CLINICAL REVIEW

Application Type	sNDA
Application Number(s)	022416 (S-009)
Priority or Standard	Priority
Submit Date(s)	3/13/17
Received Date(s)	3/13/17
PDUFA Goal Date	9/13/17
Division / Office	DNP
Reviewer Name(s)	Natalie Getzoff, MD
Review Completion Date	8/16/17
Established Name	Eslicarbazepine acetate
Trade Name	Aptiom
Therapeutic Class	Anticonvulsant
Applicant	Sunovion
Formulation(s)	Oral tablet
Dosing Regimen	200 mg-1200 mg daily based on weight
Indication(s)	Monotherapy or adjunctive treatment of partial-onset seizures
Intended Population(s)	≥ 4 years of age

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

There is adequate support for approval of Aptiom for use as adjunctive and monotherapy for patients with partial onset seizures who are ≥ 4 to 17 years of age. The recommended dosing in the pediatric population is based on weight bins and is as follows: 11-21 kg: 400-600 mg; 22-31 kg: 500-800 mg; 32-38 kg: 600-900 mg; >38 kg: 800-1200 mg. These doses are based on PK simulations derived from pediatric patients with partial onset seizures (POS) and PK data collected from adult patients. In general, the safety analysis did not identify any concerns outside of the AEs seen in the Phase 3 adjunctive epilepsy studies.

1.2 Risk Benefit Assessment

Aptiom has established efficacy as an adjunctive and monotherapy treatment in adult patients with POS. There is no new risk related to the active ingredient that has not already been identified by the experience with the drug in the adult studies.

This application was supported by data from three studies for use as therapy in treating POS in pediatric patients ≥ 4 years of age. One was an open-label Phase 2 study of PK and safety of ESL in patients with refractory POS ages 4-17 (Study 202). The other two were randomized, placebo-controlled trials of ESL as adjunct therapy in patients with refractory POS who were 4-17 years of age (Studies 208 and 305). Safety results from adolescent patients enrolled in adult studies were also described but not pooled with the three primary studies. The pharmacokinetic analysis provided support for doses in the pediatric population that provide similar exposures to efficacious doses in the adult population, and no safety signal was identified.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

No new PMRs are recommended. Continue current safety PMRs and routine postmarket surveillance.

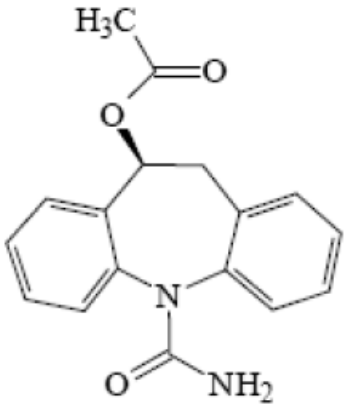
2 Introduction and Regulatory Background

2.1 Product Information

Eslicarbazepine Acetate (ESL) is a voltage-gated sodium channel blocker. It can be considered a member of a third generation in the dibenz[b,f]azepine anticonvulsant family in which carbamazepine (CBZ) would be considered as first generation and oxcarbazepine (OCB) as second generation.

When administered orally, eslicarbazepine acetate metabolizes to S- and R-licarbazepine and oxcarbazepine, as does Trileptal (oxcarbazepine, OXC); however, the ratio of these metabolites is different between OXC and eslicarbazepine (ESL). There are other differences between ESL and CBZ/OCB. For example, carbamazepine neither auto-induces its own metabolism nor is it metabolized to the epoxide form. Oxcarbazepine is metabolized to a mixture of eslicarbazepine and R-licarbazepine, as well as persistent parent molecule. Following oral administration, eslicarbazepine acetate is metabolized to yield mainly S-licarbazepine (eslicarbazepine) and to minor metabolites, R-licarbazepine and (minimally) oxcarbazepine.

Figure 1: Eslicarbazepine molecule



Molecular weight: 296.32
Molecular formula: $C_{17}H_{16}N_2O_3$

Aptiom (eslicarbazepine acetate, ESL) was approved in the United States (US) on November 8, 2013 (New Drug Application [NDA] 022416) for adjunctive treatment of partial onset seizures (POS) in adults. Aptiom was approved for monotherapy treatment of POS in adults on August 27, 2015.

Proposed dosing strengths remain unchanged: 200 mg, 400 mg, 600 mg, and 800 mg. The expanded indication is monotherapy or adjunctive treatment of partial onset seizures in patients 4 years of age and older.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1: AEDs Currently Available for Adjunctive Therapy and/or Monotherapy In Pediatric POS

AED	Adjunctive therapy in Pediatric POS	Monotherapy in Pediatric POS
Topiramate	Yes (≥ 2 years, weight-based 2 to < 10 years)	Yes (≥ 2 years, weight-based 2 < 10 years)
Oxcarbazepine	Yes (≥ 4 years, weight-based)	Yes (≥ 4 years, weight-based)
Valproic Acid	Yes (age not specified in dosing but label mentions age 3 months)	Yes (≥ 10 years)
Lamotrigine	Yes (≥ 2 years, weight-based 2-12 years)	No (but yes ≥ 16 years)
Gabapentin	Yes (≥ 3 years, weight-based ages 3-11)	No
Tiagabine	Yes (≥ 12 years)	No
Levetiracetam	Yes (≥ 1 month, weight-based dosing)	No
Perampanel	Yes (≥ 12 years)	No
Vigabatrin	Yes (10-16 years), but not first line use due to safety issues	No
Phenobarbital	seizure type not specified in label	No
Primidone	Yes, generally	No
Phenytoin	Yes (age not specified, weight-based)	No
Carbamazepine	Yes, though language is general	No
Felbamate	Not for POS, but yes for patients 2-14 years with LGS	No (but yes in adults)
Ezogabine	No	No
Lacosamide	No	No
Pregabalin	No	No
Zonisamide	No	No

2.3 Availability of Proposed Active Ingredient in the United States

Eslicarbazepine acetate is approved in the US for monotherapy and adjunctive treatment of partial onset seizures, as noted in section 2.1.

2.4 Important Safety Issues with Consideration to Related Drugs

Carbamazepine and oxcarbazepine are chemically similar to eslicarbazepine acetate.

The prescribing information for Tegretol® (carbamazepine) includes the following information (in the last approved labeling dated 8/28/2015):

- Boxed Warning:
  - Serious Dermatologic Reactions and HLA-B*1502 Allele
  - Aplastic Anemia and Agranulocytosis
- Warnings section:
  - SJS/TEN and HLA-B*1502 Allele
  - Hypersensitivity Reactions and HLA-A*3101 Allele

  - Aplastic Anemia and Agranulocytosis
  - Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/ Multi-organ hypersensitivity
  - Suicidal Behavior and Ideation
  - General: mild anticholinergic activity (intraocular pressure)
    - activation of latent psychosis (relationship to tricyclic compounds)
    - avoided in patients with hepatic porphyria
    - withdrawn gradually to minimize increased seizure frequency
- Precautions section:
  - General:
    - Use with caution in patients with a mixed seizure disorder due to increased frequency of generalized convulsions
    - AV heart block (second and third degree block)
    - Hepatic effects, ranging from slight elevations in liver enzymes to rare cases of hepatic failure
  - Laboratory Tests:
    - Hyponatremia
    - Thyroid function tests: decreased values
    - Recommended testing: HLA-B*1502 genotype, blood counts, liver tests, eye examinations, urinalysis, BUN, blood levels

The prescribing information for Trileptal® (oxcarbazepine) includes the following information in the Warnings and Precautions section of the last approved labeling (dated 03/23/2017):

- Hyponatremia (including SIADH)
- Anaphylactic Reactions and Angioedema
- Patients with a past history of Hypersensitivity Reaction to Carbamazepine
- Serious Dermatologic Reactions (Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported and association with HLA-B*1502 is noted)
- Suicidal Behavior and Ideation
- Withdrawal of AEDs
- Cognitive/Neuropsychiatric Adverse Events (cognitive symptoms, somnolence/ fatigue, and coordination abnormalities, and specific reference to pediatric data)
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multi-Organ Hypersensitivity
- Hematologic Events (rare postmarketing reports of pancytopenia, agranulocytosis, leukopenia)
- Seizure control during pregnancy
- Risk of seizure aggravation (primary generalized seizures)

2.5 Summary of Presubmission Regulatory Activity Related to Submission

As noted above, Aptiom was approved on November 8, 2013 for adjunctive treatment of adult patients with POS and August 27, 2015 for monotherapy treatment of adult patients with POS. Interactions with the sponsor on the pediatric indication included the following:

- Type C meeting (12/14/2011) in which questions on a variety of pediatric-related questions were answered, including ones regarding potential studies to support absence or primary generalized tonic clonic seizures;
- Type C meeting (10/6/2014) in which the sponsor was told that a Proposed Pediatric Study Request (PPSR) should include prospective studies in the full pediatric population ages 0 to < 18 years (including for neonatal seizures);
- General Advice letter (11/15/2015) sent to all companies with approval for adjunctive treatment of POS outlining the Division's decision to accept extrapolation of efficacy from adult to pediatric patients with POS and the data necessary to support such a submission;
- Pediatric Written Request sent to sponsor on 7/8/2016, which was materially revised from the sponsor's original submission on 12/19/2014 and took into consideration the information needed to support pediatric extrapolation for efficacy in patients with POS;
- Type B meeting (7/20/2016, 8/9/2016, 8/18/2016) to discuss the regulatory pathway and data necessary to support a sNDA for pediatric extrapolation, including an updated dosing table. DNP noted that there was insufficient number of pediatric subjects at 1600 mg/day, the highest approved dose of Aptiom. The sponsor provided a rationale that dosing above 1200 in the pediatric population is unlikely and that there are adequate pediatric exposure data up to 1200 mg/day (follow-up submission on 8/9/16). Further discussion included general structure of the sNDA, planned subgroup analyses, and the need to provide update from the ongoing adult trials that includes information on any deaths and SAEs;
- General advice letter (9/13/2016) on the acceptability of extrapolation to POS monotherapy in AEDs approved for adjunctive therapy in POS;

2.6 Other Relevant Background Information

FDA conducted a lengthy review process and determined that it is acceptable to extrapolate to pediatric patients 4 years of age and older the effectiveness of drugs approved for the treatment of partial onset seizures (POS) in adults. This determination was based on similarity of the underlying disease in the adult and pediatric populations, as well as a similar exposure-response relationship in pediatric and adult patients with POS. This extrapolation does not apply to patients < 4 years of age or to other types of epilepsy. In order to support an indication for treatment of POS in pediatric patients ≥ 4

years of age based upon extrapolation, sponsors were instructed to provide the following in a General Advice Letter dated November 12, 2015:

- *Approved indication for the treatment of POS in adults.*
- *A pharmacokinetic analysis to determine a dosing regimen that provides similar drug exposure (at levels demonstrated to be effective in adults) in pediatric patients 4 years of age and older and in adult patients with POS. This analysis will require pharmacokinetic data from both the adult and pediatric (4 years of age and older) populations.*
- *Long-term open-label safety study(ies) in pediatric patients 4 years of age and older.*

A second General Advice Letter was sent to sponsors dated September 13, 2016, which stated that the Division of Neurology Products (DNP) had *"determined that it is acceptable to extrapolate efficacy and safety of drugs approved as adjunctive therapy for the treatment of partial onset seizures (POS) to their use as monotherapy for the treatment of POS. This extrapolation applies to both adult and pediatric populations, provided that efficacy and safety as adjunctive therapy for the treatment of POS have been previously established in the respective age range."* This determination was based on FDA analysis of drugs approved for both adjunctive and monotherapy demonstrating that dosages and exposures of drugs when used as monotherapy are within the ranges of dosages and exposures for those drugs when used as adjunctive therapy for POS.

2.7 Summary of 915 Review

The postmarket safety experience 18 months after approval and after use of Aptiom by at least 10,000 patients was summarized in an FDAAA Section 915 New Molecular Entity (NME) Postmarket Safety Summary Analysis ("915 review"), completed on 30 May 2017. The 915 review identified the following new safety signals:

1. Pancreatitis: Three reported cases of acute pancreatitis were identified. All three cases had a reasonable time to onset (TTO) and positive dechallenge; however, all cases were confounded by concomitant drugs. None of the cases suggest a probable causality of eslicarbazepine in pancreatitis due to confounding factors, but ESL could not be ruled out as a cause. Because of the small number of cases and lack of probable causality, the 915 safety team opted to continue postmarket monitoring.
2. Hematologic events: Six cases reporting hematologic events were identified that provided reasonable evidence of a causal association with eslicarbazepine, two of which were associated with possible DRESS. These cases reported the adverse events of leukopenia (2), agranulocytosis and thrombocytopenia (1), thrombocytopenia (1), megaloblastic anemia (1), and pancytopenia (1). Eslicarbazepine is labeled for hematological abnormalities associated with

DRESS in the Warnings and Precautions section. It is not labeled for hematologic events occurring independently of DRESS. Because of the reasonable evidence of causal relationship between ESL and the hematologic events, as well as oxcarbazepine (identical active moiety) being labeled for hematologic events in the Warnings and Precautions section, it was decided to add hematologic events (independent of DRESS) in the Warnings and Precautions Section of the Aptiom label.

3. Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH): Four cases reporting SIADH that provided reasonable evidence of a causal association with eslicarbazepine were identified in the 915 review. Eslicarbazepine is labeled for hyponatremia in the Warnings and Precautions section, but it is not labeled for SIADH. Oxcarbazepine and carbamazepine are labeled for hyponatremia possibly associated with SIADH in the Warnings and Precautions section. Because of the probable causal relationship of ESL with SIADH and the inclusion of SIADH in the Warnings and Precautions section of the OXC and CBZ label, DNP decided to add SIADH to the Hyponatremia Warning in the Aptiom label.
4. Atrioventricular (AV) Block: Three cases reporting AV block that provided some evidence of a causal associated with ESL. All three cases reported a plausible temporal relationship, and a positive dechallenge after ESL discontinuation. Two of the cases had confounding concomitant medications and two cases reported treatment for the event (external pacing device or “surgery”). Literature review identified a prior pooled analysis of three premarketing phase III controlled studies revealed no deaths attributable to cardiac arrhythmia, along with no clinically relevant electrocardiogram (ECG) abnormalities. Because the causal relationship to ESL was unclear, it was determined to continue postmarket monitoring for AV block.

Please see the 915 review for a full discussion of the new safety signals identified.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

No data or analysis quality issues were identified Studies 208, 202, or 305.

3.2 Compliance with Good Clinical Practices

No sites were discontinued due to protocol violations or deviations.

3.3 Financial Disclosures

According to Sunovion, none of the principal investigators in studies 208, 202, or 305 had disclosable financial interests during their study participation. The sponsor noted that signed financial disclosure forms were obtained for all principal investigators and sub-investigators and none *"received compensation for Categories 1 and 3, or compensation beyond the acceptable limits for Categories 2 ($25,000) and 4 ($50,000)."*

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

No new CMC studies were performed. The sponsor submitted labeling and chemistry, manufacturing and controls (CMC) information to support the use of a professional sample for the 200 mg strength of APTIOM tablets. These were found to be acceptable by CMC.

4.2 Clinical Microbiology

No Clinical Microbiology studies were performed.

4.3 Preclinical Pharmacology/Toxicology

No new nonclinical pharmacology/toxicology studies were performed in support of this supplement.

4.4 Clinical Pharmacology

Efficacy in pediatric patients with POS ≥ 4 years of age is based on extrapolation of dose-exposures in the adult population to that of the pediatric population.

4.4.1 Mechanism of Action

APTIOM is extensively converted to eslicarbazepine, which is considered to be responsible for therapeutic effects in humans. The precise mechanism(s) by which eslicarbazepine exerts anticonvulsant activity is unknown but is thought to involve inhibition of voltage-gated sodium channels. (ref. approved Aptiom labeling)

4.4.2 Pharmacodynamics

There were no clinically significant effects of Aptiom on vital signs or ECG findings in the studies submitted in this application. The effect of APTIOM on cardiac repolarization

was evaluated in a randomized, double-blind, placebo- and active-controlled 4-period crossover trial in healthy adult men and women. No significant effect on the QTc interval was detected, and the results of this study are included in the Aptiom label.

4.4.3 Pharmacokinetics

The sponsor performed a pooled population PK analysis based on data collected from pediatric patients with refractory POS in Studies 202 and 305. Using the pediatric population PK model, the sponsor conducted PK simulations to arrive at pediatric dose selections which are likely to match exposures in adults receiving approved ESL doses. Using pediatric data from the pop-PK analysis, the sponsor conducted PK simulations in virtual adult patients and virtual pediatric patients in order to derive pediatric dosing for initial dosing and maintenance dosing.

The sponsor had originally proposed (b) (4) 38 kg: 800-1200 mg. Titration would occur weekly based on response and tolerability to the maximum once daily dose. In their review, the Office of Clinical Pharmacology noted that (b) (4) *the effect of drug interactions on ESL PK is expected to be comparable between adults and pediatric patients."* (b) (4) The OCP conducted its own PK monotherapy simulations to better define pediatric dose selection. Based on their simulations, the dose ranges were adjusted slightly (b) (4), as follows: 11-21 kg: 400-600 mg; 22-31 kg: 500-800 mg; 32-38 kg: 600-900 mg. Proposed dosing in the > 38 kg weight group remained unchanged. The sponsor agreed to the revised dosing.

During final labeling negotiations, however, the sponsor requested that the initial and titration doses for the 22 to 31 kg weight range be increased to 300 mg. The rationale behind this change was that with the revised dosing, the initial and maximum titration increment dosage should be 300 mg, which is about one half of the lowest maintenance dose. This change would be consistent with adult dosing and titration. OCP agreed to this change. Final dosing recommendations to be included in the dosing section of the PI are described in Table 2 below.

Table 2: Final Agreed dosing for patients aged 4 to < 17 years

Body Weight Range	Initial and Maximum Titration Increment Dose (mg once daily)	Maintenance Dose (mg once daily)
11 to 21 kg	200	400 to 600
22 to 31 kg	300	500 to 800
32 to 38 kg	300	600 to 900
>38 kg	400	800 to 1200

Please see the Office of Clinical Pharmacology review for a full discussion of methods and issues related to pharmacokinetics in the pediatric studies.

5 Sources of Clinical Data

The clinical review is limited primarily to safety and concentrated on the controlled, double-blind parts of Studies 305 and 208 (see Table 3) and the uncontrolled, open label extensions of these studies, as well as uncontrolled data from Studies 202, 045, 046, 050, and 311. The pediatric studies are described further in Section 5.2, Section 5.3 and Section 9.4.

5.1 Tables of Studies/Clinical Trials

Table 3: Primary Pediatric Clinical Safety Studies of Eslicarbazepine Acetate

Study No.; Phase; Study Type; Country	Objective(s) of Study	Study Design and Type of Control	Product(s); Dosage Regimen; Route of Administration	Number of Dosed Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment (Excluding Tapering)	Study Status
BIA-2093-208 Phase 2 Adjunctive Non-US	Part 1: Effects of ESL on cognition, safety, tolerability, and efficacy of ESL in children and adolescents with refractory POS	Randomized, double-blind, PBO-controlled, parallel-group, multicenter	ESL 10-30 mg/kg/day (maximum of 1200 mg QD) with a target ESL dose of 30 mg/kg/day or PBO QD Oral tablets	123 subjects (112 completed)	6- to 16-year-olds (inclusive) with POS refractory to treatment with 1 or 2 AEDs	12 weeks (4 weeks titration and 8 weeks maintenance)	Completed and reported
	Parts 2-3: Safety, tolerability, and sustainability of the therapeutic effect of ESL in children and adolescents with refractory POS	Open-label, uncontrolled, multicenter, 1-3 year extension of Part 1	ESL 10-30 mg/kg/day (maximum of 1200 mg QD) Oral tablets	Part 2: 112 subjects, (95 completed) Part 3: 42 subjects, (31 completed)	6- to 16-year-olds (inclusive) with POS refractory to treatment with 1 or 2 AEDs	1 Year	Completed and reported
BIA-2093-305 Phase 3 Adjunctive Non-US	Part 1: Efficacy, safety, and tolerability of ESL in children and adolescents with refractory POS	Randomized, double-blind, PBO-controlled, parallel-group, multicenter	ESL 10-30 mg/kg/day (maximum of 1200 mg QD) with a target ESL dose of 20 mg/kg/day or PBO QD Oral suspension (2-6 year-olds) Oral tablets	304 subjects, including 41 IMP recall (267 completed, including 29 IMP recall)	2- to 16/17/18-year-olds, depending upon country, with POS refractory to treatment with 1 to 2 AEDs	18 weeks (6 weeks titration and 12 weeks maintenance)	Completed and reported
	Parts 2-5: Safety and tolerability of ESL in children and adolescents with refractory POS	Open-label, uncontrolled, multicenter, extension of Part 1	ESL 10-30 mg/kg/day (maximum of 1200 mg QD) Oral suspension (2-6 year-olds) Oral tablets	Part 2: 260 subjects, (183 completed) Part 3: 152 subjects, (107 completed) Part 4: 81 subjects, (62 completed) 13 ongoing post cut date not included in CSR Part 5: 56 subjects, (4	2- to 16/17/18-year-olds, depending upon country, with POS refractory to treatment with 1 to 2 AEDs	1 -5 Years	Completed and reported

Study No.; Phase; Study Type; Country	Objective(s) of Study	Study Design and Type of Control	Product(s); Dosage Regimen; Route of Administration	Number of Dosed Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment (Excluding Tapering)	Study Status
				completed) 13 ongoing post cut date not included in CSR 7 ongoing as of 08 July 2016			
BIA-2093-202 Phase 2a Adjunctive Non-US	PK, tolerability and efficacy of ESL as add-on therapy in children and adolescents with refractory POS	Open-label, uncontrolled, dose escalating, single center	ESL 5, 15, and 30 mg/kg/day (maximum of 1800 mg QD) Oral suspension and tablets	31 subjects (26 completed)	2- to 17-year-olds (inclusive) with POS refractory to treatment with 1 to 3 AEDs	12 weeks (3 treatment periods of 4 weeks each)	Completed and reported

Modified from Sponsor's Summary of Clinical Safety 2.7.4, Table 1

5.2 Review Strategy

The clinical review is limited primarily to safety and concentrated on one randomized, controlled, double-blind phase 3 efficacy study of adjunctive use of ESL in children and adolescents with POS (BIA-2093-305, "Study 305") and one randomized, controlled, double-blind, phase 2 study assessing cognition and safety in children and adolescents with refractory POS on adjunctive ESL (BIA-2093-208, "Study 208"). The sponsor also provided supportive safety data from one open-label, uncontrolled phase 2 PK study of ESL in pediatric patients with POS (BIA-2093-202, "Study 202") and the few adolescents who were enrolled in two historically-controlled phase 3 efficacy and LTE studies of ESL monotherapy in adults with POS (093-045, 093-046, and 093-050) and a double blind, active comparator phase 3 efficacy study of ESL vs. CBZ monotherapy in adult patients with POS.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Study BIA-2093-305

Please see Section 9.4.1 for a full description of the study design of Study 305.

