MULTIPLE AND SINGLE DOSE STUDIES (EQUIGEN) IN PATIENTS WITH EPILEPSY

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DISCLOSURES

- Consultant: Upsher-Smith, Eisai

GOALS

- Describe the design of the Equigen studies
- Present Equigen study results
- Consider implications of Equigen study results

QUESTIONS

- Are results from bioequivalence studies generalizable to patients with epilepsy taking antiepileptic drugs?
- Can a patient be switched between disparate generic products?
- What is the within-patient variability seen with the brand product and generic products?

LAMOTRIGINE CHOICE

- Reports of problems with substitution in the MedWatch program
- Commonly used newer antiepileptic drug
- Retrospective studies suggested problems with substitution

EQUIGEN STUDIES

- Chronic dose study
  - Patients with epilepsy receiving lamotrigine
  - Switch between 2 disparate generic lamotrigine products
  - Two PK analyses for each generic product
- Single dose study
  - Patients with epilepsy NOT receiving lamotrigine
  - Received 25 mg dose of brand product, generic-low, generic-high products
  - Two PK analyses for each product

DISPARATE PRODUCT SELECTION

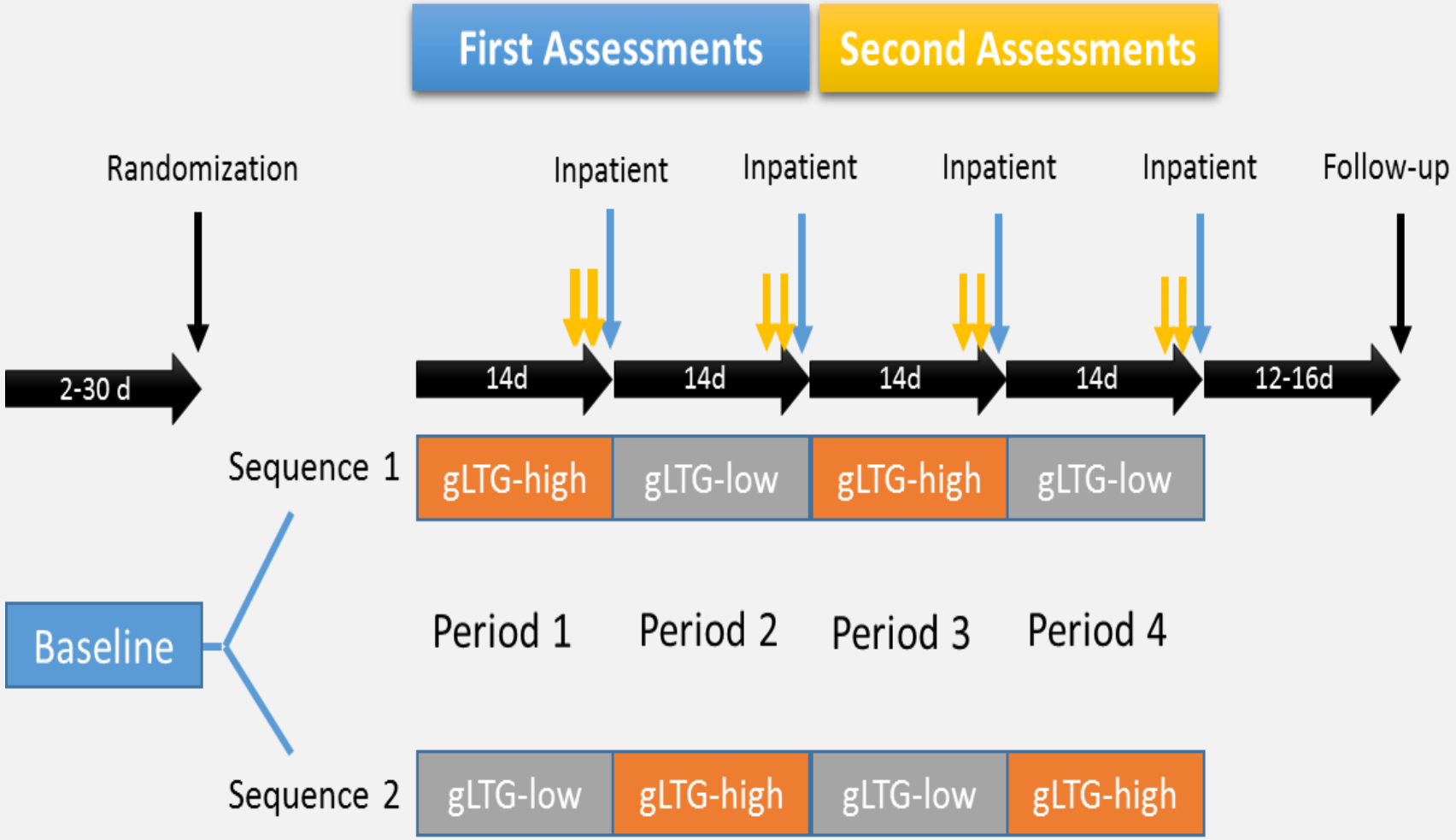
- ANDA data from FDA files
- Dissolution and content uniformity data from independent lab testing
- Excipient composition
- Market availability of single lots

