\sigma_{W,R}$ (%)[a]	19.0	[13.7; 22.0]	20.2	[16.6; 22.3]
$\sigma_{W,T}$ (%)[a]	23.6	[16.8; 27.2]	23.6	[17.9; 26.9]
σ_D (%)[b]	1.35	[0.33; 9.06]	5.10	[0.75; 15.7]
η	−2.01	[−2.63; −1.35]	−2.13	[−2.68; −1.53]
C_{max}				
$\mu_T - \mu_R$ (%)	−2.5	[−8.6; 3.8]	−1.3	[−8.1; 3.6]
$\sigma_{B,R}$ (%)[a]	22.0	[13.6; 27.3]	19.4	[11.0; 22.6]
$\sigma_{B,T}$ (%)[a]	16.5	[8.75; 22.1]	17.9	[13.2; 25.0]
ρ	1.00	[0.82; 1.00]	0.96	[0.66; 1.00]
$\sigma_{W,R}$ (%)[a]	18.1	[13.2; 20.9]	20.4	[16.8; 23.0]
$\sigma_{W,T}$ (%)[a]	20.0	[13.8; 22.4]	19.6	[14.3; 22.0]
σ_D (%)[b]	5.39	[0.84; 14.1]	5.75	[0.94; 15.1]
η	−2.31	[−2.79; −1.86]	−2.58	[−3.05; −2.11]

AUC_{0-inf}, area under the serum concentration-time curve from predose to infinity; CI, confidence interval; C_{max}, maximal concentration; $\mu_T - \mu_R$, difference between estimates of population average serum levels of Neurontin and Gabasandoz; σ_B(%), coefficient of variation between subjects for Neurontin ($\sigma_{B,R}$(%)) and Gabasandoz ($\sigma_{B,T}$(%)); ρ, the covariance in the between subject variability for Neurontin and Gabasandoz; σ_W(%), coefficient of variation within subjects for Neurontin ($\sigma_{W,R}$(%)) and Gabasandoz ($\sigma_{W,T}$(%)); σ_D(%), subject-by-formulation variability; η, individual bioequivalence criterion.
[a]Coefficient of variation (%) is calculated according to: $\sqrt{e^{(\sigma^2)}-1} * 100\%$. [b]Derived from final model parameters according to Eq. 1.

for both gabapentin formulations, the magnitude of within-subject variability was large (19.0% and 23.6% on AUC_{0-inf} for Neurontin and Gabasandoz, respectively). As such, observed between-batch and between-formulation differences (**Figure 3**) are likely dominated by the within-subject variability. Indeed, as shown in **Table 4**, adding another batch only slightly increased the within-subject variabilities to 20.2% and 23.6%, respectively. This shows that the between-batch variability did not substantially contribute to the overall variability in the present study. Thus, if an individual patient switches between Neurontin and Gabasandoz and altered blood concentrations would be observed, these are most likely the result of the difference in occasion, not the difference in batch and/or formulation. However, although differences in potencies and/or *in vitro* dissolution between batches have been found, as only two different randomly obtained batches were examined, it cannot be excluded that other batches may yield a less favorable result. It is remarkable that although potencies of Neurontin tablets were closer to 800 mg than those of Gabasandoz, the *in vitro* dissolution did not differ between Gabasandoz batches, whereas similarity was doubtful between the two Neurontin batches.

