seizure types and Total seizure burden. ZX008 may represent an effective new treatment option for Dravet syndrome.

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Fenfluramine HCl Provides Long-Term Clinically Meaningful Reduction in Seizure Frequency: Results of an Open-Label Extension Study

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Introduction: Fenfluramine (FFA) has demonstrated superior efficacy compared to placebo for the reduction in frequency of convulsive seizures in children and young adults (2-18 years old) with Dravet syndrome in two recently completed Phase 3 clinical trials. Here we report the preliminary interim analysis of the effectiveness and tolerability of FFA in a long-term open label extension study.

Methods: Dravet syndrome patients completing one of the Phase 3 clinical trials were eligible to enroll in the open-label extension (OLE) study. All patients entering the OLE initiated FFA at a dose of 0.2 mg/kg/day regardless of what dose they were receiving in the core trial. After 4 weeks, the dose could be titrated up in 0.2 mg/kg/day increments up to a maximum of 0.8 mg/kg/day (max 30 mg/day; 0.5 mg/kg/day [max 20 mg/day] if patient was also on stiripentol). Effectiveness and safety were assessed at months 1, 2, and 3 and then 3-month intervals thereafter.

Results: A total of 232 patients have enrolled in the study as of March 13, 2018. A total of 128 (55.2%) were male, and the mean ± SD age was 9.1 ± 4.7 years. A total of 22 (9.5%) patients discontinued treatment: lack of efficacy (16), subject withdrawal (2), adverse event (1), death (1, SUDEP), physician decision (1), and withdrawal by caregiver (1). Median duration of treatment with FFA was 256 days (range, 58-634 days). The median percent reduction in monthly convulsive seizure frequency over the entire OLE treatment period as compared with the baseline frequency established in the core Phase 3 studies was 66.8%. A clinically meaningful reduction in convulsive seizure frequency was noted at the first observation (month 1) during OLE and continued over time (Figure). Over the entire observation period, 64.4% of patients demonstrated a 50% reduction in convulsive seizure frequency and 41.2% demonstrated a 75% reduction. At 12 months 70.4% of caregivers and 77.8% of investigators rated patients as "much improved" or "very much improved." The most common non-cardiovascular adverse events occurring in ≥10% of patients were pyrexia (21.6%), nasopharyngitis (19.4%), decreased appetite (15.9%), influenza (11.6%), diarrhoea (10.8%), and upper respiratory infection (10.3%). No patient showed echocardiographic or clinical signs of cardiac valvular heart disease or pulmonary hypertension at any time.

Conclusions: These preliminary OLE study results demonstrate FFA to provide clinically meaningful and substantial reductions in convulsive seizure frequency over time; while generally well tolerated. FFA represents a novel, highly effective antiepileptic treatment option for DS patients.

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Long-Term Cardiovascular Safety of Fenfluramine HCl in the Treatment of Dravet Syndrome: Interim Analysis of an Open-Label Safety Extension Study

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Introduction: In two recently completed Phase 3 clinical trials, fenfluramine (FFA) has demonstrated superior efficacy vs placebo for convulsive seizure reduction in children and young adults (2-18 years old) with Dravet syndrome (DS). FFA, previously marketed for weight loss, was withdrawn from the market in 1997 following reports of cardiac valvular heart disease (VHD) and pulmonary hypertension in obese adults treated with ≥60 mg/day. Here we report the cardiovascular safety findings from an interim analysis of the long-term safety extension study of low-dose FFA for DS in children and young adults.

Methods: Patients with DS who successfully completed a Phase 3 study were eligible for this open-label extension (OLE) study. Patients with current cardiac VHD, pulmonary arterial hypertension, or any degree of aortic or mitral valve regurgitation were excluded from the Phase 3 trials. All patients in the OLE were started on FFA at 0.2 mg/kg/day, after 4 weeks the dose could be titrated 0.2 mg/kg/day every 2 weeks based on effectiveness and tolerability to 0.8 mg/kg/day to maximum 30 mg/day (0.5 mg/kg/day and 20 mg/day if they were taking concurrent stiripentol). Echocardiography was performed at extension study baseline, Week 6, and 3 monthly thereafter to assess cardiac valve function and pulmonary artery pressure. Cardiac VHD was defined as

presence of ≥ moderate mitral regurgitation and/or ≥ mild aortic regurgitation. Pulmonary hypertension was considered present when pulmonary artery systolic pressure exceeded 35 mmHg.

