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Ethosuximide, Valproic Acid and Lamotrigine in Childhood Absence Epilepsy: Initial Monotherapy Outcomes at 12 months

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Abstract

Purpose—Determine the optimal initial monotherapy for children with newly diagnosed childhood absence epilepsy based on 12 months of double blind therapy.

Methods—A double-blind, randomized controlled clinical trial compared the efficacy, tolerability and neuropsychological effects of ethosuximide, valproic acid and lamotrigine in children with newly diagnosed childhood absence epilepsy. Study medications were titrated to clinical response and subjects remained in the trial unless they reached a treatment failure criterion. Maximal target doses were ethosuximide 60 mg/kg/day or 2000 mg/day, valproic acid 60 mg/kg/day or 3000 mg/day and lamotrigine 12 mg/kg/day or 600 mg/day. Original primary outcome was at 16–20 weeks and included a video EEG assessment. For this report, the main effectiveness outcome was the freedom from failure rate 12 months after randomization and included a video EEG assessment; differential drug effects were determined by pairwise comparisons. The main cognitive outcome was the percentage of subjects experiencing attentional dysfunction at the Month 12 visit.

Key Findings—A total of 453 children were enrolled and randomized; seven were deemed ineligible and 446 subjects comprised the overall efficacy cohort. There were no demographic differences between the three cohorts. By 12 months after starting therapy, only 37% of all enrolled subjects were free from treatment failure on their first medication. At the Month 12 visit, the freedom-from-failure rates for ethosuximide and valproic acid were similar (45% and 44%,

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The study was provided study medication free of charge by Pfizer Inc., Abbott Laboratories, and GlaxoSmithKline. Dr. Glauser has received consulting fees from Eisai, UCB Pharma and Johnson & Johnson, Supernus, Sunovion, Questcor, Lundbeck and Upsher Smith along lecture fees from Eisai, UCB Pharma, Johnson & Johnson, and Questcor. Dr. Shinnar reports receiving consulting fees from Eisai, Johnson & Johnson, King Pharmaceutical and Questcor along with lecture fees from Eisai, UCB Pharmam and Questcor. Dr Adamson reports grant support from Abbott Pharmaceutical for oncology focused research. No other potential conflict of interest relevant to this article was reported.
We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

respectively; odds ratio with valproic acid vs. ethosuximide, 0.94; 95% confidence interval [CI], 0.60 to 1.48; P = 0.82) and were higher than the rate for lamotrigine (21%; odds ratio with ethosuximide vs. lamotrigine, 3.09; 95% CI, 1.86 to 5.13; odds ratio with valproic acid vs. lamotrigine, 2.90; 95% CI, 1.74 to 4.83; P<0.001 for both comparisons). The frequency of treatment failures due to lack of seizure control ($p < 0.001$) and intolerable adverse events ($p < 0.037$) were significantly different among the treatment groups. Almost two thirds of the 125 subjects with treatment failure due to lack of seizure control were in the lamotrigine cohort. The largest subgroup (42%) of the 115 subjects discontinuing due to adverse events were in the valproic acid group. The previously reported higher rate of attentional dysfunction seen at 16–20 weeks in the valproic acid group compared with the ethosuximide or lamotrigine groups persisted at 12 months ($p < 0.01$).

Significance—As initial monotherapy, the superior effectiveness of ethosuximide and valproic acid compared to lamotrigine in controlling seizures without intolerable adverse events noted at 16–20 weeks persisted at 12 months. The valproic acid cohort experienced a higher rate of adverse events leading to drug discontinuation as well as significant negative effects on attentional measures that were not seen in the ethosuximide cohort. These 12 month outcome data coupled with the study's prespecified decision making algorithm indicates that ethosuximide is the optimal initial empirical monotherapy for childhood absence epilepsy. This is the first randomized controlled trial meeting ILAE criteria for Class I evidence for childhood absence epilepsy (or for any type of generalized seizure in adults or children). (NCT00088452.)

Keywords

Randomized Clinical Trial; Pediatric Epilepsy; Epilepsy Syndrome Treatment

Introduction

Childhood absence epilepsy (CAE) is the most common pediatric epilepsy syndrome, occurring in 10% to 17% of all children with epilepsy with an annual incidence of 6.3 to 8/100,000 in children < 15 years of age (Berg et al., 2000; Jallon et al., 2001). The classic characteristics include very frequent (several to many per day) absence seizures in an otherwise appearing normal child with 3 Hz bilateral, synchronous, symmetrical spike-wave pattern with normal background activity on EEG (International League Against Epilepsy, 1989). Previously considered benign, growing evidence indicates that children with childhood absence epilepsy have a high rate of baseline attentional deficits unrelated to seizure frequency along with long term psychosocial difficulties and variable remission rates (Bouma et al., 1996; Pavone et al., 2001; Wirrell et al., 1997).

There have been no published Class I or Class II initial monotherapy clinical trials for the three most commonly used antiepileptic medications (ethosuximide, lamotrigine and valproic acid) in this population (Glauser et al., 2006). In 2003 the National Institute of Neurological Disorders and Stroke (NINDS), National Institutes of Health funded a trial to compare the efficacy and effectiveness for these three medications. The primary endpoint was at 16–20 weeks but built into the trial was an examination of longer term outcomes. The short term data showed that ethosuximide and valproic acid were more effective than lamotrigine in controlling the absence seizures and that ethosuximide was associated with fewer adverse attentional effects compared to valproic acid. This short term data indicated that ethosuximide was a "sensible choice for initial empirical monotherapy in childhood absence epilepsy" (Glauser et al., 2010).

Ideally, optimal initial monotherapy is the medication that provides the best short (4–5 months), medium (1 year post diagnosis) and long term (> 2 years post diagnosis) outcomes. For multiple reasons, it is not guaranteed that the short term initial monotherapy results of

the CAE trial would match medium and long term outcomes. For example, as children with CAE get older, there is an increased risk of generalized tonic–clonic seizures (Callenbach et al., 2009; Charlton & Yahr, 1967; Currier et al., 1963; Dieterich et al., 1985; Grosso et al., 2005; Livingston et al., 1965; Loiseau et al., 1983; Trinka et al., 2004; Wirrell et al., 2001), and ethosuximide has previously been reported to be ineffective in preventing these types of seizures (Glauser, 2002). Second, chronic drug toxicities, such as weight gain with valproic acid, may become treatment limiting later rather than in the short term (16–20 week) period (Glauser, 2007). Medium and long term outcomes need to be combined with short term results to determine the optimal initial monotherapy. The main purpose of this report is to expand the 16–20 week initial monotherapy data for childhood absence epilepsy to outcomes at 12 months of initial therapy in subjects participating in a long term double-blind, randomized comparative trial. A secondary purpose is to provide sufficient methodological detail and data to qualify this study as a Class I study using the 2006 ILAE classification criteria (Glauser et al., 2006). These medium term (12 month) results will be combined with the short term (16–20 weeks) results to help better determine the optimal initial empirical monotherapy for children with childhood absence epilepsy.

