Bioequivalence Assessment of Brand and Generic Lamotrigine Extended-Release Tablets

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BACKGROUND AND OBJECTIVES

- Lamotrigine is one of the mostly prescribed anti-epileptic drugs due to its availability of generic forms, broad spectrum efficacy, and good tolerability.[1] Neurologists have concerns about risk of switching between brand and generic lamotrigine products.
- Recent clinical studies funded by the FDA have demonstrated bioequivalence (BE) in patients with epilepsy following brand-to-generic and generic-to-generic switching of lamotrigine immediate-release (IR) product[2,3], addressing neurologists' concern on IR products.
- In contrast, due to the complexity in control release mechanism, formulation design, and in vivo pharmacokinetics (PK) profile, neurologists continue to raise concerns on lamotrigine ER products.
- Lamotrigine ER tablets have multiple strengths (25 mg, 50 mg, 100 mg, 200 mg, 250 mg, and 300 mg). Prior to January 2016, generic applicants were recommended to demonstrate in vivo BE of 50 mg strength. All other strengths were eligible for waiver of in vivo testing if they met all criteria in product-specific guidance.
- Recent study from FDA showed that Generic A 200 mg strength originally approved as a waiver had the most difference from the reference (Lamictal XR) in a dissolution media simulating fed condition.[4]
- This study aims to (1) evaluate whether Generic A and Lamictal XR 200 mg tablet products are bioequivalent under most discriminatory fed condition, and (2) assess whether additional data (i.e., intra-subject variability of study products) from fully replicated study is needed to support the approval of generic lamotrigine ER tablet products.

METHODS

- A randomized, 2-sequence, 2-treatment, 4-period, single dose, fully replicated crossover PK study of Generic A and Lamictal XR tablets (200 mg) was conducted in healthy subjects under fed condition.
- Blood samples were collected at multiple sampling time points and lamotrigine plasma concentrations were measured by a validated HPLC/MS/MS method (Table 1).
- PK metrics, including the peak plasma concentration (C_{max}) and the area under the plasma concentration time curve (AUC), were analyzed for BE assessment.
- Simulated lamotrigine plasma concentrations after repeated dosing (200 mg tablet, once daily) were obtained using a nonparametric superposition method in Phoenix WinNonlin 6.4.
- Total seizure frequency (FREQ) was described by the following equation[5]:

$$log_e(FREQ) = -1.17 - 0.0452 \cdot Cp - \frac{0.833 \cdot nday}{18.1 + nday} + 0.47 \cdot baseline$$

where *Cp* is lamotrigine plasma concentration (mcg/mL), *nday* is time after the first dose (day), *baseline* is set at 0.3 based on study LAM100034 from Lamictal XR application.[5]

RESULTS

- Details of PK study design are described in Table 1. Mean PK profiles of two lamotrigine ER tablet products are shown in Fig 1.

Table 1. Study design of in vivo testing of generic A and Lamictal XR tablets.

Identifier	NCT02821338 at ClinicalTrials.gov
Study Title	A Randomized, 2-Sequence, 2-Treatment, 4-Period, Open-Label, Single Dose, Fully Replicated Comparative Bioavailability Crossover Study of Two Formulations of Lamotrigine Extended Release Tablets in Healthy Subjects Under Fed Condition
Clinical Site	Vince & Associates Clinical Research, Inc. 10103 Metcalf Avenue Overland Park, Kansas 66212
Treatments	Two treatments administered in the morning after a 10-hour overnight fast and 30 minutes after the start of a high-fat, high-calorie breakfast: • Treatment A: one dose of Generic A ER tablet 200 mg (test) • Treatment B: one dose of Lamictal XR tablet 200 mg (reference)
Study Subjects	30 healthy adult subjects. Age 20 to 49 (mean 32) years; 19 males and 11 females; 14 White, 15 Black or African American, and 1 Asian
Washout Time	Minimum 14-day washout between doses
Safety Assessment	Vital signs, physical exams, safety laboratory tests, ECGs, adverse events, Columbia Suicide Severity Rating Scale, and concomitant medication
PK Sampling	22 blood samples collected at pre-dose, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 27, 30, 33, 36, 48, 72, 96, 120 and 144 hours post-dose
Analyte	Lamotrigine in plasma
Bioanalytical Method	Validated HPLC/MS/MS method

- Generic A and Lamictal XR achieve C_{max} at different time (T_{max}). The median (range) T_{max} of Generic A and Lamictal XR is 10 (4-27) hours and 22 (10-48) hours, respectively (Fig 1).

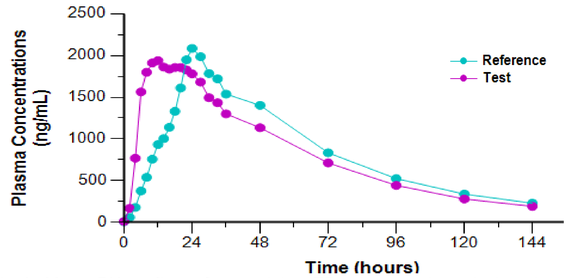

Fig 1: Mean PK profiles of lamotrigine ER tablet products in healthy subjects. Total number of subjects in four periods is 45 for Test and 46 for Reference.

