

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Supplement #: 22251/S-17, 20241/S-53, 20764/S-46

Drug Name: Lamictal ODT (lamotrigine) Orally Disintegrating Tablets

Indication(s): Maintenance treatment of Bipolar I Disorder in patients (b) (4)

Applicant: GlaxoSmithKline LLC

Date(s): July 18, 2014

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1 EXECUTIVE SUMMARY

In this submission the Sponsor provides the data of the pivotal efficacy study SCA102833 on the use of LAMICTAL™ (lamotrigine [LTG]) for the maintenance treatment of Bipolar I Disorder (BPD) in children and adolescents age 10 to 17 years of age. Supporting data from two previously conducted controlled studies of LTG in adults with BPD (Studies SCAB2003 and SCAB2006) are also presented, but this statistical review is performed and pertinent only for the pediatric patients (10-17 years old).

Study SCA102833, a parallel group, placebo-controlled, double-blind, randomized withdrawal study, was designed to investigate the effectiveness of LTG in the maintenance of pediatric BPD. The primary objective of the study was to compare the efficacy of LTG with placebo (PBO) in delaying the time to the occurrence of a bipolar event (TOBE) in subjects who had been responsive to OL LTG treatment added to their conventional mono- or dual-bipolar therapy. The TOBE is the primary endpoint in the SCA102833 study. Secondary endpoints in the study included several time to event variables: Time from randomization to Intervention for a Mood Episode (TIME), to intervention for mania/hypomania (TIMan), to depression (TIDep), to a mixed episode (TIMix), and to withdrawal from the study for any cause (TTW).

The pivotal efficacy study SCA102833 does not provide conclusive evidence ($p=0.0717$) on the efficacy of LTG over PBO in delaying the time to Bipolar Disorder (TOBE) in the overall patient population (from 10 to 17 years of age). (b) (4)

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2 INTRODUCTION

This submission provides data on the use of LAMICTAL™ (lamotrigine [LTG]) for the maintenance treatment of Bipolar I Disorder (BPD) in children and adolescents 10 to 17 years of age. Supporting data from two previously conducted controlled studies of LTG in adults with BPD (Studies SCAB2003 and SCAB2006) are also presented.

The primary objective of Study SCA102833 (the subject of this review) is to compare the efficacy of LTG versus placebo (PBO) in delaying the time to the occurrence of a bipolar event in subjects who have been responsive to open-label LTG treatment added to their conventional mono- or dual bipolar therapy.

2.1 Overview

LAMICTAL (LTG), a sodium channel blocker and a glutamate release inhibitor, was first approved in 1990 in Ireland for adjunctive treatment of partial seizures in adults, and is currently approved in the United States (US), European Union countries, Japan and over 70 other countries.

LTG was approved by the Agency in June 2003 (NDA 020241 S-017 Tablets, NDA 020764 S-011 Chewable Dispersible (CD) Tablets) for the prevention of mood episodes (depression, mania, hypomania, mixed episodes) in adult patients (≥ 18 years of age) with Bipolar I Disorder (BPD). LTG is not approved for the treatment of bipolar disorder in patients below 18 years of age in any country.

In the February 1, 2001 Pre-sNDA meeting for LTG Tablets (NDA 020241/S-017) and CD Tablets (NDA 020764/S-011) in the treatment of adult Bipolar I disorder, the Agency granted a waiver for a pediatric assessment in patients under 13 years of age and a deferral for patients 13 to 17 years of age and the Sponsor agreed to conduct the deferred study. The sNDAs were approved on June 20, 2003 as maintenance treatment of BPD to delay the time to occurrence of mood episodes in patients ≥ 18 years of age treated for acute mood episodes with standard therapy. In this approval letter, the Agency did not require a pediatric assessment as a formal post-marketing commitment because the FDA Pediatric Rule was being challenged in court at the time. Nevertheless, the Sponsor tried to fulfill this commitment by submitting a concept protocol SCA102833 in December 2004.

LTG and its associated labelling supplements were approved on May 8, 2009. At that time, the Agency formally waived the requirement for a pediatric assessment in children below the age of 10 years with bipolar disorder and formally established the following post-marketing requirement (PMR) for the three bioequivalent products:

Deferred pediatric study under PREA for the maintenance treatment of Bipolar I disorder in pediatric patients ages 10 to 17 years.

In February 2001, the Agency requested that Sponsor investigate the effects of LTG in children and adolescents with bipolar disorder to fulfill obligations under the Pediatric Research Equity Act (PREA) for NDAs 020241, 020764, and 022251. A controlled clinical Study SCA102833 was designed to compare the time to occurrence of a bipolar event in children and adolescents (10 to 17 years of age) who have been responsive to OL LTG treatment added to their conventional mono- or dual-bipolar therapy.