Synopsis:
Part 1 of Study 305 was a Phase 3, double-blind, randomized, placebo-controlled, parallel-group study of adjunctive ESL in patients 2 to 16, 17, or 18 years of age (depending upon country) with POS refractory to treatment with 1 or 2 AEDs. ESL doses ranged from 10-30 mg/kg/day with a target dose of 20 mg/kg/day and a maximum of 1200 mg/day. The purpose of the study was to demonstrate the efficacy and safety of ESL as adjunctive therapy in pediatric patients with refractory POS. Parts 2-5 of Study 305 were long-term open-label extensions available to patients who had completed the prior stage(s).

Patients with a diagnosis of partial epilepsy for 6-24 months prior to enrollment (depending on country), prior treatment with ≥ 3 AEDs, current (stable) treatment with 1-2 AEDs (excluding oxcarbazepine) for 1 month prior to enrollment, ≥4 partial onset seizures during the month prior to screening, at least 4 partial-onset seizures during each 4-week interval of the 8-week baseline period and without primary generalized epilepsy were enrolled in the study.

Patients were randomized (1:1) to receive ESL or administered orally once daily. Randomization was stratified based on age (2-6 years, 7-11 years, or 12-18 years). Patients in the treatment group received ESL 10-30 mg/kg/day (target of 20 mg/kg/day and maximum of 1200 mg/day). The titration period was 6 weeks, and the maintenance period was 12 weeks at the titrated dose.

"The primary efficacy variable was the responder rate during the maintenance period, defined as the proportion of patients with at least a 50% decrease in the standardised 4-week seizure frequency from the baseline period to the 12-week maintenance period." Important secondary endpoints in part 1 of Study 305 included the Standardized seizure frequency per period of the baseline, titration, maintenance, and tapering-off periods as compared with placebo, safety endpoints (TEAEs, clinical laboratory tests, vital signs, and ECG), and changes in a variety of neurocognitive assessments.

5.3.2 Study BIA-2093-208

Please see Section 9.4.2 for a full description of the study design of Study 208.

Synopsis:
Part 1 of Study 208 was a Phase 2, double-blind, randomized, placebo-controlled, parallel-group study of adjunctive ESL in patients 6 to 16 years of age with POS refractory to treatment with 1 or 2 AEDs. ESL doses ranged from 10-30 mg/kg/day with a maximum of 1200 mg/day. The purpose of the study was to examine the effects of ESL on cognition in comparison to placebo. Parts 2 and 3 of Study 208 were long-term open-label extensions available to patients who had completed the prior stage(s). Patients were randomized (2:1) to receive ESL or placebo administered orally once daily. Randomization was stratified based on age (7-11 years or 12-16 years). Patients in the treatment group received ESL 10-30 mg/kg/day (target dose 30 mg/kg/day, maximum of 1200 mg/day). Titration period was 6 weeks, and the maintenance period was 8 weeks at the titrated dose.

"The primary endpoint was change from baseline to the end of the Part I (DB period) in the composite Power of Attention measure, in order to assess information processing speed and attention/psychomotor speed." Important secondary endpoints in part 1 of Study 208 included the relative reduction from baseline in seizure frequency over the evaluation period as compared with placebo, safety endpoints (TEAEs, clinical laboratory tests, vital signs, and ECG), and changes in a variety of neurocognitive assessments.

5.3.2 Study BIA-2093-202

Synopsis:
This clinical study was an open-label, single-center, multiple-dose Phase 2 study, in 30 pediatric epileptic patients, 10 each in three age groups: 2-6 years [Group 1], 7-11 years [Group 2], and 12-17 years [Group 3]. The study was consisted of a 4-week baseline phase, followed by 3 consecutive 4-week treatment periods with ESL in which patients received ESL once-daily at the following dosage regimens: 5 mg/kg/day (weeks 1–4), 15 mg/kg/day (weeks 5–8) and 30 mg/kg/day or 1800 mg/day, whichever was less (weeks 9–12). At the end of each 4-week treatment period, patients were hospitalized

and serial blood samples for PK assays were obtained. After the last treatment period or in the event of premature discontinuation, the dose was down-titrated during a 2-week period. After the last treatment period patient could continue receiving ESL if it was determined to be in the patient's best interest. A follow-up visit occurred ~4 weeks after the last hospitalization or early discontinuation.

5.3.3 Adult Studies in Which Adolescents Were Enrolled

Adolescents were enrolled in Studies 093-045, 093-046 and 093-050, Study BIA-2093-304, and Study BIA-2093-311

Synopses:

- Studies 093-045 and 093-046 are completed Phase 3 randomized, historical-controlled, parallel-group, ESL monotherapy (1600 mg or 1200 mg QD) studies in subjects aged 16 to 70 years with partial-onset seizures not well controlled by 1 or 2 current AEDs. There was no concurrent placebo or pseudo-placebo arm in either of these studies. Study 093-050 was the LTE study of monotherapy in this population. A total of 13 adolescents (ages 16 to <18) were enrolled.
- Study BIA-2093-304 was a Phase 3, randomized, double-blind, placebo-controlled, parallel-group pivotal study hat assessed the safety and effectiveness of ESL in the treatment of seizures in adult patient with partial onset epilepsy refractory to 1-3 AEDs. A total of 15 patients 16-17 years of age were enrolled.
- Study BIA-2093-311 is an ongoing Phase 3, double-blind, double-dummy, active-controlled, parallel-group study in subjects ≥ 18 years with newly-diagnosed partial-onset seizures (800-1600 mg ESL or 400-1200 mg total CBZ daily dose). One subject was 17 years old at the time of randomization.

6 Review of Efficacy

Efficacy Summary

As noted in Section 2.6 above, DNP and OCP conducted a lengthy review and determined that it is acceptable to extrapolate to pediatric patients 4 years of age and older the effectiveness of drugs approved for the treatment of partial onset seizures (POS) in adults. This determination was based on similarity of the underlying disease in the adult and pediatric populations, as well as a similar exposure-response relationship in studies of pediatric and adult patients with POS. This extrapolation does not apply to patients < 4 years of age or to other types of epilepsy.

The Division has also deemed it acceptable to extrapolate the safety and efficacy of drugs used in the treatment of POS to their use as monotherapy for the same population. This determination was based on FDA analysis of drugs approved for both adjunctive and monotherapy demonstrating that dosages and exposures of drugs when

used as monotherapy are within the ranges of dosages and exposures for those drugs when used as adjunctive therapy for POS.

As part of their development program, Sunovion conducted Study BIA-2093-305 a safety and efficacy study of Aptiom (eslicarbazepine acetate) in the treatment of partial onset seizures in patients 2-17 years of age. The prespecified primary efficacy endpoint for this study was the responder rate (proportion of patients with at least a 50% reduction in seizure frequency during the maintenance period). A key secondary endpoint was the relative change in standardized 4-week mean seizure frequency from baseline to maintenance period. This study did not achieve either of these endpoints.

As noted by the sponsor in the final clinical study report of Study 305, the least square (LS) mean relative change in the standardized 4-week seizure frequency from the baseline period to the 12-week maintenance period was higher in the ESL group (-18.1%) than in the placebo group (-8.6%); however, the LS mean difference of 9.5% was not statistically significant (p=0.2490). A post hoc analysis of the reduction of seizure frequency during titration + maintenance periods revealed -16.4% in the ESL group and -4.7% in the placebo group with a non-significant LS mean difference of 11.7% (p=0.1169). The sponsor notes in the discussion of these results that the median standardized 4-week seizure frequency during baseline was lower in the ESL group (11.5 [3.7, 605.8]) than in the placebo group (17.0 [3.9, 1972.5]). The median relative changes in standardized seizure frequency between baseline and maintenance periods were -26.1% (-100.0%, 366.7%) in the ESL group and -25.9% (-100.0%, 264.5%) in the placebo group.

With respect to responder rate, 41 patients (30.6%) in the ESL group compared to 40 (31.0%) in the placebo group were responders, resulting in a non-significant odds ratio of 0.97 (p=0.9017). The sponsor performed a post hoc analysis analyzing the responder rate in the titration + maintenance periods. Thirty-four patients (25.4%) in the ESL group compared to 29 (22.5%) in the placebo group were responders, resulting in a non-significant odds ratio of 1.15 (p=0.6218).

The data from Study 305 was included in the analysis performed to establish the acceptability of extrapolation of efficacy and safety from pediatric exposure data and open label safety data in pediatric patients. Potential reasons for failure of Study 305 to demonstrate efficacy were identified as part of the wider analysis.

The major active moiety (S-licarbazepine) is the same for eslicarbazepine acetate and oxcarbazepine, which would suggest similarity in treatment response. DNP has extensive experience with the major active moiety of eslicarbazepine acetate: it has been studied in five adequate and well controlled clinical trials in adults (Trileptal, Oxtellar XR, and Aptiom) and one controlled study in pediatric patients (Trileptal), besides the Aptiom pediatric trial. The trial designs were very similar, other than a longer titration period in the pediatric trial and use of comparison to maintenance period

only for the Aptiom pediatric trial, as opposed to titration + maintenance periods in the other trials.

The number of background AEDs was similar between adult and pediatric patients in the Aptiom trials; however the specific drugs used differed. Carbamazepine (25% and 50% in pediatric and adult studies, respectively) and valproic acid (49% and 20% in pediatric and adult studies, respectively) use was not similar in the adult and pediatric trials. This level of imbalance was not seen in other pediatric and adults drug studies.

The dose-response was generally similar between Trileptal (adult and pediatric), Oxtellar XR (adult) and Aptiom (adult) and Aptiom (pediatric); however, there was a notably higher placebo response in the Oxtellar XR (adult) and Aptiom (pediatric) trials. Higher placebo response was observed in non-US sites for the Oxtellar XR trial, Aptiom adult trial and Aptiom pediatric trial (particularly Eastern Europe). This placebo response was especially high in the 2-6 (-34.12) and 4-6 (-37.43) age groups. A numerical trend favoring treatment was observed in patients ≥ 7 years of age, as seen in Table 4 below.

Table 4: Efficacy comparison by age-bins for Aptiom pediatric trial

	Median % CFB in seizure frequency/28 days			
	Efficacy dataset (n=263) (≥ 2 years)		Efficacy dataset (n=245) (≥ 4 years)	
	Placebo	Treatment	Placebo	Treatment
Overall	**-25.94 (129)**	**-26.08 (134)**	**-26.35 (124)**	**-26.80 (121)**
Stratum I (2-6 yrs)	-34.12 (31)	-18.91 (31)		
Stratum I (4-6 yrs)			-37.43 (26)	-18.04 (18)
Stratum II (7-11 yrs)	-16.13 (53)	-22.59 (52)	-16.13 (53)	-22.76 (52)
Stratum III (12-16 yrs)	-25.94 (45)	-38.88 (51)	-25.95 (45)	-38.88 (51)

Source: Angela Men, Internal discussion

Overall median exposures in all of the trials were similar; however, notably lower exposures (Cminss) were observed in the 2-6 years (23.4 µmol/L) and 4-6 years age-bins (18.04 µmol/L) in the Aptiom pediatric trial, as compared to the 7-11 years (37.0 µmol/L) and 12-16 years (38.2 µmol/L) age-bins.

Based on the analysis above, it was felt that lower exposures in the younger pediatric patients, higher placebo response (especially in the younger patients), imbalance in the baseline seizure frequency in the pediatric Aptiom trial, and the differences in the concomitant AEDs were all factors that may have contributed the lack of demonstration of efficacy of Aptiom in pediatric patients with partial onset seizures. Additionally the data from Study 305 was included in the larger analysis intended to support the extrapolation of efficacy from adults to patients ages 4-17 with POS.

In their brief discussion of the failed efficacy results of Study 305, the sponsor identified four patients who developed new seizure types during the trial which may be inconsistent with partial onset seizures (astatic or atonic seizures and “atypical non

partial onset seizures"). The sponsor also noted that 59 patients in the ESL group were diagnosed with "mental retardation" which they posit have contributed to the lack of demonstration of efficacy.

Reviewer's Comments: It is possible that excessive enrollment of patients with primary generalized epilepsies into a trial of treatment for POS might impact the efficacy results, if the drug under investigation has been demonstrated to cause seizure aggravation in patients with primary generalized epilepsy. However, the sponsor identified only 4 patients who experienced new seizure types that may be consistent with previously undiagnosed primary generalized epilepsy. The sponsor also considered the inclusion of patients with intellectual disabilities in Study 305 as a potential factor for lack of efficacy; however, there is no reason to expect that patients with intellectual disability would be less likely to respond to Aptiom. Additionally, there is no reason to believe that intellectual disability is inherently associated with primary generalized epilepsy.

The reasons that Study 305 did not achieve its primary efficacy endpoint are not likely caused by patients who developed new seizure types during the study, but rather due to lower exposures in the younger pediatric patients, higher placebo response (especially in the younger patients), imbalance in the baseline seizure frequency in the pediatric Aptiom trial, and possibly the differences in the concomitant AEDs.

7 Review of Safety

Safety Summary

Aptiom has been available for use in adults for adjunctive treatment of partial onset seizures since 2013 in the US and in Europe since 2009. It has been available for monotherapy use in adults in the US since 2015. This drug has the same active moiety as oxcarbazepine (Trileptal and Oxtellar XR) and is chemically similar to carbamazepine (Tegretol and Carbatrol). Aptiom was studied in four Phase 3 randomized, placebo-controlled, adjunctive epilepsy trials and the safety was assessed in those trials, as well as two Phase 2 epilepsy trials and a number of small phase 2 non-epilepsy trials. It was also studied in two historical-controlled monotherapy studies in adults. To support the indication for adjunctive and monotherapy use in treatment of POS, Aptiom was studied in a Phase 2 PK and safety study and two randomized, placebo-controlled trials of ESL as adjunct therapy in patients with refractory POS who were 4-18 years of age. The safety of the drug in the controlled pediatric studies is similar to the safety profile that is currently in the drug label.

The total number of pediatric patients 2-17 years of age who were exposed to ESL during clinical studies (Studies 202, 208, 305, 045, 046, 304, and 311) was 485, 421 of whom were ages 4-17 at the time of enrollment. Primary safety analyses were

performed on an integrated safety database that included data from 362 patients pooled from the controlled, double blind parts of two pediatric POS studies: Study 208 (n=120) and Study 305 (n=260). This primary safety analysis population excluded patients who were ages 2-3 (n=44) at the time of enrollment or received the oral suspension which was recalled due to stability issues (n=21). Safety data was also analyzed for the open label study including patients from study 212 and the OLE phases from studies 208, and 305, as well as the IMP recall patients (n=393). Further information was presented on the 2-3 year-old patients, IMP recall patients, and adolescents enrolled in other studies. See Table 5 for overall summary of TEAEs.

There were 5 deaths during Studies 305, 208, and 202. The overall mortality rate during the pediatric ESL controlled studies was 0.55%, with 0.50% and 0.63% in the ESL and placebo groups respectively. The overall mortality rate for patients ages 4-17 was 0.71% (3/420). These rates are similar to the mortality rate seen in the monotherapy studies (0.55%), but less than that in the adult adjunctive studies (ESL: 1/1313, 0.08% and PBO: 2/560, 0.36%). The causes of death do not raise clinical concerns. Please see Section 7.3.1 for further information on deaths during the studies.

The overall incidence of treatment-emergent SAEs (TESAEs) was higher in in the ESL group (9.9%) than in the placebo group (5.0%). The most-commonly reported serious TEAEs in the ESL and placebo groups were partial seizures (2.5% and 1.9%, respectively) and status epilepticus (2.0% and 0%, respectively); each remaining serious TEAE was reported by 1 or 2 patients.The overall SAE rate in the adjunctive studies was 4.3% or 5.3% depending on the analysis method used. The types of SAEs were similar to those in the adult studies, however.

The discontinuation rate in the controlled double-blind study pool was 5.4% in ESL group and 2.5% in the placebo group. The most common cause of discontinuation due to TEAE in the ESL group was allergic dermatitis (1.0%) and partial seizures (1.9%) in the placebo group. A much higher percentage of patients discontinued due to TEAEs in the Phase 3 adult adjunctive epilepsy studies (22.2%) compared to placebo (3.8%).

The overall incidence of sponsor-identified medically significant events of allergic reactions was 5.0% in the ESL group and 1.3% in the placebo group in the double-blind safety pool. When a wider search of potential allergic reactions was performed, the incidences were 10.9% and 6.9% respectively. There were no cases of Stevens-Johnson syndrome or toxic epidermal necrolysis in the pediatric studies. There was 1 case of DRESS identified by the Investigator in Study 305. Two cases of DRESS were reported in the adjunctive trials, and ESL is labeled for DRESS.

There were no cases of drug induced liver injury. No patient met Hy's law criteria. During the double-blind study period, two patients (one in each group) had ALT and/or AST > 3 x ULN, but neither discontinued treatment. Overall, three patients had ALT and

AST > 3 x ULN and 5 had either ALT or AST > 3 x ULN. No patients discontinued treatment due to LFT abnormalities or liver dysfunction.

One patient discontinued treatment due to SIADH with blood chloride decreased (low chloride level), blood osmolarity decreased (decreased serum osmolality), inappropriate antidiuretic hormone secretion (SIADH) as reported TEAEs along with a serum sodium < 125 mEq/L.

The most common TEAEs overall in the double-blind controlled pediatric safety pool were headache (ESL 13.9%; PBO 11.3%), somnolence (ESL 9.4%; PBO 5.0%), vomiting (ESL 7.9%; PBO 5.0%), nasopharyngitis (ESL 7.4%; PBO 10.0%), pyrexia (ESL 7.4%; PBO 8.8%), and partial seizures (ESL 7.4%; PBO 8.8%). The most common TEAEs in the adjunctive trials were dizziness (20% and 28% in 800 mg and 1200 mg groups, respectively), somnolence (11% and 18%), headache (13% and 15%), nausea (10% and 16%), and diplopia (9% and 11%). In general, the common AEs were similar between the pediatric and adult POS studies, with rates that are not dissimilar.

In summary, review of the safety database from the studies of Aptiom in pediatric patients with POS demonstrated no new safety signals. The safety profile was generally consistent with that of the adult epilepsy safety profile in the current Aptiom label.

Table 5: Summary of TEAEs in Aptiom Studies in Pediatric Patients with POS

Parameter	Double Blind		Open Label Uncontrolled		
	PBO (Pooled Studies 208 and 305) n (%)	ESL (Pooled Studies 208 and 305) n (%)	Phase 2 PK ESL (Study 212) n (%)	One-year ESL (Pooled Studies 208 and 305, parts 2) n (%)	Post One-year ESL (Pooled Studies 208 and 305, parts 3-5) n (%)
N	N = 160	N = 202	N = 28	N = 337	N = 177
Subjects with any TEAE	105 (65.6)	137 (67.8)	20 (76.9)	216 (64.1)	93 (52.5)
Severe TEAE	10 (6.3)	18 (8.9)	2 (7.7)	27 (8.0)	11 (6.2)
Serious TEAE	8 (5.0)	20 (9.9)	2 (7.7)	30 (8.9)	18 (10.2)
Fatal TEAE	1 (0.6)	1 (0.5)	0	0	0
Discontinued Due to TEAE	4 (2.5)	12 (5.9)	2 (7.7)	14 (4.2)	1 (0.6)

7.1 Methods

7.1.1 Primary Studies/Clinical Trials Used to Evaluate Safety

The sponsor provided data from three studies to support safety of Aptiom for use as therapy in treating partial onset seizures in pediatric patients ≥ 4 years of age. One was an open-label Phase 2 study of PK and safety of ESL in patients with refractory POS ages 4-17. The other two were randomized, placebo-controlled trials of ESL as adjunct therapy in patients with refractory POS who were 4-18 years of age. Safety results from

adolescent patients enrolled in adult studies were also described but not pooled with the three primary studies. Please see Table 3 for further information on the studies.

- Study BIA-2093-305 (Study 305): completed Phase 3 randomized, placebo-controlled, parallel-group, ESL adjunctive therapy (10-30 mg/kg/day, maximum 1200 mg QD) study in patients 2-18 years of age with partial-onset seizures not well controlled by 1 or 2 current AEDs. The primary objective was to assess efficacy of ESL in treating partial seizures in patients 2-18 years of age. This study did not achieve its primary efficacy endpoint.
- Study BIA-2093-208 (Study 208): completed Phase 2 randomized, placebo-controlled, parallel-group, ESL adjunctive therapy (10-30 mg/kg/day, maximum 1200 mg QD) study in patients 4-16 years of age with partial-onset seizures not well controlled by 1 or 2 current AEDs. The primary objective was to assess cognitive effects of ESL in pediatric patients.
- Study BIA-2093-202 (Study 202): completed Phase 2 open-label PK and safety study of ESL adjunctive therapy (10-30 mg/kg/day, maximum 1800 mg QD) study in patients 4-16 years of age with partial-onset seizures not well controlled by 1 or 2 current AEDs.

7.1.2 Categorization of Adverse Events

Adverse events were defined as *"any undesirable change in the function, structure, or chemistry of the body occurring to a patient during a clinical study whether or not considered related to the investigational product. Adverse events can be symptoms, signs, or clinically relevant laboratory abnormalities occurring during the course of the study. Any worsening of a pre-existing condition occurring during the study is also an AE."*

For the purpose of the safety analysis, treatment emergent adverse events (TEAEs) were defined *"any AE that started on or after the first dose of study treatment… AEs with partial or missing start dates were considered TEAEs unless the non-missing components confirmed otherwise."*

A serious adverse event was defined as follows:
An SAE is any untoward AE which a patient suffers during the course of the study that:

- *Results in death,*
- *Is life-threatening,*
- *Requires inpatient hospitalization or prolongation of existing hospitalization. 'Inpatient hospitalization' is defined as a period of at least 24 hours in hospital or overnight stay,*
- *Results in persistent or significant disability/incapacity,*
- *Is a congenital anomaly/birth defect, or*
- *Is any other medically important condition. Note: medical and scientific judgment should be exercised in deciding whether an AE meets serious criteria in other situations, such as important medical events. 'Important medical events' are defined as events that may not*

be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the serious outcomes listed above.

AEs were collected from the date of informed consent for all trials and until 28 days after the last dose and were followed until resolution or lost to follow-up. For each study, AEs were originally coded or were recoded using the Medical Dictionary for Regulatory Activities (MedDRA) version 13.1.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The sponsor notes that several different analysis cohorts are used in their safety analyses:

- Safety Population
  - Double-blind controlled study pool: all patients who received at least 1 dose of study treatment (either PBO or ESL) during Part 1 of Studies 208 or 305. This population excluded all IMP recall patients identified below.
  - One-year open-label uncontrolled study pool: all patients who received at least 1 dose of ESL during Part 2 of Studies 208 or 305 (including IMP recall patients who received at least 1 dose of ESL during Part 2).
  - Post-one year open-label uncontrolled study pool: all patients who received at least 1 dose of ESL during Part 3 of Study 208 or Parts 3-5 of Study 305 (including IMP recall patients).

- ESL Safety Population
  - Combined pediatric ESL controlled and uncontrolled study pool: all patients who received at least 1 dose of ESL during the entirety of Studies 202, 208, or 305 (including IMP recall patients who received at least 1 dose of ESL during Parts 2-5).

