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Long-term safety and effectiveness of stiripentol in patients with Dravet syndrome: Interim report of a post-marketing surveillance study in Japan

Miyuki Yamada [a,*], Katsuyoshi Suzuki [a], Daisuke Matsui [a], Yushi Inoue [b], Yoko Ohtsuka [c]

[a] Safety Vigilance & Management Dept., Reliability & Quality Assurance Division, Meiji Seika Pharma Co., Ltd., Tokyo, Japan
[b] Department of Clinical Research, National Epilepsy Center, NHO Shizuoka Institute of Epilepsy and Neurological Disorders, Shizuoka, Japan
[c] Department of Child Neurology, Asahigawaso Rehabilitation and Medical Center, Okayama, Japan

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ABSTRACT

Background: A post-marketing surveillance study is investigating the safety and effectiveness of stiripentol during real-world clinical use in Japanese patients with Dravet syndrome (DS).

Methods: The safety and effectiveness of stiripentol were prospectively investigated over 104 weeks in all patients with DS who were administered the drug from November 2012 through July 2019 in Japan. Patients administered stiripentol for the first time after its approval were defined as "new patients," and those who continued to take the drug after participating in domestic clinical studies were defined as "continuous-use patients." The responder rate was defined as the proportion of patients with a ≥50 % decrease in seizure episodes at the time of assessment of stiripentol effectiveness compared with the 4 weeks before starting stiripentol. Overall improvement was evaluated by the physician in charge based on the comprehensive assessment of the patient's condition after stiripentol treatment.

Results: Of 411 patients whose information was collected, 410 patients (376 new and 34 continuous-use) were included in the safety analysis set, and 409 (376 new and 33 continuous-use) were included in the effectiveness analysis set. The median age of new patients was 7 years (range: 0.5–50 years) at the time of stiripentol initiation; 99 % of patients were taking concomitant sodium valproate and 93 % clobazam. Adverse drug reactions occurred in 70 % of new patients; the most common were somnolence (39 %) and loss of appetite (25 %). No new safety concerns due to stiripentol were observed. The responder rate in new patients was 43 % (110/257 patients) for convulsive seizures (tonic-clonic and/or clonic convulsions), 55 % (58/105 patients) for focal impaired awareness seizures, and 62 % (56/90 patients) for generalized myoclonic seizures and/or generalized atypical absence seizures. Overall improvement (after 104 weeks or at the time of drug discontinuation) was rated as marked or moderate in 160/353 of new patients (45 %).

Conclusion: Stiripentol is safe and effective during long-term use in patients with DS in routine clinical practice.

1. Introduction

Dravet syndrome (DS) is one of the most difficult-to-treat epileptic syndromes, with a high rate of drug-refractoriness (Dravet et al., 2005). The prevalence is estimated to be one in 15,700 people in the United States (Wu et al., 2015) and one in 20,000–30,000 in France (Yakoub et al., 1992). The prevalence of DS in Japan has been reported as nine in 2220 patients with epilepsy aged <13 years in Okayama Prefecture, and nine of 250,990 people aged <13 years in the general population as of December 31, 1999 (Oka et al., 2006). From these studies, the total number of patients with DS in Japan is estimated to be between 3000 and 6,000.

Abbreviations: ADR, adverse drug reaction; CLB, clobazam; CYP2C19, cytochrome P450 2C19; DS, Dravet syndrome; GABA, γ-aminobutyric acid; GGT, γ-glutamyl transferase; GPSP, Good Postmarketing Study Practice; ICH, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; ILAE, International League Against Epilepsy; MedDRA/J, Japanese language version of the Medical Dictionary for Regulatory Activities; SCN1A, sodium channel voltage-gated type 1 alpha subunit; VPA, sodium valproate.

* Corresponding author at: Safety Vigilance & Management Department, Reliability & Quality Assurance Division, Meiji Seika Pharma Co., Ltd., 2-4-16, Kyobashi, Chuo-ku, Tokyo, 104-8002, Japan.

E-mail addresses: miyuki.yamada@meiji.com (M. Yamada), katsuyoshi.suzuki.aa@meiji.com (K. Suzuki), daisuke.matsui@meiji.com (D. Matsui), yinoue-jes@umin.net (Y. Inoue), ohtsuka@okayama-u.ac.jp (Y. Ohtsuka).

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Stiripentol (STP) is an antiseizure medication (ASM) with a unique structure and multiple mechanisms of action, including augmentation of γ-aminobutyric acid (GABA)-mediated neurotransmission (Frampton, 2019). The efficacy of STP in combination with clobazam (CLB) and sodium valproate (VPA) for DS was first shown in two randomized double-blind studies conducted in France and Italy (Chiron et al., 2000; Kassai et al., 2008), and STP (in combination with CLB and VPA) is recommended as second-line therapy for the treatment of DS (Cross et al., 2019). The unique efficacy of STP in DS has also been reported in South Korea (Cho et al., 2018), Austria (Dressler et al., 2015), the United Kingdom (Myers et al., 2018), Australia (Myers et al., 2018), the United States (Wirrell et al., 2013), and Turkey (Yildiz et al., 2019).