- As shown in Table 2, the intra-subject standard deviation of the reference and test product is similar (σ_{WT} and σ_{WR}). Subject-by-formulation interaction variance is below 0.03 (σ_D^2 and upper bound). T/R ratio of C_{max} and AUC has 90% confidence interval (CI) within 80-125%.

Table 2. BE assessment of PK study result following a single dose.

Metric	σ_{WT}	σ_{WR}	σ_D^2	σ_D^2 95% upper bound	Geometric LSmean[a]		Ratio (%)	90% CI (%)
					Test (n=45)[b]	Reference (n=46)[b]		
C_{max}	0.082	0.084	0.003	0.012	2334.2	2229.4	104.7	100.8-108.8
AUC_{0-T}	0.052	0.063	0.001	0.005	115252.8	117222.9	98.3	95.7-101.0
$AUC_{0-\infty}$	0.059	0.063	0.002	0.008	124252.7	126920.4	97.9	94.9-101.0

[a] units are ng/mL for C_{max} and ng·h/mL for AUC_{0-T} and $AUC_{0-\infty}$.
[b] n is the total number of subjects receiving each treatment in four periods.

- Treatment-emergent adverse events are listed in Table 3. There were no deaths or other serious adverse events.

Table 3. Summary of treatment-emergent adverse events.

Adverse Events	Test (no. subject =30)	Reference (no. subject = 30)
Total number of adverse events [n]	6	7
Subjects with at least one adverse event[n(%)]	3 (10.0)	6 (20.0)
Blood Pressure Systolic Increased [n(%)]	1 (3.3)	0
Heart Rate Increased [n(%)]	0	1 (3.3)
Liver Function Test Elevated [n(%)]	0	1 (3.3)
Bradycardia [n(%)]	0	1 (3.3)
Tachycardia [n(%)]	1 (3.3)	0
Diarrhea [n(%)]	0	1 (3.3)
Nausea [n(%)]	1 (3.3)	0
Musculoskeletal Pain [n(%)]	1 (3.3)	1 (3.3)
Headache [n(%)]	1 (3.3)	0
Paraesthesia [n(%)]	1 (3.3)	1 (3.3)
Rash [n(%)]	0	1 (3.3)

- Generic A was predicted to have a higher AUC for the first 2 dose intervals (left panel in Fig 2). At steady-state, T/R ratio of $C_{mean,ss}$, $C_{max,ss}$, $C_{min,ss}$, and $AUC_{interval}$ met BE criteria (right panel in Fig 2).

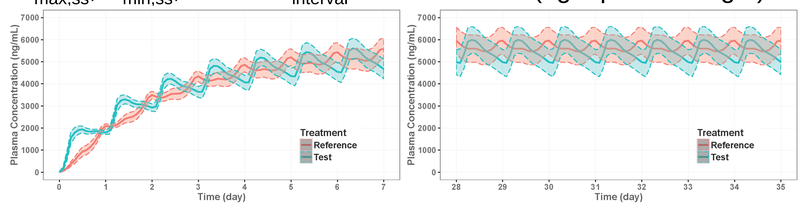

Fig 2: Simulated PK profiles of lamotrigine ER tablet products after repeated dosing. Left,1st week; right, 5th week with steady-state achieved. Solid line represents mean concentration; shaded area represent 90% CI.

- Total seizure frequency was predicted to be lower in subjects taking Generic A for the first 2 intervals (left panel in Fig 3). No significant difference in total seizure frequency was found between Generic A and Lamictal XR at steady-state (right panel in Fig 3).

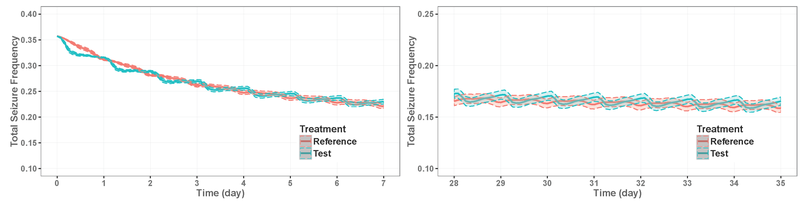

Fig 3: Simulated total seizure frequency of lamotrigine ER tablet products after repeated dosing. Left,1st week; right, 5th week. Solid line represents mean FREQ; shaded area represent 90% CI.

CONCLUSIONS

- Based on the single dose, fully replicated PK study of Generic A and Lamictal XR 200 mg tablets, BE was demonstrated in healthy subjects under fed condition. In addition, steady-state simulation predicted that PK metrics (i.e., $C_{mean,ss}$, $C_{max,ss}$, $C_{min,ss}$, and $AUC_{interval}$) met BE criteria and total seizure frequency was similar.
- Both Generic A and Lamictal XR exhibited very low intra-subject variability (i.e., σ_{WT} and σ_{WR} <0.10) with no differing clinical implications, suggesting that currently recommended two-way crossover PK study design is appropriate.

REFERENCES AND DISCLAIMER

- References: (1) Werz MA, *Ther Clin Risk Manag*, 2008. 4:1035-46; (2) Ting TY et al., *Epilepsia*, 2015. 56: 1415-24; (3) Privitera MD et al., *Lancet Neurol*, 2016. 15: 365-72; (4) Chow EC et al., *2016 AES Annual Meeting*. Houston, TX; (5) Clinical Pharmacology Biopharmaceutical Review of Lamictal XR Tablets. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022115s000_ClinPharmR.pdf
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