Methods

Subject population

Subjects were eligible for enrollment if they had i) a clinical diagnosis of Childhood Absence Epilepsy consistent with the International League against Epilepsy (ILAE) Proposal for Revised Classification of Epilepsies and Epileptic Syndromes (International League Against Epilepsy, 1989), ii) an interictal EEG demonstrating bilateral synchronous symmetrical approximate 3 Hz spike waves on a normal background with at least one burst lasting ≥ 3 seconds, iii) an age older than 2.5 years but less than 13 years of age at study entry, iv) a body weight 10 kilograms and a Body Mass Index for age less than the lower limit of the 99th percentile, v) AST/ALT < 2.5 times the upper limit of normal, vi) total bilirubin < 1.5 times the upper limit of normal, vii) an absolute neutrophil count ≥ 1500/mm^3, viii) platelet count ≥ 120,000/mm^3 and ix) if female, premenarchal at the time of enrollment and willing to agree to abstinence for the duration of the study.

Subjects were excluded if they had any of the following: i) received treatment for CAE with AEDs for a period of greater than 7 days prior to randomization, ii) a history of a major psychiatric disease (e.g. psychosis, major depression), iii) a history of autism or pervasive development disorder, iv) a history of non-febrile seizures (e.g. an afebrile generalized tonic clonic seizure) other than typical absence seizures, v) clinical signs and symptoms consistent with a diagnosis of juvenile absence epilepsy or juvenile myoclonic epilepsy as delineated by the ILAE Proposal for Revised Classification of Epilepsies and Epileptic Syndromes (International League Against Epilepsy, 1989), vi) a history of recent or present significant medical disease (i.e. cardiovascular, hepatic, renal, gynecologic, musculoskeletal, metabolic or endocrine), vii) a history of a severe dermatologic reaction (e.g. Stevens Johnson Syndrome, Toxic Epidermal Necrolysis) to medication, or viii) used a systemic contraceptive for any indication, including acne. Subjects were also ineligible if they or their parent/legal guardian were not reasonably expected to be compliant with study procedures or to complete the study, or if they had participated in a trial of an investigational drug or device within 30 days prior to screening.

The study was approved by the institutional review boards of each of the 32 United States participating sites, the coordinating center, and the NINDS- appointed data and safety monitoring board (DSMB) which provided oversight throughout the study. Families of children with newly diagnosed CAE meeting the above inclusion/exclusion criteria were offered the opportunity to participate to the trial. Parent/legal guardian(s) signed an

institutional review board approved informed consent and subject assent was obtained when appropriate and as dictated by the local institutional review board. A Medical Safety Monitor reviewed all serious adverse events (SAEs) reported during the conduct of the study.

Details of the cohort as well as the outcomes at 16–20 weeks of double blind therapy after randomization have been reported previously (Glauser et al., 2010).

Study design

The study was a parallel, randomized, double blinded study, with partial crossover to open label (at treatment failure only) with subsequent follow-up (Figure 1). The first 16–20 weeks of double blind therapy was called the Titration phase; subsequent double blind therapy was called the Treatment phase. During the Titration phase, clinic visits were scheduled every 4 weeks (with a window of up to one week delay) with a telephone contact at Week 2. During the Treatment phase, visits occurred at 26 weeks post randomization, then every 3 months thereafter until the subject reached the 24 month seizure free mark, the first time weaning study medication for treatment success was considered.

Subjects reaching a treatment failure criterion in the double blind Treatment phase were given the opportunity to enter into the open label phase. In the open label phase, subjects were randomized to one of the two other AEDs. This approach maintained the integrity of the original blinding while allowing subjects to receive one of the other appropriate AEDs.

Baseline visit

After written informed consent was obtained and before randomization and start of study medication, children had a baseline visit which included a detailed medical history, physical and neurological examination, liver function tests and blood counts, a 1 hour video EEG, an age specific battery of neuropsychological testing, a quality of life assessment and a 24 hour diet recall. The baseline EEG (and all subsequent study EEGs) was a simultaneous time locked EEG and video recording performed with the subject awake, lasting 1 hour in duration with two periods of hyperventilation (each 3–5 minutes) and one period of photic stimulation. The neuropsychological test battery included an age-appropriate Conners' Continuous Performance Test (CPT-II for children ≥6 years of age, and K-CPT for children 4 to <6 years of age) (Conners, 2002); standardized tests of verbal and nonverbal intelligence (Brown, 1997; Wechsler, 1991; Wechsler, 2003), vocabulary (Dunn, 1997), memory (Korkman et al., 1998; Korkman et al., 2005; Sheslow & Adams, 2003), learning skills (Sheslow & Adams, 2003), visuomotor integration (Beery et al., 1997), executive function (Heaton, 1981; Heaton, 1993), and academic achievement (Wilkinson, 1993; Woodcock et al., 2007). Baseline neuropsychological testing was performed either before or within 7 days after the start of the study medication. Questionnaires on behavior (Child Behavior Checklist) and quality of life (Quality of Life in Childhood Epilepsy) were also obtained (Achenbach & Rescorla, 2000; Achenbach & Rescorla, 2001; Sabaz et al., 2000).

Stratification and Randomization

Eligible subjects were randomized equally to ethosuximide, lamotrigine, or valproic acid by the Coordinating Center at the Children's Hospital of Philadelphia. Group randomization schedules were generated using permuted blocks of size three within two age strata: < 6 years and ≥ 6 years and within site. Study site personnel were blinded to treatment allocation. Patients experiencing treatment failures were randomized to one of the two other treatments based on randomization schedules generated for each of the three initial drugs using permuted blocks of size four within the two age strata, but overall sites combined, and

subject to the restrictions shown in Figure 1 (if a restriction was met, that assignment was not done and the next assignment on the schedule was given).

Study medication and dosing

The study used two different formulations of ethosuximide (250mg capsules, 250 mg/5 mL syrup), three different formulations of lamotrigine (5mg chewable tablets, 25 mg chewable tablets, 25 mg tablets) and two formulations of valproic acid (250mg capsules, 125mg sprinkles) provided by Pfizer, GlaxoSmith-Kline, and Abbott Laboratories respectively. These companies had no role in the design of the study, data collection, data analysis, or manuscript preparation.

Study medication was titrated as tolerated in predetermined increments every 1–2 weeks over these 16 weeks (Table 1). The maximal target doses were ethosuximide 60 mg/kg/day or 2000 mg/day (whichever was lower), valproic acid 60 mg/kg/day or 3000 mg/day (whichever was lower) and lamotrigine 12 mg/kg/day or 600 mg/day (whichever was lower). The maximum dose of ethosuximide and valproic acid was chosen to be above the highest previously reported dosage used successfully in previous Childhood Absence Epilepsy trials (Glauser et al., 2006). The maximum lamotrigine dose (and titration schedule) was determined by combining pharmacokinetic modeling of the potential serum concentration at different parts of titration with a maximum titration duration of 16 weeks. This analysis was done by the study's pharmacokinetics core using published and unpublished lamotrigine monotherapy data in adults and children. The study's lamotrigine titration schedule was devised to give lower serum concentration with a slower rate of rise than in the adult population at every step of the titration in order to minimize the risk for severe rash. This modeling resulted in a maximal dose for lamotrigine of 12 mg/kg/day by the week 16 visit. Only one previous Childhood Absence Epilepsy clinical trial used higher doses; in that study 7% (2/30) of subjects needed 14–15 mg/kg/day of lamotrigine to become seizure free while the remaining 93% (28/30) became seizure free at doses of ≤ 10 mg/kg/day (Frank et al., 1999). Each study drug's maximal dose and titration schedules were discussed with and approved by the US FDA prior to starting the study.

The titration was not a forced titration. Titration continued until the subject either a) achieved seizure freedom by clinical and EEG criteria, b) reached the maximal allowed study drug dose or c) reached the maximal tolerated dose, whichever came first. Up to the Week 16 visit, subjects could be declared treatment failures due to intolerable adverse events or occurrence of generalized tonic clonic seizures but not due to persistence of absence seizures.