- **IMP Recall Subjects**:
  Due to stability issues, the oral suspension formulation administered to younger patients in Study 305 was withdrawn by Bial. Patients who could swallow tablets were switched to the tablet formulation of ESL. A total of 41 subjects in Stratum 1 (2-6 year age group) who had initially taken the OS formulation and were switched to tablets were excluded from the double-blind controlled study pool. Safety analyses were performed separately and in combination with the safety population.

Please see Table 16 for enumeration of 4-17 year old patients in each study pool described above.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations of Target Populations

A total of 485 pediatric patients ages 2-17 were exposed to ESL (i.e., at least 1 dose) in Studies 202, 208, 305, 304, 311, and 045/046/050. The total pediatric population includes 58 patients 2 to < 4 years of age at the time of enrollment, who are excluded from the primary safety analysis dataset due to age. As the sponsor is seeking approval treatment of POS in patients ages 4-17, the full safety analysis population includes patients ages 4-17 at the time of enrollment in studies 202, 208, and 305 (n=393).

The double blind controlled study pool included a total of 362 patients with 202 patients receiving ESL and 160 patients receiving placebo. The overall median extent of exposure was similar in the ESL (139.0 days, range: 3 to 247 days) and placebo (141.0 days, range: 10 to 182 days) groups, 139.0 days (range: 3 to 247 days) and 141.0 days (range: 10 to 182 days, respectively. There were a total of 69.9 subject-years of exposure for ESL subjects and 59.1 for PBO subjects. The overall median of the average daily ESL dose was 798.4 mg/day (range: 150 to 1160 mg/day) over the double-blind period. For the combined controlled and uncontrolled study pool, overall, 315 subjects ages 4-17 had a duration of ESL exposure of more than 6 months, 265 subjects had a duration of ESL exposure of more than 1 year, and 130 subjects had a duration of ESL exposure of more than 2 years. (Table 6)

With respect to modal daily dose, a total of 241 patients had > 1 year exposure at or above the revised proposed efficacious dose (by weight categories), and 279 had > 6 month exposure at or above the revised proposed efficacious dose. See Section 4.4.3 above and the Office of Clinical Pharmacology's review for more information on the revised dosing.

Table 6: Extent of Exposure by Body Weight (kg) and Modal Daily Dose (mg/day) in Patients with >1 Year Exposure for the combined ESL Safety Population

Body Weight	Revised Dose Range Maintenance Therapy (mg/day), (Minimum-Maximum)	Total Patients (N)	# Patients with > 6 mos. exposure AT OR ABOVE revised dose (by modal daily dose)	# Patients with > 1 year exposure AT OR ABOVE revised dose (by modal daily dose)
11-21 kg	400-600	60	37	34
22-31 kg	500-800	86	60	50
32-38 kg	600-900	53	36	31
>38 kg	800-1200	194	146	126
	Total:	**343**	**279**	**241**

Source: Sponsor's Table 6.4.4.1a

Reviewer's Comments: The number of patients who had at or above the revised proposed dose for 6 or 12 month exposures was adequate.

7.2.2 Disposition and Demographics of Safety Populations

7.2.2.1 Patient Disposition

The primary safety populations of interest are the pooled double-blind safety pools from Studies 208 and 305, pooled open-label uncontrolled 1-year safety population from studies 208 and 305, pooled post-one-year open-label safety populations from studies 208 and 305, and combined safety populations from studies 208, 202, and 305 (patients ages 4-17). Subject disposition for these studies is summarized in Table 7.

A total of 160 patients were enrolled in the pooled placebo double-blind arm and 202 patients in the pooled ESL double-blind arm. In the double-blind controlled safety population, more than 90% of patients completed the double-blind period (90.1% of ESL patients and 91.9% of PBO patients), while 9.9% of ESL patients and 8.1% of PBO patients discontinued early. For ESL patients, the most common reasons for discontinuation during the double-blind period were adverse event (4.5% of ESL patients; 0% of PBO patients) and withdrawal of consent (2.5% of ESL patients; 3.8% of PBO patients). These rates were similar across treatments. Other reasons for discontinuation included death (1 ESL patient; 1 PBO patient), adverse event and/or lack of efficacy (1 ESL patient; 2 PBO patients).

For the one-year open-label uncontrolled safety pool, 76.3% of patients completed the one-year open-label extension and 23.7% discontinued early. The most commonly reported reasons for discontinuation were “other” (9.5%) and withdrawal of consent (7.7%). “Other” reasons consisted of lack of efficacy (n=26), adverse event (n=3), logistical reason/commercially available ESL (n=2), and IMP recall (n=1).

Only 34.5% of patients completed the post one-year open-label uncontrolled study; 65.5% discontinued early. Most patients (73.4%) completed Part 3; however, completion rates were low for Study 305 Parts 4 (44.0%) and 5 (3.0%), which the sponsor believes was primarily due to administrative reasons (specifically, switch to compassionate use). The most common reason reported for discontinuation was “administrative reasons” (44.1%), and was primarily due to the development of a compassionate use/donation program. The next most common reasons for discontinuation were “other” (10.7%) and withdrawal of consent (9.0%). “Other” reasons included lack of efficacy (n=8), lost to follow-up (n=3), aged out of the study (n=4), logistical reason/commercially available ESL (n=4).

Table 7: Subject Disposition for the Various Study Populations (ages 4-17)

Parameter	Double-Blind Study Pool		Up to 1 year Uncontrolled Study Pool	>1 year Uncontrolled Study Pool
	Total PBO N = 160 n (%)	Total ESL N = 202 n (%)	Total ESL N = 337 n (%)	Total ESL N = 177 n (%)
Number of Subjects who Completed the Period	147 (91.9)	182 (90.1)	257 (76.3)	61 (34.5)
Number of Subjects who Discontinued during the Period	13 (8.1)	20 (9.9)	80 (23.7)	130 (73.4)
Completed Part 3				60 (33.9)
Completed Part 4				4 (2.3)
Completed Part 5				116 (65.5)
Adverse event	0	9 (4.5)	5 (1.5)	1 (0.6)
Withdrawal of consent	6 (3.8)	5 (2.5)	26 (7.7)	16 (9.0)
Administrative reasons	2 (1.3)	2 (1.0)	8 (2.4)	78 (44.1)
Other	3 (1.9)	2 (1.0)	32 (9.5)	19 (10.7)
Fatal	1 (0.6)	1 (0.5)	0	0
Non-fatal	2 (1.3)	1 (0.5)	32 (9.5)	19 (10.7)
Disallowed concomitant medication	0	1 (0.5)	0	0
Lack of compliance	1 (0.6)	1 (0.5)	1 (0.3)	0
Exacerbation of seizures	1 (0.6)	0	8 (2.4)	1 (0.6)
Unknown	0	0	0	1 (0.6)

Source: ISS, Tables 14, 17, 20, verified

Aptiom in the pediatric population will be dosed by weight category, rather than mg/kg or age. When disposition by weight category is considered, ≥ 81.0% of ESL patients and ≥ 84.6% of PBO patients completed the double-blind period for each of the weight categories. Overall incidences of DB discontinuation and most common reasons for DB discontinuation (adverse event, withdrawal of consent) were similar for ESL and PBO patients without a consistent pattern across weight categories. Generally, lighter patients had greater discontinuation rates for in both ESL and PBO groups. See Table 17 for a summary of disposition by weight (dosing) category.

7.2.2.2 Demographics of Safety Populations

The sponsor presented demographics for several pooled populations from the primary studies, as follows: double-blind study pool (ages 4-17), double-blind study pool (all ages), one-year open label study pool (4-17), one-year open label study pool (all ages), combined controlled and uncontrolled study pool (4-17), and combined controlled and uncontrolled study pool (all subjects, "ESL Safety Population"). The sponsor categorized the demographic characteristics into the following population subgroups: age group (4-6 years, 7-11 years, 12-17 years), sex (male, female), race (Caucasian, Hispanic, Black, Asian, Other), weight (CDC %), number of AEDs, and baseline AED use.

With respect to other characteristics of the double-blind study populations, there were no notable differences between the placebo or ESL groups with respect to epilepsy history or concomitant AEDs. There were minor between-study differences.

For the double-blind controlled study pool, all ESL and PBO patients reported at least one concomitant AED medication. The most commonly reported concomitant AED medications in ESL patients included valproic acid (VPA) (49.0% of ESL and 53.1% of PBO patients), CBZ (30.2% of ESL and 26.3% of PBO patients), lamotrigine (LTG) (24.8% of ESL and 28.1% of PBO patients), topiramate (TPM) (24.8% of ESL and 25.0% of PBO patients), and levetiracetam (LEV) (19.3% of ESL and 18.1% of PBO patients). These concomitant AED medication rates were generally higher in Study BIA-2093-305 compared with Study BIA-2093-208.

Reviewer's Comments: In general, the demographics and background characteristics of the ESL and placebo populations were similar in the pooled double-blind safety population (ages 4-17).

7.2.2 Explorations for Dose Response

Study 202 did not include a placebo group and thus is not appropriate for assessing a dose response. Dose titration in the placebo-controlled studies (208 and 305) was based on tolerability, and explorations for dose response with respect to efficacy were not performed. Efficacy in the pediatric population is based on extrapolation from adult exposure data.

7.2.3 Special Animal and/or In Vitro Testing

None in this supplement

7.2.4 Routine Clinical Testing

Routine clinical testing for each of the pediatric studies is as follows.

In Study 208, laboratory samples were collected at screening, end of maintenance period, post study visit, and early termination in Part 1 and at 8, 28, and 52 weeks, post study visit, and early termination in Part 2. Laboratory samples were not collected in Part 3. In Study 305, laboratory samples were collected at screening, end of titration period, end of maintenance period, post study visit, and early termination in Part 1; at 4, 16, 24, 36, and 48 weeks, post study visit, and early termination in Part 2; 12, 24, 36, and 48 weeks, post study visit, and early termination in each of Parts 3 and 4; and at 26, 52, 78, and 104 weeks, follow-up (post study visit), and early termination in Part 5. For each study, clinical laboratory parameters consisted of hematology, serum chemistry (including lipid), urinalysis, thyroid, and pregnancy testing. In Study 202202, laboratory samples were collected at screening, 4, 8, and 12 weeks, follow-up visit, and early termination, and consisted of hematology, serum chemistry, coagulation, and urine pregnancy testing.

Electrocardiograms (ECGs) were analyzed at a central facility, and the following ECG parameters were manually assessed: ventricular rate, PR interval, RR interval, QRS duration, and QT interval. ECGs were collected in Study 208 at screening, end of titration period (4 weeks), end of maintenance period (12 weeks), end of tapering, post study visit, and early termination in Part 1; at 2, 8, 28, and 52 weeks, post study visit, and early termination in Part 2; at 8, 12, 20, and 24 months, post study visit, and early termination in Part 3. During Study 305, 12-lead ECGs were collected at screening, end of titration period (6 weeks), end of maintenance period (18 weeks), follow-up, and early termination in Part 1; at 8, 24, and 48 weeks, follow-up, and early termination in Part 2; 12, 24, 36, and 48 weeks, follow-up, and early termination in each of Parts 3 and 4; and at 26, 52, 78, and 104 weeks, follow-up, and early termination in Part 5.

Vital signs were collected at all visits in each study, and included systolic blood pressure, diastolic blood pressure, pulse rate, body temperature (Study 305 only), and weight. Height was not assessed.

7.2.5 Metabolic, Clearance, and Interaction Workup

The reader is referred to the Clinical Pharmacology Review.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Labels for CBZ and OXC (ADRs most similar to ESL) include warnings and precautions for SJS/TEN, hypersensitivity reactions, suicidal ideation/behavior, DRESS, AV block, hyponatremia, hypothyroidism and cognitive/neuropsychiatric adverse events. The sponsor monitored specifically for most of these events. The sponsor provided adequate safety monitoring and there were no new or unexpected events identified for the ADRs in the ESL clinical trials.

7.3 Major Safety Results

7.3.1 Deaths

A total of 5 deaths were reported in the pooled controlled and uncontrolled safety population, including adolescents enrolled in the adult studies. Two patients (1 ESL and 1 PBO) in the double-blind study population had TEAE's leading to death. One death occurred in a patient taking ESL during Parts 4-5 of Study 305, a two year-old patient died during the LTE phase of Study 305 and one patient on ESL in Study 304 (pivotal adult study) died of a TEAE. These deaths are described below.

- Double Blind Study Population:

- Subject 2093-305-185-02, a 6 year-old girl receiving ESL, died on study day 55. She developed “cluster seizures”, was treated with two doses of rectal diazepam, but became apneic and unresponsive to resuscitation. Autopsy revealed brain herniation, brain edema, and bronchopneumonia. The death was not considered related to ESL.
- Subject 2093-305-225-02 was a 5 year-old girl in the placebo arm. On day 135, she was found unconscious at home with a plastic bag in her mouth. Resuscitation attempts were unsuccessful, and cause of death was ruled asphyxia. Concomitant seizure could not be ruled out, but the death was considered not drug-related.

- Uncontrolled safety population:
  - Subject 2093-305-313-01: This patient was a 9 year old boy (5 years old at enrollment) who developed elevated transaminases during the study (3 years prior to his death) which persisted (concomitant phenobarbital and VPA were considered confounding factors). On study day 1445, he *“developed 'disseminated intravascular coagulation secondary to severe infection' and 'severe infection' of severe intensity”* and was seen in a pediatric ED 4 days later (study day 1449) and declared dead on arrival. The infection and DIC were considered causally unrelated to ESL in large part due to the long time to onset.
  - Subject 2093-305-311-02 was 4 year old girl who was enrolled at age 2 and randomized to placebo in Study 305 then transitioned to ESL during the LTE phase. She had several bouts of pneumonia during the blinded and unblinded phases of the study. On study day 817 she developed fever, cough, and dyspnea and was initially treated with paracetamol and salbutamol. She presented at and was admitted to the hospital on study day 824 with worsening symptoms. She was diagnosed with broncho-pneumonia and treated with cefuroxime. She had partial seizures while eating on study day 826 and became unresponsive. CPR was performed but the patient was not revived. An autopsy was not performed; however the cause of death was reported as bronchopneumonia.
  - Subject 2093-304-010-10 was a 19 year-old woman who was initially enrolled at age 17 in Study 304. On study day 418, she was found lying unresponsive on the floor with an injury on her nose. She was determined to be dead at the scene. Toxicology reports were negative, and the autopsy revealed cardiomegaly and obesity. The cause of death was reported as SUDEP.

- Adult Studies Population:
  - Subject 050-0200-S008: One death in the adult studies occurred during the required reporting period (23 SEP 2014 to 8 JUL 2016). On (b) (6) 973 days after the open-label study drug was initiated, the patient, a 23 year-old woman, was found face down in water in the bathtub. Based

on autopsy results, cause of death was ruled as drowning, although a seizure or SUDEP could not be ruled out as a precipitating factor. The death was considered to be unrelated to ESL, based on the length of treatment.

Reviewer's Comments: Only two deaths occurred in the double-blind period, one in a patient taking ESL (brain herniation, cerebral edema, increased seizures) and one in a patient on placebo (asphyxiation from a plastic bag). The overall mortality rate in the pooled blinded population was 0.55%, with 0.50% and 0.63% in the ESL and placebo groups respectively. These mortality rates are greater than those seen in the phase 2/3 controlled studies in adult patients with POS (ESL: 1/1313, 0.08% and PBO: 2/560 0.36%). However, the relatively small number of subjects in the pediatric studies makes it difficult to draw any substantive conclusions regarding differences in mortality rates between the adult and pediatric populations.

There were a total of 3 deaths in pediatric patients exposed to ESL in the controlled and uncontrolled study population who were ages 4-17 at time of death, for a mortality rate of 0.71% (3/420). When the full pediatric population is considered, which includes adolescent patients enrolled in studies 304 and 045/046/050 who began treatment at <18 years of age and patients who were enrolled and received the first dose of ESL prior to age 4, the mortality rate is 0.86% (4/467). This population includes one patient (#2093-304-010-10) who was 19 at the time of her death, although she was enrolled in Study 304 at age 17.

The deaths, in general, do not appear to be related to ESL and do not raise new clinical concerns.

7.3.2 Nonfatal Serious Adverse Events

The sponsor defined serious adverse events (SAEs) as any adverse event that resulted in death, was life-threatening, required inpatient hospitalization (≥24 hrs in the hospital or an overnight stay) or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity or a congenital anomaly/birth defect. Additionally, other important medical events that could jeopardize the subject or required intervention to prevent one of the serious outcomes were also considered to be SAEs by the sponsor.

The overall incidence of treatment-emergent SAEs (TESAEs) was higher in in the ESL group (9.9%) than in the placebo group (5.0%). The most-commonly reported serious TEAEs in ESL patients were seizure-related: partial seizures (ESL 2.5%; PBO 1.9%), status epilepticus (ESL 2.0%; PBO 0%), and convulsion (ESL 1.5%; PBO 0.6%); each remaining serious TEAE was reported by ≤1.0% of ESL patients.

Table 8: Serious Treatment-Emergent Adverse Events for the Pooled Double-Blind Controlled Study Population (4-17 year-olds)

MedDRA version 13.1 System Organ Class / Preferred Term	Total PBO N = 160 n (%)	Total ESL N = 202 n (%)
Subjects with any Serious TEAE	**8 (5.0)**	**20 (9.9)**
Blood and Lymphatic System Disorders	**0**	**1 (0.5)**
Anemia	0	1 (0.5)
Cardiac Disorders	**0**	**1 (0.5)**
Mitral valve incompetence	0	1 (0.5)
Ear and Labyrinth Disorders	**0**	**1 (0.5)**
Vertigo	0	1 (0.5)
Gastrointestinal Disorders	**0**	**1 (0.5)**
Coeliac disease	0	1 (0.5)
General Disorders and Administration Site Conditions	**0**	**2 (1.0)**
Device malfunction	0	1 (0.5)
Drug withdrawal syndrome	0	1 (0.5)
Infections and Infestations	**2 (1.3)**	**4 (2.0)**
Bronchopneumonia	0	2 (1.0)
Infectious mononucleosis	0	1 (0.5)
Pneumonia	1 (0.6)	1 (0.5)
Viral infection	0	1 (0.5)
Bronchitis	1 (0.6)	0
Injury, Poisoning and Procedural Complications	**0**	**4 (2.0)**
Brain herniation	0	1 (0.5)
Fall	0	1 (0.5)
Inflammation of wound	0	1 (0.5)
Shunt malfunction	0	1 (0.5)
Investigations	**0**	**1 (0.5)**
Gamma-glutamyltransferase increased	0	1 (0.5)
Metabolism and Nutrition Disorders	**0**	**1 (0.5)**
Diabetes mellitus	0	1 (0.5)
Type 1 diabetes mellitus	0	1 (0.5)
Nervous System Disorders	**5 (3.1)**	**12 (5.9)**
Partial seizures	3 (1.9)	5 (2.5)
Status epilepticus	0	4 (2.0)
Convulsion	1 (0.6)	3 (1.5)
Brain edema	0	1 (0.5)
Grand mal convulsion	0	1 (0.5)
Nervous system disorder	0	1 (0.5)
Partial seizures with secondary generalization	0	1 (0.5)
Epilepsy	1 (0.6)	0
Respiratory, Thoracic and Mediastinal Disorders	**1 (0.6)**	**0**
Asphyxia	1 (0.6)	0
Skin and Subcutaneous Tissue Disorders	**0**	**2 (1.0)**
Drug rash with eosinophilia and systemic symptoms	0	1 (0.5)
Vascular purpura	0	1 (0.5)
Surgical and Medical Procedures	**1 (0.6)**	**0**
CSF shunt operation	1 (0.6)	0
Medical device change	1 (0.6)	0

Source: ISS, Tables 74 and 7.1.13.1.1 (verified in JMP)

When compared to the phase 3 adult epilepsy controlled pool (Studies 301, 302, and 304), the TESAE rates in the pediatric population on ESL were slightly higher; however, the absolute number of patients enrolled in the pediatric studies was significantly lower, making a direct comparison somewhat difficult.

Table 9: Incidence of Treatment Emergent SAEs in Adult and Pediatric with POS (Double Blind Study Populations)

Patients with any TESAE	Placebo n (%)	ESL n (%)
Number of Pediatric Epilepsy Patients	160	202
Using ADAE dataset	8 (5.0)	20 (9.9)
Study 208 Part 1	2 (5.0)	3 (3.6)
Study 305 Part 1	6 (5.0)	17 (14.3)
Number of Adult Epilepsy Patients	426	1021
Using ADAE dataset	11 (2.6)	44 (4.3)
Study 301 Part 1	4 (3.9)	15 (5.0)
Study 302 Part 1	0	12 (4.1)
Study 304 Part 1	7 (3.1)	17 (4.0)
Using ADEVENTX	12 (2.8)	54 (5.3)
Study 301 Part 1	4 (3.9)	20 (6.7)
Study 302 Part 1	1 (1.0)	17 (5.8)
Study 304 Part 1	7 (3.1)	17 (4.0)

Sources: ADAE dataset, AESER, AETRTEM1, AGESELFL, EXCLDBFL, TRTP1/ ARM; Dr. Mary Doi's Safety Review of original 022416 NDA submission (6 Sep 2013)

When TESAEs were analyzed by weight category, the analysis did not show a consistent trend in treatment differences across the weight categories. The pattern and incidence of overall TESAEs were consistent in subsets with the pattern seen in the overall population. Most common SAEs were too uncommon to allow for any conclusions regarding differences across weight subsets to be drawn.

TESAEs were also analyzed by modal daily dose (adult equivalents). In this analysis, the incidence of overall serious TEAEs did not show a consistent trend toward greater frequency for subjects of differing weight (either greater or lower weight), although incidence of TESAEs was higher in ESL patients than placebo patients in all weight groups. Additionally, overall serious TEAEs did not show a dose response within any of the weight groups.

Lastly, TESAEs were analyzed by age for potential trending or significant differences. Although the incidence of TESAEs in the double-blind population was higher in the youngest patients (17.4% in ESL patients ages 4-6) than in the older age groups (8.3% in ESL patients ages 7-11 and 9.5% in ESL patients in the 12-17 age group), there was not an overall trend of decreasing incidence of TESAEs with age.

Serious TEAE results for the OLE study pools were similar to the results for the DB controlled study pool. Notable SAEs for the one-year open-label uncontrolled study pool included rash vesicular and conduct disorder (1 [0.3%] ESL patient each). For the

combined controlled and uncontrolled study pool, the overall incidence of treatment-emergent SAEs was 16.3%. The most-commonly reported TESAEs were partial seizures (2.8% of ESL patients), status epilepticus (2.0% of ESL patients), convulsions (1.8% of ESL patients), and pneumonia (1.5% of ESL patients). For Study 202Study 202, one patient had 2 treatment-emergent SAEs (laryngitis and acute respiratory insufficiency), deemed unrelated to the study drug.

7.3.3 Dropouts and/or Discontinuations

Discontinuations due to TEAEs were more common in the ESL double-blind pooled study population than in the placebo group, although the absolute numbers of discontinuations were small. A total of 11 (5.4%) ESL patients and 4 (2.5%) placebo patients discontinued participation in the blinded phase due to a TEAE.

