

# Efficacy and safety evaluation of pregabalin treatment over 52 weeks in patients with diabetic neuropathic pain extended after a double-blind placebo-controlled trial

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## ABSTRACT

**Aims/Introduction:** Diabetic peripheral neuropathy (DPN) is often associated with pain, and thus a new treatment option is anticipated. We recently showed the efficacy of pregabalin in a randomized, double-blind, placebo-controlled, 14-week trial in Japanese patients with painful DPN. In the present study, we evaluated the long-term efficacy and safety of pregabalin for the relief of painful DPN.

**Materials and Methods:** A total of 123 patients were enrolled in a 52-week open-label study, from among those who participated in the preceding double-blind trial. The subjects received pregabalin 150–600 mg/day. Pain intensity was measured using the short-form McGill pain questionnaire (SF-MPQ: total score, visual analog scale and present pain intensity).

**Results:** The efficacy parameter SF-MPQ showed a decrease over the treatment period. The changes in visual analog scale and present pain intensity at the final evaluation were  $-25.4$  mm and  $-0.7$ , respectively, suggesting an analgesic effect of pregabalin. Commonly reported adverse events were somnolence, weight gain, dizziness and peripheral edema, but most of them were mild to moderate in intensity. No new concerns about safety as a result of long-term administration of pregabalin were identified.

**Conclusions:** The findings from this trial suggest that long-term treatment with pregabalin is beneficial for pain relief in patients with DPN. This trial was registered with ClinicalTrials.gov (no. NCT00553280). (*J Diabetes Invest*, doi: 10.1111/j.2040-1124.2011.00122.x, 2011)

**KEY WORDS:** Diabetic peripheral neuropathy, Neuropathic pain, Pregabalin

## INTRODUCTION

Neuropathy, mainly associated with disorders of sensory nerves and autonomic nerves, is one of the most common complications in diabetic patients. It can be classified into two categories: diffuse symmetric neuropathy and mononeuropathy. In the clinical setting, sensorimotor and autonomic neuropathy occurs most commonly as polyneuropathy, thereby causing symptoms in the distal extremities, such as pain, dysesthesia, paresthesia and numbness, and autonomic symptoms<sup>1</sup>. These symptoms are often associated with psychosocial distress, such as sleep disorder, lowered quality of life and anxiety/depression<sup>2,3</sup>.

Diabetic peripheral neuropathy (DPN) is one of the disorders that typically causes chronic neuropathic pain<sup>4</sup>. The International Association for the Study of Pain defines neuropathic pain as 'pain arising as a direct consequence of a lesion or disease affecting the somatosensory system'<sup>5</sup>. Some clinical symptoms might be accompanied by stimulation-independent pain (spontaneous pain), hyperalgesia and allodynia induced by minor tactile stimuli.

Pregabalin, a  $\gamma$ -aminobutyric acid derivative used for the treatment of neuropathic pain, is considered to produce its analgesic effect as follows: it binds to  $\alpha_2\delta$  subunits of voltage-dependent calcium channels to reduce the influx of calcium ions at nerve presynapses, resulting in the decreased release of various excitatory neurotransmitters, including glutamic acid<sup>6,7</sup>. Pregabalin is recommended as one of the first-line drugs in the pharmacological treatment guidelines for neuropathic pain in European countries and the USA<sup>8,9</sup>. Also, in Japan, it is expected to provide a new treatment option for painful DPN. In one previous 14-week, phase III, randomized, double-blind, placebo-controlled trial carried out in Japan<sup>10</sup>, pregabalin

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HbA<sub>1c</sub> is expressed by National Glycohemoglobin Standardization Program value.

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Received 2 December 2010; revised 21 February 2011; accepted 3 March 2011

(300 and 600 mg/day, given b.i.d.) significantly lessened the pain at all time-points during the 13-week treatment period when compared with the placebo. However, the long-term efficacy and safety of pregabalin treatment remain unclear. The present study is of patients with painful DPN who continued to receive 150–600 mg/day pregabalin after completion of the 13-week treatment in the preceding phase III trial<sup>10</sup> in an open-label manner for 52 weeks to evaluate its efficacy and safety.

The present study was carried out from February 2008 to January 2010 as a collaborative work at 36 medical institutions (Appendix S1). It was carried out in accordance with Good Clinical Practice after being reviewed and approved by the Institutional Review Board at each participating institution before initiation.