Pharmacy dosing schedules were constructed that maintained the patient within a 20% margin of the weekly mg/kg target dose throughout titration after week 2. Based on the available dosing formulations and the wide range of weights involved, this was accomplished using variable weight group ranges (from a 3 kg range in the smallest children and lowest doses, to a 5 kg range for larger children and higher doses). Further, once the doses for each treatment, dose step, and weight group were defined, the maximum required number of capsules was defined. Subjects received the same number of capsules for all treatments at any given step and weight group so that blinding could be maintained.

For children between 10kg and 50.9 kg, a double dummy double blind design was used with the liquid formulation of ethosuximide and a capsule that contained crushed chewable (LTG) with filler or sprinkles (valproic acid) with filler, in order to enable children who could not swallow capsules to participate in the study. Participants were allowed to open the capsules and put the content in applesauce or other food. The capsules and liquid had appropriate matching placebo. The placebo formulations had similar color, taste and

appearance as the active drug. If children learned to swallow capsules, they could switch from double dummy study medication to over encapsulated study medication at any time after the initial month.

For children 51 kg and over, over-encapsulation was available for blinding the capsule formulation of ethosuximide, the tablet formulation of lamotrigine and the coated tablet formulation of valproic acid. Subjects had a choice of double dummy double blind or double blind encapsulated formulation. Further, children could start on the double dummy double blind formulation, learn to swallow and switch to the double blind encapsulated formulation. If the child was not able to learn how to swallow pills by week 16 but was seizure free and willing to continue on the double dummy arm then the subject could stay in the study and receive the double dummy blinded medication. If the child was not able to learn how to swallow pills by week 16 but was seizure free and unwilling to continue on the double dummy arm then the subject discontinued from the study. All capsules had the same appearance and were packaged by the study's central pharmacy (based at Cincinnati Children's Hospital). Throughout the double blind portion of the trial, the central pharmacy prepared and sent to sites subject specific "study kits" as prescribed by the local site investigator based on the subject's clinical response and the study protocol. The site pharmacy dispensed the double blind study drug kits to the subject. All site pharmacies received bulk drug for the open-label phase and dispensed those directly.

Titration phase and Week 16–20 visit

During the titration phase, a subject was considered seizure free if they did not have: i) any clinical seizures since the last clinic visit per parent/guardian report, ii) no clinical seizures during two 5 minute periods of hyperventilation under the direct observation of the physician, coordinator and the parent (or legal guardian), and iii) no electrographic seizures during a 1 hour awake EEG. The 1 hour EEG performed while the patient was awake used 3 or more seconds of generalized spike-and-wave discharge on EEG as the definition of a seizure.

All subjects had a 1 hour awake video EEG performed at the week 16-study visit. At the week 16 visit, subjects at their maximal allowed or tolerated dose with either clinical seizures or electrographic seizures were declared treatment failures. For those subjects, the double blind treatment was tapered off and subjects were candidates to be randomized to one of the two other treatments (Figure 1). Those subjects tolerating study medication but who had not yet reached their maximal allowed dose had a single additional dose escalation and returned for a 1-hour video EEG four weeks later for a week 20 visit. If at the week 20 visit, subjects continued with clinical seizures or electrographic seizures, then they were declared treatment failures and the double blinded treatment was tapered off. If at the week 20 visit, subjects were clinically seizure free with no evidence of spike wave bursts ≥ 3 seconds on the 1 hour video EEG, then they were declared free from treatment failure and continued receiving double blind medication.

Treatment phase

Subjects continued receiving double blind study medication in the Treatment phase as long as they did not meet any treatment failure criteria (Table 2). Subsequent visits occurred at 26 weeks post randomization, then every 3 months thereafter until the subject reached the 24 month seizure free mark, the first time weaning study medication for treatment success was considered. In depth efficacy and toxicity assessments (1 hour video EEG, neuropsychological battery, including attention testing, and quality of life assessment) were performed at the double blind Month 12 and Month 24 visits.

If a subject did not meet a treatment failure criteria at the Week 16 visit, was at less than the maximum allowed study dose at Week 16, and then later experienced a recurrence of clinical and electrographic absence seizures in the double blind treatment phase, then one additional dose escalation was allowed. If the dose escalation was tolerated, then a repeat 1 hour video EEG was performed four weeks later. On the repeat EEG, subjects found to have electrographic seizures were considered treatment failures and removed from the double blind Treatment phase. On the repeat EEG, subjects found to be seizure free continued to be treated at that dose and continued to be considered free from failure.

Evaluations

At every double blind visit, random nonfasting blood samples were obtained for study medication serum concentration, complete blood count and liver panel. Serum study medication concentrations were not used to guide drug dosing; samples were analyzed in batches and the results utilized in an ancillary population pharmacokinetic study. At the Week 16 or Week 20 visit (if a dose escalation step occurred at Week 16), a sparse pharmacokinetic profile was obtained (pre-dose and 2 samples post-dose) for population pharmacokinetic analysis along with a random spot urine for metabolomic analysis. Assessments of subject's nutrition status were evaluated using a 24 hour recall system at the baseline, Week 16–20 visit and Month 12 visit. Adherence assessments were performed by pill counts, measurement of liquid returned and formal questions regarding the number of missed doses in the past week and the number of missed doses in the period since the last visit. For each subject enrolled in the study, a single blood sample was obtained for pharmacogenetic analyses along with a single blood sample from a healthy adult (unrelated to any subject in the study and without a history of epilepsy) matched for race and ethnicity to serve as a control for pharmacogenetic analyses. The results from these ancillary studies (population pharmacokinetics, nutritional, metabolomics, and pharmacogenetic) will be detailed in separate reports.

Outcomes

The main effectiveness outcome was the freedom from treatment failure rate 12 months after randomization. Treatment failure was defined as failure either due to lack of seizure control, or meeting safety exit criteria, or withdrawal from the study for any other reason (Table 2). The main cognitive outcome was the percentage of subjects 4 years of age or older with a Confidence Index (CI) ≥ 0.60 on the Conners' Continuous Performance Test at the Month 12 visit (or the latest data from any subject's visit after the Week 16–20 visit up to and including their Month 12 visit).

Since multiple outcome measures were used in the trial, a decision making algorithm was constructed prior to breaking the blind. The goal of the algorithm was to facilitate interpretation of study results in a predefined, meaningful, and objective way that would inform clinical practice. In this algorithm, study medications were compared using four study outcomes in a sequential manner to identify the optimal initial monotherapy. The four outcomes were freedom from failure (the overall study's primary outcome), medication impact on attention (measure by Conners' Continuous Performance Test), medication impact on behavior (measured by Child Behavior Checklist scores), and medication impact on quality of life (measured by Quality of Life in Childhood Epilepsy scores). If the first outcome did not identify a single optimal study treatment, then the best 2 or 3 medications using that outcome were compared using the next outcome. This process was repeated until a single medication was identified as optimal or all outcomes were examined (whichever came first).

Statistical Analysis

Baseline characteristics and safety variables for the three treatments were compared by either an exact chi-square test or a two-way analysis of variance (with treatment as one factor and age stratum as the other factor), depending on whether the characteristic being analyzed was discrete or continuous.