The most-commonly reported TEAEs resulting in discontinuation in ESL subjects were allergic dermatitis (1.0% of ESL subjects; 0% of PBO subjects) and edema (1.0% of ESL subjects; 0% of PBO subjects); the most commonly reported TEAE leading to discontinuation was partial seizures for PBO (0.5% of ESL subjects; 1.9% of PBO subjects). Only two TEAEs leading to discontinuation occurred in more than one patient: allergic dermatitis (n=2) and partial seizures (n=4), the rest occurred in a single patient. See Table 10 below for specifics.

Table 10: TEAEs Resulting in Discontinuation for the Double-blind Controlled Study Pool (4-17 year-olds)

MedDRA version 13.1 System Organ Class / Preferred Term	Total PBO N = 160 n (%)	Total ESL N = 202 n (%)
Subjects with any TEAE Leading to Discontinuation	**4 (2.5)**	**11 (5.4)**
Ear and Labyrinth Disorders	**0**	**1 (0.5)**
Vertigo	0	1 (0.5)
Gastrointestinal Disorders	**0**	**2 (1.0)**
Abdominal pain	0	1 (0.5)
Dysphagia	0	1 (0.5)
General Disorders and Administration Site Conditions	**1 (0.6)**	**3 (1.5)**
Edema	0	2 (1.0)
Asthenia	0	1 (0.5)
Pyrexia	0	1 (0.5)
Drug ineffective	1 (0.6)	**0**
Infections and Infestations	**0**	**1 (0.5)**
Infectious mononucleosis	0	1 (0.5)
Investigations	**0**	**2 (1.0)**
C-reactive protein increased	0	1 (0.5)
Nervous System Disorders	**3 (1.9)**	**3 (1.5)**
Dizziness	0	1 (0.5)
Partial seizures	3 (1.9)	1 (0.5)
Status epilepticus	0	1 (0.5)
Skin and Subcutaneous Tissue Disorders	**0**	**5 (2.5)**
Dermatitis allergic	0	2 (1.0)

MedDRA version 13.1 System Organ Class / Preferred Term	Total PBO N = 160 n (%)	Total ESL N = 202 n (%)
Drug rash with eosinophilia and systemic symptoms	0	1 (0.5)
Macule	0	1 (0.5)
Petechiae	0	1 (0.5)
Rash	0	1 (0.5)
Vascular purpura	0	1 (0.5)

Source: JMP, ADAE, AETRTEM1, AEACN, AGESELFL, EXCLDBFL, TRTP1/ARM,

Discontinuation due to treatment emergent adverse events was analyzed by weight category and age groups. There was no obvious trend towards discontinuation when patients were analyzed by weight category (Table 19). Numbers of patients in each weight category who discontinued treatment due to TEAEs were very small, making it difficult to draw any firm conclusions from the analysis. There were similar findings when discontinuation due to TEAEs was analyzed by age groups (Table 18).

Reviewer's Comments: The incidence of discontinuation in the ESL group (5.9%) was more than twice that in the placebo group (2.5%) during the double blind study period. The overall number of patients who discontinued was relatively low, and none discontinued because of unanticipated AEs. The rate of discontinuations due to TEAEs in the pediatric DB controlled pool (5.4%) is notably lower than that seen in the adult POS adjunctive studies (13.6%), although the incidence of discontinuation due to TEAEs in the adult placebo group was similar (2.8%). There was a strong dose-related effect on discontinuations in the adult epilepsy controlled pool with 6.1% discontinuing due to TEAEs in the 400 mg dose group, 10.1% in the 800 mg group, and 20.7% in the 1200 mg group. For pediatric patients, dosing will be by weight, and there were no obvious trends based on weight category. The absolute number of pediatric patients who discontinued due to TEAEs was low, making it difficult to draw any useful conclusions from the analysis.

Of note, one patient in the ESL group who discontinued treatment during the study due to TEAEs appears to have been included incorrectly in the DB period. A 9 year-old girl enrolled in the ESL group (#2093-305-185-18503) experienced multiple TEAEs leading to discontinuation (blood chloride decreased, blood osmolarity decreased, and inappropriate antidiuretic hormone secretion) which were coded in the dataset as occurring during the DB period. However, these events appear, based on the information in the narrative, to have occurred during the OLE period. She did have a single reported decreased sodium level during the double-blind period but was not discontinued from treatment at that time.

When TEAEs leading to discontinuation were analyzed in the one-year open-label uncontrolled study pool (4-17 year-old patients), the overall incidence was 4.2%. The most-commonly reported TEAE resulting in discontinuation in ESL patients was partial

seizures (1.5%). The overall incidence of discontinuation due to TEAEs in the combined controlled and uncontrolled study pool (4-17 year-old patients) was 6.9%. The most commonly reported TEAE resulting in discontinuation in in the combined population was also partial seizures (n=6, 1.5%). As a comparison, the overall rate of discontinuation due to TEAEs was 15.3% in the combined controlled and uncontrolled Phase 3 Epilepsy Pool (pivotal adult adjunctive studies).

7.3.4 Significant Adverse Events

7.3.4.1 Allergic Reaction, Including Rash and Hypersensitivity

The sponsor provides a discussion of allergic reactions in the ISS. This discussion analyzed the double blind and the full safety populations (pooled uncontrolled and controlled patients). As seen in Table 11, the overall incidence of sponsor-identified MSE's of allergic reactions in the double blind population was 5.0% in ESL patients and 1.3% in PBO patients. There was one reported case of drug rash with eosinophilia and systemic symptoms (DRESS) in the pediatric population (see description below of subj #2093305-211-21109). This case was reviewed by Dr. Doi in the safety review of the original NDA. There were no reported pediatric cases of Stevens-Johnson syndrome or toxic epidermal necrolysis. The most-commonly reported allergic reaction MSEs were allergic dermatitis (3.0% of ESL patients, 0% PBO patients) and rash (1.0% ESL patients, 1.3% of PBO patients). Each remaining allergic reaction MSE was reported by 1 subject (0.5%). Only one of the allergic reaction MSE's resulted in discontinuation (the DRESS case referenced above and described below); however, 4 other patients discontinued the drug due to skin reactions.

Table 11: Sponsor-Identified Treatment-Emergent MSEs of Allergic Reaction for the Double-Blind Controlled Study Pool (4-17 year-old Patients)

MedDRA version 13.1 System Organ Class / Preferred Term	Total PBO N = 160 n (%)	Total ESL N = 202 n (%)
Subjects with any Allergic Reaction MSE	**2 (1.3)**	**10 (5.0)**
Skin and subcutaneous tissue disorders	**2 (1.3)**	**10 (5.0)**
Dermatitis allergic	0	6 (3.0)
Rash	2 (1.3)	2 (1.0)
Drug rash with eosinophilia and systemic symptoms	0	1 (0.5)
Pruritus	0	1 (0.5)

Source: ISS, modified from Sponsor's Table 96

When the double blind safety population was examined for all rash-related and other TEAEs potentially indicative of allergic reactions, multiple other adverse events were identified. Overall, the rate of potentially immune-mediated/allergic reactions was greater in the ESL group than in the placebo group (10.9% and 6.9%, respectively); however, this analysis is complicated by the fact that all of the patients in the adjunctive

pediatric studies were on concomitant AEDs and a lack of dechallenge/rechallenge information. The incidence of rash-related TEAEs was greater in the ESL patients (8.9%) than in the placebo patients (6.3%) in the double-blind study pool; however the difference in incidence between the groups was relatively small.

Table 12: TEAEs Potentially Indicative of Allergic Reactions in Double-Blind Safety Population (4-17 years)

MedDRA version 13.1 System Organ Class Preferred Term	Total Placebo n (%) N = 160	Total ESL n (%) N = 202
Subjects with any Potential Identified Allergic Reaction	**11 (6.9)**	**22 (10.9)**
General Disorders And Administration Site Conditions	**0**	**2 (0.9)**
Edema	0	2 (0.9)
Eye Disorders	**0**	**1 (0.5)**
Eye Swelling	0	1 (0.5)
Skin and Subcutaneous Tissue Disorders	**10 (6.3)**	**18 (8.9)**
Dermatitis	0	1 (0.5)
Dermatitis allergic	1 (0.6)	6 (3.0)
Dermatitis contact	1 (0.6)	1 (0.5)
Drug rash with eosinophilia and systemic symptoms	0	1 (0.5)
Erythema	1 (0.6)	1 (0.5)
Macule	0	1 (0.5)
Petechiae	0	1 (0.5)
Photodermatosis	0	1 (0.5)
Pruritus	1 (0.6)	1 (0.5)
Rash	5 (3.1)	4 (2.0)
Rash pruritic	0	1 (0.5)
Skin ulcer	0	1 (0.5)
Vascular purpura	0	1 (0.5)

Source: JMP, ADAE

Table 13: Rash-related TEAEs in ESL Subjects > Placebo, Adult Phase 3 Epilepsy Controlled Pool

MedDRA PT	Placebo (%) n=426	ESL (%) n=1021
TEAEs		
Rash	4 (0.9)	19 (1.9)
Pruritus	4 (0.9)	12 (1.2)
Dermatitis contact	1 (0.2)	3 (0.3)
Dermatitis	0	2 (0.2)
Drug eruption	0	1 (0.1)
Exfoliative rash	0	1 (0.1)
Leukocytoclastic vasculitis	0	1 (0.1)
Rash pruritic	0	1 (0.1)
Purpura	0	1 (0.1)
Skin disorder	0	1 (0.1)

Source: Table 53, Dr. Doi's safety review original submission NDA 022416

Reviewer's Comments: Aptiom includes a warning for serious dermatologic reactions in the package insert (Section 5.2) and rash is identified as an adverse drug reaction in

Section 6.1. The incidence of rash and other potentially immune-mediated skin reactions is greater in the ESL group than placebo group in the double blind pediatric population and overall greater than that reported in the double-blind adult adjunctive trials. However, this difference was not larger (2.6%) and may be complicated by the much lower number of patients in the DB safety populations of the pediatric epilepsy trials (n=362) vs adult epilepsy trials (n=1447). Lastly, the incidence of allergic reaction MSEs in the monotherapy studies (ITT safety population, 10.2%) was similar to that in the pediatric double-blind safety population (10.9%), although the monotherapy studies were not placebo-controlled.

The combined controlled and uncontrolled population (ages 4-17) safety population was examined for all rash-related and other TEAEs potentially indicative of allergic reactions, multiple other adverse events. In this population, the rate of potentially immune-mediated/allergic reactions was 13.9%.The incidence of rash-related TEAEs was greater in the ESL patients (8.9%) than in the placebo patients (6.3%) in the double-blind study pool; however the difference was not notable.

Drug rash with eosinophilia and systemic symptoms (DRESS):
Subject 2093305-211-21109 had a history of epilepsy and developed dysphagia and fever to 40.7 degrees C on Day 6 of study drug (ESL or PBO). She was evaluated by her general practitioner who diagnosed her with a throat infection and started treatment with amoxicillin/clavulanate. Two days later, she developed edema on upper eyelids, ears, and lips and then started to have perioral macular skin changes that spread to the ears, neck, chest, and arms. Lymphadenopathy was also noted during physical examination. She was hospitalized, and the study medication was discontinued. A chest x-ray revealed “pneumonia infiltration.” Antibiotic therapy was modified to imipenem. Oxygen therapy was initiated. Labs revealed elevated AST, ALT, GGT, LDH, and titers of EBV IgM/IgG, Coxsackie B IgM, and Enterovirus B18 IgM. The patient slowly recovered and was discharged after a month long hospitalization. The sponsor diagnosed this case as infectious mononucleosis with elevated EBV titers, although it was eventually felt to be DRESS.

Reviewer’s Comments: Aptiom is already labeled for “Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan Hypersensitivity” in Warnings and Precautions (Section 5.3). The pediatric case of DRESS identified in this supplement was included in the safety review of the original NDA for Aptiom. The sponsor has not proposed a change to the package insert based on the information included in this efficacy supplement. No revisions are necessary.

7.3.4.2 Suicidality

Suicidality was not assessed prospectively in the pediatric studies that form the basis of this review. However, suicidality was considered an adverse event of special interest and was specifically searched for in the primary safety analysis.

For the double-blind controlled study pool and uncontrolled study pool, there were no treatment-emergent suicidal ideation/behavior MSEs. Note that depression was not reported as a TEAE in the DB, OLE, or post 1-year OLE study pools.

During the postmarketing reporting period (23 September 2014 through 08 July 2016), there were no spontaneously-reported serious pediatric cases of suicidal attempts and no pediatric cases of completed suicide; 2 pediatric cases (2 events) reported suicidal ideation. Detailed postmarketing results are discussed in Section 8.

Reviewer's Comments: The label for Aptiom contains a warning (Section 5.1) for suicidal behavior ideation. This is a class warning in all AED labels. Based on the information in this supplement and the rarely reported suicidality in the clinical trials of Aptiom in adults with epilepsy, there is no reason to revise the class warning already in the label.

7.3.4.3 Homicidal Ideation/Behavior

For the double-blind controlled study pool and uncontrolled study pool, there were no treatment-emergent homicidal ideation/behavior events based on TEAEs or CIOMS data. Additionally, no pediatric cases of homicidal ideation or behavior were reported during the postmarketing reporting period (23 September 2014 through 08 July 2016).

7.3.4.4 Hepatic Events

The MSE category of hepatic disorders included all subjects with:

- *TEAEs contained in MedDRA SMQ of "drug-related hepatic disorders (severe)" that were serious, resulted in discontinuation, or were otherwise medically significant.*
- *Lab values: any post-dose ALT or AST > 3 x upper limit of normal (ULN)*

The sponsor also evaluated hepatic events by summarizing ALT, AST, total bilirubin, alkaline phosphatase (ALP) elevations, INR, TEAEs, and various combination categories. *"AST/ALT elevations were programmatically assessed by subject to determine persistence (defined as an elevation on 2 consecutive tests that were separated by at least 2 weeks) for"* cut points of > 3 x ULN and > 5 x ULN.

Hepatic Disorders Based on TEAEs or Laboratory Values of ALT or AST > 3 x ULN

In the double-blind study pool, no ESL or PBO subject met Hy's law criteria or had persistent ALT/AST elevations. ALP > 1.5 ULN was reported in 3.0% of ESL subjects and 1.9% of PBO subjects. A single patient in the placebo group (#2093-305-184-07) had transient elevations of both ALT and AST > 3 x ULN several times during the DB portion of the study (PBO) and during the OLE phase, when he was taking ESL. He was hospitalized on Day 1556 due to symptoms related to elevated liver enzymes; however, ESL was not discontinued.

For the combined controlled and uncontrolled study pool (all patients), no patient met Hy's law criteria. One (0.2%) pediatric patient had persistent ALT elevations > 3 x ULN; none had persistent AST elevations. The overall incidence of hepatic events based on TEAEs or laboratory data was 8.5% of ESL patients. The most common hepatic events based on laboratory data were ALP > 1.5 x ULN (6.0%) and ALT > 3 x ULN (1.6%). Eight ESL patients had ALT and/or AST > 3 x ULN. Of these 8 patients, 4 ESL patients had ALT > 3 x ULN, 1 ESL patient had AST > 3 x ULN, and 3 ESL patients had both ALT and AST > 3 x ULN. Two patients (2093-305-184-07 and 2093-305-233-03) had their first elevated LFT while on PBO treatment during Part 1 of the study. Patient 2093-305-184-07, as described above, developed elevated AST and ALT > 3x ULN during the double blind portion of the study. All 8 patients with ALT and/or AST > 3 x ULN had total bilirubin within normal limits at all times. Most of these patients were asymptomatic and had transient elevations. ESL was not discontinued in any of these patients.

Reviewer's Comments: In general, the evaluation for DILI did not identify any issues inconsistent with what was seen in the trials of Aptiom as adjunctive or monotherapy in patients with POS. There were no pediatric patients who met Hy's Law, although one patient met the criteria in one of the adult adjunctive POS trials (evaluated by Dr. Doi in her safety review of the original Aptiom NDA submission). Incidences of hepatic lab value outliers were generally low and similar to those seen in the adult POS trials.

7.3.4.5 Hyponatremia

The medically-significant event category of hyponatremia included all patients with the following:

- TEAEs with PT of "hyponatremia" or "sodium decreased".
- Laboratory findings of serum sodium ≤ 125 mEq/L.

For the double-blind controlled study pool, there were no treatment-emergent hyponatremia MSEs based on TEAEs. One patient had a reported post-dose sodium ≤ 125 mEq/L, but it did not appear to lead to discontinuation or change in dose. However, this patient (#2093-305-185-18503) discontinued treatment on Study Day 335 due to adverse events of blood chloride decreased (low chloride level), blood osmolarity

decreased (decreased serum osmolality), inappropriate antidiuretic hormone secretion (SIADH). A TEAE of hyponatremia was also reported. A decrease from baseline Na ≥10 mEq/L was observed in 3 (1.5%) ESL patients and 1 (0.6%) PBO patient.

In the combined controlled and uncontrolled safety population, one TEAE of hyponatremia and two post-dose sodium values < 125 mEq/L were reported. The TEAE is described above.

Select TEAEs were analyzed by sodium level. Only a few ESL patients with low sodium (≤ 125 mEq/L or > 125 to ≤ 130 mEq/L) had TEAEs that are obviously correlated linked to low sodium by physiology (1 ESL patient with sodium ≤ 125 mEq/L each had vomiting, blood antidiuretic hormone decreased, blood osmolarity decreased, and/or inappropriate antidiuretic hormone secretion). No sodium-related TEAE showed a clear pattern of incidence associated with low sodium level.

Please see Section 7.4.2.3 for discussion of sodium laboratory values.

Reviewer's Comments: Aptiom's package insert already includes a warning for hyponatremia. The rates of hyponatremia in the pediatric study were lower than seen in the adult adjunctive POS studies and raise no clinical concerns.

As noted in Section 2.7, four cases of SIADH were identified in the course of the 915 review, which were probably or possibly causally related to administration of Aptiom. The major active moiety is the same for both Aptiom and Trileptal. SIADH was recently added to the hyponatremia warning in the Trileptal label, due to a number of reported cases that were considered probably causally related to Trileptal administration. Because the active moieties of Trileptal and Aptiom are identical and SIADH cases have been reported with Aptiom, addition of SIADH to the already-existing hyponatremia warning is warranted.

7.3.4.6 Hypothyroidism

As per the ISS SAP, the medically-significant event category of hypothyroidism included patients with TEAEs contained in MedDRA SMQ of "hypothyroidism" that were fatal, serious, resulted in discontinuation, or required treatment for hypothyroidism.

In the double-blind controlled study pool (4-17 year-olds), there were 2 (1.0%) ESL patients (#2093-305-172-02 and #2093-305-223-05) and 1 (0.6%) placebo patient (#2093-208-505-07) with a TEAE of hypothyroidism. One patient experienced a TEAE of goiter diagnosed by ultrasound after approximately 6 months of ESL exposure. The AE term of goiter was not included in the hypothyroidism MSE search. Free T3 and TSH remained within the range of normal, and free T4 was transiently below the lower limit of normal with recovery at the end of the study. No thyroid medication was administered.

The relationship of the goiter, without clinically meaningful abnormality or change from baseline in thyroid function tests, to ESL treatment is uncertain.

When the full uncontrolled study pool was analyzed, 4 (1.6%) patients with a TEAE of hypothyroidism were identified. Please see Table 20 for specific information on all of the identified hypothyroidism cases.

Reviewer's Comments: No cases of hypothyroidism were identified in the adult studies. The incidence of hypothyroidism in the pediatric studies was similar in the ESL and placebo groups (1.0% and 0.6%, respectively). The overall incidence in the open label extension period was also low (1.6%). No patients stopped ESL during the study, so no positive or negative dechallenges were reported. All of these patients had confounding factors: all were on at least one concomitant AED, one patient developed the TFT changes while on placebo, and 2 patients had elevated TSH levels at baseline, prior to starting ESL. Identifying causal relationship to ESL is difficult in all cases.

Thyroid Parameters

Thyroid testing was performed during Parts 1 and 2 (not in Part 3) of Study 208 and Parts 1-5 of Study 305. Thyroid parameters consisted of total and free triiodothyronine (T3), total and free thyroxine (T4), and thyroid stimulating hormone (TSH).

In the double-blind controlled study pool, there were no apparent mean changes of clinical significance from baseline to the lowest/highest on-treatment values for free T3, free T4, or TSH. Mean changes were small, but were generally larger for ESL patients compared with PBO patients.

Shifts from normal at baseline to out-of-range low/high for the lowest/highest on-treatment values for free T3, free T4, and TSH were as follows.

- Free T3 shifted from normal at baseline to out-of-range low for the lowest on-treatment value in 5.8% of ESL patients and 1.9% of PBO patients.
- Free T4 shifted from normal at baseline to out-of-range low for the lowest on-treatment value in 40.3% of ESL patients and 7.1% of PBO patients.
- TSH shifted from normal at baseline to out-of-range high for the highest on-treatment value in 12.6% of ESL patients and 10.4% of PBO patients.

Though larger in the ESL group, the magnitude of the change in free T4 was small for the mean change from baseline to the lowest on-treatment value (-0.206 ng/dL for ESL patients; -0.054 for PBO patients). There were no treatment-emergent post-baseline PCS thyroid parameters (total T3, total T4, or TSH) with an incidence > 5% of ESL subjects. No ESL or PBO patient had free T4 < 0.75 ng/dL and concurrent elevated/ depressed values for sodium, chloride, CPK, cholesterol, LDL, HDL, or triglycerides. See Table 21 and Table 22 for specifics.

Reviewer's Comments: Evaluation of thyroid laboratory parameters in the double-blind pediatric study pool revealed a greater incidence of patients with a reduction in free T4 in the ESL group (40.3%) vs that seen in the placebo group (7.1%). Almost all of the patients who had elevated free T4 had normal TSH values. As noted above, there were a total of 3 cases of hypothyroidism identified in the double-blind safety population (2 ESL, 1 PBO) and 5 cases during the OLE phases. Determination of causal relationship to ESL is difficult in all cases.

Aptiom includes a warning for abnormal thyroid tests in the package insert (Section 5.9), which states the following: "Dose-dependent decreases in serum T3 and T4 (free and total) values have been observed in patients taking APTIOM. These changes were not associated with other abnormal thyroid function tests suggesting hypothyroidism. Abnormal thyroid function tests should be clinically evaluated." Given the imbalance in the incidence of the shift from normal to low free T4 values between ESL (40.3%) and PBO (7.1%) arms, low incidence of hypothyroidism identified in the pediatric studies, and the lack of clarity as to causal relationship, no changes to the label with respect to hypothyroidism or thyroid testing should be made at this point. The sponsor has recently completed a PMR study ("Ex-vivo Study to Evaluate Serum Free Thyroxine (FT4) and Free Triiodothyronine (FT3) Measurements using Equilibrium Dialysis (ED) and Automated Kit Assay for Subjects Treated with Eslicarbazepine Acetate") intended to prospectively evaluate the effect of eslicarbazepine on T3 and T4 measurements. The results of that study are currently under review.