CHRONIC DOSE STUDY

CHRONIC DOSE ADHERENCE

- Careful monitoring of adherence
  - Diary
  - Tablet counts
  - Computerized prescription bottle caps
- Rigorous standards for adherence
  - 3 days prior to PK, take doses within 1 hour of scheduled time
  - No missed doses for week prior to PK

EQUIGEN Study Design: Chronic Dose



*19 blood levels over 12 hours at each inpatient PK visit

CHRONIC DOSE RESULTS

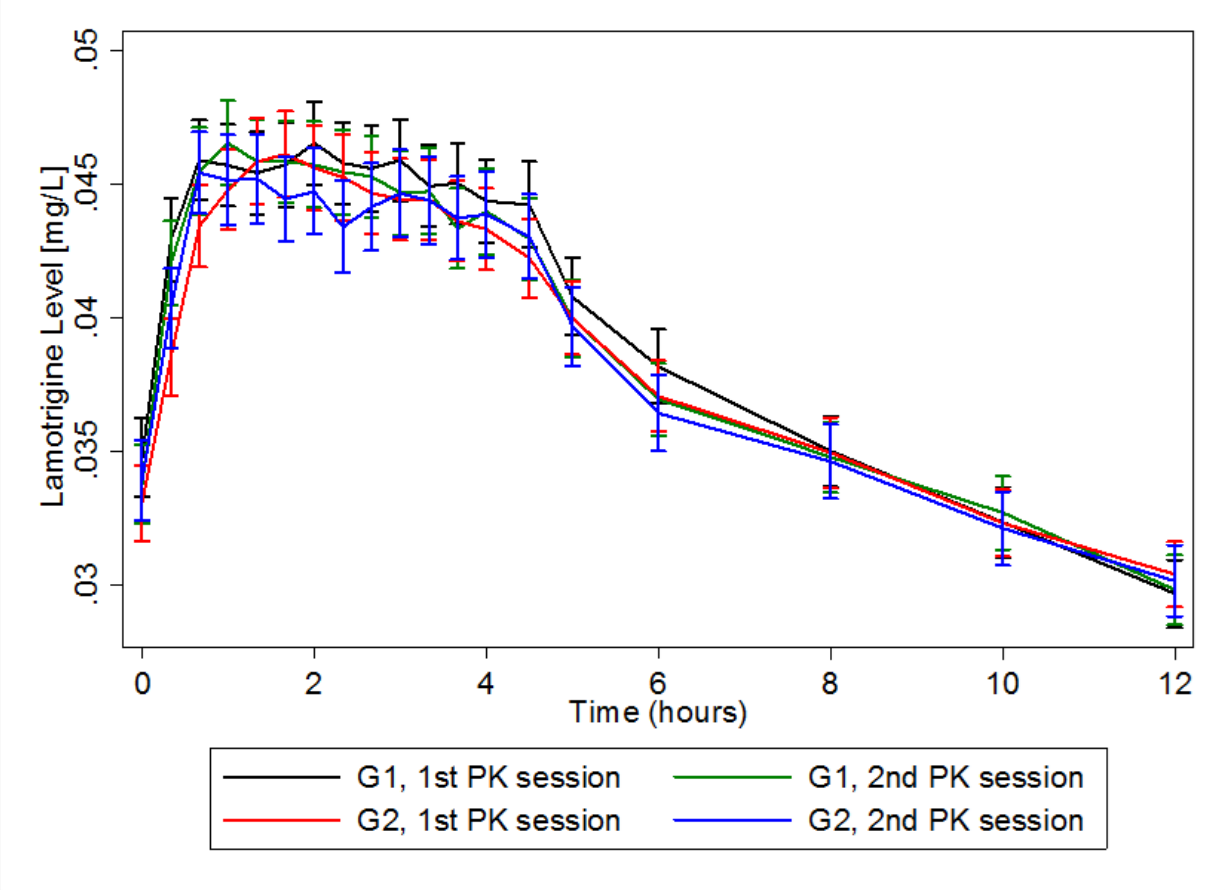
- 33 subjects
- 58% received other antiepileptic drugs
  - 18% on enzyme inducing drugs with known interactions with lamotrigine
  - Enzyme inhibiting drug (i.e., valproate) excluded
- No loss of seizure control
- No unexpected adverse effects
- Side effect measure scores not different between products