Rates of freedom from failure were compared using Fisher's exact test for the pairwise comparisons between treatments with a P value of 0.017 considered to indicate statistical significance (accounting for a Bonferroni correction for the three pairwise comparisons). Odds-ratio calculations with a 95% confidence interval were performed. Kaplan–Meier curves were constructed to show the time to treatment failure over the 12 month study period. A logrank test of the three pairs of study drugs was performed at Month 12 visit.

McNemar test was used to investigate the change in the percentage of subjects (4 years of age or older) experiencing attentional dysfunction as measured by a Confidence Index of 0.60 or higher on the Conners' Continuous Performance Test between the baseline visit and the Month 12 visit. A Tukey–Kramer analysis of attentional function at Month 12 visit incorporated baseline attentional differences. All analyses were carried out using SAS software, version 9.1 (SAS Institute), and StatXact software, version 8.0 (Cytel Software).

The primary objective of the study was to detect a 20% difference in freedom from failure rates between the three medications at 16–20 weeks of double blind therapy. Sample size calculations were based on detecting this difference with 80% power using the binomial outcome at 16-weeks with a two-sided p-value of 0.017 for significance along with one interim analysis. The interim analysis, performed when 50% of subjects reached the primary outcome, was for both efficacy and futility, with the use of an O'Brien–Fleming boundary for stopping the study and adjustment with the Lan–DeMets spending function. Given the two stratification factors and the expected dropout; the sample size then was expanded by 5% twice (two stratification factors), and corrected for an expected 5% dropout, resulting in a required sample size of 446 subjects. This sample size was determined to be large enough to detect a meaningful difference of 0.5 standard deviations in the Confidence Index on the age appropriate Conner's Continuous Performance Tests (with >80% power and α=.017) at the Week 16–20 visit.

Results

Patient population

A total of 453 children enrolled in the CAE trial between July 2004 and October 2007, meeting the study's enrollment goals only 4 months later than originally projected (Figure 2). Out of the 1,188 screened children, 820 (69% of screened) subjects were eligible and 453 subjects (55% of eligible) enrolled and were randomized. Among the 453 subjects enrolled, seven were withdrawn due to ineligibility at baseline including three cases not meeting EEG criteria and single cases with abnormal neutrophil count, BMI greater than the 99th percentile, family withdrew consent on the day of randomization before subject took any study drug, and subject discovered to meet an exclusion criterion after randomization but before subject took any study drug. Thus 446 subjects are included in subsequent effectiveness analyses and 451 subjects are included in subsequent safety analyses.

A total of 32 sites across the entire United States participated in the study. The highest recruiting sites were: Cincinnati Children's Hospital (n=50, 11%), The Children's Hospital of Philadelphia (n=33, 7%), University of California San Diego (n=26, 6%), Denver Children's Hospital (n=26, 6%), Baylor College of Medicine in Houston (n=25, 6%), Nationwide Children's Hospital in Columbus (n=24, 5%), and Children's Hospital Univ. of

Alabama at Birmingham (n=21, 5%). Ten other sites recruited 10–19 subjects each, and fifteen sites recruited 1–9 subjects each. Thus, a total of seven sites recruited 203 (45%) of the study subjects and the remaining 25 sites recruited the other 55% of subjects.

The median age of the 453 children enrolled in the CAE trial was 7 years 5 months (range 2 years 7 months to 12 years 11 months) (Table 3). More female subjects (57%) enrolled than male subjects (43%). The most commonly self reported race was white (72%) followed by Black or African-American (19%). Twenty-two percent (22%) of the subjects are of Hispanic ethnicity. The median percentile weight for age and median percentile BMI for age (for both age groups) was approximately at the 75th percentile. The interquartile range for BMI for age was from the 43% to the 89%.

There were no significant differences among the treatment groups within each age stratum or with respect to overall demographic characteristics (Table 3). The Confidence Index on the Conners' Continuous Performance Test was elevated (≥0.60) in 142 of 399 subjects (36%) who could be evaluated.

Freedom from Treatment Failure

Overall, 37% (165/446) of subjects were free from treatment failure at the Month 12 visit. Subjects receiving ethosuximide (45%) or valproic acid (44%) had higher freedom-from failure rates compared to those given lamotrigine (21%, $p < 0.001$ for both comparisons) (Table 4). The odds ratio for freedom from treatment failure for ethosuximide versus lamotrigine was 3.09 (95% confidence interval [CI]: 1.86–5.31) and valproic acid versus lamotrigine was 2.90 (95% CI: 1.74–4.83). The freedom from treatment failure rate analysis within each age stratum along with the log-rank test of time to treatment failure until the visit at 12 months (Figure 3) gave similar results. There was no significant difference between the freedom from failure rates for ethosuximide and valproic acid (Table 4).

The remaining 63% (281/446) of subjects experienced treatment failure during the first 12 months of initial therapy. The most common reasons for treatment failure were lack of seizure control (28%, 125/446) and intolerable side effects (26%, 115/446). There were significant differences among the treatment groups in the frequency of treatment failures due to lack of seizure control ($p < 0.001$) and intolerable adverse events ($p < 0.037$). The majority of the 125 subjects with treatment failure due to lack of seizure control were in the lamotrigine cohort. The largest percentage of the 115 subjects discontinuing due to adverse events were in the valproic acid group.

The category of nervous system, behavioral and psychological adverse events was the overall most common cause for treatment discontinuation due to intolerable adverse events but there was no difference in its occurrence between treatment groups. The only adverse event leading to discontinuation that occurred more frequently in one treatment group compared to the others was an increase in BMI meeting the pre-specified treatment failure criteria (Table 2). During the first year of therapy, 12 subjects in the valproic acid group discontinued due to BMI increases meeting treatment failure criteria compared to one subject in the lamotrigine and no subjects in the ethosuximide cohorts. In eight subjects, treatment was discontinued owing to generalized tonic–clonic seizures: three subjects in the ethosuximide group, four in the valproic acid group, and one in the lamotrigine group. There were 14 subjects who developed a rash that led to treatment failure (ethosuximide n=6, lamotrigine n=6, valproic acid n=2, p=0.34). In these subjects, the rash was considered possibly drug-related and judged to be moderate to severe in severity. None of the subjects developed Stevens–Johnson syndrome. There were no significant differences among the treatment groups in the frequency of treatment failures due to withdrawal from the study.

Between the Week 16–20 primary study outcome and the Month 12 visit, treatment failure occurred in an additional 7% (11/154) of ethosuximide subjects, 8% (12/146) of lamotrigine subjects and 14% (21/146) of valproic acid subjects. Treatment failure due to loss of seizure control between the Week 16–20 primary outcome and the Month 12 visit was more common in the lamotrigine cohort (5%, 7/146) compared to the ethosuximide (1%, 1/154) and valproic acid (1%, 1/146) cohorts. Treatment failure due to intolerable adverse events between the Week 16–20 primary outcome and the Month 12 visit was more common in the valproic acid cohort (9%, 13/146) compared to the ethosuximide (1%, 1/154) and lamotrigine (3%, 4/146) cohorts. The most common cause for valproic acid related intolerable adverse event treatment failure during this interval was BMI increases of ≥ 3.0 kg/m^2 by the Month 12 visit in 8 subjects (compared to none in the other treatment groups). Over the entire first 12 months, the body mass index treatment failure criteria reached by the 12 valproic acid patients occurred at a median of 6.8 months (range 2.8 to 11.9 months). Only one additional patient (on lamotrigine) developed a rash meeting treatment failure criteria between the Week 16–20 primary outcome and the Month 12 visit.