In Japan, the efficacy of STP in patients with DS was first reported in a multicenter study (Inoue et al., 2009). Based on these results, as well as subsequent short- and long-term clinical studies (Inoue et al., 2014, 2015), STP was approved as combination therapy with CLB and VPA for the treatment of DS in Japan in November 2012. However, because of the small number of patients enrolled in two domestic clinical studies (Inoue et al., 2014, 2015), the Ministry of Health, Labour and Welfare (MHLW) required, as a condition of its approval, that the safety and effectiveness of STP be examined by conducting post-marketing surveillance in all DS patients who had been administered STP after its approval. This surveillance is now currently underway and will continue until September 2022. However, an interim analysis was performed using information collected up to July 2019.

2. Methods

2.1. Study design

All patients with DS in whom STP had been administered since its approval in November 2012 were included in this surveillance. Patients who were administered STP for the first time after its approval were defined as "new patients", and those who had been given STP since before its approval (i.e., those who had continued to take the drug after participating in the domestic clinical studies (Inoue et al., 2014, 2015)) and those who had obtained the drug through private import were defined as "continuous-use patients." The planned observation period is for up to 156 weeks after starting STP administration or until drug discontinuation, whichever comes first. Physicians used a central registration process to register all patients with DS who were administered STP, and entered their data and information into the survey sheets. This interim analysis was conducted in July 2019, and included information on STP administration for up to 104 weeks.

This surveillance is currently underway in compliance with the protocol that received MHLW approval, as well as the Good Post-marketing Study Practice (GPSP; Ordinance of the Ministry of Health, Labour and Welfare No. 171, December 20, 2004). According to the GPSP Ministerial Ordinance, deliberations at the Institutional Review Board and patient consent were not required for post-marketing surveillance. Patient confidentiality was maintained by anonymizing patient information. A plan for this surveillance has been registered as JapicCTI-205180 in the Japan Pharmaceutical Information Center.

2.2. Patients

The following background information was collected for each patient: sex, age at the time of initiation of STP administration for new patients or at the time of starting this surveillance for continuous-use patients, age at disease onset, sodium channel voltage-gated type 1 alpha subunit (*SCN1A*) genetic testing, cytochrome P450 (CYP) 2C19 genetic polymorphism testing, family history of epilepsy or febrile convulsions (within second-degree relative), status of STP administration, and status of concomitant ASM administration. In female patients of childbearing age, information was collected about pregnancy and lactation status.

Each attending physician made a diagnosis of DS based on the following clinical symptoms and electroencephalogram (EEG) findings (Dravet et al., 2012): 1) onset of seizures during the first year of life; 2) initial occurrence of "convulsive seizures" (generalized or unilateral clonic seizures or generalized tonic-clinic seizures) often triggered by fever and evolving into status epilepticus; 3) subsequent appearance of myoclonic seizures and/or atypical absences as well as complex partial seizures (although DS could be diagnosed in patients without generalized myoclonic seizures and/or atypical absences if the patient had "convulsive seizures" with/without complex partial seizures associated with other typical symptoms and clinical course of DS, since not all DS patients develop myoclonic seizures and/or atypical absences); 4) normal development before the onset of seizures, but developmental retardation and other progressive neurological symptoms such as ataxia and/or pyramidal signs emerging after the first year of life; 5) normal EEGs at the onset of seizures; 6) generalized spike-wave and/or generalized multiple spike-wave complexes and/or multifocal spike-waves appear after the first year of life; 7) basic pattern of EEG showing a deteriorating tendency over time; 8) early photosensitivity (not present in all cases of DS). Even if all of the above criteria were not met, all cases with a final diagnosis of DS from the attending physician were included in this study. Genetic testing was undertaken at the discretion of the treating physician.

2.3. Safety

Adverse events (AEs) that occurred between the start of STP administration and the end of the observation period were recorded and graded according to the degree of seriousness. AEs were considered serious if, according to the physician in charge, the event (1) led to death; (2) was life-threatening; (3) required hospitalization or prolongation of hospital stay for treatment; (4) resulted in persistent or significant disability and/or dysfunction; (5) caused congenital anomalies/birth defects; or (6) constituted other medically important conditions. AEs were defined as "adverse drug reactions (ADRs)" if the physician in charge determined that there was a causal relationship to STP. The causal relationship between each adverse event and STP was evaluated as either "clearly", "probably", "possibly", "none", and "not evaluable"; all AEs other than "none" were classified as ADRs. The ADRs were defined using the preferred terms of the Japanese language edition, version 22.0, of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Medical Dictionary for Regulatory Activities (MedDRA/J). The incidence of ADRs was calculated.

2.4. Effectiveness

In the previous local clinical studies (Inoue et al., 2014, 2015), symptoms were mainly classified according to the International League Against Epilepsy (ILAE) 1981 seizure criteria (International League Against Epilepsy, 1981), but considering the uniqueness of seizures in patients with DS, tonic-clonic seizures and/or clonic seizures were additionally classified as "convulsive seizures," and other seizures were classified as complex partial seizures, myoclonic seizures, and/or atypical absence seizures. The same classification was also used to determine the frequency of seizures, except for the following revisions made as a result of a new seizure classification by the ILAE published in 2017 (Fisher et al., 2017): complex partial seizures were classified as focal impaired awareness seizures, myoclonic seizures as generalized myoclonic seizures, and atypical absence seizures as generalized atypical absence seizures. We classified convulsive seizures without distinguishing between generalized and focal types because discriminating between these types is difficult.