## MATERIALS AND METHODS

### Subjects

The subjects were patients who had completed 13 weeks of treatment in the preceding phase III trial<sup>10</sup>. The patients had no serious adverse events for which a causal relationship with pregabalin was suspected, nor did they have any problems with respect to treatment compliance. The inclusion criteria of the preceding phase III trial were: (i) patients with a diagnosis of peripheral symmetry sensorimotor polyneuropathy as a result of diabetes mellitus (type 1 or 2) based on a modified version of the simplified diagnostic criteria for distal symmetric polyneuropathy proposed by the Diabetic Neuropathy Study Group in Japan<sup>11</sup>; (ii) patients whose glycemic control was judged to be constant; (iii) patients aged 18 years and over; (iv) patients whose duration of pain was 1 year or more; (v) patients with a visual analog scale (VAS) value of 40 mm or more; and (vi) patients with a mean pain score in the 7-day screening period recorded in a pain diary of 4 or more. The exclusion criteria were: (i) a disease that might affect pain assessment; (ii) arm/leg (excluding toes) amputation; and (iii) creatinine clearance (CLCr) of 30 mL/min or less. Before the study, the investigator gave each subject full written information regarding the content of the study and obtained his/her consent in writing to voluntarily participate in the present study.

### Administration Method

The study schedule is shown in Figure 1. The dose of pregabalin was set at 150 mg/day (b.i.d.) for the first week, and then adjusted in increments or decrements of 150 mg/day, within the range of 150–600 mg/day (b.i.d.), at every hospital visit. Treatment was carried out for 52 weeks. However, because this drug is excreted unchanged from the kidney, a decrease in CLCr of 50% might increase the exposure to the drug by approximately twofold. Therefore, in patients with CLCr of 60 mL/min or less, the highest dose was set at 300 mg/day (b.i.d.). Furthermore, in patients who had received a dose of 300 mg/day or more, the treatment was completed through a 1-week dose reduction phase.

## Observations/Evaluations and Evaluation Methods

Observations and evaluations were made according to the schedule shown in Figure 1. Efficacy was evaluated using the short-form McGill pain questionnaire (SF-MPQ)<sup>12</sup>. The SF-MPQ consisted of three components: (i) the presence or absence of pain in the last 1 week (15 pain descriptors [sensory, affective] were rated on a four-score scale of 0 [none] to 3 [severe], and the scores were summed [sensory, affective and total scores]); (ii) pain intensity in the last 1 week (VAS value) rated on a 100-mm VAS scale; and (iii) present pain intensity (PPI) score (rated on a six-score scale of 0 [no pain] to 5 [excruciating]). Furthermore, the presence or absence of allodynia or hyperalgesia was also evaluated before treatment with the study drug and at the final evaluation.

In the safety evaluation, 'adverse event' was defined as any untoward medical occurrence in a subject who received the study drug, and the type of adverse event, time of onset, severity, measures taken, outcome and causal relationship with the study drug were evaluated. Laboratory tests were carried out with respect to hematology, blood biochemistry and urinalysis. The resulting data were regarded as laboratory abnormalities when they were out of the prespecified range, regardless of whether the pretreatment values were in or outside the range.

### Statistical Analysis

Efficacy analysis was carried out in the full analysis set of subjects who had received at least one dose of the study drug and had undergone efficacy evaluation at least once. The results of SF-MPQ as the efficacy end-point were summarized in the descriptive statistics, and no inferential analysis was carried out. Safety analysis was carried out in the set of subjects who had received at least one dose of the study drug.

## RESULTS

### Patient Background

Of the 317 subjects enrolled in the preceding phase III trial, 123 subjects received pregabalin in the present study and 97 (78.9%) completed the 52-week treatment. A total of 26 subjects withdrew from the study – 19 withdrew because of an adverse event (causality related to the study drug, 12; causality unrelated, 7), three withdrew because of insufficient therapeutic response and four withdrew for other reasons. No subjects were excluded from the efficacy or safety analysis set.

The demographic data and baseline characteristics of the subjects are summarized in Table 1. Male subjects predominated; mean age was 61.7 years and HbA<sub>1c</sub> was 7.4%<sup>13</sup>. The mean duration of illness was 14.1 years for type 1 diabetes mellitus, 13.8 years for type 2 diabetes mellitus and 4.4 years for painful DPN.

