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Efficacy and safety of vigabatrin in Japanese patients with infantile spasms: Primary short-term study and extension study

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ABSTRACT

Vigabatrin was approved for the treatment of infantile spasms by the US Food and Drug Administration, but not in Japan at the time of initiating this clinical study because of concerns about irreversible peripheral visual field defects (VFDs). This study evaluated the efficacy and safety of vigabatrin for Japanese patients with infantile spasms. Of 15 patients (aged ≥4 weeks and <2 years) enrolled, with the exception of two patients who did not receive vigabatrin, 13 were treated with a titrated dosage of vigabatrin (50–150 mg/kg/day; limited to 3000 mg/day). Twelve out of 13 patients receiving vigabatrin had spasms that were treatment refractory; these patients were concurrently treated with at least one other antiepileptic drug. One patient received vigabatrin monotherapy. Eight of the 13 patients (61.5% [95% CI: 31.6–86.1%]) had a ≥ 50% reduction during the dose-adjustment phase compared with baseline in the frequency of spasms, with efficacy maintained through a 2-week maintenance phase. Spasms disappeared in six out of nine patients (66.7% [95% CI: 29.9–92.5%]) who transitioned to the maintenance phase and hypsarrhythmia on electroencephalography also resolved in four patients. Hypsarrhythmia was improved in another two patients. Six out of seven patients who continued treatment through Week 32 of an extension study reported ongoing efficacy for vigabatrin. The most common adverse events (AEs) were psychiatric disorders and nervous system disorders (n = 8; 61.5%) that were generally mild in severity. No treatment-related peripheral VFDs were observed. No severe AEs or AEs resulting in discontinuation of vigabatrin therapy were reported. An abnormality in magnetic resonance images was observed in one patient during the extension period. Vigabatrin was deemed to be clinically effective and well tolerated in Japanese patients with infantile spasms.

1. Introduction

Infantile spasms, or West syndrome, is classified as an "epileptic encephalopathy" by the International League Against Epilepsy (ILAE) Classification system [1] and is characterized by spasms, neurodevelopmental regression, and hypsarrhythmia on electroencephalography (EEG) in children mainly under the age of 2 years old [2]. Infantile spasms can be caused by a variety of underlying pathologies, including pre-, peri-, and postnatal brain insults; but a significant number of cases have an unknown etiology [3]. In most cases, the long-term developmental and seizure outcomes are devastating.

Currently approved treatments for infantile spasms in Japan include synthetic adrenocorticotrophic hormone (ACTH). Adrenocorticotrophic hormone is considered to be the most effective treatment for infantile spasms in Japan, but a high proportion (>40%) of Japanese patients had spasms that relapsed after discontinuing treatment [4]. Treatment is also associated with a high risk of adverse events (AEs), including potentially life-threatening serious AEs (SAEs) [5], so a short-duration/low-dose ACTH regimen is often used in Japan to reduce the risk of SAEs [6]. Meanwhile, other treatment options are urgently required.

Vigabatrin has been well evaluated for the treatment of infantile spasms in many countries, especially in Europe [7,8], and is considered to be particularly efficacious in patients with tuberous sclerosis [9,10]. It is a structural analog of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) that functions as a long-acting anticonvulsant by irreversibly binding GABA-transaminase, the primary GABA-degrading enzyme, increasing GABA levels in the brain [11].

However, an increased risk of peripheral visual field defects (VFDs) following prolonged administration of vigabatrin (>12 months) has been reported in both adult and pediatric patients [10]. It has been suggested that vigabatrin-related peripheral VFDs are a result of vigabatrin inhibiting taurine uptake in the gastrointestinal tract, leading to taurine

Abbreviations: ACTH, adrenocorticotrophic hormone; ADR, adverse drug reaction; AE, adverse event; AED, antiepileptic drug; AESI, adverse events of special interest; ALT, alanine aminotransferase; BID, twice daily; CI, confidence interval; CLB, clobazam; ECG, electrocardiography; EEG, electroencephalography; ERG, electroretinography; FDA, US Food and Drug Administration; GABA, γ-aminobutyric acid; HA, hypsarrhythmia; ILAE, International League Against Epilepsy; LEV, levetiracetam; LTG, lamotrigine; MRI, magnetic resonance imaging; NZP, nitrazepam; PB, phenobarbital; SAE, serious adverse event; TPM, topiramate; VFD, visual field defect; VPA, valproic acid; ZNS, zonisamide.

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deficiency-related retinal toxicity [12–16]. Other studies have reported reversible abnormal magnetic resonance imaging (MRI) scan signal intensity and/or restricted diffusion-weighted imaging in patients with infantile spasms administered vigabatrin [17,18].

Clinical trials aiming to support the official approval of vigabatrin in Japan began in 1990, but were terminated in 1997 because of reports of irreversible VFDs. In 1997, an approvable letter from the US Food and Drug Administration (FDA) for vigabatrin was rescinded in light of concerns about VFDs [11]. However, the FDA subsequently approved vigabatrin for the treatment of epilepsy, including infantile spasms in 2009, once it became clear that VFDs were likely related to prolonged, cumulative exposure to vigabatrin [19]. Vigabatrin is also approved for the treatment of infantile spasms in Taiwan, Hong Kong, and South Korea, leading to renewed interest in vigabatrin as a potential treatment for infantile spasms in Japan.