The responder rate was defined as the proportion of patients who experienced a decrease of $\geq$50 % in the number of seizure episodes in the 4 weeks immediately before the effectiveness assessment compared

with the 4 weeks before starting STP (baseline period). Effectiveness assessments were undertaken after approximately 3 months (13–16 weeks), 12 months (49–52 weeks), and 2 years (101–104 weeks) of treatment. In the cohort of new patients, effectiveness was assessed in those who had ≥ 1 seizure episodes during the 4-week baseline period and who had sufficient data on seizure frequency during the assessment periods. Patients with missing data on seizure frequency were excluded from the analysis only during the assessment period in which data were missing. Patients who discontinued STP were classified as "non-responders" in all assessments after drug discontinuation.

The physician in charge comprehensively compared the patient's condition, including the frequency of seizures after the start of STP administration, the duration and the intensity of seizures, and ability to undertake activities of daily living, with those before the start of STP administration, and rated the overall improvement on a 5-point scale (marked, moderate, mild, unchanged, or worsened) or as undetermined according to the impression of each attending physician. The proportion of patients in whom overall improvement was rated as marked or moderate was defined as the rate of overall improvement. New patients whose degree of overall improvement was rated as undetermined were excluded from the analysis.

2.5. Statistical analyses

No pretrial sample size was defined because all patients taking STP in Japan after November 2012 were included in this analysis.

All statistical analyses were performed using the SAS software version 9.1.3. Factors affecting the safety and effectiveness were analyzed using Fisher's test (2 × 2) or $\chi 2$ test (2 × n), with $P < 0.05$ (two-sided) as the significance level. Analyses of safety and effectiveness in patient subgroups included only those patients with known data in each subgroup category. In this study, the safety and effectiveness were evaluated by background factors for exploratory purposes, and multiple comparisons were not performed.

3. Results

3.1. Patients

A total of 594 patients were registered in the central database from November 2012 to July 2019, with completed survey forms available for 411. Of these 411 patients, 410 (376 new patients and 34 continuous-use patients) were included in the safety analysis set. The excluded patient did not visit the hospital again after receiving the first prescription of STP. One additional patient was found not to have DS, but this patient was included in the safety analysis set according to the protocol. The effectiveness analysis set included 409 patients, (376 new patients and 33 continuous-use patients); the one patient without DS was excluded. Among the new patients in the effectiveness analysis set, 101 patients with tonic-clonic and/or clonic seizures (convulsive seizures), 264 with focal impaired awareness seizures, and 278 with generalized myoclonic seizures and/or generalized atypical absence seizures were excluded from the responder rate analyses because they had < 1 seizure episode during the baseline period or missing data. Therefore, a large proportion of cases were excluded from the analysis of responder rate. Moreover, 23 patients were excluded from the analysis of overall improvement because the degree of their improvement was undetermined.

Table 1 shows the demographic and clinical characteristics of the 410 patients included in the safety analysis set. None of the female subjects were pregnant or lactating. New patients were aged between 6 months and 50 years (median age 7.0 years) at the time of starting STP treatment. The attending physicians performed genetic testing in 231/409 patients with DS (56.5 %), and 180/231 patients (77.9 %) had *SCN1A* gene mutations. Five patients did not receive VPA (all new patients) and 28 patients did not receive CLB (25 new patients and 3 continuous-use patients); none of the patients received STP without either VPA or CLB. The mean (standard deviation [SD]) dose of VPA at the start of the surveillance was 22.1 (9.6) mg/kg/day for new patients and 20.8 (7.6) mg/kg/day for continuous-use patients. The mean (SD) dose of CLB at the start of the investigation was 0.3 (0.2) mg/kg/day for both new and continuous-use patients. Excluding VPA and CLB, 92.3 % of the new patients (347/376 patients) used a mean (SD) of 2.3 (1.3) concomitant ASMs (range: 1–8) and 73.5 % of the continuous-use patients (25/34 patients) used a mean (SD) of 1.6 (0.7) drugs (range: 1–3). Excluding VPA and CLB, the most commonly used ASM was bromide.

Fig. 1 shows changes in STP doses in new patients. The mean (SD) dose for new patients was 13.4 (6.2) mg/kg/day at the start of treatment and increased to 16.2 (8.0) mg/kg/day 2 weeks later and 20.9 (10.7) mg/kg/day 4 weeks later. From then, the mean (SD) doses were 32.5 (14.9) mg/kg/day after 52 weeks and 32.7 (14.5) mg/kg/day after 104 weeks. Among new patients, only 101/376 patients (26.9 %) had their dose titrated to the maximum approved dose of 50 mg/kg/day.

STP was continuously administered for 104 weeks in 305/410 patients (74.4 %). One hundred and five patients discontinued STP: 74

Table 1
Patient demographic and clinical characteristics.