CHRONIC DOSE AUC AND C_{MAX}

	Generic LTG-high			Generic LTG-low		
	First PK (n=33)	Second PK (n=33)	Mean Within Subject % change	First PK (n=33)	Second PK (n=33)	Mean Within Subject % change
Dose-normalized $AUC_{(0\text{-}120)}$ (µg-mL/min)	2723 (1145)	2727 (1173)	1.09% (16.76; -4.6 to 6.8)	2710 (1129)	2704 (1200)	-0.58% (10.35; -3.0 to 4.1)
Dose-normalized C_{max} (µg/mL)	5.03 (1.8)	5.02 (1.9)	0.58% (14.83; -4.5 to 5.6)	4.96 (1.9)	4.95 (1.9)	0.73 (13.93; -4.0 to 5.5)

Data are mean (SD) or mean (SD; 95% CI). Dose normalized to 100 mg.

CHRONIC DOSE CURVES



CHRONIC DOSE CONCLUSION

- No statistical difference in AUC or C_{max} when switching between disparate generic products.
- Within-subject variability average <10% (2 subjects >30%).
- No change in clinical response detected.
  - Not powered for statistical comparison.

REFERENCE

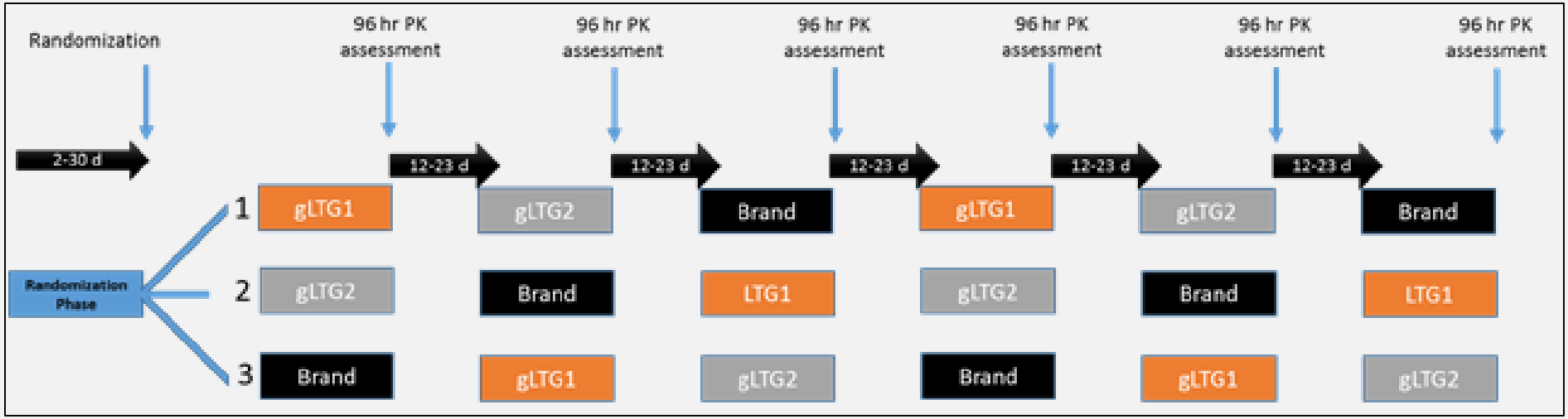
- Privitera MD, Welty TE, Gidal BE, et.al. Generic-to-generic lamotrigine switches in people with epilepsy: the randomized controlled EQUIGEN trial. Lancet Neurol 2016;15 (4):365-72.

