Synopsis – Study 14362B

Study Title A multi-site, prospective, open-label, long-term, flexible-dose, interventional study to evaluate the safety and tolerability of clobazam as adjunctive therapy in paediatric patients aged ≥1 to ≤16 years with Dravet Syndrome
Investigators 2 principal investigators at 2 sites in the United States
Study Sites Patients were enrolled at 2 sites in the United States
Publications None (as of the date of this report)
Study Period *First patient first visit* – 28 July 2015 (the date when the first *Informed Consent Form* was signed) *Study terminated* – 24 August 2015 *Last patient last visit* – 12 October 2015 (the date of the last protocol-specified contact with any patient)
Objectives • *Primary objective*: – to investigate the long-term safety and tolerability of clobazam when administered for 1 year as adjunctive therapy in paediatric patients aged ≥1 to ≤16 years with Dravet Syndrome, including height/length and weight, behavioural and neurocognitive endpoints, serious skin rashes, urinary retention, hypothermia (both alone or accompanied by shock or anaphylaxis), exacerbation of any seizure type, suicidality and neurological adverse events (such as somnolence, sedation, fatigue, impaired gait, impaired coordination, falls) • *Secondary objectives*: – to investigate the effect of clobazam on the frequency of tonic-clonic and clonic seizures over various time periods – to evaluate the occurrence of tachyphylaxis
Study Methodology • This was an interventional, multi-national, multi-site, open-label, long-term safety study in patients with Dravet Syndrome. • The study consisted of the following periods and visits: – a 2-week Screening Period (only for the patients who had not been enrolled in lead-in Study 14362A) – a 2-week Baseline Period (only for the patients who had not been enrolled in lead-in Study 14362A) – a 52-week Treatment Period – a Completion/Withdrawal Visit: on Day 360 or as soon as possible after withdrawal – a Safety Follow-up Visit: 30 days after the last dose of Investigational Medicinal Product (IMP) • During the Baseline Period, daily counts of seizures, focusing on tonic-clonic and clonic seizures, were captured (only for the patients who had not been enrolled in Study 14362A). • During the Treatment Period, daily counts of seizures, focusing on tonic-clonic and clonic seizures, were captured in a seizure diary for the first 30 days after each study visit, except for Visit 9 (Completion/ Withdrawal) for which daily seizure counts were to be collected for 30 days prior to the visit. • Safety data were collected at regular intervals throughout the study.

Study Methodology – continued

- The daily dose of IMP was to be calculated based on the patient's body weight and then divided into 2 preferably equal doses of IMP/day. Patients who participated in Study 14362A were to continue on the IMP formulation that they were administered when completing or withdrawing from the lead-in study. Patients who did not participate in Study 14362A continued to receive their current dose of IMP as either tablets or oral suspension. Details about the dosing of IMP and dose adjustments are available in the *Clinical Study Protocol*.
- The study was terminated by the sponsor in August 2015 due to recruitment challenges.
- This *Abbreviated Clinical Study Report* presents selected study data for the 1 patient who received IMP.

Number of Patients Planned

At least 40 patients were planned for enrolment.

Diagnosis and Main Selection Criterion

Outpatients with a diagnosis of Dravet syndrome supported by:

- onset of seizures in the first year of life
- history of fever-induced prolonged seizures as determined by the investigator
  - these may include prolonged (approximately 15 minutes or longer) hemi-clonic seizures
- multiple seizure types may include:
  - generalised tonic-clonic (required for inclusion)
  - clonic (required for inclusion)
  - myoclonic jerks/seizures
- history of normal development prior to seizure onset followed by development delay or regression after seizure onset
- abnormal electroencephalogram consistent with Dravet Syndrome

A patient could be enrolled if they fulfilled the following criteria:

- The patient is a boy or girl, aged ≥1 and ≤16 years at Baseline (in either Study 14362A or in this study).
- The patient is treated with at least 1 but no more than 3 antiepileptic drugs (AEDs) [Vagal Nerve Stimulator (VNS) and ketogenic diet will not be considered an AED].
- The patient either completed or withdrew due to lack of efficacy from lead-in Study 14362A and:
  1) received at least 4 weeks of blinded maintenance treatment (Maintenance Period A in Study 14362A) OR
  2) withdrew after they had experienced an increase in seizure frequency >100% over baseline AND
  3) had not had a serious or severe adverse event that was determined by the investigator to be related to IMP and according to the investigator would make it unsafe for the patient to continue receiving IMP.