Characteristic, n (%)	Continuous-use patients[a] (n = 34)	New patients[b] (n = 376)
Sex		
Male	14 (41.2)	193 (51.3)
Female	20 (58.8)	183 (48.7)
Age at the time of initiation of STP administration[c]		
0–2 years	0	95 (25.3)
3–5 years	5 (14.7)	66 (17.6)
6–11 years	18 (52.9)	70 (18.6)
12–18 years	6 (17.7)	67 (17.8)
≥19 years	5 (14.7)	78 (20.7)
Age at disease onset[d]		
0–3 months	5 (15.2)	68 (18.1)
4–6 months	14 (42.4)	185 (49.2)
7–9 months	10 (30.3)	76 (20.2)
10–11 months	3 (9.1)	18 (4.8)
1 year	1 (3.0)	15 (4.0)
≥2 years	0	7 (1.9)
Unknown	0	7 (1.9)
SCN1A mutations present[e]		
Yes	19 (95.0)	161 (76.3)
No	1 (5.0)	50 (23.7)
CYP2C19 genotype[e]		
Extensive metabolizer	12 (80.0)	16 (80.0)
Poor metabolizer	3 (20.0)	4 (20.0)
Family history of epilepsy or febrile convulsions		
No	19 (55.9)	288 (76.6)
Yes	13 (38.2)	65 (17.3)
Unknown	2 (5.9)	23 (6.1)
Concomitant antiseizure medications (used by >40 % of patients in either group)[f]		
Sodium valproate	34 (100.0)	371 (98.7)
Clobazam	31 (91.2)	351 (93.4)
Bromide	15 (44.1)	183 (48.7)
Topiramate	12 (35.3)	153 (40.7)

CYP2C19: cytochrome P450 2C19; *SCN1A*: sodium channel voltage-gated type 1 alpha subunit; STP: stiripentol.

[a] Patients who had been taking STP since before its approval, such as those who had continuously taken the drug from the domestic clinical studies and those who had obtained the drug through private import.

[b] Patients who took STP for the first time after its approval in November 2012.

[c] For continuous-use patients, age at the start of this surveillance.

[d] One of the continuous-use patients did not have Dravet syndrome.

[e] Only the patients who underwent tests are shown.

[f] Concomitant drug usage during the observation period.

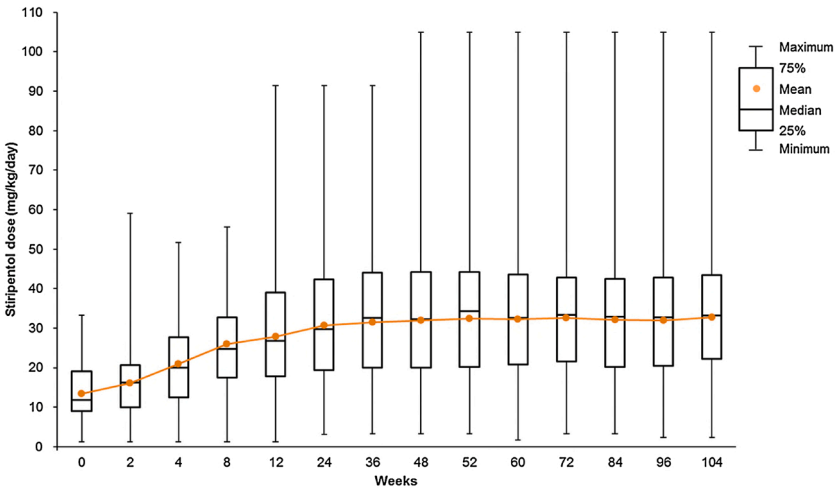

Fig. 1. Changes in stiripentol doses over time in new patients (patients who took stiripentol for the first time after its approval in November 2012). The approved dosage of stiripentol in Japan is a starting dose of 20 mg/kg/day or 1000 mg/day (in patients with body weight > 50 kg), increased by 10 mg/kg increments at 1-week intervals up to a maximum of 50 mg/kg/day or 2500 mg/day (body weight > 50 kg).

patients in the first 52 weeks of treatment and 31 patients between 53 and 104 weeks after the start of this surveillance. The most common reasons for STP treatment discontinuation were insufficient efficacy (n = 54) and occurrence of AEs (n = 50); patients could have more than one reason for treatment discontinuation.

3.2. Safety

Table 2 shows the ADRs that occurred in ≥1 % of patients in the safety analysis set. The overall incidence of ADRs was 70.0 % (263/376 patients) for new patients and 44.1 % (15/34 patients) during the surveillance period for continuous-use patients. Moreover, the incidence of serious ADRs was 14.4 % (54/376 patients) for new patients and 11.8 % (4/34 patients) for continuous-use patients.

Several unexpected ADRs were observed, including seizures, convulsive seizures, tonic convulsions, myoclonic seizures, and atonic seizures in 18 new patients (exacerbation of seizures in all cases); aspiration pneumonia in six new patients; and hypersalivation in five new patients and one continuous-use patient. However, all of these ADRs were strongly suspected to be affected by the primary disease (DS) or concomitant ASMs, or had an unevaluable causal relationship to STP. Of the 18 patients who experienced exacerbation of seizures, the main combinations of concomitant ASMs were VPA + CLB + bromide in nine patients and VPA + CLB in five patients. *SCN1A* genetic testing was performed in 8/18 patients and mutations were detected in 6/8 patients. Other factors suspected of contributing to seizure exacerbation were the patient's primary disease (DS), pyrexia, and dose reduction/blood concentration reduction of concomitant ASMs (CLB and VPA). In cases in which the primary disease (DS) was judged to be a suspected factor, there was a possibility of exacerbation of seizures as a symptom of DS. Pyrexia or decreased ASMs at the time of the exacerbation was found in 7/18 of patients. The time of onset was within 3 months after the start of STP in seven patients, within 4–6 months in two patients, within 7–12 months in three patients, and within 13–24 months in six patients. Twenty-four new patients and two continuous-use patients had an increase in the blood concentration of their concomitant ASMs, which included VPA (n = 23), CLB (n = 5) or its metabolite N-desmethyl CLB (n = 2), phenytoin (n = 2), and phenobarbital (n = 2). These increases in the drug concentration were associated with other ADRs (e.g., somnolence and loss of appetite). All patients who developed hyperammonemia were receiving concomitant VPA. Dose adjustment of STP or concomitant ASMs was required in all patients, but no patients discontinued STP. Of these patients with hyperammonemia, three also developed increased γ-glutamyl transferase levels as ADRs.