Adverse events reported by ≥ 5% of the subjects in at least one treatment group are shown in Table 5. Overall, the most common of these 20 different adverse events were fatigue and headache. Stomach upset, nausea, and vomiting occurred more frequently (defined as 5% greater occurrence in one treatment group compared to either of the other treatment groups) in the ethosuximide group. Weight increase, hyperactivity, attention problems, hostility, decreased concentration, personality change, and sleep problems were reported more frequently in the valproic acid group. No side effect occurred more frequently in the lamotrigine cohort compared to the other treatment cohorts.

By the Month 12 visit, eight subjects (2%) had had serious adverse events that required hospitalization: four in the ethosuximide group and two each in the lamotrigine and valproic acid groups. Reasons for hospitalization included generalized tonic–clonic seizures in three subjects (ethosuximide n=2, valproic acid n=1), and one subject each had nonepileptic events, longer in duration than previous absence seizures, episodes of acting out, salmonella enteritis, and pneumonia with diarrhea and vomiting.

Confidence Index Scores on Continuous Performance Test

Among 166 subjects who were 4 years of age or older at baseline and had Month 12 visit data, 89% (148/166) had Confidence Index results from the Conners' Continuous Performance Test both at the baseline visit and the Month 12 visit. This Confidence Index data was available in 91% (64/70) of ethosuximide subjects, 88% (28/32) of lamotrigine subjects, and 88% (56/64) of valproic acid subjects. Among the subjects 4 years and older, there were no statistically significant differences in the baseline demographics between those who had a Conners' Continuous Performance Test performed at a Month 12 visit and those who did not have one performed at a Month 12 visit for any reason (e.g. never made it to Month 12, test not performed at Month 12 visit).

At the Month 12 visit, a higher rate of Confidence Index scores ≥ 0.60 was noted in the valproic acid group (56%) compared to either the ethosuximide group (29%) or the lamotrigine group (27%) ($p < 0.01$, Table 6). Even after adjustment for baseline Confidence Index scores, the valproic acid group had worse Confidence Index scores at the 16–20 week visit and the 12 month visits compared to the ethosuximide ($p<0.001$, $p=0.0043$ respectively) and lamotrigine ($p<0.001$, $p=0.055$ respectively) groups while there was no difference between the ethosuximide and lamotrigine groups at either time point ($p=0.43$, $p=0.97$ respectively). Analysis of Month 12 data after adjustment for Week 16–20 Confidence Index scores showed no statistical difference between the three groups.

A significant number of subjects in the valproic acid group experienced a change in their Confidence Index score from normal (CI < 0.60) to abnormal (CI ≥ 0.60) between baseline and the Month 12 visit (p=0.012). In contrast, this significant change from normal to abnormal was not seen in the ethosuximide and lamotrigine cohorts.

Among the 44 subjects who reached treatment failure criteria after the Week 16–20 visit but before the Month 12 visit, baseline and last visit Confidence Index data is available for an additional 14 subjects. The same valproic acid effect was seen if these subjects are included in the analysis and again no effect was seen in the ethosuximide or lamotrigine cohorts.

Discussion

After 12 months of initial monotherapy in subjects with childhood absence epilepsy, ethosuximide and valproic acid were significantly more effective than lamotrigine in controlling seizures without intolerable side effects. In addition, a significant number of subjects in the valproic acid cohort experienced negative effects on attentional measures; this was not seen in the ethosuximide or lamotrigine cohort. At 12 months of double blind therapy, treatment failure due to lack of seizure control was much more common in the lamotrigine group while intolerable adverse events were more common in the valproic acid group. Valproic acid associated increases in BMI were not seen at a higher rate than the other treatments by the 16–20 week of therapy but by the 12 month visit, this specific adverse event was more evident in the valproic acid group, further differentiating it from ethosuximide. There were specific side effects that occurred more frequently in the ethosuximide group or valproic acid group that did not result in discontinuation and were generally transient. These 12 month outcome data provide further support that not only in the short term, but also in the medium term, ethosuximide is the optimal initial empirical monotherapy for childhood absence epilepsy. This is the first randomized controlled trial meeting ILAE criteria for Class I evidence for childhood absence epilepsy (or for any type of generalized seizure in adults or children) (Glauser et al., 2006).

The study's inclusion/exclusion criteria were constructed to identify and enroll a homogeneous, well defined, recognizable subject population of children with childhood absence epilepsy. To minimize subject selection bias, 32 sites across the United States participated in the study. The diversity of study sites, both geographically and in terms of racial and ethnic composition, provided comprehensive representation of the pediatric population of CAE in the U.S. which minimized subject selection bias while maximizing the generalizability of the results. The age characteristics of this 453 subject national CAE cohort is similar to the 69 CAE subjects with absences only at study entry from the Connecticut prospective, community-based study of 613 children with newly diagnosed epilepsy (median 7 years, range 3.2–10.3 years) (Berg et al., 1999). The distribution of weight is consistent with general trends in the U.S. population. The CAE cohort's demographic characteristics were representative of both the US population and smaller community-based CAE cohorts. A strength of the study was the successful recruitment of minority participants with a distribution similar to the US general population. Based on the study cohort's demographics, we expect our findings in this population to be generalizable to subjects with CAE.

One of the greatest challenges in designing pediatric epilepsy trials is determination of a clearly justified target dosing, titration rate and titration duration for each study intervention. A key decision is whether the study will use a "fixed" approach (fixed target dose, fixed titration rate, fixed titration duration) or a "flexible" approach. The fixed approach is a common and successful design for pediatric epilepsy trials of investigational antiepileptic medication studied for regulatory purposes. However, the fixed approach misses the

opportunity to gain a better understanding of how dosing is practiced in the clinical setting. A flexible design uses the clinically relevant approach of "titration to clinical response". It allows for study of the entire dosing range for each intervention with a titration that optimizes the balance between the risk of continued seizures and the risk for adverse events. A completely flexible titration schedule or duration is not practical for a blinded clinical trial. In some cases too much flexibility would also be unethical because families and study staff will not tolerate continued seizures indefinitely due to ineffective study medications. By avoiding forced titration schedules, fixed target doses and shortened titration duration, the study design tried to avoid biasing outcome due to differential titration characteristics of the three study medications.

In this study, initial drug dosages, titration and administration schedules, criteria for treatment failure, time until weaning, and use of sequential monotherapy was designed to match clinical practice. There was not forced titration to high dosages, rather upper limits of study medication dosages were set high to allow for a full exploration of the dosing range for each study medication. Using these approaches, the study did not force clinicians to act radically differently from regular clinical practice. As such, clinician comfort with study design was high which translated into few protocol violations, no need for major protocol revisions during the course of the trial, and a low dropout rate over the course of 12 months.

To determine if the subject was seizure free during titration, the study used a stepwise process (parental/guardian report, bedside hyperventilation, 1 hour video EEG) where the next step only occurred if the patient was reported as seizure free at the previous step. Clinical history and hyperventilation alone were not considered adequate to determine and confirm seizure freedom. Comparison of parental report of clinically obvious seizures with measures on EEG has found that parental report frequently underestimated the seizure burden by five- or ten-fold (Browne et al., 1983). The office-based hyperventilation test is associated with unacceptably high rates of false positive and false negative test results (Aicardi, 1994; Epstein et al., 1994; North et al., 1990; Wirrell et al., 1996). This study's previously reported short term results demonstrated that 31% (34/109) of the subjects having treatment failure due to lack of seizures only had seizures noted on the 1 hour video EEG when the other assessment methods indicated the patient was seizure free. At the Week 16–20 and Month 12 visits, all three steps were performed to determine seizure control.