Results: 232 patients enrolled in the study as of cut off at March 13, 2018 and received ≥ one dose of FFA, (9.5%) patients have discontinued treatment due to: lack of efficacy (16), subject withdrawal (2), adverse event (1), death (1, SUDEP), physician decision (1), or withdrawal by caregiver (1). Demographics include 128 (55.2%) male patients, mean ± SD age of 9.1 ± 4.7 years. The median FFA treatment duration was 256 days (58-634 days). No patient demonstrated cardiac VHD or pulmonary arterial hypertension during the study. The most common finding was intermittent and transient physiologic/trace valve regurgitation, also seen in normal healthy children and young adults.

Conclusions: The results of this long-term safety study demonstrate no development of cardiac VHD or pulmonary hypertension after daily treatment with FFA for ≤ 21 months in DS patients. Together with the efficacy data from the Phase 3 trials, fenfluramine appears to have a positive benefit-risk profile in this patient population.

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A Study of Trends of Intravenous Antiepileptic Drugs in Patients with Status Epilepticus

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Background and Objective: Status epilepticus (SE) called the neurological emergency. Currently, we have many kinds of intravenous antiepileptic drugs (AEDs) despite conventional antiepileptic drugs and new antiepileptic drugs. Therefore, objective of this study is acquiring for trends and cumulative cost of intravenous AEDs in patients with SE.

Methods: The study was a descriptive, retrospective study. Data from electronic hospital database were collected between 1st October 2015 to 30st September 2018 (financial year 2016 to 2018) in patients with SE who received intravenous AEDs (conventional AEDs; phenytoin, sodium valproate, phenobarbital and newer AEDs; levetiracetam) at Srinagarind hospital.

Results: The results showed that 190 SE patients (93 men and 97 women) whose mean age 39.14 years ± 24.24. Convulsive status epilepticus was most common (294 events, 98%) vs non-convulsive status epilepticus (6 events, 2%). Consideration of hospital admission rate of conventional AEDs, we found phenytoin and phenobarbital were decreased (phenytoin; 39.20% in 2016, 36.64% in 2017, 33.60% in 2018 and phenobarbital 14.86% in 2016, 14.85% in 2017, 5.60% in 2018) and sodium valproate was increased in 2018 (14.86% in 2016, 13.86% in 2017, 16.80% in 2018). If considerate proportions of hospital admission rate who received each type of intravenous AEDs between conventional AEDs and newer AEDs were associated with a decreased rate of conventional AEDs used (conventional AEDs; 68.92% in 2016, 65.35% in 2017, 56.00% in 2018 and newer AEDs; 31.08% in 2016, 34.65% in 2017, 44.00% in 2018). Moreover, proportions of first- line treatment of intravenous AEDs were increased in newer AEDs (28.57% in 2016, 30.00% in 2017 and 47.78% in 2018; 19.21% increasing).

Conclusion: Trends of newer AEDs used were increased, it appears that trends of intravenous AEDs used were changed. This study will be a useful basic information for evaluate pharmacy purchasing system and drug use evaluation.

Key words: trends, intravenous antiepileptic drugs

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Cost and Expense of Intravenous Levetiracetam for Treatment of Acute Seizure in Tertiary Hospital in Thailand

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Background: Epilepsy is a chronic condition that required long-term treatment with antiepileptic agents. Levetiracetam is the new generation antiepileptic agent which is commonly used for treatment of various type of seizure, as well as status epilepticus. The costs of treatment are very impact on patients with epilepsy and health system. The availability of an intravenous preparation is advantage, but with the high price, intravenous levetiracetam treatment tends to be more expensive than conventional treatments. This study aimed to describe the cost and expense of intravenous levetiracetam used to control symptoms in patients with acute seizure.

Methods: A retrospective descriptive study conducted at Khon Kaen University Hospital in Thailand. Patients over 15 years old who had diagnosed as acute seizure and had received intravenous levetiracetam treatment between January 1, 2010 and December 31, 2014 were enrolled into the study. The cost of levetiracetam used and the expense of treatment that the patients had to pay for control seizure were determined. Data of all eligible patients were analyzed by descriptive statistics. The cost and expense of intravenous levetiracetam treatment are expressed in term of median and interquartile range (IQR).

Results: During the study period, 332 patients with acute seizure receiving intravenous levetiracetam were included. Among these patients, 91 were status epilepticus and 241 were non-status epilepticus. The average age of patients was 55.7 (20.4) years with qual sex distribution. Most patients received intravenous levetiracetam for loading dose of 1,000 mg (167 patients: 50.3%) and maintenance dose of 1,000 mg/day (254 patients: 76.5%), respectively. The median cost of intravenous levetiracetam used per admission for patients with acute seizure was 9,095 THB (363.8 USD). From the patient's perspective, the median total expense per admission was 162,609 THB (6,504.4 USD), which was due to the expense for intravenous levetiracetam 12,384 THB (495.4 USD)