Table 3 shows the association between patients' baseline characteristics and the incidence of ADRs. Age at the time of initiating STP treatment was associated with a significant difference in ADR incidence, with the incidence increasing in older age groups. However, no significant difference in ADR incidence was seen between other groups based on demographic or clinical characteristics.

Major ADRs that led to the discontinuation of STP treatment were: somnolence in 17 patients, loss of appetite in 13 patients, aggravation of seizures in six patients, weight reduction in five patients, ataxia/vertigo and agitation in four patients each, and mood changes in three patients.

Five patients died during this study, all from the new patient group. The causes of death were: drowning in two patients (girls aged 11 and 13 years); sudden death (a boy aged 4 years); liver damage (a girl aged 1 year); and hepatobiliary cancer (a woman aged 34 years). Drowning (two patients) occurred 10 months after the start of STP administration; sudden death and liver damage (one patient each) occurred 2 months after starting STP; and hepatobiliary cancer occurred 18 months after starting STP. The attending physician evaluated the two cases of drowning and one of hepatobiliary cancer as having no causal relationship to STP, the sudden death as having an unevaluable causal relationship to STP, and the liver damage as having a possible causal relationship to STP. In all deaths, additional possible causes of death other than STP were recorded by the attending physician, namely "aging" in the case of hepatobiliary cancer, "concomitant ASMs (VPA and CLB)" in the case of the patient with liver damage, and "primary disease" (DS) in the sudden death and the two cases of drowning, since the circumstances surrounding the two drowning deaths suggested that they were also related to sudden death. The liver damage was suspected to be drug-induced based on the fact that levels of alanine aminotransferase and aspartate aminotransferase decreased after discontinuation of all drugs (STP, VPA and CLB), but the causal drug could not be determined. Despite drug discontinuation, the patient's liver dysfunction progressed to multiple organ failure, and she died of acute respiratory distress syndrome.

3.3. Effectiveness

Table 4 shows the responder rate according to seizure type among new patients in the effectiveness analysis set. In all seizure types, the responder rate was consistent over the 104-week observation period. A pooled analysis of the number of cases in which seizures were reduced by 75 % was performed in patients in the responder analysis set (i.e. the

Table 2
Adverse drug reactions occurring in ≥1 % of patients.

ADRs[a], n (%)	Continuous-use patients[b] (n = 34)		New patients[c] (n = 376)	
	Non-serious	Serious	Non-serious	Serious
Somnolence	4 (11.8)	0	137 (36.4)	8 (2.1)
Loss of appetite	5 (14.7)	1 (2.9)	80 (21.3)	14 (3.7)
Weight reduction	2 (5.9)	1 (2.9)	12 (3.2)	9 (2.4)
Ataxia/Vertigo	3 (8.8)	0	51 (13.6)	2 (0.5)
Seizures/Convulsive seizures/Tonic convulsions/ Myoclonic seizures/ Atonic seizures (all exacerbation of seizures)	0	0	9 (2.4)	9 (2.4)
Agitation	1 (2.9)	0	9 (2.4)	1 (0.3)
Insomnia	0	0	9 (2.4)	1 (0.3)
Vomiting	1 (2.9)	0	4 (1.1)	2 (0.5)
Irritability	0	0	5 (1.3)	1 (0.3)
Aspiration pneumonia	0	0	0	6 (1.6)
Asthenia	0	0	5 (1.3)	1 (0.3)
Constipation	0	0	6 (1.6)	0
Hypersalivation	1 (2.9)	0	4 (1.1)	1 (0.3)
Dyskinesia	0	0	3 (0.8)	2 (0.5)
Tremors	1 (2.9)	0	4 (1.1)	0
Aggression	0	0	2 (0.5)	2 (0.5)
Eating disorders	0	0	2 (0.5)	2 (0.5)
Mood changes	0	0	4 (1.1)	0
Nausea	0	0	3 (0.8)	1 (0.3)
Rash	0	0	4 (1.1)	0
Malaise	0	0	4 (1.1)	0
Drug concentration increase[d]	2 (5.9)	0	19 (5.1)	5 (1.3)
Decreased platelet count/ Thrombocytopenia	1 (2.9)	0	14 (3.7)	8 (2.1)
Ammonia increase/ Hyperammonemia	0	0	17 (4.5)	1 (0.3)
Liver dysfunction	0	0	10 (2.7)	1 (0.3)
GGT increase	0	0	10 (2.7)	0

ADR: adverse drug reaction; GGT: γ-glutamyl transferase.

[a] Based on the preferred terms of the Japanese language edition, version 22.0, of ICH Medical Dictionary for Regulatory Activities (MedDRA); if multiple ADRs occurred in one patient, the number of patients (%) for each ADR is shown.