The 1 hour awake EEG used ≥ 3 seconds of generalized spike-and-wave discharge on EEG as the definition of a seizure. Studies have defined an absence "seizure" as a generalized spike-and-wave discharge lasting at least three seconds (Frank et al., 1999; Holmes et al., 1987). The "three seconds" rule is clinically reasonable, since more than 90% of generalized spike-and-wave discharges lasting at least three seconds are accompanied by some clinical manifestation (Holmes et al., 1987). The 1 hour awake EEG (using a seizure definition of ≥ 3 second burst of generalized spike wave) allows for an objective, valid, reliable and reproducible measurement of AED efficacy. Even if the study EEG was normal or showed generalized spike wave bursts all less than 3 seconds, the study drug was considered a failure if the family reported a history of a clinical event since the last visit.

For children with epilepsy, outcome measures should include measures of medication efficacy (seizure control) and effectiveness (the combination of efficacy and tolerability) along with measures of cognitive function, behavior and quality of life. This study's primary outcome measure focused on effectiveness. The study's secondary outcome was a cognitive measure since in children cognitive side effects can be an important factor when one is selecting a drug from among medications that are equally effective. Attention was specifically selected for the secondary outcome since it is considered a fundamental part of absence epilepsy (just as memory deficits are for patients with temporal lobe epilepsy)

(Caplan et al., 2008; Holdsworth & Whitmore, 1974; Killory et al., 2011; Mitchell et al., 1992; Vega et al., 2010).

The study's freedom from failure results at the Month 12 visit are similar to those measured at the Week 16–20 visit; both ethosuximide and valproic acid demonstrated better efficacy and effectiveness than lamotrigine (Glauser et al., 2010). There is no clear reason for the discrepancy between this study's lower efficacy rates for lamotrigine and smaller open-label studies that have shown much higher efficacy rates despite similarities in dose ranges, maximal daily doses, drug exposures, and efficacy end points.

Although lamotrigine's lack of efficacy was previously noted at the Week 16–20 visit, valproic acid's elevated rate of discontinuations due to adverse events is a new finding and was not noted in the short term results. The greatest increase in valproic acid-treated subjects meeting failure criteria between the Week 16–20 visit and the Month 12 visits was for increases in body mass index. Overall 8% (12/146) of the valproic acid cohort reached treatment failure due to this criterion. In previous studies (not randomized clinical trials), the incidence of valproic acid associated excessive weight gain in children with epilepsy ranged from 9% to 44% and was reported to occur within the initial 3 months of therapy (Easter et al., 1997; Egger & Brett, 1981; Jallon & Picard, 2001; Novak et al., 1999). In contrast, in this study, the body mass index treatment failure criteria was reached at a median of 6.8 months (range 2.8 to 11.9 months) indicating the weight gain causing the increased body mass index may not always be seen in the short term.

Children with childhood absence epilepsy can exhibit cognitive, behavioral, and psychosocial co-morbidities. For these children, attentional deficits are the most important marker of cognitive dysfunction and often associated with reduced academic performance. The study used the Conners' Continuous Performance Test Confidence Index to provide an overall indication of whether a subject had attentional problems (Conners, 2002). A Confidence Index of 0.60 or higher was used as an indicator of clinically significant difficulties with attention (Conners, 2002; Glauser et al., 2010). This measure is not, and was not used as, a test for a diagnosis of attention deficit disorder. Both the prespecified and post hoc analyses showed that by the Month 12 visit, valproic acid negatively affected attention in a higher percentage of children than did ethosuximide.

Prior to breaking the blind, an algorithm was established that created a hierarchy of the study's outcome measures, clearly indicating how the data should be interpreted when the trial is complete. This study's algorithm started with effectiveness and then used effects on attention, behavior and quality of life as sequential comparisons. This pre-specified approach was aimed at identifying an optimal initial monotherapy without being biased by knowledge of the study's primary and secondary outcome results. This algorithm would also minimize the risk of misinterpreting clinical trial results later when readers might focus only on outcomes that match their own pre-existing biases. Since the optimal initial therapy for 12 month outcomes was established using effectiveness and attentional data, data on behavior and quality of life will be presented in a separate report.

The efficacy, effectiveness and attentional outcomes of this study measured at the 12 month visit are similar to the short-term outcomes measured at the Week 16–20 visit. Some chronic toxicities of valproic acid are now apparent (such as weight gain). Conversely, some of the early acute toxicities (e.g. rash, fatigue) were no longer a significant problem past 16 weeks. Overall, the results for the 16 week primary outcome in terms of freedom from failure, seizure freedom, and adverse events rates remain substantially unchanged at the 12 month visit.

These results reinforce that ethosuximide is the optimal choice for initial empirical monotherapy in childhood absence epilepsy. However, there is still significant room to improve since even the best empirical initial monotherapy fails in 55% of children over the first 12 months of treatment.

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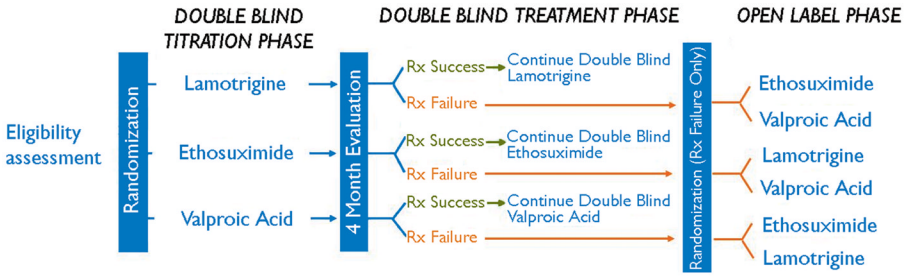

Figure 1.

Overall study design. Note that subjects exiting the double blind phase due to a generalized tonic clonic seizure were not randomized to ethosuximide for the open label phase; subjects exiting the double blind phase due to a rash were not randomized to lamotrigine for the open label phase; subjects exiting the double blind phase due to hepatitis/pancreatitis were not randomized to valproic acid for the open label phase; subjects exiting the double blind phase and starting a systemic contraceptive were not randomized to lamotrigine.