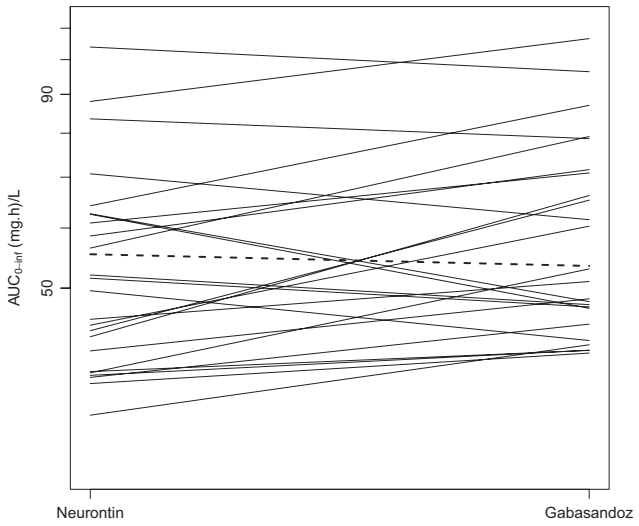

Figure 2 Individual differences in area under the concentration-time curve from zero to infinity (AUC_{0-inf}) between Neurontin and Gabasandoz 800 mg tablets. The individual differences in AUC_{0-inf} between the two formulations are shown by the solid lines with the left and right ends of the line representing the AUC_{0-inf} after Neurontin and Gabasandoz, respectively; the dashed line represents the population average. Data are calculated from serum levels of batch 1 of each formulation.

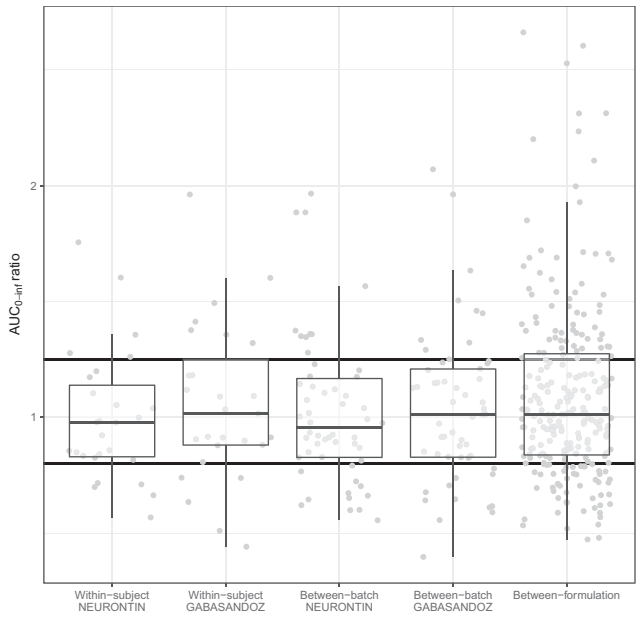

Figure 3 Within-subject, between-batch, and between-formulation variability in area under the concentration-time curve from zero to infinity (AUC_{0-inf}). Solid circles denote the individual ratios in AUC_{0-inf} between: (i) the first and second administration of the same batch (within-subject; R1 replicate 1 vs. replicate 2, T1 replicate 1 vs. replicate 2), (ii) different batches (between-batch; R1 replicate 1 vs. R2, R1 replicate 2 vs. R2, T1 replicate 1 vs. T2, T1 replicate 2 vs. T2), and (iii) different formulations (between-formulation; R1 replicate 1 vs. T1 replicate 1, R1 replicate 2 vs. T1 replicate 1, R2 vs. T1 replicate 1, R1 replicate 1 vs. T1 replicate 2, etc.). R1, Neurontin 800 mg batch 1 (1269012); R2, Neurontin 800 mg batch 2 (1091082); T1, Gabasandoz 800 mg batch 1 (CJ7435); T2,: Gabasandoz 800 mg batch 2 (CT9850).

During long-term treatment with one formulation, a patient inevitably is changing to other batches. Therefore, it has been suggested that the relevant basis for the individual comparison of the test and reference products should actually be the batch-to-batch variations observed within each of the two formulations in each subject.[15] In the present study, the subject-by-formulation variability did not differ from the subject-by-batch variability.

Recently, a nonparametric population PK model for gabapentin was developed to identify subpopulations with AUC and/or C_{max} ratios outside the 80–125% ABE margin when subjects are exposed to average-bioequivalent formulations. However, the data supporting this model were derived from a nonreplicated crossover trial and, therefore, provide no estimate of within-subject variability.[16] Data from the present study might be useful to validate this model and lead to further refinements.