In its correspondence letter of November 26, 2007, the Agency expressed its concerns on the use of TIME as the primary endpoint despite it being used in Sponsor's adult BPD studies, because many of the premature discontinuations who met TIME requirements were not considered to have been reasonably related to bipolar disorder. In the amendment submitted to the Agency on June 5, 2008, the sponsor proposed to use the Time to the Occurrence of a Bipolar Event (TOBE) as the primary endpoint, which was accepted by the Agency.

In June 2007, the Agency initially agreed to Sponsor's proposal to include adolescents 13 to 17 years of age, a population where it is accepted that the presentation is similar to the clinical presentation in adults. However, in October 2007, the Agency requested that children aged 10-12 years of age be added to the population. The Sponsor agreed, but included a pre-specified subgroup analysis for the age subgroups 10 to 12 years of age and 13 to 17 years of age in the reporting and analysis plan (RAP).

Study SCA102833 is the only efficacy study conducted in children and adolescents with BPD and is the focus of this sNDA, therefore is selected for the full statistical review. Per previous agreement with the Agency, data from the two studies in adults (Studies SCAB2003 and SCAB2006) are also presented for comparison. These two studies are not directly related to the indication (b) (4) in this submission, therefore will not be selected for full statistical review.

Study SCA102833 is a multicenter, parallel group, placebo-controlled, double-blind, randomized withdrawal study evaluating the efficacy, safety, and tolerability of LTG as add-on maintenance therapy compared to maintenance mono- or dual-therapy alone in male and female children and adolescents, 10 to 17 years of age, who had been diagnosed with BPD.

This study consisted of 4 phases: a Screen Phase (approximately 2 weeks), an Open-label (OL) Phase (up to 18 weeks), a Randomized Phase (up to 36 weeks), and a Taper and Follow-up Phase (up to 4 weeks), which may have been either OL or double-blind depending on the phase of the study. The study was conducted at 32 centers in the US. The first subject was enrolled into the study on July 31, 2008. The date of last subject last visit was August 7, 2013. Of those enrolled, 298 subjects were included in the OL ITT population. A total of 173 subjects were randomized into the Randomization Phase of the study, 66 subjects in the 10 to 12 year-old subgroup, and 107 subjects in the 13-17 year-old subgroup. The design is depicted in Table 2.1.

Table 2.1 Study Design for Study SCA102833

	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
SCA102833	A multicenter, parallel group, placebo-controlled, double-blind, randomized withdrawal study. It has 4 phases: screen phase, OL phase, randomized phase and tape and follow up phase.	Randomized phase of 36 weeks	Tape and follow up phase up to 4 weeks	LTG: 87 randomized / 24 completed Placebo: 86 randomized / 25 completed	Children and adolescents (10 to 17 years of age) who have been responsive to OL LTG treatment

Source: Study SCA 102833 Clinical Study Report

2.2 Data Sources

The sponsor's data sources were stored in the directory of [\\CDSESUB1\evsprod\NDA022251\0125](#) of the Center's electronic document room of the Agency. Data sources include all material reviewed, i.e., study reports, raw data sets, data sets analyzed, protocol amendments, individual data listings, reporting and statistical analysis plan, and literature referenced, etc. The SAS data sets are stored in the directory of [\\CDSESUB1\evsprod\NDA022251\0125\m5\datasets\sca102833\analysis\legacy\programs\sca102833](#). The analysis software is also stored in the same directory.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The sponsor provides high quality data sets along with the programs to produce the analysis data sets and efficacy results which allow the statistical reviewer to duplicate the efficacy results. The reviewer is also able to verify the randomized treatment assignments by comparing the treatment assignment sheet with the analysis data set.

According to the Clinical Study Report (CSR), subject data were entered into GSK-defined electronic case report forms (eCRFs), transmitted electronically to GSK, and combined with data provided from other sources (e.g., laboratory data) in a validated data system. Clinical data management was performed in accordance with applicable GSK standards and data cleaning procedures with the objective of removing errors and inconsistencies in the data which impacted the analysis and reporting objectives, or the credibility of the CSR. Adverse events and concomitant medications terms were coded using MedDRA Version 16.1 and GSKDrug, an internal validated medication dictionary. In all cases, subject initials were not collected nor transmitted to GSK.

According to CSR, subjects and investigators were blinded to the investigational product during the Randomized Phase. The Double-blind Taper Phase was blinded only to the subjects.

All study treatment was supplied in identical blister cards as LTG and PBO tablets to match. Blinding was maintained throughout the study for subjects, investigators and any personnel with direct contacts with the sites, until completion of the final assessment for the final subject had been entered onto the database and the final database lock had been performed. The GSK biostatistics and programming team were unblinded once all data were considered final and locked.