In addition, patients aged ≥1 and ≤16 years who had not participated in Study 14362A could be enrolled in Study 14362B if they were currently receiving a stable dose of at least 0.5 mg/kg/day of clobazam for the previous ≥3 months and if they had been approved for screening or enrolment by the sponsor.

Investigational Medicinal Product, Dose and Modes of Administration, Batch Number

Clobazam – a maximum of 2.0 mg/kg/day (maximum 80 mg/day) twice daily (BID); clobazam oral suspension (2.5mg/mL) or clobazam tablets (10 mg), orally; batch no. 1302936 (tablets)

Duration of Treatment

52 weeks

Efficacy Assessments

Daily seizure diaries

Safety Assessments

- Adverse events, clinical safety laboratory tests, vital signs, weight, height/length, electrocardiograms (ECGs), and physical and neurological examinations
- Columbia Suicide Severity Rating Scale (C-SSRS; for patients ≥6 years)
- Vineland Adaptive Behavioural Scale (VABS)

Endpoints

- *Primary endpoints*:
  - number and incidence of adverse events, including serious skin rashes, urinary retention, hypothermia (both alone or accompanied by shock or anaphylaxis), and neurological adverse events (such as somnolence, sedation, fatigue, impaired gait, impaired coordination, falls) and suicidality
  - absolute values and changes from baseline in clinical safety laboratory tests, vital signs, weight, height/length and ECG parameters
  - incidence of potentially clinically significant clinical safety laboratory test values, vital signs, weight, height/length, and ECG parameter values
  - C-SSRS categorisation based on Columbia Classification Algorithm of Suicide Assessment (C-CASA) categories (1, 2, 3, 4, and 7) for patients aged ≥6 years
  - change from the baseline in behavioural, neurocognitive measures (VABS).
- *Secondary endpoints*:
  - change from baseline in mean weekly number of tonic-clonic and clonic seizures at Days 30, 60, 90, 180, 270, 360 and upon Study Completion/Withdrawal.
  - the number and percentage of initial treatment responders who returned to their baseline tonic-clonic and clonic seizure rate during the study (an assessment of tachyphylaxis)

Statistical Methodology

Selected study data for patient S2001 were listed.

Patient Disposition

- 3 patients were enrolled. None of these 3 patients had participated in lead-in Study 14362A.
- 1 patient (S2001) was treated. At the time of study termination, the other 2 patients had not yet received IMP and were therefore classified as screening failures.
- None of the patients completed the study.

Demography, Exposure to IMP, and Baseline Characteristics

- A 13-year-old White girl, with a height of 151 cm and a weight of 78 kg was enrolled and treated. The patient received IMP (60 mg/day) for 33 days during the study.
- Diagnosis and seizure history are presented in Listings 1 and 2.
- Medical history and concomitant medication are presented in Listings 3 and 4, respectively.
- The patient had been treated with clobazam (60 mg/day) since January 2012.

Efficacy Results

Seizure diary data are presented in Listing 5.

Safety Results

- No adverse events were reported in this study.
- Clinical safety laboratory test and vital signs results are presented in Listings 6 and 7, respectively. The reference ranges for the clinical safety laboratory tests are presented in Listing 8. A few isolated clinical safety laboratory values were outside the reference ranges; leukocytes values decreased from $3.9x10^9$/L at Baseline (lower reference range: $4.2x10^9$/L) to $3.6x10^9$/L at the Follow-up Visit.
- ECG data are presented in Listing 9. The ECG test was abnormal, but not clinically significant, at the Completion Visit (Day 33); the baseline ECG results were normal.

Conclusions

The study was terminated due to recruitment challenges. Only one patient received IMP and no safety or efficacy conclusions can be drawn based on study data.

Report Date

20 January 2016

This study was conducted in compliance with the principles of *Good Clinical Practice*.