[b] Patients in whom stiripentol had been administered prior to its approval because of continuous administration of the drug from the domestic clinical studies and because of private import.

[c] Patients who were given stiripentol for the first time after its approval in November 2012.

[d] Increase in the concentration of concomitant antiseizure medication.

same patient cohort as shown in Table 4). Among those with convulsive seizures, there was at least a 75 % reduction in seizures in 95/260 patients (36.5 %) after 13–16 weeks, 86/264 (32.6 %) after 49–52 weeks, 90/257 (35.0 %) after 101–104 weeks; in those with focal impaired awareness seizures, the number was 50/105 (47.6 %), 47/103 (45.6 %) and 53/105 (50.5 %), respectively, at these timepoints. In those with generalized myoclonic seizures and/or generalized atypical absence seizures, the number was 46/91 (50.6 %) after 13–16 weeks, 53/95 (55.8 %) after 49–52 weeks, and 51/90 (56.7 %) after 101–104 weeks. Of the new patients, seven patients maintained a seizure-free status for at least 1 year.

Among new patients in the effectiveness analysis set, overall improvement after 104 weeks or at the time of drug discontinuation was rated as marked in 18.7 % (66/353 patients), moderate in 26.6 % (94/353 patients), mild in 20.1 % (71/353 patients), unchanged in 29.5 % (104/353 patients), and worsened in 5.1 % (18/353 patients). The rate of moderate or higher improvement was 45.3 % (160/353 patients). Table 5 shows the rate of overall improvement in patient groups based on baseline demographic and clinical characteristics.

Table 3
Adverse drug reactions in new patients (patients who took stiripentol for the first time after its approval in November 2012) stratified by patient background characteristics.

Characteristic	Patients with ADRs, n/N	Incidence, %	P-value
Sex			
Male	135/193	70.0	1.00
Female	128/183	70.0	
Age at the time of initiation of STP administration			
0–2 years	58/95	61.1	0.002
3–5 years	41/66	62.1	
6–11 years	46/70	65.7	
12–18 years	51/67	76.1	
≥19 years	67/78	85.9	
Age at disease onset			
0–3 months	44/68	64.7	0.63
4–6 months	136/185	73.5	
7–9 months	50/76	65.8	
10–11 months	12/18	66.7	
1 year	12/15	80.0	
≥2 years	5/7	71.4	
SCN1A mutations present			
Yes	116/161	72.1	0.86
No	35/50	70.0	
CYP2C19 genotype			
Extensive metabolizer	10/16	62.5	1.00
Poor metabolizer	3/4	75.0	
Family history of epilepsy or febrile convulsions			
No	202/288	70.1	1.00
Yes	46/65	70.8	

ADR: adverse drug reaction; CYP2C19: cytochrome P450 2C19; *SCN1A*: sodium channel voltage-gated type 1 alpha subunit; STP: stiripentol.

4. Discussion

This is a large-scale surveillance study involving Japanese patients with DS who have been treated with STP in a real-world clinical setting for up to 7 years. The current interim report describes the safety and effectiveness of STP for 2 years, and shows that ADRs occurred in 70.0 % of the new patients (263/376 patients), which was lower than the incidence of 91.7 % (22/24 patients) seen in previous clinical studies conducted in Japan (Inoue et al., 2014, 2015). In those clinical studies, the incidence of ADRs was highest during the early stages of treatment, occurring in 83.3 % of patients in the first 4 weeks of drug administration, 75.0 % in weeks 5–16, and 66.7 % from 17 to 56 weeks (Inoue et al., 2014, 2015). The approved dosage of STP in Japan is based on the clinical trials conducted in Japan (Inoue et al., 2014, 2015), which used a starting dose of 20 mg/kg/day or 1000 mg/day (in patients weighing >50 kg) and increased the dose to the defined maximum level relatively rapidly. The dosage could be increased by 10 mg/kg at 1-week intervals up to 50 mg/kg/day or 2500 mg/day (body weight >50 kg) (Inoue et al., 2014, 2015). On the other hand, our surveillance study of real-world clinical use of STP found that the mean initial dose for new patients was 13.4 mg/kg/day, and 4 weeks were required to exceed the recommended initial dose of 20 mg/kg/day. The drug continued to be used thereafter at a dose lower than the approved dosage. Therefore, one possible reason for the low incidence of ADRs in our surveillance study is that low initial doses of STP were used, and that the dose of STP was carefully increased during the early weeks of treatment when ADRs are most likely to occur, and thereafter, according to the patient's condition.

Apart from VPA and CLB, bromide was the most frequently used concomitant ASM in this study. This may be due to the fact that bromide

Table 4
Changes in the responder rate over time in new patients (patients who took stiripentol for the first time after its approval in November 2012).