### Duration of Administration and Dose

The total number of subjects treated for 52 weeks or longer was 95, and the median duration of administration was 369 days (range 5–378 days). The dose at the final evaluation was

Phase III trial (Study No. A0081163)	Long-term treatment (Study No. A0081164)																
Double- blind	Open-label																
	Dose adjustment/maintenance phase															Dose reduction phase	
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**Figure 1** | Study design. (●) Carried out at hospital visit made at week 13 of the phase III trial. <sup>a</sup>Creatinine clearance (CLcr) was calculated by the Cockcroft–Gault formula using the data of the preceding phase III trial. In subjects with CLcr > 30 and ≤60 mL/min, the highest dose was set at 300 mg/day. <sup>b</sup>Hospital visit 1 of the present study corresponds to the hospital visit made at week 13 of the phase III trial. <sup>c</sup>Final visual acuity testing and fundus photography were carried out within 1 week of the final hospital visit. <sup>d</sup>Carried out on the day of the final hospital visit (visit 16 or 17). <sup>e</sup>Taken within 1 week of the final hospital visit (visit 16 or 17).

150 mg/day in 28 subjects, 300 mg/day in 38 subjects, 450 mg/day in 16 subjects and 600 mg/day in 41 subjects, and the mean dose was 384.8 mg/day. Furthermore, the principal diabetic medicines concomitantly used during the present study were insulin (48 subjects), glimepiride (36 subjects), metformin (32 subjects), voglibose (30 subjects) and pioglitazone (26 subjects).

### Efficacy

The mean SF-MPQ total score was 9.4 at baseline, but it decreased to 4.7 at the final evaluation (change from baseline: −4.7). The mean VAS value and PPI score were 52.8 mm and 1.9, respectively, at baseline, but they decreased to 27.4 mm and 1.2, respectively, at the final evaluation (change from baseline: −25.4 mm and −0.7, respectively; Table 2, Figure 2). These findings suggest an analgesic effect of pregabalin when used over a long period.

The percentage of subjects who achieved complete relief of pretreatment allodynia or hyperalgesia was 73.7% (14/19 subjects) for allodynia and 45.8% (11/24) for hyperalgesia at the final evaluation. In contrast, the percentage of subjects in whom allodynia or hyperalgesia had newly appeared at the final evaluation accounted for 2.9% (3/104 subjects) and 4.0% (4/99), respectively.

### Safety

#### Adverse Events

Treatment-related adverse events occurred in 87 subjects (70.7%). The most common/frequent events were somnolence in 28 subjects (22.8%), weight gain in 27 subjects (22.0%), dizziness in 25 subjects (20.3%) and peripheral edema in 19 subjects (15.4%; Table 3). These adverse events ranged from mild to moderate in severity in most subjects, and the serious treatment-related

**Table 1** | Demographic data and baseline characteristics of subjects

No. subjects	123
Sex (male/female)	100/23
Age (years), <i>n</i> (%)	
18–44	6 (4.9)
45–64	71 (57.7)
≥65	46 (37.4)
Mean (±SD)	61.7 (10.0)
Range	36–85
Height (cm)	
Mean (±SD)	164.2 (8.4)
Range	140.7–182.3
Body weight (kg)	
Mean (±SD)	66.2 (11.7)
Range	41.3–104.5
Body mass index (kg/m <sup>2</sup> )	
Mean (±SD)	24.5 (3.8)
Range	17.3–38.3
Diabetes type (type 1/type 2)	7/116
Duration of type 1 diabetes (years)	
Mean (±SD)	14.1 (5.9)
Median	16.0
Range	5.2–21.5
Duration of type 2 diabetes (years)	
Mean (±SD)	13.8 (8.8)
Median	11.8
Range	1.5–40.9
Duration of peripheral neuropathic pain (years)	
Mean (±SD)	4.4 (3.0)
Median	3.3
Range	1.4–19.8
HbA <sub>1c</sub> (NGSP value [%])*†	
Mean (±SD)	7.4 (1.0)
Median	7.4
Range	5.7–10.5
Estimated CLcr‡ (mL/min)	
Mean (±SD)	96.0 (32.8)
Median	91
Range	36.0–251.0
Low CLcr stratum, <i>n</i> (%)§	14 (11.4)
Normal CLcr stratum, <i>n</i> (%)§	109 (88.6)

\*Baseline data. The baseline value in the phase III trial was used for the subjects who received pregabalin in the preceding phase III trial, and the baseline value in the present study was used for those who received the placebo in the phase III trial.