Therefore, a short-term study, followed by a long-term extension study, was conducted to examine the efficacy and safety of vigabatrin in Japanese patients with infantile spasms with the aim of supporting marketing approval in Japan. In this manuscript, results of the primary short-term study, and an interim analysis at Week 32 of the extension study, are presented.

2. Material and methods

2.1. Study design

A Phase III, single-blind study of vigabatrin in patients with infantile spasms across four medical centers and five university hospitals in Japan (JapicCTI-142558; EudraCT Number 2017-000230-62; see supplementary material for full details of participating hospitals) was conducted in accordance with the Declaration of Helsinki. The study was approved by the Ethics Committees at each participating site.

All patients stayed in hospital for the duration of the study and were accompanied by their parent(s) or guardian(s) who were trained to act as observers, accurately recording seizures in a seizure diary.

This study consisted of screening, dose adjustment, maintenance, and taper phases. Each patient underwent assessment during the screening phase (4–14 days). The dose-adjustment phase (6 days–8 weeks) was designed to achieve optimal dosing for each patient. Patients who completed the dose-adjustment phase were then treated using a consistent dose of vigabatrin during a 2-week maintenance phase.

On completion of the maintenance phase, patients who were (based on each investigator's judgment) determined to be suitable for continued vigabatrin therapy, and for whom consent was provided, entered into an extension study (JapicCTI-142559; EudraCT Number 2017-000611-17) with continuing follow-up. For patients who did not enter into the extension study, the dose of vigabatrin was gradually decreased over 3 weeks (taper phase) and follow-up continued for 12 weeks thereafter. The length of each treatment phase could be shortened at the investigators' discretion due to inadequate efficacy or safety issues, but temporary treatment discontinuation was not allowed during the study period.

Study participants were administered vigabatrin 50–150 mg/kg/day (25–75 mg/kg twice daily [BID]). Dosing was adjusted by weight on the first day of each treatment phase and total daily dosing limited to 3000 mg.

2.2. Enrolment criteria

Patients were required to meet all of the following criteria to be eligible for the study: a diagnosis of infantile spasms with hypsarrhythmia on EEG according to the 1989 ILAE Classification [20]; ≥4 weeks and <2 years of age at the date of initial dosing with vigabatrin; and signed informed consent from the patient's legal guardian.

Patients were excluded from the study if they met any of the following criteria: concurrent severe liver or renal disease; cardiac disease associated with a severe conduction disorder; a serious gastrointestinal disorder; any other serious disorder or disease; treatment with ACTH products or corticosteroids within 28 days of formal registration in the study; previous or current treatment with vigabatrin; concomitant Lennox–Gastaut syndrome; or current or prior participation in another clinical study within 6 months. Patients with a history of an ophthalmologic complication, or any condition that was considered to interfere with assessment of retinal function were also excluded from the study.

Concomitant antiepileptic drugs (AEDs) which were initiated before enrolment were continued until completion of the maintenance phase without change of regimens. Furthermore, additional AED use was prohibited from enrolment to completion of the maintenance phase.

2.3. Dosing

2.3.1. Dose-adjustment phase

During the first 3 days of the dose-adjustment phase, a placebo solution was administered BID to control for any placebo effect on seizure frequency. This placebo phase was single blind to the patients and observers. From Day 4 of the dose-adjustment phase onwards, vigabatrin 50 mg/kg/day (25 mg/kg BID) was administered. If spasms were not controlled by Day 7, and there were no safety concerns, vigabatrin dosage was uptitrated by 25–50 mg/kg/day every 3 days thereafter until spasms were controlled.

Control of spasms was defined as no spasms being observed during spasm assessment days. Dose adjustment could be delayed for up to 7 days on the basis of safety concerns. Accordingly, each investigator sought the optimal dose for the individual patient during the dose-adjustment phase (6 days to 8 weeks).

Dose reduction due to safety or tolerability concerns was permitted, including for patients whose spasms remained uncontrolled. If safety and tolerability concerns resolved following dose reduction, and spasms remained uncontrolled, uptitration was to proceed every 3 days. Dose uptitration following a temporary dose reduction was only permitted once.

Patients were permitted to enter the maintenance phase of the study once spasm control had been achieved or the maximum dose reached. For any patients with inadequate spasm control at the maximum dose, or unacceptable drug safety or tolerability, treatment was to be discontinued and the patient immediately transitioned to the taper phase.

2.3.2. Maintenance phase

Patients entering the maintenance phase continued vigabatrin treatment for 14 days on the dose determined in the dose-adjustment phase to offer spasm control, or the maximum permitted dose. Dose escalation was only permitted for patients who experienced a recurrence/aggravation of spasms during the first 7 days of the maintenance phase, following the dose escalation protocol used in the dose-adjustment phase. Dose escalation was only permitted once during the maintenance phase.

Dose reduction was permitted once during the maintenance phase without subsequent dose re-escalation.

If exacerbation or no improvement was observed in the maintenance phase of the study, despite being administered the maximum dose of vigabatrin, vigabatrin was discontinued and the patient immediately transitioned to the taper phase.

2.3.3. Taper phase

Dose tapering was recommended at the rate of a 25–50 mg/kg/day reduction in vigabatrin dose every 3–4 days, except where the investigators believed there was a need for immediate discontinuation. Investigator discretion could be used to manage dose tapering, as appropriate.