Treatment codes could be unblinded by the investigator or treating physician only in the case of a medical emergency or in the event of a serious medical condition, when knowledge of the investigational product was essential for the clinical management or welfare of the subject. GSK Global Clinical Safety and Pharmacovigilance (GCSP) staff could unblind treatment codes in the event of a serious adverse event (SAE). The date and reason for the unblinding must have been recorded in the appropriate data collection tool.

A Reporting and Statistical Analysis Plan (RSAP) is included in the submission in which detailed statistical reporting and analysis plan was provided. This document was developed on May 28, 2013 which was before the study completion date of August 7, 2013. It is reported that the SAP was submitted to the Agency on August 16, 2013. It was not clearly stated in the RSAP if the SAP was submitted before study data unblinding.

(b) (4)

3.3 Evaluation of Safety

NA.

3.4 Benefit-Risk Assessment

NA.

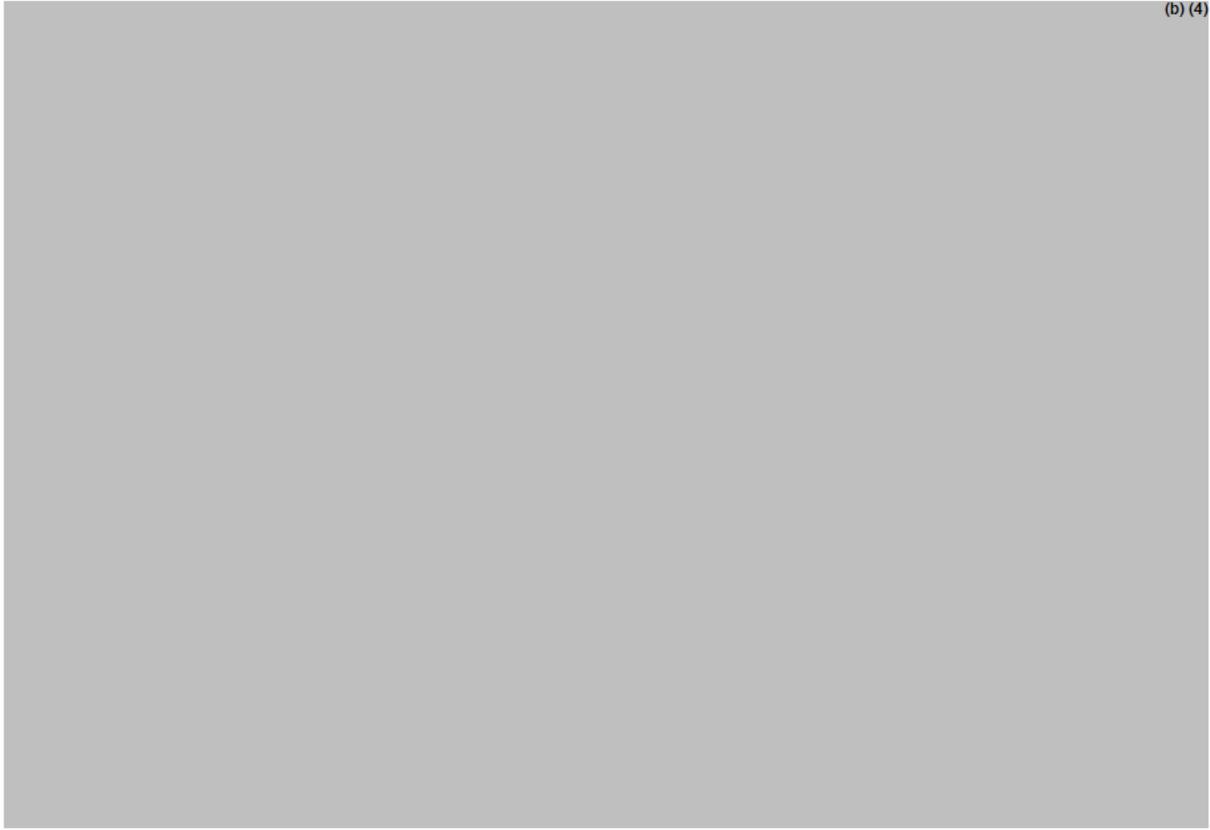


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(b) (4)

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues



5.3 Conclusions and Recommendations

The pivotal efficacy study SCA102833 does not provide conclusive evidence (b) (4) the effectiveness of LTG over PBO in delaying the time to Bipolar Disorder in the overall patient population of 10 to 17 years of age. (b) (4)



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/s/

FANHUI KONG
03/19/2015

PEILING YANG
03/19/2015

I concur that efficacy is not demonstrated in this trial.

HSIEN MING J HUNG
03/19/2015