7.3.4.7 Hematologic Events

The medically-significant event category of cytopenia included all patients with TEAEs with the HLT of "anaemias NEC", "marrow depression and hypoplastic anaemias", "leukopenias NEC", or "neutropenias" that were fatal, serious, severe intensity, resulted in discontinuation, or had other action taken.

For the double-blind controlled study pool, the overall incidence of treatment-emergent cytopenia MSEs was 2.0% of ESL patients (4/202) and 0% of PBO patients, and consisted of neutropenia in 3 ESL patients (1.5%) and anemia in 1 ESL patient (0.5%). In the uncontrolled safety pool (4-17 years), 2 more patients (0.5%) experienced pancytopenia and 1 (0.25%) experienced anemia. Two further patients experienced cytopenia MSEs (anemia) but are not included in the above analyses, as they were under age 4 at enrollment (though one was > 4 years at the time the anemia presented). ESL was not discontinued in any of these patients due to the hematologic event. Of these cases, two occurred after the ESL was discontinued (neutropenia diagnosed in one patient about 20 days after ESL stopped for DRESS and 29 days after discontinuation for abdominal pain in another patient). One patient developed

neutropenia. His ESL dose was not changed, and the neutropenia persisted. He discontinued ESL treatment due to "abnormal behavior" and no further information was provided on the neutropenia. One patient had anemia in the setting of surgery and received a blood transfusion. Another patient developed anemia during hospitalization for bronchopneumonia. Two other cases of anemia were treated with ongoing iron supplementation. Two patients developed pancytopenia with no reported precipitating factors, although both were on other AEDs. No changes were made to Aptiom dosing in either of these patients and the events resolved.

Reviewer's Comments: The overall incidence (and absolute number) of medically significant hematologic events in the pediatric studies was low, although the incidence was greater in the ESL group (2%) than the placebo group (0%). The types of events reported in the pediatric studies were varied: anemia (4), neutropenia (3), and pancytopenia (2). The causal relationship between Aptiom and these hematologic events is unclear, as all patients were on at least one AED, many of which are labeled for hematologic events in either the Warnings or Postmarket Experience Sections. Aptiom was not discontinued due to a hematologic event during the pediatric studies, so there are no positive dechallenges or rechallenges. There were at least 3 negative dechallenges, in which the patient remained on ESL with no change in dose and the hematologic lab parameters returned to baseline.

There were 6 cases of hematologic events with reasonable evidence for association with ESL identified during the 915 review. Aptiom is labeled for hematologic abnormalities associated with drug reaction with eosinophilia and systemic symptoms (DRESS) in the Warnings and Precautions section, but it is not labeled for hematologic abnormalities in the absence of DRESS. There was one case of agranulocytosis associated with DRESS reported. Causal relationship between the DRESS-related agranulocytosis and eslicarbazepine was possible due to a reasonable time to onset (TTO) and positive dechallenge, although all concurrent drugs were discontinued along with the eslicarbazepine. There were seven cases of hematologic abnormalities reported in the absence of DRESS. Of these seven cases, three (megaloblastic anemia, leukopenia, and pancytopenia) were possibly related to eslicarbazepine, based on reasonable temporal association and positive dechallenge, but were confounded by factors such as multiple concomitant drugs and concurrent medical illness. Causal relationship in three cases (thrombocytopenia [2] and neutropenia [1]) was unclear due to lack of positive dechallenge and/or ongoing event. Causal relationship in one case (anemia) was unlikely due to lack of positive dechallenge in the setting of improving anemia. In their review, OSE identified 15 cases of hematologic disorders in FAERS, 6 of which provided reasonable evidence of a causal association, some of which overlapped the cases included in the PADERs. Because of the 6 hematologic events with reasonable evidence of causal relationship to Aptiom administration [leukopenia (2), agranulocytosis and thrombocytopenia (1), thrombocytopenia (1), megaloblastic anemia (1), and

pancytopenia (1)] identified during the 915 review, as well as oxcarbazepine being labeled for such events, "hematologic events" has been added to the Warnings and Precautions Section of the Aptiom package insert.

7.3.4.8 AV Block

For the entire pediatric safety population, there were no treatment-emergent medically-significant events of 2nd degree or 3rd degree atrioventricular block based on TEAE or ECG data.

Reviewer's Comments: Three cardiovascular events with reported AV block, QT prolongation, or symptomatic bradycardia were identified in the 915 review. None of the cases were considered probably related to eslicarbazepine due to lack of information (TTO, concomitant drugs, confounding factors, dechallenge), prolonged TTO, lack of positive dechallenge, continued treatment with eslicarbazepine or other confounding factors (concomitant drugs). Continued pharmacovigilance for AV block and other cardiac rhythm events will continue, especially because two structurally similar products are labeled for AV block in Precautions (carbamazepine) and Postmarket Experience (oxcarbazepine).

7.3.4.9 Seizure Exacerbation

The medically-significant event category of seizure exacerbation included all subjects with TEAEs in the MedDRA HLT of "seizure".

In the controlled pediatric study pool, there was 1 ESL case of partial seizures resulting in death, as described above in Section 7.3.1. The overall incidence of seizure exacerbation MSEs was 8.9% in the ESL group and 6.3% in the placebo group. The incidence of seizure exacerbation MSEs was much greater in Study 305 (ESL: 14.3%, placebo: 7.5%) than in Study 208 (ESL: 1.2%, PBO: 2.5%). The sponsor posits that the inclusion criterion in Study BIA-2093-208 requiring an IQ ≥ 70 may have played a role but provided no rationale for that assumption other than to note that 59 patients enrolled in Study 305 had a baseline finding of mental retardation.

One patient discontinued participation in the study during the double blind period due to seizure exacerbation. The patient was a 10 year old boy (#2093-208-411-41101) who was randomized to ESL and developed status epilepticus on study day 5. He was treated with rectal diazepam and discontinued treatment on study day 6 due to the episode of SE.

The most-commonly reported seizure types were partial seizures (ESL 4.5%, PBO 4.4%), convulsion (ESL 2.5%, PBO 0.6%), and status epilepticus (ESL 2.0%, PBO 0.6%). Each remaining seizure type was reported by one ESL patient (0.5%).

Table 14: Incidence of Seizure TEAEs in the Double-Blind Safety Pool (4-17 years)

MedDRA version 13.1 System Organ Class / Preferred Term	Study 208		Study 305		Total	
	PBO N = 40 n (%)	ESL N = 83 n (%)	PBO N = 120 n (%)	ESL N = 119 n (%)	PBO N = 160 n (%)	ESL N = 202 n (%)
Subjects with any Seizure Exacerbation MSE	**1 (2.5)**	**1 (1.2)**	**9 (7.5)**	**17 (14.3)**	**10 (6.3)**	**18 (8.9)**
Source: Adverse Event Data (TEAEs)						
Nervous System Disorders	**1 (2.5)**	**1 (1.2)**	**9 (7.5)**	**17 (14.3)**	**10 (6.3)**	**18 (8.9)**
Partial seizures	1 (2.5)	0	6 (5.0)	9 (7.6)	7 (4.4)	9 (4.5)
Convulsion	0	0	1 (0.8)	5 (4.2)	1 (0.6)	5 (2.5)
Status epilepticus	0	1 (1.2)	1 (0.8)	3 (2.5)	1 (0.6)	4 (2.0)
Epilepsy	0	0	1 (0.8)	1 (0.8)	1 (0.6)	1 (0.5)
Grand mal convulsion	0	0	0	1 (0.8)	0	1 (0.5)
Partial seizures with secondary generalization	0	0	0	1 (0.8)	0	1 (0.5)

Source: ISS Table 115, verified in JMP

When the entire safety study pool is considered, the overall incidence of seizure exacerbation MSEs was 12.2%. The most-commonly reported seizure exacerbation type was partial seizure (5.8%), convulsion (3.7%), status epilepticus (1.8%), and epilepsy (1.6%); each remaining seizure type was reported by at most 5 (1.2%) patients. Three patients discontinued participation during the OLE period due to seizure exacerbation, although none of these events were serious.

Reviewer's Comments: Seizure exacerbation is a real concern in patients with any type of epilepsy. Many factors may aggravate seizures in patients with epilepsy including sleep deprivation, intercurrent illness, noncompliance with therapy, alcohol and other recreational drugs, OTC drugs, seizure-inducing drugs, drug-drug interactions (DDIs), change from one AED to a less effective AED, development of drug resistance, natural history of the epilepsy, overdosage, inappropriate AED choice (some drugs have been shown to increase absence and other primary generalized seizure types), AED-induced encephalopathy, and metabolic effects. It is difficult to establish Aptiom as the proximate cause of seizure exacerbation in the pediatric patients in whom this event was reported, because it is difficult to rule out all (or even most) of the potentially contributing factors.

A significant difference in exacerbation of seizures between ESL and placebo groups was not reported in the adult epilepsy trials, although the incidence of seizure SAEs was higher in the ESL than placebo in the adult phase 3 epilepsy study pool (1.4% vs 0.5%).

Because of the lack of clear causal relationship between Aptiom and seizure exacerbation in the pediatric studies, inability to rule out potentially contributing factors, no significant difference between pediatric ESL and placebo groups with respect to incidence of seizure exacerbation, no changes to the labeling are recommended.

7.3.5 Submission Specific Primary Safety Concerns

N/A

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

For the double blind study pool, a total of 137 of 202 patients in the ESL group (67.8%) and 105/160 patients (65.6%) in the placebo group experienced any TEAE. As seen in Table 24, the most common TEAEs overall in the double blind population were headache (13.9% and 11.3%), somnolence (9.4% and 5.0%), vomiting (7.9% and 5.0%), nasopharyngitis (7.4% and 10.0%), pyrexia (7.4% and 8.8%), and partial seizures (7.4% and 8.8%) in ESL and placebo patients respectively. The most common TEAEs in patients taking ESL in the double-blind phase of the adjunctive POS trials were dizziness (22%), somnolence (14%), headache (13%), nausea (12%), and diplopia (10%). The incidence and types of TEAEs observed in the double blind pediatric study pool were consistent with those observed in adult patients with partial-onset seizures. Pyrexia and various infections were more frequently observed in pediatric patients than adult subjects; however in the pediatric population, infections (overall) and pyrexia were not more frequent with ESL treatment.

When the double-blind controlled study pool (4-17 year-olds) were analyzed by weight category and modal daily dose category, the incidence of overall TEAEs and most common TEAEs as identified above (headache, somnolence, vomiting, nasopharyngitis, pyrexia, and partial seizures) did not show a consistent trend toward greater frequency for patients of differing weight (either greater or lower weight). Overall TEAEs and most common TEAEs did not show a dose response within any of the weight groups. The largest difference seen was in the incidence of skin and subcutaneous tissue disorders SOC, where the treatment difference was greatest in the 11-21 kg category (26.1% of ESL patients; 11.5% of PBO patients); however, in higher weight children, there was no consistent trend in treatment differences.

Overall TEAEs were analyzed by age group (4-6, 7-11, and 12-17 years). In general, the pattern and incidence of overall TEAEs and most common TEAEs were consistent in subsets with the pattern seen in the overall population and did not show a consistent trend in treatment differences across the age groups. As with the lowest weight

category, the greatest difference in any age group was the incidence of skin and subcutaneous tissue disorders SOC in the 4-6 year-old group (26.1% of ESL patients; 10.3% of PBO patients), which decreased in older children.

A separate safety assessment of the patients enrolled in Study 305 who received the recalled oral suspension ("IMP patients") was conducted by the sponsor. A total of 41 IMP patients were excluded from the primary double blind safety pool (ESL arm: n = 21; placebo arm: n = 20). For these patients (2-6 year-olds), there was a higher overall incidence of TEAEs seen in the ESL group (61.9%) than in the PBO group (50.0%). The most-commonly reported TEAEs in ESL patients were vomiting (19.0% ESL patients and 0% PBO patients), diarrhea (ESL 14.3% [n=3], placebo 5.0% [n=1]), respiratory tract infection (ESL 14.3% and 5.0% PBO), and rhinitis (ESL 14.3%, placebo 5.0%); a trend for higher ESL incidences than PBO was observed.

Reviewer's Comments: The meaningfulness of the trend towards higher incidence of TEAEs in the ESL group who received the recalled oral suspension is unclear. The overall number of these patients is low (ESL: n = 21; placebo: n = 20), making it difficult to draw any significant conclusions. It is unclear if the recalled medical product contributed specifically to these TEAEs.

For 4-17 year old patients in the one-year open-label uncontrolled study pool (Table 25), the overall incidence of TEAEs was 64.1%. The most-commonly reported TEAEs were nasopharyngitis (10.1%), partial seizures (10.1%), vomiting (9.5%), pyrexia (8.6%), headache (8.0%), and somnolence (6.8%). When TEAEs in the uncontrolled 1 year safety population were analyzed, the pattern and incidence of overall TEAEs and most common TEAEs in subsets were consistent with the pattern seen in the overall population and did not show a consistent trend across the weight categories.

When TEAEs in all patients in the one-year open-label uncontrolled study pool were analyzed, the overall incidence of TEAEs was 64.0%. The most-commonly reported TEAEs in this population similar to those reported in the 4-17 year-old population: partial seizures (10.2%), nasopharyngitis (9.9%), vomiting (9.9%), pyrexia (9.4%), headache (7.5%), and somnolence (6.7%).

When TEAEs in the one-year open-label uncontrolled study pool were analyzed by age, the pattern and incidence of overall TEAEs and most common TEAEs (except headache and somnolence) trended more common in the youngest age group (4-6 years) and decreased in older children.

The overall incidence of TEAEs in the post one-year open-label uncontrolled study pool (4-17 year-olds) was 52.5% (93/177) with the most common TEAEs similar to those seen in the one-year open-label uncontrolled study pool: partial seizures (10.7%), pyrexia (9.0%), nasopharyngitis (8.5%), headache (7.9%), and vomiting (6.8%).

When TEAEs in the full uncontrolled safety study population (Studies 202, 208 Parts 2-3, and 305 Parts 2-5) are assessed, the overall incidence of TEAEs was 69.9% (255/365 patients) with the most common TEAEs of partial seizures (12.9%), vomiting (12.3%), pyrexia (11.2%), nasopharyngitis (10.7%), headache (10.4%), and somnolence (9.0%). See Table 23 for a comparison of the most common TEAEs (≥5% incidence) in all of the study pools.

Reviewer's Comments: The incidence and types of common TEAEs in the uncontrolled safety pool do not differ significantly from those seen in the controlled study pool. While some common TEAEs were more frequent in the controlled pediatric population and some were more frequent in the controlled adult population, there was very little difference in the pattern and incidence of common TEAEs in the adult and pediatric studies.

7.4.2 Laboratory Findings

7.4.2.1 Measures of Central Tendency and Shift Changes

When changes from baseline to lowest or highest on-treatment values were analyzed in the double-blind study pool, there were no changes of clinical significance for the hematology, serum chemistry (including lipid parameters), urinalysis, or coagulation parameters for either the ESL or placebo group.

GGT shifted from normal at baseline to out-of-range high for the highest on-treatment value in 27.2% of ESL patients and 0.9% of PBO patients. Also, GGT shifted from normal at baseline to out-of-range high for the lowest on-treatment value in 16.7% of ESL patients and 0% of PBO patients. Elevated GGT was not a defined cause of study discontinuation. Very few of the GGT changes were accompanied by > 3 x ULN change in ALT, AST, or bilirubin, and were therefore of uncertain significance.

For the one-year open-label uncontrolled study pool (4-17 year-old patients), there were no apparent mean changes of clinical significance from baseline to the lowest or highest on-treatment values for any hematology or serum chemistry (including lipid) parameters.

When all patients (2-17 years) in the one-year open-label uncontrolled study pool were analyzed, the parameters with the most patients with shifts from normal at baseline to out-of-range low/high for the lowest and highest on-treatment values were very similar to those seen in the 4-17 population.

For the post one-year open-label uncontrolled study pool (4-17 year-old patients), there were no apparent mean changes of clinical significance from baseline to the lowest or highest on-treatment values for any hematology or serum chemistry parameters.

7.4.2.2 Potentially Clinically Significant Laboratory Data

Individual laboratory values were evaluated according to sponsor-defined criteria determined using age-specific criteria to identify potentially clinically significant (PCS) values. Post-baseline PCS data were examined for subjects with non-PCS values at baseline in order to identify treatment-emergent post-baseline PCS laboratory parameters with an incidence > 5% of ESL patients.

For the double-blind controlled study pool (4-17 year-olds), treatment-emergent post-baseline PCS laboratory parameters were generally similar for ESL and PBO patients and did not raise any clinical concerns.

7.4.2.3 Minimum Post-dose Sodium Levels

In the primary double-blind controlled study pool (4-17 year-old patients), the incidences were low for the minimum post-dose sodium ≤ 125 mEq/L (ESL 0.5%; PBO 0%), > 125 to ≤ 130 mEq/L (ESL 1.0%; PBO 0%), > 130 to ≤ 135 mEq/L (ESL 3.6%; PBO 1.9%), and decrease from baseline more than 10 mEq/L (ESL 1.5%; PBO 0.6%) categories. Incidences were similar for ESL and PBO patients for each minimum post-dose sodium category.

For the one-year open-label uncontrolled study pool (4-17 year-olds), the incidences for the minimum post-dose sodium categories were as follows: ≤ 125 mEq/L (0%), > 125 to ≤ 130 mEq/L (0.3%), > 130 to ≤ 135 mEq/L (5.7%), and decrease from baseline more than 10 mEq/L (1.5%).

Reviewer's Comments: In general, the incidence of hyponatremia was low in the pediatric studies. Very low post-dose sodium levels (≤ 125 mEq/L) occurred in a single patient in the controlled double-blind and uncontrolled study pools.

7.4.3 Vital Signs

Vital signs measurements were collected at all visits and included systolic blood pressure, diastolic blood pressure, pulse rate, body temperature (Study 305 only), and weight; blood pressure was measured after sitting for at least 5 minutes There were no reported changes of clinical significance from baseline to the lowest or highest on-treatment values for any vital sign parameter (diastolic blood pressure, systolic blood pressure, pulse rate, supine pulse rate, or weight) in the double-blind study pool (4-17

years), the uncontrolled 1-year safety pool, or the post one-year uncontrolled safety pool.

With respect to weight, a greater percentage of ESL patients than placebo patients lost weight or gained weight during the double blind period, but the changes were not clinically significant.

Reviewer's Comments: It is difficult to derive any meaningful conclusions from the weight data, other than to state that some patients may gain weight and some may lose weight. Longer exposure may lead to greater changes in weight, but the long-term data is confounded by the fact that subjects were not specifically restricted to ESL monotherapy, and other AEDs have been linked to weight changes. These findings were similar to those seen in the controlled adjunctive and historically-controlled monotherapy studies of Aptiom in adults.

7.4.4 Electrocardiograms (ECGs)

For Study 305, 12-lead ECGs were collected at screening, and multiple time points during Parts 1-5 of the study (see Section 7.2.4 for study visits at which ECGs were collected). A central facility was used for the analysis and interpretation of ECGs. Ventricular rate, PR interval, RR interval, QRS duration, and QT interval were assessed.

For Study 208, 12-lead ECGs were collected at screening and various times throughout Parts 1-3. Only an assessment of normal or abnormal was recorded.

A formal QT study that examined the effect of ESL on cardiac repolarization was reviewed as part of the original NDA. The FDA Interdisciplinary Review Team (IRT) for QT studies reviewed Study 116. These data are already described in the label.

In Part 1 of Study 305, there were no apparent changes of clinical significance from baseline to the lowest or highest on-treatment values for any ECG parameter. The incidence of ECG abnormalities was 2.8% of ESL patients and 4.0% of PBO patients at end of maintenance period compared with baseline abnormalities of 4.5% and 4.4%, respectively. The incidence of ECG abnormalities was higher for the post one-year open-label uncontrolled study pool (≤19.4% of ESL subjects at each post-baseline visit; baseline abnormalities of 5.6%); however, none of these ECG changes were correlated with any clinical abnormalities or TEAEs.

7.4.5 Special Safety Studies/Clinical Trials

N/A

7.4.6 Immunogenicity

N/A

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

There were no pediatric studies with a design that was appropriate for assessing a dose response. Study 202 did not include a placebo group. In placebo-controlled Studies 208 and 305, ESL-treated patients had their dose titrated based on tolerability.

7.5.2 Time Dependency for Adverse Events

The overall incidence of AEs/TEAEs was lowest during the tapering-off period (ESL 18.5%; PBO 14.2%) and the double-blind follow-up period (ESL 15.2%; PBO 17.2%). Each TEAE was reported in < 5.0% of ESL patients. Incidence during the baseline period (ESL 32.2%; PBO 20.6%) was lower than that in the titration period (ESL 48.0%; PBO 36.9%) and maintenance period (ESL 45.8%; PBO 48.1%). The overall incidence of TEAEs had a gradual, although unsteady, general decline over the weeks of the double-blind period for each treatment group.

The median time to first occurrence of any TEAE was shorter for ESL subjects (14.0 days) than PBO subjects (26.0 days). Median time to first occurrence of some of the common TEAEs was shorter in the ESL group than in the placebo group and longer for others without a specific pattern noted. The median maximum duration of any TEAE was longer for ESL patients (30.0 days) than PBO patients (20.0 days). As with time to first occurrence, median maximum duration was longer in the ESL group for some common TEAEs and shorter for others with no obvious pattern.

7.5.3 Drug-Demographic Interactions

The pattern and incidences of overall TEAEs and most common TEAEs were consistent in subsets with the pattern seen in the overall population and did not show a consistent trend in treatment differences across either the age groups (4 to 6, 7 to 11, 12 to 17 year-old) or the weight categories (11 to 21, 22 to 31, 32 to 38, >38 kg) in the double blind safety pool.

Differences in incidences of overall and most common TEAEs across each of the gender, race, and region subgroups for treatment differences (ESL-PBO) were generally small, and were not considered clinically meaningful. For partial seizures, the treatment difference was greater in Western Europe (ESL 18.2%; PBO 7.7%) compared

with Eastern Europe (ESL 4.9%; PBO 8.6%). There were too few non-Caucasian patients (<5%) to allow for any conclusions to be drawn regarding differences across race categories.

7.5.4 Drug-Disease Interactions

Assessments and recommendations for hepatic and renal impairment were made in the original NDA review. Please see the Clinical Pharmacology review for any new information in this supplement.

7.5.5 Drug-Drug Interactions

Incidence of TEAEs trended up with the baseline number of AEDs, but the differences between groups were not significant. The low overall numbers of patients on ≥3 AEDs (ESL n=13; PBO n=11) makes it difficult to draw any conclusions from this trend.

There were only two TEAEs with ≥10% difference between groups. For headache, the treatment difference was greater for 1 baseline AED (ESL 19.7%; PBO 5.4%) compared with 2 baseline AEDs (ESL 10.9%; PBO 13.4%). Similarly for nasopharyngitis, the treatment difference was greater for 1 baseline AED (ESL 8.2%; PBO 2.7%) compared with 2 baseline AEDs (ESL 7.0%; PBO 11.6%). Otherwise, the incidences for overall TEAEs and most common TEAEs did not show any ≥ 10% difference across the baseline AED use categories for treatment differences. With respect to specific AEDs, in general, there were no patterns in TEAEs dependent on baseline AED.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

N/A

7.6.2 Human Reproduction and Pregnancy Data

The APTIOM labeling cautions that because of the potential for serious adverse reactions in nursing infants from APTIOM, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

There have been no clinical studies of ESL in pregnant women. There is insufficient information to support a conclusion about the use of ESL during pregnancy. The APTIOM package insert warns that ESL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

There were no pregnancies reported in pediatric studies. Two patients had positive screening pregnancy tests, but each was followed by negative tests. Two pediatric patients reported pregnancies in the postmarketing period with no negative outcomes (see Section 8.1 for specific information on these pregnancies).

