



**ESLICARBAZEPINE ACETATE  
STUDY NO. 093-050  
PROTOCOL AMENDMENT HISTORY**

**LONG-TERM ESLICARBAZEPINE ACETATE EXTENSION STUDY**

**IND No. 67,466**

**EudraCT No. 2010-019000-22**

15 November 2013

Original Protocol Version 1.0 (24 Sep 2008)  
Amendment No.1, Protocol Version 2.0 (16 Apr 2009)  
Amendment No. 2, Protocol Version 3.0 (24 Jul 2009)  
Non-substantial Amendment No. 1 (22 Apr 2010)  
Amendment No. 3, Protocol Version 4.0 (09 Jun 2010)  
Amendment No. 4, Protocol Version 5.0 (17 Aug 2010)  
Czech Republic-specific Amendment No. 1 (16 Nov 2010)  
Non-substantial Amendment No. 2 (12 Dec 2011)  
Non-substantial Amendment No. 3 (03 Dec 2012)  
Amendment No. 5, Protocol Version 6.0 (07 Jun 2013)  
Non-substantial Amendment No. 4 (15 Nov 2013)

## 1. SUMMARY OF AMENDMENT HISTORY

The original protocol (Version 1.0), dated 24 Sep 2008, was globally amended 5 times. There was also 1 country-specific amendment for the Czech Republic and 4 non-substantial amendments (administrative letters). Brief summaries of the changes are outlined in the sections below.

A country-specific amendment for Russia was also developed; this amendment is not included in this document or the clinical study report as the study was never conducted in Russia.

## 2. AMENDMENT 1, PROTOCOL VERSION 2.0 (16 APRIL 2009)

FDA feedback received from a Special Protocol Assessment (SPA) request necessitated an amendment to Protocol 093-045 version 1.0 (25 July 2008). Based on amended Protocol 093-045, version 2.0 (04 March 2009) the following changes were made to the protocol:

- Throughout the text, new wording “not well controlled by” replaced the previous wording “unresponsive to” so as not to confuse subjects enrolled in the present study with patients who have become refractory to other AEDs.
- Allowance of lorazepam, other benzodiazepines, and newer generation sleep medications as occasional sleep medicines (up to once a month).
- Clarified provision of rescue medication (lorazepam would be provided locally by investigator as standard-of-care and not through the sponsor).
- Addition of testing for creatinine phosphokinase (indicator of muscle lysis caused by seizure activity); and elimination of testing for tricyclic antidepressant as part of urine drug screen.
- Addition of diazepam rectal gel dosing chart.
- Replacement with new versions of medical events calendar, seizure diary, and QOLIE-31 scale.
- Elimination of criteria for independent blinded rater for the MADRS scale (as improvement in MADRS was not a primary endpoint of the study and this requirement would be better suited for clinical studies of depression. Suicidality would be better assessed through the C-SSRS).

### **3. AMENDMENT 2, PROTOCOL VERSION 3.0 (24 JULY 2009)**

Protocols 093-045 (Version 2.0, 04 March 2009) and 093-050 (Version 2.0, 16 April 2009) were reviewed by Health Canada as part of a CTA application and at an Investigator's meeting held in the USA (3-5 June 2009). Based on feedback received from the regulatory authority and by US investigators the following major changes were made to the protocol:

- Removal of requirement that efficacy and safety assessments must occur in a specific order. However, vital signs and ECGs were to be collected prior to blood draws.
- Further clarification regarding permitted use of benzodiazepines as sleeping medications.
- Addition of dose adjustment requirement for concomitant medications whose plasma levels may increase after taper/discontinuation of certain enzyme inducing antiepileptic drugs.
- Allowance of change in setting of vagal nerve stimulator in subjects with a clinically significant worsening of seizures or increase in seizure frequency.
- In cases of subject discontinuation/withdrawal due to need for >2 AEDs, provision of instructions that study drug taper schedule would be at Investigator's discretion and an unscheduled visit to record adverse events and return unused study drug.
- Simplification of seizure diary.

### **4. NON-SUBSTANTIAL AMENDMENT 1 (22 APRIL 2010)**

The purpose of this non-substantial amendment (administrative letter) was to notify the Investigators of the following administrative clarifications to Sepracor Protocol 093-050 (Version 3.0, 24 July 2009):

- The EudraCT number for this study is 2010-018684-42. Sites were provided with a self-adhesive label citing this EudraCT number that should have been affixed to the title page of the protocol.
- The telephone and fax numbers for 24-hour SAE Reporting was updated.
- Section 7.3.3, Health Outcomes Assessments: The site staff could use the review of subject entries in the Medical Events Calendar (MEC) as a source to determine if further data about the subject's utilization of health care services should be obtained.