Single doses of 800 mg gabapentin were moderately well tolerated by healthy volunteers. The most common AEs were somnolence/fatigue, headache, and dizziness. This is in line with those reported in the Summary of Product Characteristics for Neurontin and with the AEs reported in another study.[12,17] AEs did not differ in number, type, or severity between the two formulations.

Because gabapentin 800 mg showed a broader range of CIs than lower doses,[13] it is likely that the conclusions of the present study can be extrapolated to lower doses of gabapentin. The results can probably not be extrapolated to other compounds, including other AEDs, as gabapentin has a relatively simple PK profile (good absorption, no protein binding, and no metabolization).[17] As only one generic product of 800 mg gabapentin was available on the Belgian market at study onset, we did not include other generics and could, therefore, not investigate whether a so-called "generic drift" effect (i.e., larger differences between generics because each generic is only proven to be bioequivalent to the reference/innovator product[18]) between different generics was present. However, previous studies with gabapentin could not detect a "generic drift" effect using a brand and three generic formulations of 800 mg gabapentin.[12,13]

Despite strict regulation by governmental authorities and many studies confirming average bioequivalence between brands and generics, prescribers, mainly neurologists, remain reluctant toward switching from a brand to a generic AED in seizure-free patients until individual (within-patient) bioequivalence data on generic AEDs are available.[6,11] The present study does not answer the question whether the neurologists' position is right or wrong, neither whether the IBE method is superior to ABE for demonstrating switchability. This study does show there is significant within-subject variability for Neurontin and Gabasandoz and that despite this variability both formulations can be regarded as bioequivalent, both on the population and the individual levels.

CONCLUSIONS

Bioequivalence on an average and individual subject level was demonstrated between the brand (Neurontin) and the generic formulation (Gabasandoz) of 800 mg gabapentin tablets. Mimicking a real-life situation by adding another batch of both formulations did not change this result. Changing between the two

formulations or between batches did not add much to the high degree of within-subject variability and was negligible. Although successful treatment is not only based on the clinical effect of medicinal products but also on correct medication use and adherence, we can conclude that provided correct medication use and adherence, switching between the brand (Neurontin) and the generic formulation (Gabasandoz) of 800 mg gabapentin tablets, and probably also lower doses, should be possible without affecting the clinical outcomes in patients with epilepsy.

METHODS

Study design

The study was a two-part, single-blind, randomized six-way crossover study in healthy volunteers. Study medication was obtained from a Belgian licensed pharmacy and consisted of two different batches of the RLD (Neurontin) and its generic counterpart (Gabasandoz). Neurontin 800 mg tablets were manufactured by Pfizer (New York, NY; R1: batch 1269012; R2: batch 1091082). Gabasandoz 800 mg tablets were manufactured by Sandoz (Holzkirchen, Germany; T1: batch CJ7435; T2: batch CT9850). Study medications were given as a single oral dose on six occasions with a minimum washout of 4 days between occasions. All trial procedures (except the serum gabapentin analyses) were performed at the Drug Research Unit Ghent, the unit for early phase clinical drug research of the Ghent University Hospital, Belgium.

The study design was based on the four-period, two-sequence crossover trial recommended by the FDA for the establishment of IBE with subjects randomized over two different fixed sequences (R1/T1/R1/T1 or T1/R1/T1/R1).[1] For the secondary objective, to evaluate whether batch-to-batch variability has a significant impact on switchability, two additional periods were added on which another batch of the RLD and its generic counterpart (R2 and T2, respectively) were administered. To minimize the influence of potential drug carryover, these two additional periods were randomized around the fixed four-period, two sequences resulting in a six-way crossover study with 12 possible sequences (**Table 1**). Therefore, randomization was performed in blocks of 12. A randomization list was produced by lot drawing before the start of the study by staff members not involved in the allocation process. On enrollment, healthy volunteers received an allocation number in sequential order.

On each occasion, subjects were fasted overnight prior to receiving the study medication, which was taken in the morning with ~ 240 mL of water. Subjects were blindfolded, and study drug administration was witnessed by study staff. During the course of the trial food intake was standardized. The study was approved by the institutional review board (Ghent University Hospital; EC/2013/210) and received EudraCT-number 2013-001157-57. All subjects gave their written informed consent. The study was registered in the clinicaltrials.gov database (ID number NCT01821235).