7.6.3 Pediatrics and Assessment of Effects on Growth

Formal assessments of growth were not performed in Studies 202, 208, and 305.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were no overdose/drug toxicity-related deaths, no overdose/ drug toxicity SAEs, and no drug toxicity TEAEs reported in pediatric studies.

ESL is not a controlled substance. The abuse potential of ESL was evaluated in animal and human studies included in the original NDA submission. The sponsor plans to (b) (4) One SAE in an ESL patient of "drug withdrawal syndrome" was reported. The sponsor did not consider this event related to ESL as ESL dosing had been stable for 3 weeks prior to development of the symptoms. However, the TESAE did resolve after the ESL dose was increased. One patient reported a TEAE of visual hallucination.

7.7 Additional Submissions / Safety Issues

None

8 Postmarket Experience

8.1 Postmarketing Data

As of the postmarketing cut-off date for this sNDA (08 JUL 2016), eslicarbazepine (200 mg, 400 mg, 600 mg, and 800 mg tablets for oral use) was authorized for marketing in 42 countries under the trade name of Zebinix® or Exalief®.

An estimate of the number of patients exposed to marketed ESL was calculated by the sponsor from combined worldwide sales volumes from 4th Quarter of 2014 to the 2nd Quarter of 2016, which is the closest available exposure time-frame matching the adverse event data received from the postmarketing reporting period (23 SEP 2014 through 08 JUL 2016). This exposure was estimated based on the assumption that each subscription unit (or number of tablets sold) was used in patients on a dosage

regimen of 1 tablet per day where 1 subscription unit represented one 800 mg tablet taken per day and the sum of all subscription units represented the total patient-days of exposure. Patient-days of exposure were then converted to patient-years of exposure by dividing the patient-days of exposure by 365.25. There was a total of (b) (4) subscription units sold during the reporting interval, representing (b) (4) patient-years of exposure.

None of the below-mentioned actions relating to safety were considered by regulators during the postmarketing reporting period:

- Marketing authorization withdrawal or suspension
- Failure to obtain a marketing authorization renewal
- Restrictions on distribution
- Clinical trial suspension
- Dosage modification
- Changes in target population or indications
- Formulation changes
- Urgent safety restriction

The number of cases with adverse events reported in postmarketing in the Global Safety database between 23 September 2014 and 08 July 2016 are summarized in Table 15 below.

Table 15: Estimated Number of Postmarketing Adverse Event Cases by Country

Country	Pediatric Cases	Adult & Unknown Age Cases	Total Cases
United States	5	420	425
France	1	63	64
Spain	1	51	52
Germany	3	34	37
Portugal	3	17	20
Canada	0	15	15
United Kingdom	0	11	11
Ireland	2	7	9
Greece	0	6	6
Italy	1	5	6
Czech Republic	0	2	2
Norway	0	2	2
Russia	0	1	1
Ukraine	1	0	1
Denmark	0	1	1
Total	17	635	652

Source: ISS Table 150

The 17 pediatric postmarketing cases occurred in 6 males and 10 females (gender not reported in 1 patient), and the youngest patient was 7 years old (age was not reported in 2 patients). There were 45 reported events, 9 of which were serious, and no fatalities. Two pediatric reports described pregnancy (both in patients age 16). Of the 9 serious

events, 5 were events of seizure exacerbation, 2 were of suicidal ideation (1 in a patient with a history of suicide attempts in the past), and 1 case had 2 serious events of acute pancreatitis and urinary tract infection.

There were no pediatric deaths in the reporting period. In the reporting interval from 23 September 2014 through 08 July 2016, the most commonly-reported events (≥ 2) with at least 1 serious event for pediatric patients were seizure (4 events) and suicidal ideation (2 events).

Pediatric postmarketing events of interest include the following:

- Suicidal ideation:
    - 16 year-old girl with history of hospitalization for attempted suicide in the past developed suicidal thoughts while on ESL. Her symptoms resolved after ESL was discontinued. No other significant information was provided for this event.
    - 15 year-old girl who developed suicide intentions, but was not hospitalized. ESL was discontinued, but no information was given regarding any further treatment or outcome.
- Hyponatremia: a single report from a physician of hyponatremia that occurred in a "teenager". The patient developed hyponatremia at an unknown date after starting ESL. Her symptoms resolved after the physician *"adjusted the patient's fluid intake"*, but ESL was not discontinued.

Reviewer's Comments: The pediatric postmarketing reports are consistent with ADRs included in Aptiom's labeling and do not appear to present any new safety signals for the use of Aptiom in the pediatric population.

There were 12 fatal cases in the adult population during the postmarket reporting period. The associated SAEs included "sudden death" (2), seizure/drowning (1), infection (1), respiratory disorder (1), "natural causes" (1), and pneumonia (1). Associated events and/or cause of death were unknown or not reported in 5 cases.

The most common SAEs (≥5 cases) reported in adult patients during the postmarketing period were seizure (90 cases), epilepsy (10), GTCS (5), partial seizures (7), suicidal ideation (12), hyponatremia (63), decreased serum sodium (11), IADH (6), suicidal ideation (12), rash (7), vomiting (5), and "death" (6). Of note, numerous skin and subcutaneous disorders were reported (n=30), with 3 cases of DRESS and 1 case each of SJS, TEN, or erythema multiforme.

Reviewer's Comments: The spontaneously-reported SAEs and common AEs in adult patients are consistent with the safety profile obtained from clinical trials. The review of postmarketing SAEs and AEs in adults did not show any new safety concerns compared to

the current labeling.

8.2 120 Day Safety Update

Ongoing studies include BIA-2093-305 (Part 5), 093-050, BIA-2093-131, BIA-2093-304 (Part 3), BIA-2093-311 (Double-blind + Extension), 093-050, and SEP093-453.

During the Safety Update reporting period (09 July 2016 to 28 February 2017), a total of 10 pediatric patients were ongoing in Part 5 of Study 305; 6 of these patients were 4-17 years old at study entry and 4 were 2-3 years old at study entry. Four adolescent patients who were 16-17 years-old at entry to Study 045/046 were ongoing in Study 050 during the SU reporting period. No pediatric patients in Study BIA-2093-305 Part 5 or adolescent patients in Study 093-050 completed or withdrew from the study during the SU reporting period; all were ongoing as of 28 February 2017. No deaths or discontinuations due AEs were reported in pediatric patients enrolled in these studies.

One SAE of pneumonia was reported in a 7 year old patient enrolled in Study 305 (2 years old at study entry). This patient has a prior history of asthma and had an exacerbation of her asthma 2 days prior to developing the pneumonia. No changes were made to her ESL dosing, and her pneumonia is reported as resolved.

One adult patient enrolled in Study 131 (#2093311-2414-008) died during the SU reporting period. He was a 77 year old man with a history of cardiovascular disease who died of a pulmonary embolism on (b) (6) No further information was provided by the family.

There were 7 SAEs reported in adult patients in the ongoing studies: pulmonary embolism (patient described above), abdominal hernia, viral respiratory tract infection, lumbar intervertebral disc protrusion/back pain, partial seizures with secondary generalization, seizure, atrial fibrillation, and intestinal hemorrhage (h/o diverticulitis).

Reviewer's Comments: The information gathered from the 120 Day Update is consistent with what was seen in the pediatric and adult epilepsy studies and does not raise any clinical concerns at this time.

9 Appendices

9.1 Literature Review/References

See footnotes

9.2 Labeling Recommendations

See final approved labeling.

9.3 Advisory Committee Meeting

The Division did not present this sNDA to an Advisory Committee.

9.4 Full Description of Studies 208 and 305

9.4.1 Study BIA-2093-305

Part 1 of Study BIA-2093-305 was a Phase 3, double-blind, randomized, placebo-controlled, parallel-group study of adjunctive ESL in patients 2 to 16, 17, or 18 years of age (depending upon country) with POS refractory to treatment with 1 or 2 AEDs. ESL doses ranged from 10-30 mg/kg/day with a target dose of 20 mg/kg/day and a maximum of 1200 mg/day. The purpose of the study was to demonstrate the efficacy and safety of ESL as adjunctive therapy in pediatric patients with refractory POS. Parts 2-5 of Study BIA-2093-305 were long-term open-label extensions available to patients who had completed the prior stage(s).

Screening and Baseline Periods

Subjects who met eligibility requirements during screening entered an 8-week, non-interventional baseline phase to establish a 28-day baseline seizure frequency. The baseline seizure frequency criterion was ≥ 4 partial seizures with at least 1 seizure occurring in each 28-day interval of the 8-week baseline period.

Dose Blind Treatment Period

Patients who met the baseline seizure criteria entered the dose-blind treatment phase (~18 weeks) and were randomized (1:1) to receive ESL or administered orally once daily. Randomization was stratified based on age (2-6 years, 7-11 years, or 12-18 years). Patients in the treatment group received ESL 10-30 mg/kg/day (target of 20 mg/kg/day and maximum of 1200 mg/day). During the titration period, subjects underwent escalation to the ESL target dose. For the first 2 weeks, 10 mg/kg/day ESL (maximum 800 mg/day) was given. If the patient developed an intolerable AE while in

10/mg/day, he or she was withdrawn from the study. After 2 weeks, the ESL dose was increased to 20 mg/kg/day (maximum 1200 mg/day) for 4 weeks. If a patient developed intolerable AE(s), the patient was down-titrated to 10 mg/kg/day. After the titration period, patients entered the 12-week maintenance period. At the beginning of the maintenance period (after 4 weeks on 20 mg/kg/day), patients who had an inadequate therapeutic response but were tolerating the dose were permitted a final dose increase to 30 mg/kg/day. If the dose and response were tolerable, patients remained at 20 mg/kg/day. After the 12-week maintenance period, the study drug was tapered off every 2 weeks, followed by a 4-week observational follow-up period. However, if a patient experienced an increase in seizure frequency (e.g., more than 100% increase over baseline) during tapering-off or follow-up in Part I, the patient was to proceed directly with the long-term, open-label extension.

Study Population

Key Inclusion Criteria: males or females ages 2 to 16, 17, or 18 years of age (depending on country) with a diagnosis of partial epilepsy for 6-24 months prior to enrollment (depending on country), prior treatment with ≥ 3 AEDs, current (stable) treatment with 1-2 AEDs (excluding oxcarbazepine) for 1 month prior to enrollment, ≥4 partial onset seizures during the month prior to screening, and at least 4 partial-onset seizures during each 4-week interval of the 8-week baseline period.

Key Exclusion Criteria: primary generalized seizures, baseline seizure frequency substantially different from usual seizure frequency, known progressive neurological disorders, seizures of non-epileptic origin, status epilepticus within the 3 months prior to enrollment, second or third degree AV block, Lennox-Gastaut or West syndrome, or impaired renal function.

Analysis populations

- Intent-to-treat (ITT) population: all randomized patients treated with at least 1 dose of study medication, and with at least 1 post-baseline seizure frequency assessment, excluding IMP recall patients.
- Modified intent-to-treat (mITT) set: all randomized patients treated with at least 1 dose of study medication after randomization, and with at least 1 post-baseline seizure frequency assessment, including stratum I patients who were randomized before the IMP recall.
- Safety set: all patients who received at least 1 dose of double-blind study treatment excluding stratum I patients who were randomized before the IMP recall.
- Combined safety set: All patients who received at least 1 dose of double-blind study treatment, i.e. safety set and stratum I patients randomized before IMP recall combined.

Endpoints

Primary efficacy endpoint:
The primary efficacy variable was the responder rate during the maintenance period, defined as the proportion of patients with at least a 50% decrease in the standardised 4-week seizure frequency from the baseline period to the 12-week maintenance period.

Secondary Efficacy Endpoints (Part 1 of study)

1. Standardized seizure frequency per period of the baseline, titration, maintenance, and tapering-off periods.
2. Relative change in seizure frequency from the baseline period to the 12-week maintenance period (≥25%; >–50% to <25%; ≥–75% to ≤–50%; <–75%).
3. Proportion of patients who are seizure-free during the maintenance period.
4. Standardized seizure frequency by seizure type (simple partial, complex partial, partial evolving to secondary generalized, unclassified, other) during the maintenance period. Seizures with missing seizure type information were considered as unclassified for the analysis.
5. Seizure duration (as classified in the diary): <30sec, ≥30 sec - <1 min, ≥1 min - <5 min, ≥5 min, unknown.
6. Seizure severity assessed with the 13-item Hague seizure severity scale.
7. Number of days with seizures (standardized to 4-week time period).
8. Treatment retention time, defined as the time to first occurrence of one of the following during the titration or maintenance period: withdrawal of study medication due to AEs or withdrawal of study medication due to lack of efficacy (defined as seizure exacerbation ≥100% compared to the baseline period).
9. Seizure exacerbations during tapering-off or follow-up period.

Safety Endpoints

1. Reports of adverse events (AEs), including serious adverse events (SAEs).
2. Safety laboratory (hematology, biochemistry, and urinalysis).
3. Vital signs, 12-lead electrocardiogram (ECG) parameters
4. Physical and neurological examinations.
5. Sexual maturation assessment.

9.4.2 Study BIA-2093-208

Part 1 of Study BIA-2093-208 was a Phase 2, double-blind, randomized, placebo-controlled, parallel-group study of adjunctive ESL in patients 6 to 16 years of age with POS refractory to treatment with 1 or 2 AEDs. ESL doses ranged from 10-30 mg/kg/day with a maximum of 1200 mg/day. The purpose of the study was to examine the effects of ESL on cognition in comparison to placebo. Parts 2 and of Study BIA-2093-208 were long-term open-label extensions available to patients who had completed the prior stage(s).

Screening and Baseline Periods

Subjects who met eligibility requirements during screening entered a 4-week, non-interventional baseline phase to establish a 28-day baseline seizure frequency. The baseline seizure frequency criterion was ≥ 2 partial seizures during the 4-week baseline period.

Dose Blind Treatment Period

Patients who met the baseline seizure criteria entered the dose-blind treatment phase and were randomized (2:1) to receive ESL or placebo administered orally once daily. Randomization was stratified based on age (7-11 years or 12-16 years). Patients in the treatment group received ESL 10-30 mg/kg/day (target dose 30 mg/kg/day, maximum of 1200 mg/day). During the titration period, subjects underwent escalation to the ESL target dose. For the first 2 weeks, 10 mg/kg/day ESL (maximum 800 mg/day) was given. If the patient developed an intolerable AE while in 10/mg/day, he or she was withdrawn from the study. After 2 weeks, the ESL dose was increased to 20 mg/kg/day (maximum 1200 mg/day) for 2 weeks. If a patient developed intolerable AE(s), the patient was down-titrated to 10 mg/kg/day. If the patient experienced no intolerable AEs, the dose was increased after 2 weeks to 30 mg/kg/day. Maintenance period was 8 weeks at the titrated dose. After the 8-week maintenance period, the study drug was tapered off by 10 mg/kg/day every 2 weeks, followed by a 4-week observational follow-up period. When a patient down-titrated to 10 mg/kg/day, he or she could either enter the OLE phase of the study or discontinue the drug.

Study Population

Key Inclusion Criteria: ages 2 to16, a diagnosis of partial epilepsy for 12 months prior to enrollment, IQ of at least 70 as assessed within the 1 year prior to screening, current (stable) treatment with 1-2 AEDs (excluding oxcarbazepine) for 1 month prior to enrollment, ≥2 partial onset seizures during the month prior to screening, and at least 2 partial-onset seizures during the 4-week baseline period.

Key Exclusion Criteria: only simple partial seizures with no motor symptomatology, primary generalized seizures, baseline seizure frequency substantially different from usual seizure frequency, known progressive neurological disorders, seizures of non-epileptic origin, status epilepticus or cluster seizures (≥3 seizures within 30 minutes) within the 3 months prior to enrollment, diagnosis of ADHD and treated with stimulants, second or third degree AV block, Lennox-Gastaut or West syndrome, or estimated creatinine clearance < 60 mL/min.

Analysis populations

- Safety population: all randomized patients who received at least 1 dose of study treatment.

- Modified Efficacy Intent-to-Treat (mITT) population: all randomized patients treated with at least 1 dose of study medication after randomization and with at least 1 post-baseline seizure frequency assessment.
- Modified Cognitive Intent-to-Treat (ITT) population: all randomized patients treated with at least 1 dose of study medication and with at least 1 post-baseline assessment of cognition.
- Cognitive Per-protocol (PP) population: all patients in the Modified Cognitive ITT population who completed the 8-week maintenance period and were without Important Protocol Deviations with respect to the primary cognitive endpoint.
- Efficacy PP population – all patients in the Modified Efficacy ITT population who completed the 8-week maintenance period and without Important Protocol Deviations with respect to the secondary efficacy endpoints.

Endpoints

Primary endpoint:
The primary endpoint was change from baseline to the end of the Part I (DB period) in the composite Power of Attention measure, in order to assess information processing speed and attention/psychomotor speed.

Secondary Endpoints
Safety Endpoints

- (Parts I and II)
  - *Treatment-emergent adverse events (TEAEs).*
  - *Change from baseline in clinical laboratory tests (hematology, biochemistry, thyroid function and urinalysis).*
  - *Vital signs.*
  - *Body weight, height and head circumference.*
  - *12-lead electrocardiogram (ECG) readings.*
- Part III
  - *Treatment-emergent adverse events (TEAEs).*
  - *Vital signs.*
  - *Body weight, height and head circumference.*
  - *12-lead electrocardiogram (ECG) readings.*
  - *Physical and neurological examination.*

Efficacy Endpoints

- *Part I*
  - *Relative reduction from baseline in seizure frequency over the evaluation period as compared with placebo.*
  - *Proportion of patients with a 50% or greater reduction in seizure frequency from the baseline period to the 8-week maintenance period (responders).*
  - *Proportion of seizure-free patients (100% seizure reduction) over the 8-week maintenance period.*

  - *Proportion of patients with a 25% or greater exacerbation in seizure frequency versus baseline.*
- *Part II*
  - *Relative reduction from baseline in seizure frequency over the one-year OL-period.*
  - *Proportion of patients with a 50% or greater reduction in seizure frequency from the baseline period (responders).*
  - *Proportion of seizure-free patients (100% seizure reduction).*
  - *Proportion of patients with a 25% or greater exacerbation in standardized seizure frequency versus baseline.*
- *Part III*
  - *Treatment retention time defined as actual time on treatment.*
  - *Clinical Global Impression-Severity (CGI-S) scale change from baseline*

Neurocognitive Endpoints

- *Part I*
  - *Continuity of Attention*
  - *Quality of working memory.*
  - *Quality of episodic secondary memory (children aged ≥ 9 years only).*
  - *Word recognition (children aged ≥ 9 years only).*
  - *Picture recognition (children aged < 9 years only).*
  - *Speed of memory.*
- *Part II*
  - *Power of Attention.*
  - *Continuity of Attention.*
  - *Quality of working memory.*
  - *Quality of episodic secondary memory (children aged ≥ 9 years only).*
  - *Picture recognition (children aged < 9 years only).*
  - *Speed of memory.*

Global Cognitive, Social Competence and Quality of Life Endpoints

- *Part I:*
  - *Change from baseline to the end of Part I (DB period) in the following:*
  - *Number of correct answers on the Raven's SPM test.*
  - *Competence summary score from the CBCL.*
  - *Physical and psychosocial functioning summary score from the CHQ.*

- *Part II:*
  - *Change from baseline to the end of Part II (one-year OL-period) in the following:*
  - *Number of correct answers on the Raven's SPM test.*
  - *Competence summary score from the CBCL.*
  - *Physical and psychosocial functioning summary score from the CHQ.*

9.5 Summary Tables

Table 16: Enumeration of 4-17 year-old Patients in Pediatric ESL Studies and Adolescent Patients in Adult ESL Studies

Category/Study	PBO N	ESL N	Total Patients N
Pediatric Studies with ESL Exposure	**170**	**394**	**411**
BIA-2093-202	**-**	**28**	**28**
BIA-2093-208	**40**	**120**	**123**
BIA-2093-208 Part 1	40	83	123
BIA-2093-208 Part 2	-	112	112
BIA-2093-208 Part 3	-	42	42
BIA-2093-305[a]	**130**	**246**	**260**
BIA-2093-305 Part 1[a]	130	130	260
BIA-2093-305 Part 2[a]	-	225	225
BIA-2093-305 Part 3[a]	-	135	135
BIA-2093-305 Part 4[a]	-	78	78
BIA-2093-305 Part 5[a]	-	55	55
BIA-2093-305 Parts 4-5 Ongoing[b]	-	13	13
Double-blind Controlled Study Pool (Safety Population)[c]: Studies BIA-2093-208 Part 1 and BIA-2093-305 Part 1	160	202	362
One-year Open-label Uncontrolled Study Pool (Safety Population)[c]: Studies BIA-2093-208 Part 2 and BIA-2093-305 Part 2	-	337	337
Post One-year Open-label Uncontrolled Study Pool (Safety Population)[c]: Studies BIA-2093-208 Part 3 and BIA-2093-305 Parts 3-5	-	177	177
Combined Controlled and Uncontrolled Study Pool (ESL Safety Population)[c]: Studies BIA-2093-202, BIA-2093-208 Parts 1-3, and BIA-2093-305 Parts 1-5	-	393	393
Total Uncontrolled Study Pool: Studies BIA-2093-202, BIA-2093-208 Parts 2-3, and BIA-2093-305 Parts 2-5 (not defined by sponsor)		365	365
Adolescent (16-17 year-old) Subjects in Adult Studies	**5**	**24**	**29**
093-045/-046/-050	**-**	**13**	**13**
BIA-2093-304	**5**	**10**	**15**
BIA-2093-304 Part 1	5	10	15
BIA-2093-304 Part 2	-	13	13
BIA-2093-304 Part 3	-	8	8
BIA-2093-311 Double-blind + Extension	**-**	**1**[d]	**1**[d]

Source: ISS, Table 2

a *For Study BIA-2093-305, all data obtained for the CSR data cut on 16 June 2014 were included. Study BIA-2093-305 IMP recall subjects are counted…13 subjects were ongoing in Part 4 as of the CSR cut-off date of 16 June 2014, and 7 subjects were ongoing in Part 5 as of 08 July 2016. In the ISS, Study BIA-2093-305 IMP recall subjects were not counted in the double-blind controlled study pool, but were counted in the respective analysis populations of the remaining study pools, as applicable (see Statistical Analysis Plan Section 6 for details). In the CSR, IMP recall subjects in Stratum 1 (2-6 year age group) who took study medication before withdrawal of ESL oral suspension study medication from clinical sites due to stability issues were excluded from the safety population and safety analyses were performed separately and in combination with the safety population. This subject (2093-311-3104-048) was 17 years-old at the randomization visit of 07 October 2013 (birthdate* (b) (6) (b) (6) *) (data on file at Sunovion).*