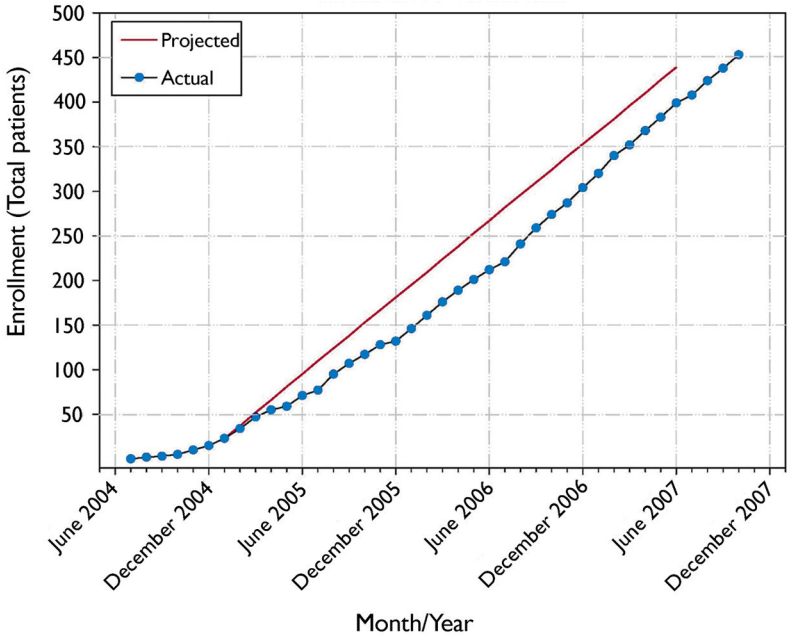

Figure 2.
Projected and Actual study enrollment

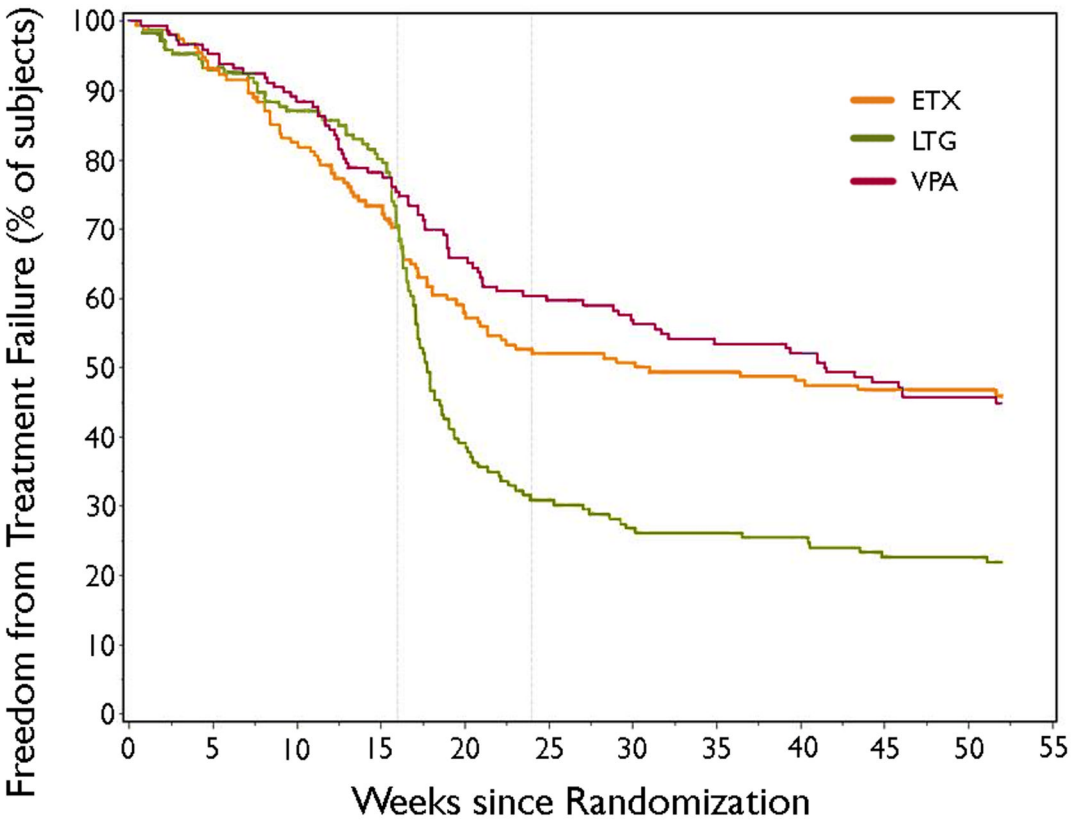

Figure 3.
Log-rank test of time to treatment failure through 12 months by treatment ($p<0.001$). Patients remained on study unless they met a treatment failure criterion. Treatment failure due to drug toxicity or a generalized tonic clonic seizure could occur at any time; treatment failure due to persistence of absence seizures could only occur on or after the 16-week visit.

Table 1

Titration Schedule for each study medication with study week target dose

Study Week	Ethosuximide	Valproic Acid	Lamotrigine
	(in mg/kg/day)		
1	10	10	0.3
2	10	10	0.3
3	15	15	0.6
4	15	15	0.6
5	20	20	1.2
6	20	20	1.8
7	30	30	2.4
8	30	30	3.0
9	40	40	4.5
10	40	40	4.5
11	50	50	7.0
12	50	50	7.0
13	60	60	9.0
14	60	60	9.0
15	60	60	12.0
16	60	60	12.0

Table 2

Treatment Failure Criteria

1. A general tonic clonic seizure of any duration
2. Persistence or relapse of absence seizures (after week 16)
    - **a.** Clinical or HV induced seizures:
        - **i.** If the subject has reached their maximal allowed or maximum tolerated dose, persistence on or recurrence after the Week 16 visit
        - **ii.** If the subject has not reached their maximal allowed or maximum tolerated dose, persistence or recurrence following the single additional dose escalation
    - **b.** Electrographic seizures:
        - **i.** If the subject has reached their maximal allowed or maximum tolerated dose: electrographic seizures on 1 hour video EEG at the Week 16, Month 12 visit or Month 24 visit
        - **ii.** If the subject has not reached their maximal allowed or maximum tolerated dose, electrographic seizures on prolonged EEG following the single additional dose escalation
3. Dose Exiting Toxicity
    - **a.** Platelets < 50,000/mm^3.
    - **b.** Absolute neutrophil count < 500/mm^3.
    - **c.** ALT/AST ≥ 10 × upper limit of normal.
    - **d.** Total bilirubin ≥ 5 × upper limit of normal.
    - **e.** Rash considered by the local investigator to be of at least moderate severity and possibly, probably, or definitely drug related.
    - **f.** Clinical symptoms consistent with pancreatitis with elevations in serum amylase or lipase.
    - **g.** An increase in the BMI of at least 3.0 kg/m^2 as compared to baseline at any time during the first 12 months of the study, or of a least 4.0 kg/m^2 as compared to baseline at any time during the second 12 months of the study. Increases after the first 24 months on drug will not be evaluated as exit criteria.
4. Subjects who develop Dose Limiting Toxicity following a single dose modification. Dose limiting toxicity is defined as
    - **a.** Platelets: 50,000/mm^3 to < 75,000/mm^3
    - **b.** Absolute neutrophil count: 500/mm^3 to < 750/mm^3
    - **c.** ALT/AST : > 5 × to < 10 × upper limit of normal
    - **d.** Total bilirubin: > 2.5× to < 5 × upper limit of normal
    - **e.** Affirmative response by parents/guardian to the question: “Are your child’s side effects intolerable?”
5. Subject/parent/guardian or physician desire for subject to withdraw for study related reasons (e.g. medication side effects, loss of desire to come to visits).

Table 3

Subject Baseline Characteristics

	Ethosuximide (N=155) no. (%)	Lamotrigine (N=149) no. (%)	Valproic Acid (N=147) no. (%)	Total (N=451) no. (%)	P-value
Age					0.96*
Under 4 years old	5 (3)	5 (3)	7 (5)	17 (4)	
≥ 4 to < 8 years old	79 (51)	81 (55)	78 (53)	243 (53)	
≥ 8 to < 12 years old	66 (43)	58 (40)	58 (40)	184 (41)	
≥ 12 to < 13 years old	4 (3)	2 (1)	3 (2)	10 (2)	
Age 6 years old and older	116 (75)	110 (74)	113 (77)	339 (75)	0.81
Male sex	65 (42)	57 (38)	71 (48)	193 (43)	0.21
Hispanic ethnicity	36 (23)	32 (22)	32 (22)	100 (22)	0.92
Race					
White	110 (71)	117 (78)	107 (73)	334 (74)	0.51
Black or African American	33 (21)	26 (18)	29 (20)	88 (20)	
Other or missing	12 (8)	6 (4)	11 (8)	29 (6)	
Attentional difficulties (CPT CI ≥ 0.60)	49/141 (35)	39/130 (30)	54/128 (42)	142/399 (36)	0.12
Neuropsychological Evaluation performed before 1st study dose	94/142 (66)	85/132 (64)	78/132 (59)	257/406 (63)	0.45

CI = Confidence Index

CPT = Conners' Continuous Performance Test

Table 4

Outcomes and Reasons for Treatment Failure in three study groups at Month 12 (numbers shown as n (%)).