†HbA<sub>1c</sub> values (%) were measured using the standard substance by Japan Diabetes Society (JDS), which are 0.4% lower than those measured by the National Glycohemoglobin Standardization Program (NGSP). The value of HbA<sub>1c</sub> (%) is estimated as a NGSP equivalent value (%) calculated by the formula  $\text{HbA}_{1c} (\%) = \text{HbA}_{1c} (\text{JDS}) (\%) + 0.4\%$ , considering the relational expression of HbA<sub>1c</sub> (JDS) (%) measured by the previous Japanese standard substance and measurement methods for HbA<sub>1c</sub> (NGSP).

‡Calculated from serum creatinine data obtained on the day of hospital visit (visit 5) at week 8 of the phase III trial.

§Low creatinine clearance (CLcr) stratum,  $30 < \text{CLcr} \leq 60$  mL/min; normal CLcr stratum,  $\text{CLcr} > 60$  mL/min.

**Table 2** | Summary of short-form McGill pain questionnaire

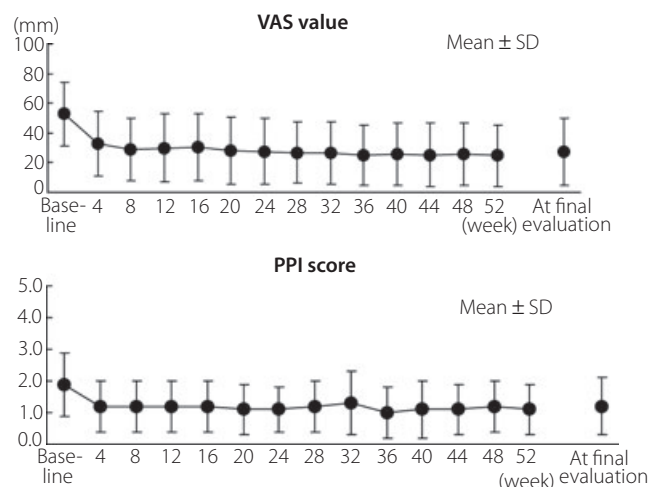
Time point	Sensory score	Affective score	Total score	VAS (mm)	PPI
Baseline*					
<i>n</i>	123	123	123	123	123
Mean (SD)	7.4 (5.5)	2.0 (2.5)	9.4 (7.5)	52.8 (21.7)	1.9 (1.0)
Median	6.0	1.0	8.0	57.0	2.0
Range	0–30	0–12	0–42	1–98	0–5
Endpoint†					
<i>n</i>	123	123	123	123	123
Mean (SD)	3.9 (4.8)	0.8 (1.9)	4.7 (6.5)	27.4 (22.7)	1.2 (0.9)
Median	3.0	0.0	3.0	22.0	1.0
Range	0–30	0–12	0–42	0–95	0–5
Change from baseline to endpoint‡					
<i>n</i>	123	123	123	123	123
Mean (SD)	−3.5 (5.1)	−1.2 (2.4)	−4.7 (6.8)	−25.4 (26.4)	−0.7 (1.1)
Median	−3.0	0.0	−4.0	−22.0	−1.0
Range	−23–12	−9–8	−32–20	−88–53	−4–3

VAS, visual analogue scale; PPI, present pain intensity; SD, standard deviation.

\*Baseline data: the baseline value in the phase III trial was used for the subjects who received pregabalin in the preceding phase III trial, and the baseline value in the present study was used for those who received placebo in the phase III trial.

†Last evaluation of each subject during the adjustment/maintenance phase or early termination assessment for subjects who discontinued the study.

‡Negative values of changes indicate an improvement in pain symptom.



**Figure 2** | Time course changes of visual analog scale (VAS) value and present pain intensity (PPI) score. The baseline value in the phase III trial was used for the subjects who received pregabalin in the preceding phase III trial, and the baseline value in the present study was used for those who received the placebo in the phase III trial. The at final evaluation value is the time at which the final evaluation was made in individual subjects during the dose adjustment/maintenance phase (or at which dosing was discontinued in the case of withdrawn subjects).