	Responders, n/N[a]	Responder rate, % (95 % CI)	Missing data, n
Convulsive seizures (tonic-clonic seizures and/or clonic seizures)			
After 13–16 weeks	120/260	46.2 (40.0–52.4)	15
After 49–52 weeks	107/264	40.5 (34.6–46.7)	11
After 101–104 weeks	110/257	42.8 (36.7–49.1)	18
Focal impaired awareness seizures			
After 13–16 weeks	57/105	54.3 (44.3–64.0)	7
After 49–52 weeks	49/103	47.6 (37.6–57.7)	9
After 101–104 weeks	58/105	55.2 (45.2–65.0)	7
Generalized myoclonic seizures and/or generalized atypical absence seizures			
After 13–16 weeks	57/91	62.6 (51.9–72.6)	7
After 49–52 weeks	60/95	63.2 (52.6–72.8)	3
After 101–104 weeks	56/90	62.2 (51.4–72.2)	8

CI: confidence interval.
[a] Only patients with one or more attacks in the baseline period (4 weeks before starting stiripentol) were included in the analysis. Among these patients, convulsive seizures were present in 275 patients, focal impaired awareness seizures in 112 patients, and generalized myoclonic seizures and/or generalized atypical absence seizures in 98 patients. The N varies from period to period because patients with missing seizure information were excluded from this analysis.

Table 5
The rate of overall improvement in new patients (patients who took stiripentol for the first time after its approval in November 2012) stratified by patient characteristics.

Characteristic	Marked or moderate improvement, n/N	Improvement rate, % (95 % CI)	P-value
Sex			
Male	80/181	44.2 (36.8–51.8)	0.67
Female	80/172	46.5 (38.9–54.3)	
Age at the time of initiation of STP administration			
0–2 years	50/92	54.4 (43.6–64.8)	0.25
3–5 years	27/62	43.6 (31.0–56.7)	
6–11 years	26/65	40.0 (28.0–52.9)	
12–18 years	29/61	47.5 (34.6–60.7)	
≥19 years	28/73	38.4 (27.2–50.5)	
Age at disease onset			
0–3 months	30/64	46.9 (34.3–59.8)	0.10
4–6 months	66/176	37.5 (30.3–45.1)	
7–9 months	39/73	53.4 (41.4–65.2)	
10–11 months	9/17	52.9 (27.8–77.0)	
1 year	8/12	66.7 (34.9–90.1)	
≥2 years	3/5	60.0 (14.7–94.7)	
SCN1A mutations present			
Yes	78/155	50.3 (42.2–58.4)	0.18
No	18/47	38.3 (24.5–53.6)	
CYP2C19 genotype			
Extensive metabolizer	9/14	64.3 (35.1–87.2)	1.00
Poor metabolizer	2/3	66.7 (9.4–99.2)	
Family history of epilepsy or febrile convulsions			
No	124/272	45.6 (39.6–51.7)	0.40
Yes	24/61	39.3 (27.1–52.7)	

CI: confidence interval; CYP2C19: cytochrome P450 2C19; *SCN1A*: sodium channel voltage-gated type 1 alpha subunit; STP: stiripentol.

is often used to treat DS-related seizures in Japan (Tanabe et al., 2008). In this surveillance study, 74.4 % of the patients (305/410 patients) continued to take STP for up to 104 weeks. This high continuation rate is similar to the continuation rate of STP administration (79.2 %; 19/24 patients) in the previous clinical studies in Japan (Inoue et al., 2014, 2015).

No marked differences were seen in the type of ADRs reported between our surveillance study and the previous clinical studies (Inoue et al., 2014, 2015), and no new safety concerns due to STP were found. Although some unexpected ADRs were observed, these events did not have definitive causality with STP. During the surveillance observation period, 24 new patients and two continuous-use patients had an ADR of increased blood concentration of a concomitant ASM that was associated with symptomatic ADRs in all cases, such as somnolence and loss of appetite. Anticonvulsive effects occur due to the interaction between STP and concomitant ASMs, especially CLB, because STP is a powerful inhibitor of CYP enzymes (Giraud et al., 2006; Tran et al., 1997). Drug–drug interactions associated with STP may also cause an increase in concentrations of phenytoin and VPA, as was seen in our surveillance study, where a number of patients showed an increase in the concentration of VPA. It has been suggested that VPA concentrations are likely to increase in patients who are taking topiramate in combination with STP and VPA (Jogamoto et al., 2017). Therefore, if a patient develops somnolence, loss of appetite, or other ADRs attributable to an increase in concomitant drug concentration during treatment with STP, physicians should consider reducing the doses of not only STP, but also the implicated concomitant drugs.

DS is characterized by a higher mortality rate compared with other epileptic syndromes. In a retrospective multicenter study conducted in Japan, the mortality rate associated with DS was 10.1 % (63/623 patients); the common causes of death included sudden death (53 %), acute encephalopathy with status epilepticus (36 %), drowning (10 %), and acute hepatopathy (1%) (Sakauchi et al., 2011). In the present surveillance study, five deaths were reported, so the mortality rate was not high (1.2 %; 5/410 patients); however, this result was obtained over a limited period of only 104 weeks.

There was a significant relationship between patient age at the time of initiation of STP and the development of ADRs. The older the patient was when they started STP treatment, the higher the incidence of ADRs. A previous study has also reported that ADRs (especially gastrointestinal symptoms, such as loss of appetite and weight reduction) with STP were more common in children with DS who were ≥12 years of age than in younger children (Thanh et al., 2002). However, the reason for this finding in the earlier study and in our surveillance study is unclear. No other patient characteristics were associated with the occurrence of ADRs.