Study population: Inclusion and exclusion criteria

The subjects were nonsmokers, aged between 18 and 55 years, and had a body mass index of 18.0–30.0 kg/m^2. All subjects were in good physical and mental health at the time of inclusion, as established by medical history, physical examination, electrocardiogram, and vital signs recording and by results of biochemistry, hematology, and urinalysis testing within 6 weeks prior to the first dose. Subjects had no history of hypersensitivity or idiosyncrasy to gabapentin or any other AEDs, reported no history of alcohol or drug abuse within the last 2 years, no cancer or surgery of the gastrointestinal tract that might interfere with absorption, and no history or presence of any significant disease. There was no use of any medication (except for contraceptive agents and paracetamol), herbal medicines, or dietary supplements from 14 days prior to the first dose. Subjects refrained from any enzyme-inducing drugs and products from 21 days prior to the first dose and did not participate in another clinical trial within 28 days prior to the first dose. Female subjects were not pregnant or breastfeeding and agreed to apply a highly effective method of birth control. All subjects were informed, orally and in writing, about this study and gave oral and written consent prior to entering the study and were willing to comply with the study protocol requirements and to complete the study.

Blood sampling and bioanalysis

Blood samples were taken prior to gabapentin administration and 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 12, 24, and 36 hours after dosing. Using an indwelling catheter in the forearm, ~ 2 mL of blood was drawn into a blood collection tube with serum cloth activator without gel separator. Prior to each sample collection, about 1 mL of blood was drawn from the catheter and discarded. After sampling, the catheter was flushed with 2.0 mL physiologic saline solution. Serum was separated within 2 hours after sampling by centrifugation at 1,300*g* at 20°C for 15 minutes. Serum was transferred into cryogenic vials (Biosigma, Cona, Italy) and stored at −70°C until analysis. The quantification of gabapentin in serum was performed with a validated ultraperformance reversed-phase liquid chromatography coupled with tandem mass spectrometry (Department of Clinical Pharmacology and Pharmacy, VU University Medical Center Amsterdam, The Netherlands). This analytical method has previously been described.[19]

Estimation of secondary PK parameters

Secondary PK parameters were calculated using noncompartmental analysis with the PK package in R[20,21] (area under concentration-time profiles ($AUC_{0-t\,last}$), AUC_{0-inf}, terminal half-life) or were deduced from the actual observed serum concentrations (time of maximum plasma concentration (T_{max}) and C_{max}). Prior to these calculations, noncompartmental analysis samples BLOQ (0.03 mg/L) were replaced by zero.

Calculation of the ABE and IBE criterion

The statistical tests to establish ABE and IBE were performed according to the FDA Guidance for Industry on "Statistical approaches to establishing bioequivalence,"[1] from here on referred to as "the guidance." For these analyses, at first, only the data from the R1 and T1 administrations were used (i.e., the classical four-period, two-sequence, crossover study). In a subsequent analysis, all data (including also R2 and T2) were used to evaluate IBE in a more real-life situation (i.e., a situation in which batch-to-batch variability is not excluded).

In line with the guidance, SAS version 9.4 was used to fit a linear mixed-effects model to the log-transformed BA measures (details on the model can be found in Appendix G of the guidance).[22] Based on this model, for each drug formulation, estimates were obtained for the population average BA measures (μ_R and μ_T and the corresponding difference $\Delta\mu$). In addition to this, the variability in BA between individuals ($\sigma_{B,R}$ and $\sigma_{B,T}$), the variability in BA within individuals ($\sigma_{W,R}$ and $\sigma_{W,T}$) and, to allow the evaluation of the IBE criterion, the subject-by-formulation variance (σ_D) was estimated. The latter was derived according to Eq. 1, based on the estimates of $\sigma_{B,R}$ and $\sigma_{B,T}$ and $\rho\sigma_{B,R}\sigma_{B,T}$ (i.e., the covariance in the between subject variability for the RLD and the generic).