**Table 3** | Treatment-related adverse events (incidence:  $\geq 3\%$ )

No. subjects included in safety evaluation	123	
No. subjects with adverse event (%)	87	(70.7)
Somnolence	28	(22.8)
Weight gain	27	(22.0)
Dizziness	25	(20.3)
Peripheral edema	19	(15.4)
Face edema	8	(6.5)
Edema	6	(4.9)

Data were compiled with reference to the Medical Dictionary for Regulatory Activities (MedDRA version 12.1).

adverse event was osteonecrosis in one subject (terminology reported by the physician: right femoral head necrosis; measures taken: drug withdrawal; outcome: recovered). Another event was cerebral infarction in one subject (severity: moderate; measures taken: drug withdrawal; outcome: relieved). The median time of onset of the central nervous system-related adverse events caused by pregabalin was 13.5 days for somnolence and 16.0 days for dizziness, and the median duration of events in subjects who completed the 52-week treatment was 61.0 days and 22.0 days, respectively. Furthermore, congestive heart failure (moderate) and angina pectoris (mild) were each observed in one subject, as cardiovascular events.

#### Laboratory Abnormalities

The most common/frequent laboratory abnormalities (incidence:  $\geq 20\%$ ) observed were blood glucose, HbA<sub>1c</sub> and triglyceride levels exceeding their respective prespecified ranges, and positive urine sugar, urinary protein and urinary occult blood. An increase in creatine kinase (three subjects), increase in alanine aminotransferase (one subject), increase in blood urea (one subject), decrease in neutrophil count (one subject), decrease in platelet count (one subject) and hyperuricemia (one subject) were reported as treatment-related adverse events. However, all but hyperuricemia (moderate) were of mild severity.

Blood glucose and HbA<sub>1c</sub> showed no notable difference in values before and after treatment (mean blood glucose level 149.4 vs 143.6 mg/dL; mean HbA<sub>1c</sub> level [National Glycohemoglobin Standardization Program value]<sup>13</sup> 7.4 vs 7.3%). This tendency was the same in the case of subjects with or without weight gain and in subjects with or without concomitant diabetic medication.

#### Other Safety Variables

Regarding blood pressure and pulse rate, a decrease in systolic blood pressure (two subjects, 1.6%), increase in systolic blood pressure (one subject, 0.8%), decrease in diastolic blood pressure (one subject, 0.8%) and increase in diastolic blood pressure (one subject, 0.8%) were observed as clinically significant changes seen at the final evaluation (events in which the values exceeded the prespecified range). Pulse rate showed no change. The mean change in bodyweight from the baseline to the final evaluation was +2.4 kg.

During the present study, peripheral edema (regardless of causality) was observed in 21 subjects (16 subjects, mild; five subjects, moderate), and its resolution by the end of treatment was confirmed in 14 (70.0%) of the 20 subjects (95.2%) who had continued treatment.

#### DISCUSSION

Chronic pain in DPN, when of sufficient severity, has been treated with tricyclic antidepressant drugs, anti-epilepsy drugs, mexiletine or, in some cases, opiates, in Japan<sup>14</sup>. In overseas countries, in contrast, the efficacy of pregabalin has been established in randomized, double-blind, placebo-controlled studies<sup>15–20</sup>, and it is recommended as one of the first-line drugs for the treatment of neuropathic pain (including painful DPN) in clinical guidelines<sup>8,9</sup>. Most recently, we found a significant improvement of pain and showed the safety profile of pregabalin treatment in a 14-week, phase III, randomized, double-blind clinical trial in Japanese patients<sup>10</sup>, confirming the results obtained from overseas trials.

In the present study, we evaluated the efficacy and safety of 150–600 mg/day pregabalin given for a longer period (52 weeks) in patients with painful DPN. The present study showed that total score, VAS value and PPI score obtained using SF-MPQ were improved at the final evaluation, as compared with the corresponding baseline data, and that the VAS value and PPI score were maintained over 52 weeks, suggesting a long-term analgesic effect of pregabalin. With regard to the proportion of patients with  $\geq 30$  and  $\geq 50\%$  improvement in VAS value from baseline, a well-known efficacy measurement method might be considered to be clinically important<sup>21</sup>; based on this method, the responder rates in these patients (65.9 and 56.1%, respectively) supported the efficacy of pregabalin. In addition, it was also suggested that pregabalin was effective against allodynia and hyperalgesia, which frequently accompany neuropathic pain.