Result	Ethosuximide (N=154)			Lamotrigine (N=146)			Valproic Acid (N=146)			Overall P value*
	At 16–20 Weeks	In between 16–20 Weeks & Month 12	At 12 Months	At 16–20 Weeks	In between 16–20 Weeks & Month 12	At 12 Months	At 16–20 Weeks	In between 16–20 Weeks & Month 12	At 12 Months	At 12 Months
Primary outcome: Freedom from treatment failure on double blind randomized treatment	81 (53)		70 (45)	43 (29)		31 (21)	85 (58)		64 (44)	< 0.001
Treatment Failures	73 (47)	11 (7)	84 (55)	103 (71)	12 (8)	115 (79)	61 (42)	21 (14)	82 (56)	
Lack of Seizure Control	23 (15)	1 (1)	24 (16)	73 (50)	7 (5)	80 (55)	20 (14)	1 (1)	21 (14)	< 0.001
Intolerable AE	37 (24)	1 (1)	38 (25)	25 (17)	4 (3)	29 (20)	35 (24)	13 (9)	48 (33)	< 0.037
Nervous system, behavioral, or psychological effects	12	1	13	9	3	12	20	3	23	
Digestive disorders	9	0	9	3	1	4	6	2	8	
Rash	6	0	6	5	1	6	2	0	2	
Fatigue	3	0	3	2	1	3	5	1	6	
Headache	3	0	3	2	0	2	2	1	3	
Body Mass Index increase meeting exit criterion	0	0	0	1	0	1	4	8	12	
Laboratory abnormality	1	0	1	2	0	2	2	1	3	
Other	4	0	4	4	2	6	5	0	5	
Study/Subject Related Withdraw	19 (12)	10 (6)	29 (19)	18 (12)	0 (0)	18 (12)	15 (10)	6 (4)	21 (14)	0.28

Note: The percentages may not add up to 100% due to rounding errors.

Table 5

Adverse events in 5% or more of subjects in any treatment group (numbers shown as n (%)).

Adverse Effect	Ethosuximide			Lamotrigine			Valproic Acid			Total
	Up to 16–20 Weeks (N=155)	In between 16–20 Weeks and Month 12 (N=81)	Up to Month 12 (N=155)	Up to 16–20 Weeks (N=149)	In between 16–20 Weeks and Month 12 (N=43)	Up to Month 12 (N=149)	Up to 16–20 Weeks (N=147)	In between 16–20 Weeks and Month 12 (N=85)	Up to Month 12 (N=147)	Up to Month 12 (N=451)
General whole body										
Fatigue	25 (16)	1(1)	26 (17)	16 (11)	3(7)	18 (12)	22 (15)	5(6)	27 (18)	71 (16)
Headache	20 (13)	5(6)	23 (15)	12 (8)	3(7)	14 (9)	12 (8)	7(8)	18 (12)	55 (12)
Bacterial infection	6 (4)	3(4)	8 (5)	3 (2)	2(5)	5 (3)	1 (1)	0(0)	1 (1)	14 (3)
Gastrointestinal										
Stomach upset	24 (15)	1(1)	24 (15)	7 (5)	1(2)	8 (5)	13 (9)	1(1)	13 (9)	45 (10)
Nausea, vomiting, or both	25 (16)	6(7)	29 (19)	2 (1)	0(0)	2 (1)	10 (7)	3(4)	12 (8)	43 (10)
Appetite increased	5 (3)	1(1)	6 (4)	9 (6)	1(2)	10 (7)	13 (9)	2(2)	15 (10)	31 (7)
Appetite decreased	9 (6)	1(1)	10 (6)	7 (5)	2(5)	9 (6)	4 (3)	4(5)	8 (5)	27 (6)
Weight increased	1 (1)	0(0)	1 (1)	3 (2)	1(2)	4 (3)	11 (7)	3(4)	14 (10)	19 (4)
Diarrhea	6 (4)	3(4)	9 (6)	2 (1)	0(0)	2 (1)	5 (3)	3(4)	7 (5)	18 (4)
Neurological – behavioral – psychiatric										
Hyperactivity	13 (8)	1(1)	13 (8)	12 (8)	0(0)	12 (8)	17 (12)	6(7)	23 (16)	48 (11)
Attention problems	6 (4)	3(4)	8 (5)	7 (5)	4(9)	11 (7)	16 (11)	9(11)	24 (16)	43 (10)
Hostility	4 (3)	1(1)	4 (3)	11 (7)	0(0)	11 (7)	19 (13)	3(4)	22 (15)	37 (8)
Concentration decreased	5 (3)	1(1)	6 (4)	5 (3)	4(9)	9 (6)	13 (9)	5(6)	18 (12)	33 (7)
Personality change	5 (3)	1(1)	6 (4)	8 (5)	2(5)	10 (7)	15 (10)	2(2)	17 (12)	33 (7)
Sleep problem	10 (6)	1(1)	11 (7)	5 (3)	0(0)	5 (3)	15 (10)	2(2)	17 (12)	33 (7)
Depression	4 (3)	2(2)	4 (3)	9 (6)	3(7)	11 (7)	8 (5)	3(4)	11 (7)	26 (6)
Slow process speed	2 (1)	1(1)	3 (2)	6 (4)	1(2)	7 (5)	8 (5)	4(5)	11 (7)	21 (5)
Memory problem	0 (0)	0(0)	0	6 (4)	2(5)	8 (5)	9 (6)	2(2)	10 (7)	18 (4)
Dizziness	9 (6)	2(2)	10 (6)	5 (3)	0(0)	5 (3)	2 (1)	0(0)	2 (1)	17 (4)
Apathy	4 (3)	1(1)	4 (3)	3 (2)	0(0)	3 (2)	7 (5)	3(4)	9 (6)	16 (4)

Note: The numbers in the “up to Month 12” and “up to 16–20 weeks” columns are the sum of unique adverse events per patient in that treatment group. The numbers in the In between column are the sum of unique adverse events that started after 16–20 weeks visit, and not including and continuing AEs from before the 16–20 week visit. The denominators for the percentages in “up to Month 12” and “up to

16–20 weeks" columns are the total number of patients randomized to that treatment group and had at least one dose of the study medicine. The denominators of the In between columns are the number of patients who had Freedom From Failure outcome at the 16–20 week visit evaluation in that treatment group

Table 6

Elevated Confidence Index Scores (CI ≥ 0.60) at Baseline visit, 16–20 week visit and Month 12 visit per treatment group.

Visit	Ethosuximide	Lamotrigine	Valproic Acid	P value at that visit
Baseline	35% (49/141)	30% (39/130)	42% (54/128)	0.12
16–20 Week visit	33% (35/107)	24% (25/104)	49% (52/106)	0.0006
12 month visit	29% (20/70)	27% (8/30)	56% (34/61)	0.0021