Table 17: Subject Disposition by Weight Category for the Double-Blind Controlled Study Pool (ages 4-17)

		Study 208		Study 305		Total	
Body Weight	**Parameter**	**PBO n (%)**	**ESL n (%)**	**PBO n (%)**	**ESL n (%)**	**PBO n (%)**	**ESL n (%)**
11-21 kg	**N**	**3**	**3**	**23**	**20**	**26**	**23**
	Number of Patients who completed the DB Period	3 (100.0)	2 (66.7)	19 (82.6)	18 (90.0)	22 (84.6)	20 (87.0)
	Number of Patients who discontinued during the DB Period	0	1 (33.3)	4 (17.4)	2 (10.0)	4 (15.4)	3 (13.0)
	Primary Reason for Discontinuation						
	Adverse event	0	1 (33.3)	0	1 (5.0)	0	2 (8.7)
	Withdrawal of consent	0	0	2 (8.7)	0	2 (7.7)	0
	Administrative reasons	0	0	1 (4.3)	0	1 (3.8)	0
	Other	0	0	1 (4.3)	1 (5.0)	1 (3.8)	1 (4.3)
22-31 kg	**N**	**1**	**16**	**31**	**26**	**32**	**42**
	Number of Patients who completed the DB Period	1 (100.0)	13 (81.3)	28 (90.3)	21 (80.8)	29 (90.6)	34 (81.0)
	Number of Patients who discontinued during the DB Period	0	3 (18.8)	3 (9.7)	5 (19.2)	3 (9.4)	8 (19.0)
	Primary Reason for Discontinuation						
	Adverse event	0	1 (6.3)	0	2 (7.7)	0	3 (7.1)
	Withdrawal of consent	0	1 (6.3)	1 (3.2)	2 (7.7)	1 (3.1)	3 (7.1)
	Administrative reasons	0	0	0	1 (3.8)	0	1 (2.4)
	Other	0	0	1 (3.2)	0	1 (3.1)	0
	Lack of compliance	0	1 (6.3)	0	0	0	1 (2.4)
	Exacerbation of seizures	0	0	1 (3.2)	0	1 (3.1)	0
32-38 kg	**N**	**6**	**14**	**21**	**11**	**27**	**25**
	Number of Patients who Completed the DB Period	6 (100.0)	14 (100.0)	21 (100.0)	9 (81.8)	27 (100.0)	23 (92.0)
	Number of Patients who discontinued during the DB Period	0	0	0	2 (18.2)	0	2 (8.0)
	Primary Reason for Discontinuation						
	Adverse event	0	0	0	1 (9.1)	0	1 (4.0)
	Disallowed concomitant medication	0	0	0	1 (9.1)	0	1 (4.0)
>38 kg	**N**	**30**	**49**	**45**	**62**	**75**	**111**
	Number of Patients who completed the DB Period	27 (90.0)	45 (91.8)	42 (93.3)	59 (95.2)	69 (92.0)	104 (93.7)
	Number of Patients who discontinued during the DB Period	3 (10.0)	4 (8.2)	3 (6.7)	3 (4.8)	6 (8.0)	7 (6.3)
	Primary Reason for Discontinuation						
	Adverse event	0	3 (6.1)	0	0	0	3 (2.7)
	Withdrawal of consent	1 (3.3)	1 (2.0)	2 (4.4)	1 (1.6)	3 (4.0)	2 (1.8)
	Administrative reasons	0	0	1 (2.2)	1 (1.6)	1 (1.3)	1 (0.9)
	Other	1 (3.3)	0	0	1 (1.6)	1 (1.3)	1 (0.9)
	Lack of compliance	1 (3.3)	0	0	0	1 (1.3)	0

Source: ISS, Table 15, verified

Table 18: Brief Summary of Treatment-emergent Adverse Events by Age Group for the Double-blind Controlled Study Pool (Safety Population)

Age Group	Parameter	Total	
		PBO n (%)	ESL n (%)
4 to 6 years	N	29	23
	Subjects with any TEAE	24 (82.8)	18 (78.3)
	Serious TEAE	1 (3.4)	4 (17.4)
	Discontinued Due to TEAE	2 (6.9)	2 (8.7)
7 to 11 years	N	65	84
	Subjects with any TEAE	41 (63.1)	63 (75.0)
	Serious TEAE	1 (1.5)	7 (8.3)
	Discontinued Due to TEAE	1 (1.5)	8 (9.5)
12 to 17 years	N	66	95
	Subjects with any TEAE	40 (60.6)	56 (58.9)
	Serious TEAE	6 (9.1)	9 (9.5)
	Discontinued Due to TEAE	1 (1.5)	2 (2.1)

Source: JMP ADAE

Table 19: TEAEs Resulting in Discontinuation by Weight Category for the Double-blind Controlled Study Pool (Ages 4-17)

Weight Group	MedDRA version 13.1 System Organ Class / Preferred Term	Study 208, Part 1		Study 305, Part 1		Total	
		PBO n (%)	ESL n (%)	PBO n (%)	ESL n (%)	PBO n (%)	ESL n (%)
All Weight Groups	N	40	83	120	119	160	202
	Subjects with any TEAE Leading to Discontinuation	0	4 (4.8)	4 (4.3)	8 (6.7)	4 (2.5)	12 (5.9)
11 to 21 kg	N	3	3	23	20	26	23
	Subjects with any TEAE Leading to Discontinuation	0	0	2 (8.7)	1 (5.0)	2 (7.7)	1 (4.3)
22 to 31 kg	N	1	16	31	26	32	42
	Subjects with any TEAE Leading to Discontinuation	0	1 (6.3)	1 (3.2)	4 (15.4)	1 (3.1)	5 (11.9)
32 to 38 kg	N	6	14	21	11	27	25
	Subjects with any TEAE Leading to Discontinuation	0	0	0	1 (9.1)	0	1 (4.0)

Source: ISS, Tables 88 and 7.1.13.1.1 (verified in JMP)

Table 20: Listing of Treatment-emergent Hypothyroidism Medically-significant Events

Category/ Subject Number	Age (years)/ Gender/Weight (kg)	Double-blind Treatment	Study Part	MedDRA version 13.1 Preferred Term	Event Start Day	Serious/ Resulted in D/C	Treatment Given in Response to Event	Outcome	Comment
2093-208-505-07	6/M/21	PBO*	1	Hypothyroidism	87	No/No	Yes	Ongoing	On Study Day 87 (Placebo), mild hypothyroidism was identified. TSH at the time was 6 µIU/mL (ULN 4.2). He was treated with levothyroxine 25 µg QD. The hypothyroidism event was considered resolved on Study Day 312; however, his TSH remained elevated. The event of hypothyroidism was considered as not related to the study drug by the Investigator.
2093-305-131-04	8/M/30	PBO	2	Hypothyroidism	410	No/No	Yes	Ongoing	The patient had intermittently low free T4 levels while on ESL with intermittently elevated TSH. Thyroxine was started ~day 400. He discontinued from the study due to lack of efficacy on day 758.
2093-305-135-05	15/F/49	ESL	3, 4, 5	Hypothyroidism	584	No/No	Yes	Ongoing	On Study/ESL Day 584, the patient was diagnosed with "moderate" hypothyroidism. At baseline, free T3 was at the LLN (2.54 pg/mL; LLN 2.54) with free T4 near the LLN (0.98 ng/dL; LLN 0.93) and normal TSH. Free T3 and free T4 were intermittently low during subsequent visits with persistently normal TSH. The patient was treated with levothyroxine 25 µg oral QD. All subsequent TFTs were normal. The event of hypothyroidism was considered ongoing and was considered not related to the study drug by the Investigator. He discontinued the study when he turned 18 and switched to Zebinix.
2093-305-172-02	13/F/47	ESL*	1	Hypothyroidism	1	No/No	Yes	Ongoing	On Study Day 1 (pre-treatment), the patient was identified as having hypothyroidism. At the screening visit, free T3 was normal, free T4 was low (0.79 ng/dL, LLN 0.93 ng/dL) and TSH was elevated (4.33 µIU/mL, ULN 4.2 µIU/mL). She was started on levothyroxine started on day 139. No action was taken with the study drug.

Category/ Subject Number	Age (years)/ Gender/Weight (kg)	Double-blind Treatment	Study Part	MedDRA version 13.1 Preferred Term	Event Start Day	Serious/ Resulted in D/C	Treatment Given in Response to Event	Outcome	Comment
									The hypothyroidism was considered as ongoing at the time of study discontinuation, though all thyroid tests were within normal limits. The event of hypothyroidism was considered not related to the study drug by the Investigator. Patient discontinued from the study due to increased seizure frequency (day 202).
2093-305-184-05	5/M/23	PBO	2	Hypothyroidism	197	No/No	Yes	Ongoing	On Study Day 197 (ESL Day 28), patient was diagnosed with hypothyroidism and was treated with levothyroxine 12.50 µg then 25 µg orally QD. The event of hypothyroidism was ongoing and considered as unlikely related to the study drug by the investigator. The patient developed decreased free T4 (0.875) and elevated TSH on study day 169. His free T4 remained low throughout the rest of the study. His TSH initially remained elevated (maximum 7.73 on day 337), but normalized on day 512. Concomitant drugs: VPA, TPM
2093-305-184-06	12/F/42	ESL	3, 4, 5	Hypothyroidism	1107	No/No	Yes	Ongoing	On Study/ESL Day 1107, the patient was diagnosed with hypothyroidism. No action was taken with the study drug. The free T3, free T4 and TSH were normal at study entry (4.36 pg/ml, 1.29 ng/dL, and 3.82 uIU/mL) respectively; free T4's were lower while taking ESL compared to baseline and were below normal range for the first time at the week 6 visit (0.81 ng/dL, LLN 0.93 ng/dL), with minimal elevation in TSH at that time (4.50 uIU/mL, ULN 4.2 uIU/mL). Free T4 remained near the LLN. On study day 1107, free T4 was 0.87 ng/dL, and TSH was 5.10 uIU/mL (maximum recorded TSH). He was treated with levothyroxine 37.5 µg QD. TSH returned to below ULN by day 1387. The event of hypothyroidism was reported as

Category/ Subject Number	Age (years)/ Gender/Weight (kg)	Double-blind Treatment	Study Part	MedDRA version 13.1 Preferred Term	Event Start Day	Serious/ Resulted in D/C	Treatment Given in Response to Event	Outcome	Comment
									ongoing and was considered not related to study drug by the Investigator. Concomitant drugs: VPA
2093-305-223-05	8/F/33.5	ESL*	1	Hypothyroidism	74	No/No	Yes	Ongoing	Baseline TSH was elevated (7.45, ULN 4.20), but free T3 and T4 were normal. She presented on study/ESL Day 74 with hypothyroidism. On Study day 48, her TSH was 7.07 and her free T4 was 0.875 (LLN 0.93). Her T3 levels remained normal throughout the study, but her free T4 levels fluctuated between low and normal. She was treated with levothyroxine 25 µg orally TIW. She was discontinued from the study at the "request of the sponsor" unclear if related to the hypothyroidism. Concomitant drugs: VPA, CLB
2093-305-261-01	10/M/35	PBO	2	Hypothyroidism	212	No/No	No	Ongoing	On study day 212 (ESL day 29), he presented with low free T4 (0.806, nl 0.93-1.69) and increased TSH (5.32, nl 0.27-4.2). He continued on ESL without change in dose or thyroid replacement. D/C'd from study on Study Day 1023 (free T4 low, but normal TSH) due to withdrawal of consent.

Source: ISS, Tables 111, 7.5.4 and narratives

Table 21: Thyroid Parameter Mean Changes from Baseline to Lowest/Highest On-treatment Values for the Controlled Study Pool (4-17 year-olds)

	Study 208		Study 305		Combined	
Parameter (Unit) Variable Statistic	PBO N = 40	ESL N = 83	PBO N = 120	ESL N = 119	PBO N = 160	ESL N = 202
Free T3 (pg/mL): Change from Baseline to Lowest On-Treatment Value						
n	37	77	114	110	151	187
Mean (SD)	-0.076 (0.6788)	-0.374 (0.5904)	-0.230 (0.6453)	-0.517 (0.5462)	-0.192 (0.6548)	-0.458 (0.5677)
Median	-0.050	-0.350	-0.195	-0.456	-0.195	-0.410
Min, Max	-1.98, 1.63	-1.76, 1.58	-4.62, 1.04	-1.89, 0.78	-4.62, 1.63	-1.89, 1.58
Free T4 (ng/dL): Change from Baseline to Lowest On-Treatment Value						
n	37	77	114	110	151	187
Mean (SD)	-0.018 (0.1533)	-0.156 (0.2056)	-0.066 (0.1246)	-0.241 (0.1607)	-0.054 (0.1333)	-0.206 (0.1849)
Median	-0.010	-0.160	-0.054	-0.236	-0.040	-0.210
Min, Max	-0.33, 0.31	-0.72, 0.38	-0.42, 0.22	-0.61, 0.26	-0.42, 0.31	-0.72, 0.38
TSH (uIU/mL):Change from Baseline to Highest On-Treatment Value						
n	37	77	113	110	150	187
Mean (SD)	-0.152 (1.3966)	0.157 (1.6668)	0.355 (1.5122)	0.459 (1.6220)	0.230 (1.4961)	0.335 (1.6429)
Median	-0.260	0.140	0.320	0.310	0.255	0.250
Min, Max	-2.62, 4.66	-4.68, 7.82	-3.96, 6.97	-7.28, 7.24	-3.96, 6.97	-7.28, 7.82

Source: ISS Table 9.1.3.1

Table 22: Thyroid Parameter Shifts from Baseline to the Lowest/Highest On-treatment Values for the Double-blind Controlled Study Pool (4-17 year-olds)

Parameter (Unit) Variable Treatment Group	Baseline Value				
	Low n (%)	Normal n (%)	High n (%)	Missing n (%)	Total n (%)
Free T4 (ng/dL): Lowest On-Treatment Value					
STUDY 208 Part 1 PBO (N = 40)					
Low	3 (8.1)	2 (5.4)	0	0	5 (13.5)
Normal	4 (10.8)	28 (75.7)	0	0	32 (86.5)
High	0	0	0	0	0
Total	7 (18.9)	30 (81.1)	0	0	37 (100.0)
STUDY 208 Part 1 ESL (N = 83)					
Low	9 (11.7)	21 (27.3)	0	0	30 (39.0)
Normal	3 (3.9)	44 (57.1)	0	0	47 (61.0)
High	0	0	0	0	0
Total	12 (15.6)	65 (84.4)	0	0	77 (100.0)
STUDY 305 Part 1 PBO (N = 120)					
Low	11 (9.4)	9 (7.7)	0	0	20 (17.1)
Normal	3 (2.6)	87 (74.4)	3 (2.6)	3 (2.6)	96 (82.1)
High	0	0	1 (0.9)	0	1 (0.9)
Total	14 (12.0)	96 (82.1)	4 (3.4)	3 (2.6)	117 (100.0)
STUDY 305 Part 1 ESL (N = 119)					
Low	10 (8.8)	56 (49.1)	2 (1.8)	2 (1.8)	70 (61.4)
Normal	1 (0.9)	38 (33.3)	3 (2.6)	2 (1.8)	44 (38.6)
High	0	0	0	0	0
Total	11 (9.6)	94 (82.5)	5 (4.4)	4 (3.5)	114 (100.0)

Parameter (Unit) Variable Treatment Group	Baseline Value				
	Low n (%)	Normal n (%)	High n (%)	Missing n (%)	Total n (%)
Total PBO (N = 160)					
Low	14 (9.1)	11 (7.1)	0	0	25 (16.2)
Normal	7 (4.5)	115 (74.7)	3 (1.9)	3 (1.9)	128 (83.1)
High	0	0	1 (0.6)	0	1 (0.6)
Total	21 (13.6)	126 (81.8)	4 (2.6)	3 (1.9)	154 (100.0)
Total ESL (N = 202)					
Low	19 (9.9)	77 (40.3)	2 (1.0)	2 (1.0)	100 (52.4)
Normal	4 (2.1)	82 (42.9)	3 (1.6)	2 (1.0)	91 (47.6)
High	0	0	0	0	0
Total	23 (12.0)	159 (83.2)	5 (2.6)	4 (2.1)	191 (100.0)
TSH (uIU/mL): Highest On-Treatment Value					
STUDY 208 Part 1 PBO (N = 40)					
Low	0	0	0	0	0
Normal	0	21 (56.8)	6 (16.2)	0	27 (73.0)
High	0	6 (16.2)	4 (10.8)	0	10 (27.0)
Total	0	27 (73.0)	10 (27.0)	0	37 (100.0)
STUDY 208 Part 1 ESL (N = 83)					
Low	0	0	0	0	0
Normal	0	49 (63.6)	8 (10.4)	0	57 (74.0)
High	0	8 (10.4)	12 (15.6)	0	20 (26.0)
Total	0	57 (74.0)	20 (26.0)	0	77 (100.0)
STUDY 305 Part 1 PBO (N = 120)					
Low	0	0	0	0	0
Normal	0	78 (66.7)	7 (6.0)	4 (3.4)	89 (76.1)
High	0	10 (8.5)	18 (15.4)	0	28 (23.9)
Total	0	88 (75.2)	25 (21.4)	4 (3.4)	117 (100.0)
STUDY 305 Part 1 ESL (N = 119)					
Low	0	0	0	0	0
Normal	0	70 (61.4)	3 (2.6)	4 (3.5)	77 (67.5)
High	0	16 (14.0)	21 (18.4)	0	37 (32.5)
Total	0	86 (75.4)	24 (21.1)	4 (3.5)	114 (100.0)
Total PBO (N = 160)					
Low	0	0	0	0	0
Normal	0	99 (64.3)	13 (8.4)	4 (2.6)	116 (75.3)
High	0	16 (10.4)	22 (14.3)	0	38 (24.7)
Total	0	115 (74.7)	35 (22.7)	4 (2.6)	154 (100.0)
Total ESL (N = 202)					
Low	0	0	0	0	0
Normal	0	119 (62.3)	11 (5.8)	4 (2.1)	134 (70.2)
High	0	24 (12.6)	33 (17.3)	0	57 (29.8)
Total	0	143 (74.9)	44 (23.0)	4 (2.1)	191 (100.0)

Source: modified from ISS Table 122

Table 23: TEAEs Reported by ≥ 5.0% of Patients in Any Study Pool (4-17 year-olds)

Study Pool	Double-blind Controlled[a]		One-year Open-label Uncontrolled	Post One-year Open-Label Uncontrolled	Combined Controlled and Uncontrolled[b]
MedDRA version 13.1 System Organ Class / Preferred Term	Total PBON = 160n (%)	Total ESL N = 202 n (%)	Total ESLN = 337n (%)	Total ESLN = 177n (%)	Total ESLN = 393n (%)
Subjects with any TEAE	**105 (65.6)**	**137 (67.8)**	**216 (64.1)**	**93 (52.5)**	**302 (76.8)**
Eye disorders	**3 (1.9)**	**19 (9.4)**	**23 (6.8)**	**3 (1.7)**	**42 (10.7)**
Diplopia	2 (1.3)	13 (6.4)	15 (4.5)	2 (1.1)	28 (7.1)
Gastrointestinal Disorders	**24 (15.0)**	**38 (18.8)**	**52 (15.4)**	**27 (15.3)**	**97 (24.7)**
Vomiting	8 (5.0)	16 (7.9)	32 (9.5)	12 (6.8)	57 (14.5)
Diarrhoea	4 (2.5)	3 (1.5)	8 (2.4)	10 (5.6)	20 (5.1)
Nausea	3 (1.9)	10 (5.0)	9 (2.7)	1 (0.6)	20 (5.1)
General Disorders and Administration Site Conditions	**22 (13.8)**	**32 (15.8)**	**54 (16.0)**	**20 (11.3)**	**86 (21.9)**
Pyrexia	14 (8.8)	15 (7.4)	29 (8.6)	16 (9.0)	51 (13.0)
Infections and Infestations	**59 (36.9)**	**67 (33.2)**	**137 (40.7)**	**57 (32.2)**	**189 (48.1)**
Nasopharyngitis	16 (10.0)	15 (7.4)	34 (10.1)	15 (8.5)	48 (12.2)
Pharyngitis	10 (6.3)	9 (4.5)	14 (4.2)	9 (5.1)	28 (7.1)
Bronchitis	8 (5.0)	6 (3.0)	14 (4.2)	10 (5.6)	27 (6.9)
Respiratory tract infection	8 (5.0)	11 (5.4)	17 (5.0)	4 (2.3)	24 (6.1)
Rhinitis	8 (5.0)	4 (2.0)	12 (3.6)	11 (6.2)	24 (6.1)
Upper respiratory tract infection	4 (2.5)	5 (2.5)	7 (2.1)	10 (5.6)	23 (5.9)
Viral infection	4 (2.5)	5 (2.5)	12 (3.6)	7 (4.0)	23 (5.9)
Nervous System Disorders	**46 (28.8)**	**73 (36.1)**	**97 (28.8)**	**35 (19.8)**	**169 (43.0)**
Headache	18 (11.3)	28 (13.9)	27 (8.0)	14 (7.9)	57 (14.5)
Partial seizures	14 (8.8)	15 (7.4)	34 (10.1)	19 (10.7)	54 (13.7)
Somnolence	8 (5.0)	19 (9.4)	23 (6.8)	2 (1.1)	49 (12.5)
Dizziness	4 (2.5)	9 (4.5)	10 (3.0)	2 (1.1)	21 (5.3)

[a] Study BIA-2093-305 IMP recall subjects were not included.
[b] TEAEs that occurred since the first dose of ESL in Studies BIA-2093-202, BIA-2093-208, and BIA-2093-305 were included in the analysis. For Study BIA-2093-305 IMP recall subjects, TEAEs that occurred in Part 1 of the study were excluded from the analysis.
Source: ISS, Table 55, verified with JMP

Table 24: All TEAEs Reported in the Double-blind Controlled Study Pool (ages 4-17)

MedDRA version 13.1 Preferred Term or Laboratory Criteria	Total PBO (N = 160)		Total ESL (N = 202)	
	n	%	n	%
Headache	18	11.3%	28	13.9%
Somnolence	8	5.0%	19	9.4%
Nasopharyngitis	16	10.0%	16	7.9%
Vomiting	8	5.0%	16	7.9%
Partial Seizures	14	8.8%	15	7.4%
Pyrexia	14	8.8%	15	7.4%
Diplopia	2	1.3%	13	6.4%
Respiratory Tract Infection	8	5.0%	11	5.4%