SINGLE DOSE STUDY

WHY DO THIS STUDY

- More sensitive to small PK differences
- Question of variability of generic products compared to brand product

EQUIGEN Single Dose Study: 3 Treatments; 6 Periods



SINGLE DOSE RESULTS

- 50 subjects randomized
  - 46 completed all 6 periods
- No outliers in accordance with statistical analysis in replicate studies[1]
- No serious adverse events

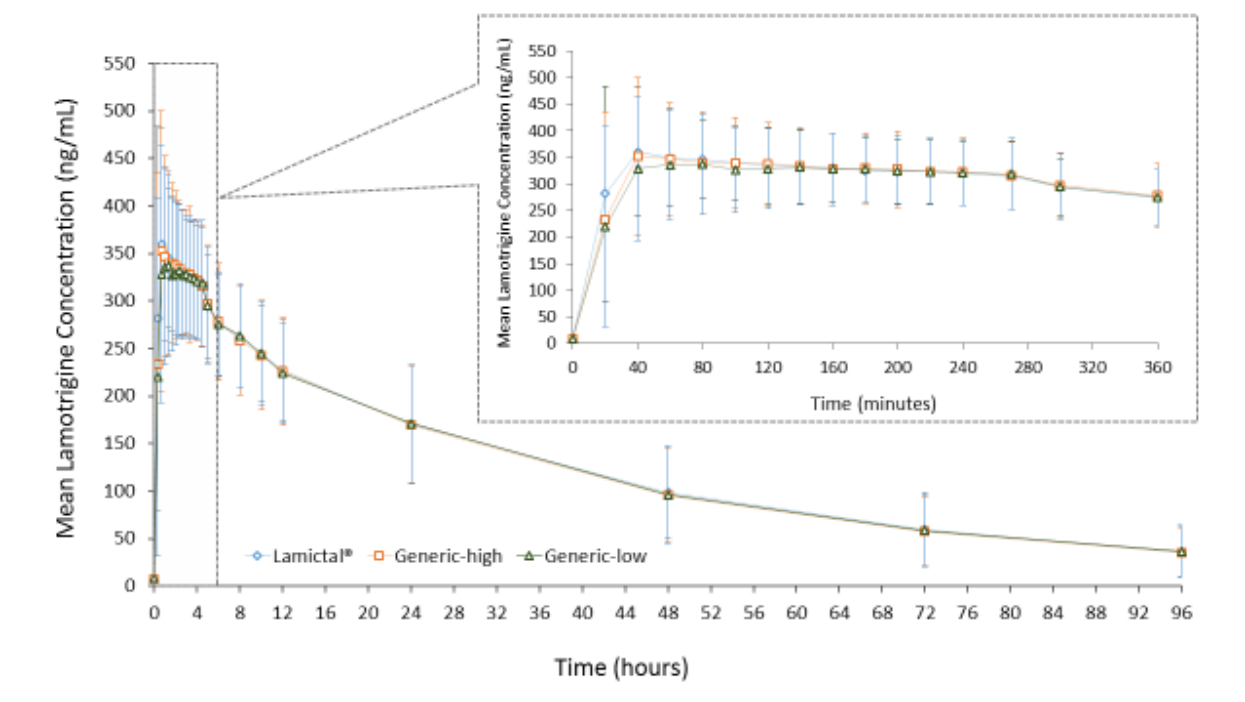
Unpublished data, manuscript submitted.