With regard to safety, somnolence, weight gain, dizziness and peripheral edema occurred as treatment-related adverse events, but they were of mild to moderate severity and did not result in study discontinuation in most subjects. Dizziness and somnolence - events with a high incidence - appeared relatively early in the course of treatment (median time of onset 13.5–16.0 days), but they disappeared in many subjects during treatment (median duration of event 22.0–61.0 days). Furthermore, although weight gain in diabetic patients might be a concern because of the effect on glycemic control, neither blood glucose nor HbA<sub>1c</sub> showed any difference between the values obtained before and after treatment. Also, in the case of peripheral edema, although its incidence was slightly high, there were no severe cases and its disappearance during treatment was confirmed in many subjects (14/21). In addition, the incidence of peripheral edema occurring with or without the concomitant use of pioglitazone, which is a diabetes drug known to cause edema, was 26.9% in subjects with concomitant use (7/26 subjects) and 14.4% in subjects without concomitant use (14/97). That is, the incidence was higher in



subjects with concomitant use, but drug withdrawal was limited to one subject (outcome: recovered). The severity of peripheral edema and other events related to edema (face edema, edema, generalized edema, etc.) were mild or moderate in subjects. The adverse events detected in the present study were the same as those observed in our phase III trial<sup>10</sup>, and no unexpected events occurred after long-term treatment.

The treatment of neuropathic pain in older patients can be challenging and complex as a result of an increased risk of adverse effects and problems with drug interactions<sup>22</sup>. In the present study, the improvement in pain was observed regardless of age (mean change from baseline in VAS: -28.7 mm in <65 years-of-age group, -19.8 mm in ≥65 years-of-age group), and the incidence of adverse events appeared to be unrelated to age (70.1% in <65 years-of-age group, 71.7% in ≥65 years-of-age group). As has been discussed, pregabalin, whose long-term efficacy and safety have been shown, is concluded to be clinically useful in the treatment of painful DPN.

## ACKNOWLEDGEMENTS

We gratefully acknowledge the contributions of all of the investigators to this study (all clinical investigators are listed in the online Appendix S1). This study was funded by Pfizer Inc. Kazurou Kaise, Shunya Sato, Kenichi Suzuki, Hiroshi Otani, Kenji Yaginuma, Seiichi Nakayama, Kuniaki Otsuka, Nobuyuki Sato, Makoto Ono, Masaaki Miyamoto, Shinichi Oikawa, Yukiko Onishi, Tetsuya Morishita, Keiichi Shimoda, Masahiko Takai, Yukio Tanaka, Michio Nakagawa, Shunichi Kojima, Hideki Okamoto, Shigeichi Shoji, Motoyoshi Ikebuchi, Koji Manabe, Tsuyoshi Torii, Kenta Sato, Jun Watanabe, Atsushi Ogo, Youichi Tatsukawa, Masaharu Hiraga, Masazumi Takeshita, Yoshito Inobe, Osamu Kanashiro, Seitaro Nakama, Hideaki Tanaka, Nobuyuki Miyake, Hajime Ishii, and Makoto Suda participated in the trials as principal investigators. Jo Satoh has received research funding, lecture fees and consultancy fees from Astellas, Banyu, Daiichi-Sankyo, Dainippon-Sumitomo, Eli Lilly, Novo Nordisk, Ono, Pfizer, Sanofi-Aventis and Takeda. Soroku Yagihashi received a consultancy fee from Pfizer for this study, and has been paid by Pfizer and Ono for giving lectures at scientific meetings. Masayuki Baba has received research funding, lecture fees and consultancy fees from Astellas, Boehringer Ingelheim, Daiichi-Sankyo, Dainippon-Sumitomo, Eisai, Eli Lilly, Kyowa-Kirin, Ono, Otsuka, Pfizer, Takeda, Tanabe-Mitsubishi and Teijin. Makoto Suzuki, Akio Arakawa and Tamotsu Yoshiyama are full-time employees of Pfizer Japan Inc.

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## SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

**Appendix S1** | List of investigators.

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