$$\sigma_D = (\sigma_{B,R} - \sigma_{B,T})^2 + 2 * \left(1 - \frac{\rho\sigma_{B,R}\sigma_{B,T}}{\sigma_{B,R}\sigma_{B,T}}\right) * \sigma_{B,R}\sigma_{B,T}. \quad (1)$$

ABE was then evaluated using the obtained estimates according to Eq. 2. In short, the null hypothesis (H_0) (i.e., both products are, on average, bioequivalent and is rejected only if the 95% UCB of the absolute difference between the average log-transformed measures of BA exceeds the limit θ_A; (according to the guidance, this should be set to ln(1.25)).

$$[|(\mu_T - \mu_R)|]^{95\%\,UCB} \leq \theta_A. \quad (2)$$

Due to the absence of an analytical solution to calculate the 95% confidence bounds, we used R and SAS to, respectively, generate bootstrap samples and fit the linear-mixed effects model to these bootstrap samples. In order to produce a reliable sampling distribution of the criterion, 5,000 bootstrap samples were used.

IBE was evaluated according to Eq. 3. The H_0 of individual bioequivalence between both formulations is rejected if the 95% UCB of the IBE criterion (η) is larger than zero.

$$\left[\frac{(\mu_T - \mu_R)^2 + \sigma_D^2 + \left(\sigma_{WT}^2 - \sigma_{WR}^2\right)}{\sigma_{W0}^2} - \theta_I\right]^{95\%\,UCB} \leq 0. \quad (3)$$

The IBE limit θ_I depends on the maximum allowable σ_D and the difference in the within-subject variability ($\sigma_{W,R}$ and $\sigma_{W,T}$) between both formulations. Based on the work of Yu *et al.*[12] and according to the FDA criteria, gabapentin (Neurontin) is a low-variability product ($\sigma_{W,R} < 0.2$). Hence, the constant-scaling approach was used, as recommended in the guidance (i.e., $\sigma_{W0} = 0.2$ and $\theta_I = 2.5$).

Interim analysis and sample size calculation

This study was conducted in two parts. In the first part, 12 subjects were enrolled, and the data were analyzed in an interim analysis. This approach was chosen because no reliable information on variability in BA (μT, μR, σW, σB, and σD) following an 800 mg dose was available in literature to set up sample size/power calculations. This interim analysis has no impact on the overall type I error rate of this study because no formal hypothesis test was conducted. The estimates from the linear mixed-effects model were used to set up a simulation study to estimate the total sample size needed to achieve 80% power in the final analysis. This simulation study was set up in R. It consisted of the generation of 1,000 virtual clinical trials, each with a prespecified sample size (ranging from 12–40 subjects) and σ_W, σ_B, and σ_D randomly sampled from the variance-covariance matrix of the estimates from the interim linear mixed-effects model. In line with the guidance, the virtual clinical trials incorporated a difference between μ_T and μ_R (i.e., Δμ) of 5%. Afterward, for each of the virtual clinical trials, the IBE criterion was calculated, and the power was calculated for the different sample size categories as the relative frequency of rejecting the H_0. Using the data from the first cohort of 12 healthy volunteers, a total sample size of 26 subjects was sufficient to achieve 80% power for the primary study objective in a four-period, two-sequence, single-batch, crossover trial. Taking into consideration potential dropout, we decided to include a total of 30 healthy volunteers in the study. For the secondary study objective, no formal power calculations were performed.

In vitro dissolution tests

The *in vitro* dissolution tests were performed according to the US Pharmacopeia[23] and compared using DDSolver software.[24]

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CONFLICT OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

G.V.L., L.V.B., and P.C. wrote the manuscript. L.V.B., G.V.L., P.C., K.B., and J.V.B. designed the research. G.V.L., B.D., and L.V.B. performed the research. P.C., K.B., E.S., A.C., and J.V.B. analyzed the data. E.S. and A.C. contributed new reagents/analytical tools.

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