Clinical studies with STP in Japan reported a ≥50 % decrease in convulsive seizures in 66.7 % of patients (16/24) after 16 weeks of treatment and in 54.2 % of patients (13/24) after 56 weeks (Inoue et al., 2014, 2015). On the other hand, our surveillance study found that the responder rates to convulsive seizures were 46.2 % (120/260 patients) 16 weeks later, 40.5 % (107/264 patients) 52 weeks later, and 42.8 % (110/257 patients) 104 weeks later, which were slightly lower than the results of clinical studies in Japan (Inoue et al., 2014, 2015). In these clinical studies, the concomitant use of three drugs (STP, CLB, and VPA) was required, concomitant use of bromide was allowed, diazepam could be used on an emergency basis, and the dose of STP was increased in compliance with the protocol (Inoue et al., 2014, 2015). In contrast, the current surveillance study was carried out in a real-world clinical setting, where the STP dose and the type and dose of concomitant ASMs were determined by the patient's treating physician. We found that, in clinical practice, physicians tended to use a lower dosage of STP than the approved dosage, and titrated it more slowly than in the previous clinical studies (Inoue et al., 2014, 2015). This was possibly associated with a lower incidence of ADRs, but may also have reduced effectiveness of STP and led to the decreased responder rates. Unlike the previous clinical studies which used predefined patient selection criteria (Inoue et al., 2014, 2015), the current surveillance study was conducted in all patients with DS who received STP. Moreover, a limitation of our surveillance study is that data on seizure frequency were missing for some patients during the observation period (including the baseline period).

In particular, a large number of patients were excluded from the responder analysis because the number of seizures in the baseline period was <1 or missing, including 101 patients with convulsive seizures, 264 with focal impaired awareness seizures, and 278 with generalized myoclonic seizures and/or generalized atypical absence seizures. These differences between the current surveillance study and the previous clinical studies in Japan (Inoue et al., 2014, 2015) may explain the difference in the reported response rates. Of note, seizure types other than convulsive seizures were not analyzed in the previous clinical studies (Inoue et al., 2014, 2015), whereas our surveillance study found similar responder rates in the other seizure types (Table 4).

The current surveillance study also evaluated overall improvement, which was not assessed in the previous clinical studies (Inoue et al., 2014, 2015). Overall improvement was rated as marked in 18.7 % (66/353 patients) and moderate in 26.6 % (94/353 patients) of new patients after 104 weeks or at the time of drug discontinuation. The combined improvement rate was 45.3 % (160/353 patients). Another 20.1 % of patients (71/353) had a slight overall improvement. On the other hand, symptoms worsened in only 5.1 % of the patients (18/353). Previous studies have suggested that the efficacy of STP was age-dependent, and was particularly effective in patients aged ≤2 years (Chiron, 2019) and less effective in adults (Balestrini and Sisodiya, 2017). In the current surveillance study, however, there were no significant differences in overall improvement rates between age groups, based on age at the time of STP initiation. Similarly, no significant differences in drug effectiveness were seen between other patient subgroups based on demographic or clinical characteristics.

A German study reported a decrease in the frequency of attacks and hospitalizations after treatment with STP (Strzelczyk et al., 2014). In Japan, previous clinical trials have shown a decrease in seizure duration (Inoue et al., 2014, 2015), which may reduce the number of emergency hospitalizations for status epilepticus. Reducing hospitalization rates would not only improve the quality of life of patients and caregivers, but also contribute to a reduction in medical costs. Unfortunately, our study did not examine the frequency of hospitalization before and after STP administration, but we recommend that future studies measure the impact of STP treatment on hospitalization rates and costs in Japan.

A strength of our study was the assessment of STP safety and effectiveness in a large number of patients with DS in a real-world setting over a long treatment duration. Therefore, our findings may be generalized to a similar (diverse) population of patients with DS. However, this type of surveillance conducted in real-world clinical setting does not include a control group, limiting our ability to accurately assess the effectiveness and tolerability of STP compared with previous clinical studies (Inoue et al., 2014, 2015). Although diagnostic criteria were presented in this study, DS was ultimately diagnosed at the discretion of the individual physician, and genetic testing was not required. Therefore, the accuracy of DS diagnosis was a potential study limitation, as well as the fact that a subjective method was used as an evaluation index of efficacy. However, we believe that conducting a large-scale survey of all patients diagnosed with DS in clinical practice, rather than limiting the survey to patients with positive genetic tests, is meaningful in order to understand the effectiveness and safety of STP in a routine clinical setting.

5. Conclusions

The present post-marketing surveillance study of all patients with DS who were given STP in Japan found that STP did not cause any new safety concerns. Thus, STP could be administered safely, effectively, and for a long period of time for the treatment of patients with DS.

Author contributions

Miyuki Yamada, Katsuyoshi Suzuki, and Daisuke Matsui were involved in implementing the surveillance, collecting and interpreting the data, and preparing the paper. Yushi Inoue and Yoko Ohtsuka, who are medical specialists for this surveillance, were involved in offering advice for the surveillance, making medical assessments of the surveillance results, and provided critical review of the paper. This assistance was funded by Meiji Seika Pharma Co., Ltd. All authors approved the final version of the paper, and agreed to accept accountability for all the items described in the paper.

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Declaration of Competing Interest

Miyuki Yamada, Katsuyoshi Suzuki, and Daisuke Matsui are employees of Meiji Seika Pharma Co., Ltd. Yushi Inoue and Yoko Ohtsuka have no conflicts of interest to declare. All authors confirm that they have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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