MedDRA version 13.1 Preferred Term or Laboratory Criteria	Total PBO (N = 160)		Total ESL (N = 202)	
	n	%	n	%
Decreased Appetite	1	0.6%	10	5.0%
Nausea	3	1.9%	10	5.0%
Dizziness	5	3.1%	9	4.5%
Pharyngitis	10	6.3%	9	4.5%
Fatigue	3	1.9%	7	3.5%
Bronchitis	8	5.0%	6	3.0%
Dermatitis Allergic	1	0.6%	6	3.0%
Vertigo	0	0.0%	6	3.0%
Weight Increased	3	1.9%	6	3.0%
Agitation	1	0.6%	5	2.5%
Convulsion	1	0.6%	5	2.5%
Upper Respiratory Tract Infection	4	2.5%	5	2.5%
Viral Infection	4	2.5%	5	2.5%
Viral Upper Respiratory Tract Infection	3	1.9%	5	2.5%
Abdominal Pain	6	3.8%	4	2.0%
Abdominal Pain Upper	0	0.0%	4	2.0%
Influenza	1	0.6%	4	2.0%
Lymphadenopathy	1	0.6%	4	2.0%
Pneumonia	4	2.5%	4	2.0%
Rash	5	3.1%	4	2.0%
Respiratory Tract Infection Viral	3	1.9%	4	2.0%
Rhinitis	8	5.0%	4	2.0%
Status Epilepticus	1	0.6%	4	2.0%
Abnormal Behaviour	0	0.0%	3	1.5%
Asthenia	1	0.6%	3	1.5%
Ataxia	1	0.6%	3	1.5%
Blood Lactate Dehydrogenase Increased	0	0.0%	3	1.5%
Blood Thyroid Stimulating Hormone Increased	2	1.3%	3	1.5%
Cough	7	4.4%	3	1.5%
Diabetes Mellitus	0	0.0%	3	1.5%
Diarrhoea	4	2.5%	3	1.5%
Electroencephalogram Abnormal	1	0.6%	3	1.5%
Epilepsy	2	1.3%	3	1.5%
Increased Appetite	0	0.0%	3	1.5%
Neutropenia	0	0.0%	3	1.5%
Oropharyngeal Pain	2	1.3%	3	1.5%
Partial Seizures With Secondary Generalisation	0	0.0%	3	1.5%
Tremor	2	1.3%	3	1.5%
Alanine Aminotransferase Increased	1	0.6%	2	1.0%
Anaemia	0	0.0%	2	1.0%
Anxiety	1	0.6%	2	1.0%
Arthralgia	1	0.6%	2	1.0%
Aspartate Aminotransferase Increased	1	0.6%	2	1.0%
Blood Calcium Decreased	0	0.0%	2	1.0%
Bronchopneumonia	0	0.0%	2	1.0%
Constipation	1	0.6%	2	1.0%
Contusion	1	0.6%	2	1.0%
Coordination Abnormal	1	0.6%	2	1.0%
Cystitis	1	0.6%	2	1.0%
Enuresis	0	0.0%	2	1.0%
Food Poisoning	1	0.6%	2	1.0%

MedDRA version 13.1 Preferred Term or Laboratory Criteria	Total PBO (N = 160)		Total ESL (N = 202)	
	n	%	n	%
Gait Disturbance	1	0.6%	2	1.0%
Gamma-Glutamyltransferase Increased	1	0.6%	2	1.0%
Gastritis	1	0.6%	2	1.0%
Gastroenteritis	1	0.6%	2	1.0%
Hyperthermia	1	0.6%	2	1.0%
Hypothyroidism	1	0.6%	2	1.0%
Insomnia	4	2.5%	2	1.0%
Intracranial Pressure Increased	0	0.0%	2	1.0%
Irritability	1	0.6%	2	1.0%
Mental Retardation	1	0.6%	2	1.0%
Mood Swings	0	0.0%	2	1.0%
Obesity	1	0.6%	2	1.0%
Oedema	0	0.0%	2	1.0%
Oral Herpes	0	0.0%	2	1.0%
Pharyngotonsillitis	1	0.6%	2	1.0%
Platelet Count Decreased	1	0.6%	2	1.0%
Post-Traumatic Pain	0	0.0%	2	1.0%
Renal Aplasia	0	0.0%	2	1.0%
Salivary Hypersecretion	0	0.0%	2	1.0%
Seasonal Allergy	0	0.0%	2	1.0%
Tachycardia	0	0.0%	2	1.0%
Tonsillitis	3	1.9%	2	1.0%
Unresponsive To Stimuli	1	0.6%	2	1.0%
Urine Analysis Abnormal	1	0.6%	2	1.0%
Varicella	3	1.9%	2	1.0%
Abdominal Abscess	0	0.0%	1	0.5%
Abdominal Distension	0	0.0%	1	0.5%
Acidosis	0	0.0%	1	0.5%
Acute Tonsillitis	1	0.6%	1	0.5%
Adenoidectomy	0	0.0%	1	0.5%
Aggression	0	0.0%	1	0.5%
Allergy To Arthropod Bite	0	0.0%	1	0.5%
Alopecia	2	1.3%	1	0.5%
Amnesia	0	0.0%	1	0.5%
Antibody Test Positive	0	0.0%	1	0.5%
Apnoeic Attack	0	0.0%	1	0.5%
Asthma	1	0.6%	1	0.5%
Atelectasis	0	0.0%	1	0.5%
Autoimmune Thyroiditis	0	0.0%	1	0.5%
Automatism	0	0.0%	1	0.5%
Balance Disorder	0	0.0%	1	0.5%
Basophil Count Decreased	0	0.0%	1	0.5%
Binocular Eye Movement Disorder	0	0.0%	1	0.5%
Blood Antidiuretic Hormone Decreased	0	0.0%	1	0.5%
Blood Bicarbonate Decreased	1	0.6%	1	0.5%
Blood Chloride Decreased	0	0.0%	1	0.5%
Blood Cholesterol Decreased	0	0.0%	1	0.5%
Blood Creatine Phosphokinase Increased	1	0.6%	1	0.5%
Blood Creatinine Abnormal	0	0.0%	1	0.5%
Blood Creatinine Decreased	0	0.0%	1	0.5%
Blood Fibrinogen Decreased	0	0.0%	1	0.5%

MedDRA version 13.1 Preferred Term or Laboratory Criteria	Total PBO (N = 160)		Total ESL (N = 202)	
	n	%	n	%
Blood Glucose Abnormal	0	0.0%	1	0.5%
Blood Immunoglobulin E Abnormal	0	0.0%	1	0.5%
Blood Osmolarity Decreased	0	0.0%	1	0.5%
Blood Pressure Increased	0	0.0%	1	0.5%
Blood Sodium Increased	0	0.0%	1	0.5%
Blood Triglycerides Increased	1	0.6%	1	0.5%
Blood Urea Increased	0	0.0%	1	0.5%
Body Temperature Increased	0	0.0%	1	0.5%
Bradyphrenia	0	0.0%	1	0.5%
Brain Herniation	0	0.0%	1	0.5%
Brain Malformation	0	0.0%	1	0.5%
Brain Oedema	0	0.0%	1	0.5%
Brain Stem Syndrome	0	0.0%	1	0.5%
Breath Sounds Abnormal	1	0.6%	1	0.5%
Bruxism	0	0.0%	1	0.5%
Bullous Impetigo	0	0.0%	1	0.5%
Candidiasis	0	0.0%	1	0.5%
Cardiac Arrest	0	0.0%	1	0.5%
Cardiac Murmur	0	0.0%	1	0.5%
Cerebral Ventricle Dilatation	0	0.0%	1	0.5%
Cerebrovascular Disorder	0	0.0%	1	0.5%
Chest Pain	0	0.0%	1	0.5%
Circulatory Collapse	0	0.0%	1	0.5%
Clonus	0	0.0%	1	0.5%
Coeliac Disease	0	0.0%	1	0.5%
Colitis Ulcerative	0	0.0%	1	0.5%
Colonic Polyp	0	0.0%	1	0.5%
Communication Disorder	0	0.0%	1	0.5%
Concussion	0	0.0%	1	0.5%
Condition Aggravated	0	0.0%	1	0.5%
Confusional State	0	0.0%	1	0.5%
Congestive Cardiomyopathy	0	0.0%	1	0.5%
Conjunctivitis	0	0.0%	1	0.5%
Coxsackie Virus Test Positive	0	0.0%	1	0.5%
C-Reactive Protein Increased	0	0.0%	1	0.5%
Cyanosis	0	0.0%	1	0.5%
Decreased Activity	0	0.0%	1	0.5%
Dermatitis	0	0.0%	1	0.5%
Dermatitis Contact	1	0.6%	1	0.5%
Device Malfunction	1	0.6%	1	0.5%
Diet Refusal	2	1.3%	1	0.5%
Drooling	0	0.0%	1	0.5%
Drug Rash With Eosinophilia And Systemic Symptoms	0	0.0%	1	0.5%
Drug Withdrawal Syndrome	0	0.0%	1	0.5%
Dry Skin	0	0.0%	1	0.5%
Dyslogia	0	0.0%	1	0.5%
Dyspepsia	0	0.0%	1	0.5%
Dysphagia	0	0.0%	1	0.5%
Dysthymic Disorder	0	0.0%	1	0.5%
Dysuria	0	0.0%	1	0.5%
Ear Infection	2	1.3%	1	0.5%

MedDRA version 13.1 Preferred Term or Laboratory Criteria	Total PBO (N = 160)		Total ESL (N = 202)	
	n	%	n	%
Ear Pain	0	0.0%	1	0.5%
Electrocardiogram PR Prolongation	0	0.0%	1	0.5%
Electrocardiogram QT Prolonged	0	0.0%	1	0.5%
Emphysema	0	0.0%	1	0.5%
Endocarditis Rheumatic	0	0.0%	1	0.5%
Enterovirus Infection	0	0.0%	1	0.5%
Enterovirus Test Positive	0	0.0%	1	0.5%
Eosinophil Count Decreased	0	0.0%	1	0.5%
Epistaxis	1	0.6%	1	0.5%
Epstein-Barr Virus Antibody Positive	0	0.0%	1	0.5%
Erythema	1	0.6%	1	0.5%
Excoriation	0	0.0%	1	0.5%
Eye Swelling	0	0.0%	1	0.5%
Fall	2	1.3%	1	0.5%
Febrile Infection	0	0.0%	1	0.5%
Feeling Abnormal	0	0.0%	1	0.5%
Feeling Hot	0	0.0%	1	0.5%
Fluid Intake Reduced	0	0.0%	1	0.5%
Gastric Disorder	0	0.0%	1	0.5%
Gastroduodenitis	1	0.6%	1	0.5%
Gastroenteritis Viral	0	0.0%	1	0.5%
Gastrointestinal Disorder	0	0.0%	1	0.5%
Genital Labial Operation	0	0.0%	1	0.5%
Goiter	0	0.0%	1	0.5%
Grand Mal Convulsion	0	0.0%	1	0.5%
Haematochezia	0	0.0%	1	0.5%
Haematocrit Increased	0	0.0%	1	0.5%
Haemoglobin Abnormal	0	0.0%	1	0.5%
Haemoglobin Decreased	0	0.0%	1	0.5%
Hand Fracture	2	1.3%	1	0.5%
Head Injury	1	0.6%	1	0.5%
Heart Sounds Abnormal	0	0.0%	1	0.5%
Helicobacter Infection	0	0.0%	1	0.5%
Helicobacter Test Positive	0	0.0%	1	0.5%
Hepatomegaly	1	0.6%	1	0.5%
Herpes Simplex	1	0.6%	1	0.5%
Hyperaemia	1	0.6%	1	0.5%
Hyperkalaemia	0	0.0%	1	0.5%
Hyperphagia	0	0.0%	1	0.5%
Hypokalaemia	0	0.0%	1	0.5%
Hypotonia	0	0.0%	1	0.5%
Inappropriate Affect	0	0.0%	1	0.5%
Inappropriate Antidiuretic Hormone Secretion	0	0.0%	1	0.5%
Infection	0	0.0%	1	0.5%
Infectious Mononucleosis	0	0.0%	1	0.5%
Inflammation Of Wound	0	0.0%	1	0.5%
Inflammatory Marker Increased	0	0.0%	1	0.5%
Initial Insomnia	0	0.0%	1	0.5%
Intention Tremor	1	0.6%	1	0.5%
Intraocular Pressure Test	0	0.0%	1	0.5%
Ischaemia	0	0.0%	1	0.5%

MedDRA version 13.1 Preferred Term or Laboratory Criteria	Total PBO (N = 160)		Total ESL (N = 202)	
	n	%	n	%
Joint Injury	0	0.0%	1	0.5%
Ketoacidosis	0	0.0%	1	0.5%
Ketonuria	0	0.0%	1	0.5%
Labia Enlarged	0	0.0%	1	0.5%
Lethargy	0	0.0%	1	0.5%
Limb Injury	0	0.0%	1	0.5%
Listless	0	0.0%	1	0.5%
Local Swelling	0	0.0%	1	0.5%
Loss Of Consciousness	2	1.3%	1	0.5%
Lung Infection	0	0.0%	1	0.5%
Lupus-Like Syndrome	0	0.0%	1	0.5%
Lymphocyte Count Decreased	0	0.0%	1	0.5%
Lymphocyte Count Increased	0	0.0%	1	0.5%
Lymphopenia	0	0.0%	1	0.5%
Macule	0	0.0%	1	0.5%
Medical Device Complication	0	0.0%	1	0.5%
Metrorrhagia	0	0.0%	1	0.5%
Migraine	0	0.0%	1	0.5%
Mitral Valve Incompetence	0	0.0%	1	0.5%
Mitral Valve Prolapse	0	0.0%	1	0.5%
Monocyte Count Abnormal	0	0.0%	1	0.5%
Monocyte Count Increased	0	0.0%	1	0.5%
Nasal Discomfort	0	0.0%	1	0.5%
Nervous System Disorder	0	0.0%	1	0.5%
Neutrophil Count Decreased	0	0.0%	1	0.5%
Neutrophilia	0	0.0%	1	0.5%
Nystagmus	0	0.0%	1	0.5%
Ocular Discomfort	0	0.0%	1	0.5%
Oedema Peripheral	0	0.0%	1	0.5%
Onychomadesis	0	0.0%	1	0.5%
Open Wound	0	0.0%	1	0.5%
Optic Atrophy	0	0.0%	1	0.5%
Otitis Externa	0	0.0%	1	0.5%
Otitis Media	1	0.6%	1	0.5%
Otitis Media Acute	0	0.0%	1	0.5%
Pachygyria	0	0.0%	1	0.5%
Pallor	2	1.3%	1	0.5%
Papilloma	0	0.0%	1	0.5%
Papilloma Excision	0	0.0%	1	0.5%
Petechiae	0	0.0%	1	0.5%
Phlebitis	0	0.0%	1	0.5%
Photodermatosis	0	0.0%	1	0.5%
Platelet Count Increased	0	0.0%	1	0.5%
Protein Total Decreased	0	0.0%	1	0.5%
Protein Total Increased	0	0.0%	1	0.5%
Prothrombin Time Prolonged	0	0.0%	1	0.5%
Pruritus	1	0.6%	1	0.5%
Rash Pruritic	0	0.0%	1	0.5%
Red Blood Cell Count Decreased	0	0.0%	1	0.5%
Respiratory Depression	0	0.0%	1	0.5%
Respiratory Disorder	0	0.0%	1	0.5%

MedDRA version 13.1 Preferred Term or Laboratory Criteria	Total PBO (N = 160)		Total ESL (N = 202)	
	n	%	n	%
Restlessness	1	0.6%	1	0.5%
Rheumatic Fever	0	0.0%	1	0.5%
Rheumatoid Factor Increased	0	0.0%	1	0.5%
Sebaceous Adenoma	0	0.0%	1	0.5%
Shunt Malfunction	0	0.0%	1	0.5%
Sinusitis	0	0.0%	1	0.5%
Skin Papilloma	0	0.0%	1	0.5%
Skin Ulcer	0	0.0%	1	0.5%
Skull Malformation	0	0.0%	1	0.5%
Sleep Talking	0	0.0%	1	0.5%
Strabismus	0	0.0%	1	0.5%
Streptococcal Infection	0	0.0%	1	0.5%
Streptococcus Test Positive	0	0.0%	1	0.5%
Stress	0	0.0%	1	0.5%
Thirst	0	0.0%	1	0.5%
Toothache	1	0.6%	1	0.5%
Tri-Iodothyronine Free Increased	0	0.0%	1	0.5%
Trismus	0	0.0%	1	0.5%
Type 1 Diabetes Mellitus	0	0.0%	1	0.5%
Urinary Incontinence	0	0.0%	1	0.5%
Urinary Tract Infection Bacterial	1	0.6%	1	0.5%
Vascular Purpura	0	0.0%	1	0.5%
Venous Insufficiency	0	0.0%	1	0.5%
Viral Pharyngitis	0	0.0%	1	0.5%
Vision Blurred	0	0.0%	1	0.5%
Visual Field Defect	0	0.0%	1	0.5%
Visual Impairment	0	0.0%	1	0.5%
Vitello-Intestinal Duct Remnant	0	0.0%	1	0.5%
White Blood Cell Count Increased	0	0.0%	1	0.5%
Wrist Fracture	0	0.0%	1	0.5%
Acute Sinusitis	2	1.3%	0	0.0%
Affective Disorder	1	0.6%	0	0.0%
Angina Pectoris	1	0.6%	0	0.0%
Apathy	1	0.6%	0	0.0%
Arthropod Bite	1	0.6%	0	0.0%
Asphyxia	1	0.6%	0	0.0%
Atrial Septal Defect	1	0.6%	0	0.0%
Back Pain	1	0.6%	0	0.0%
Biliary Dyskinesia	2	1.3%	0	0.0%
Breathing-Related Sleep Disorder	1	0.6%	0	0.0%
Cognitive Disorder	1	0.6%	0	0.0%
Cortical Dysplasia	1	0.6%	0	0.0%
CSF Shunt Operation	1	0.6%	0	0.0%
Deafness	1	0.6%	0	0.0%
Dehydration	1	0.6%	0	0.0%
Disturbance In Attention	1	0.6%	0	0.0%
Drug Ineffective	1	0.6%	0	0.0%
Drug Toxicity	1	0.6%	0	0.0%
Dyspnoea	1	0.6%	0	0.0%
Ear Haemorrhage	1	0.6%	0	0.0%
Ecchymosis	1	0.6%	0	0.0%

MedDRA version 13.1 Preferred Term or Laboratory Criteria	Total PBO (N = 160)		Total ESL (N = 202)	
	n	%	n	%
Electrocardiogram Low Voltage	1	0.6%	0	0.0%
Enteritis	1	0.6%	0	0.0%
Expressive Language Disorder	1	0.6%	0	0.0%
Face Injury	1	0.6%	0	0.0%
Flatulence	1	0.6%	0	0.0%
Fluid Retention	1	0.6%	0	0.0%
Frequent Bowel Movements	1	0.6%	0	0.0%
Gingivitis	1	0.6%	0	0.0%
Haematocrit Abnormal	1	0.6%	0	0.0%
Haematoma	1	0.6%	0	0.0%
Heat Rash	1	0.6%	0	0.0%
Herpes Zoster	1	0.6%	0	0.0%
Hypersomnia	1	0.6%	0	0.0%
Hypoxia	1	0.6%	0	0.0%
Increased Upper Airway Secretion	1	0.6%	0	0.0%
Irritable Bowel Syndrome	1	0.6%	0	0.0%
Joint Dislocation	1	0.6%	0	0.0%
Joint Sprain	1	0.6%	0	0.0%
Lip Injury	1	0.6%	0	0.0%
Liver Disorder	1	0.6%	0	0.0%
Medical Device Change	1	0.6%	0	0.0%
Metabolic Syndrome	1	0.6%	0	0.0%
Muscle Tightness	1	0.6%	0	0.0%
Mydriasis	1	0.6%	0	0.0%
Nephropathy	1	0.6%	0	0.0%
Nervousness	1	0.6%	0	0.0%
Onychomycosis	1	0.6%	0	0.0%
Oral Pain	1	0.6%	0	0.0%
Oxygen Saturation Decreased	1	0.6%	0	0.0%
Pain	1	0.6%	0	0.0%
Pain In Extremity	2	1.3%	0	0.0%
Peripheral Coldness	1	0.6%	0	0.0%
Pleural Effusion	1	0.6%	0	0.0%
Polycystic Ovaries	1	0.6%	0	0.0%
Postictal State	1	0.6%	0	0.0%
Psychomotor Hyperactivity	2	1.3%	0	0.0%
Red Blood Cell Sedimentation Rate Abnormal	1	0.6%	0	0.0%
Rhinitis Allergic	1	0.6%	0	0.0%
Rhinorrhoea	3	1.9%	0	0.0%
Scratch	1	0.6%	0	0.0%
Skin Striae	1	0.6%	0	0.0%
Syncope	1	0.6%	0	0.0%
Tinea Infection	1	0.6%	0	0.0%
Tinnitus	1	0.6%	0	0.0%
Tonsillar Inflammation	1	0.6%	0	0.0%
Tracheitis	1	0.6%	0	0.0%
Transaminases Increased	1	0.6%	0	0.0%
Tympanic Membrane Perforation	1	0.6%	0	0.0%
Upper Airway Obstruction	1	0.6%	0	0.0%
Urinary Tract Infection	1	0.6%	0	0.0%
Urine Uric Acid Abnormal	1	0.6%	0	0.0%

MedDRA version 13.1 Preferred Term or Laboratory Criteria	Total PBO (N = 160)		Total ESL (N = 202)	
	n	%	n	%
Weight Decreased	1	0.6%	0	0.0%
White Blood Cells Urine	1	0.6%	0	0.0%

Source: JMP ADAE

Table 25: TEAEs Reported by ≥ 2.0% of Subjects in the 1-Year Uncontrolled Study Pool (4-17 year-olds)

MedDRA version 13.1 System Organ Class / Preferred Term	Total ESL N = 337 n (%)
Subjects with any TEAE	**216 (64.1)**
Ear and Labyrinth Disorders	**9 (2.7)**
Vertigo	7 (2.1)
Eye Disorders	**23 (6.8)**
Diplopia	15 (4.5)
Gastrointestinal Disorders	**52 (15.4)**
Vomiting	32 (9.5)
Nausea	9 (2.7)
Abdominal pain	8 (2.4)
Diarrhea	8 (2.4)
General Disorders and Administration Site Conditions	**54 (16.0)**
Pyrexia	29 (8.6)
Fatigue	8 (2.4)
Infections and Infestations	**137 (40.7)**
Nasopharyngitis	34 (10.1)
Respiratory tract infection	17 (5.0)
Bronchitis	14 (4.2)
Pharyngitis	14 (4.2)
Rhinitis	12 (3.6)
Viral infection	12 (3.6)
Respiratory tract infection viral	10 (3.0)
Ear infection	8 (2.4)
Gastroenteritis	8 (2.4)
Acute tonsillitis	7 (2.1)
Influenza	7 (2.1)
Upper respiratory tract infection	7 (2.1)
Injury, Poisoning and Procedural Complications	**26 (7.7)**
Fall	7 (2.1)
Investigations	**38 (11.3)**
Gamma-glutamyltransferase increased	9 (2.7)
Nervous System Disorders	**97 (28.8)**
Partial seizures	34 (10.1)
Headache	27 (8.0)
Somnolence	23 (6.8)
Dizziness	10 (3.0)
Convulsion	8 (2.4)
Respiratory, Thoracic and Mediastinal Disorders	**21 (6.2)**
Cough	9 (2.7)

Source: ISS, Table 61, verified by JMP

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/s/

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