## 5. AMENDMENT 3, PROTOCOL VERSION 4.0 (09 JUNE 2010)

Based on continued feedback from the contract research organization and investigative sites enrolling subjects the following changes/clarifications were made to the protocol:

- Addition of information (in table format) on diazepam doses and formulations when used as rescue medication in countries where lorazepam as rescue medication was not available.
- Addition of information (in table format) on diazepam doses and formulations when used as emergency medication in countries where Diastat<sup>®</sup> (diazepam rectal gel) as emergency medication was not available.
- Clarification that the Medical Events Calendar (MEC) could have been used as an additional tool for collection of health outcomes assessments.
- Addition of trazodone as allowed medication.
- Addition of marijuana as a disallowed medication.
- Clarification that the PI or designee must provide a prescription for diazepam when used as emergency or rescue medication (formulation/dose as listed in Appendices XII and XIII).
- Addition of telephone and fax numbers for 24-hour SAE reporting in Europe.
- Addition of the Eudra CT number.
- Change in responsible physician.
- Increase in sample size from 270 to 348 subjects as a result of the increase in sample size for Protocols 093-045 and 093-046.

## **6. AMENDMENT 4, PROTOCOL VERSION 5.0 (17 AUG 2010)**

The sponsor extended the current study duration to beyond 1-year. This allowed subjects who demonstrated clinical benefit over a 1-year period to continue receiving study drug beyond 1-year. There was no change in sample size or change in study drug dosing resulting from the extended duration of study. The protocol has been amended to incorporate the following major changes:

- A post-1-year period that would follow the 1-year period. The post-1-year period would continue until the subject discontinues study, the study drug becomes clinically available in the subject's locale, or the sponsor terminates the study drug clinical development program.
- Addition of new post-1-year primary objective and 2 new post-1-year secondary objectives.
- Addition of a new post-1-year endpoint.
- Addition of post-1-year Patient Global Impression (PGI) scale for assessing improvement in disease.
- Addition of a continuation criterion for subjects who choose to continue into the post-1-year part of the study.

## **7. CZECH REPUBLIC-SPECIFIC AMENDMENT 1, PROTOCOL 5.1 (16 NOVEMBER 2010)**

As of October 2010, Sepracor Inc. has changed its name to Sunovion Pharmaceuticals Inc. Edits to the protocol were made to reflect the name change.

## **8. NON-SUBSTANTIAL AMENDMENT 2 (12 DECEMBER 2011)**

The purpose of this letter was to notify the Investigators of the administrative change to Sunovion Pharmaceuticals Inc. Protocol 093-050 (Version 5.0, 17 Aug 2010, Czech Republic-Specific Local Amendment Version 5.1, 16 Nov 2010, and Russia-specific Protocol Version 5.1, 14 Jan 2011).

The contact for reporting of SAEs, pregnancies, and any other immediately reportable events was updated.

## **9. NON-SUBSTANTIAL AMENDMENT 3 (03 DECEMBER 2012)**

The purpose of this non-substantial amendment (administrative letter) was to notify the Investigators of the following administrative changes to Sunovion Pharmaceuticals Inc. Protocol 093-050 (Version 5.0, 17 Aug 2010; Czech Republic-specific Local Amendment Version 5.1, 16 Nov 2010; and Russia-specific Protocol Version 5.1, 14 Jan 2011):

- For clarification, all pregnancy tests (urine and serum) were to be conducted in female subjects of child bearing potential ONLY. The definition of child-bearing potential was provided in Section 8.1 (Subject Inclusion/Exclusion Criteria) of the protocol.
- Effective 03 Dec 2012 serious adverse events, (SAEs), pregnancies, and any other immediately reportable events for Protocol 093-050 were to be reported to PPD Pharmacovigilance (PVG).

## **10. AMENDMENT 5, PROTOCOL VERSION 6.0 (07 JUNE 2013)**

The protocol was amended to remove the following post-1-year EOS/ET visit assessments: clinical laboratory evaluations (performed only if clinically indicated), coagulation testing, thyroid panel, lipid panel, bone turnover markers, and serum pregnancy tests. The post-1-year EOS/ET 12-lead ECG assessment was to be performed only if clinically indicated. The Sponsor determined that these assessments do not contribute additional information needed to evaluate the overall safety profile of eslicarbazepine acetate.

In addition, updates outlined in non-substantial amendments (administrative letters) sent to the sites such as safety reporting information, Medical Monitor contact information, and change in company name were also included in this amendment.

## **11. NON-SUBSTANTIAL AMENDMENT 4 (15 NOVEMBER 2013)**

The purpose of the non-substantial amendment (administrative letter) was to notify the Investigators of the following administrative change to Sunovion Pharmaceuticals Inc. Protocol 093-050 (Version 6.0, dated 07 Jun 2013):

Sections 11.1 (ECGs); 11.4.9 (End of Study/Early Termination); Appendix III (Cardiac Safety Monitoring); and Appendix IX (Computerized Systems Used for Source Data): A post-1-year ECG assessment, if performed, should have been over-read.