[1]Schall R, Endrenyi L, Ring A. Residuals and outliers in replicate design crossover studies. J Biopharm Stat. 20101;20(4):835-49

SINGLE DOSE RELATIVE BIOAVAILABILITY DATA

	C_{max} Estimate mean (90% CI)	$AUC_{(0-\infty)}$ Estimate mean (90% CI)	$AUC_{(0-96)}$ Estimate mean (90% CI)
G1 vs Brand	102.2% (98.7 to 105.8)	97.8% (94.9 to 100.8)	99% (96.9 to 101.2)
G2 vs Brand	96% (92.6 to 99.6)	98.5% (95.9 to 101.2)	99.4% (97.6 to 101.2)
G1 vs G2	106.4% (102.6 to 110.4)	99.3% (96.6 to102)	99.6% (97.3 to 101.9)

SINGLE DOSE CURVES



Unpublished data, manuscript submitted.

SINGLE DOSE WITHIN-SUBJECT VARIABILITY

	Brand (N=49)	gLTG-high (N=49)	gLTG-low (N=49)
$AUC_{(0-96)}$ (mg·mL/min)	7.0% (5.8 to 8.3)	8.7% (7.3 to 10.3)	7.9% (6.7 to 9.3)
$AUC_{(0-\infty)}$ (mg·mL/min)	12.1% (10.3 to 14.2)	12.9% (10.8 to 15.3)	9.9% (8.3 to 11.9)
C_{max} (mg/mL)	14.6% (12.2 to 17.4)	14.7% (12.4 to 17.6)	16.0% (13.5 to 18.9)

Data are presented as percent coefficient of variation (95% CI). Unpublished data, manuscript submitted.

SINGLE DOSE CONCLUSION

- No difference in bioavailability
- Within-subject variability similar for brand and generic products

IMPLICATIONS FOR PRACTICE

- **Generic products meet bioequivalence standards in patients with epilepsy, therefore can be safely interchanged for brand product.**
- **Disparate generic products meet bioequivalence standards in patients with epilepsy, therefore switches between generic products can be practiced safely.**
  - Resulted in change of American Epilepsy Society position statement on generic substitution.
- Same amount of variability is seen with brand product compared to generic products.

FUTURE CONSIDERATIONS: VARIABILITY

- Lower the bioavailability, higher the inter-subject variability.[1] Is the same true for within-subject variability?
- What within-patient variability is seen in clinical practice, given the following observations in ideal conditions?
  - BEEP: 6-13%
  - Equigen Chronic: <10%, 2 subjects >30% (maximum of 58% for AUC and 45% for C_{max})
  - Equigen Single: 7-16%
- How does the issue of within-patient variability impact patient response?
  - Retrospective studies?
  - Non-bioequivalence factors?

[1]Hellriegel ET, Bjornsson TD, Hauck WW. Interpatient variability in bioavailability is related to the extent of absorption: Implications for bioavailability and bioequivalence studies. Clin Pharmacol Ther 1996;60:601-7.

CONCLUSION

- No bioequivalence differences
  - Disparate generic product switches
  - Brand to generic switches
- FDA bioequivalence standards are applicable to patients with epilepsy
- Variability needs to be further investigated

STUDY TEAM

- Michael Privitera MD: University of Cincinnati
- Michel Berg MD: University of Rochester
- Timothy Welty PharmD: Drake University
- Barry Gidal PharmD: University of Wisconsin
- Ron Krebill MPH: University of Kansas Medical Center
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- Edmund Elder PhD: University of Wisconsin
- Wenlei Jiang PhD: Food and Drug Administration
- Xiaohui Jiang PhD: Food and Drug Administration
- Multiple study site coordinators