Efficacy and safety of monotherapy by pegvisomant, a growth hormone receptor antagonist, in Japanese patients with acromegaly

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Abstract. Pegvisomant is a GH receptor antagonist and strong inhibitor of insulin-like growth factor I (IGF-I) production. The treatment goal for acromegaly is to normalize serum IGF-I levels and attenuate associated symptoms. The efficacy and safety of pegvisomant as treatment for acromegaly have been reported in Caucasians, but not in Japanese. Here we report the clinical experience of using pegvisomant in Japanese patients with acromegaly. The efficacy and safety data for pegvisomant from two open-labeled clinical studies in Japan, conducted from 2004 to 2007, were re-analyzed using the new Japanese age- and sex-matched normative ranges for IGF-I. Eighteen patients with active acromegaly were enrolled in an initial pivotal study, and 16 of them were moved to a long-term (max 168 weeks) extension study. The dose of pegvisomant in the extension study was adjusted to 10–30 mg per day according to IGF-I levels. IGF-I normalization was observed in 81.3% (13/16 patients) during the extension study. The mean percentage decrease from baseline in serum IGF-I level was 64.7% at the time of last observation. The clinical symptoms and overall health status were improved, and the ring size was reduced over time until Week 12 and maintained. For safety, no clinically significant changes were observed both in the pituitary tumor size and the anti-GH antibody level. Three subjects were withdrawn from the studies due to an abnormal elevation of liver enzymes which resolved after discontinuation. Pegvisomant demonstrated excellent clinical efficacy and was well tolerated in Japanese patients with acromegaly.

Key words: Pegvisomant, Acromegaly, Insulin-like growth factor I, Adverse event

ACROMEGALY is a chronic disorder caused by growth hormone (GH) hypersecretion, which leads to excess production of insulin-like growth factor I (IGF-I) and results in a multisystem disease characterized by somatic overgrowth, multiple comorbidities, premature mortality, and physical disfigurement [1]. More than 95% of patients with acromegaly harbor a GH secreting pituitary adenoma arising from somatotroph cells [2]. The goal of treatment of acromegaly is to attenuate the symptoms due to GH hypersecretion, to reduce associated comorbidities and the mortality risk to the level of the general population while preserving normal pituitary functions [3].

The first-line strategy for the management of acromegaly is the transsphenoidal adenomectomy [3]. However, for still active patients in whom the complete removal of the tumor was unsuccessful, the medical therapy and the radiation therapy are considered as a second line strategy [3]. Pegvisomant (B2036-PEG injection; Pfizer, Inc., Tokyo, Japan) which is a drug for the medical treatment of acromegaly had a unique mechanism of action. While dopamine agonists and somatostatin analogues act directly on pituitary adenoma to inhibit GH secretion, pegvisomant is an antagonist to compete with endogenous GH at GH receptor, thereby lowering IGF-I production and ameliorating the clinical features associated with acromegaly. In the case of pegvisomant, serum IGF-I is the sole biomarker to determine the injection dosage and assess the efficacy [1, 3].

As for assessing the serum IGF-I value, population-based reference ranges for the Japanese was reported in 1996 [4, 5]. These references were widely used and acceptable in clinical practice. Since the references
of children and those of adults were established independently, they might not properly reflect data during the transition period when serum IGF-I levels rapidly decline. Therefore, the revised normative range was published in 2012 [6].

In order to get approval of pegvisomant for medical therapy of acromegaly, the initial pivotal study and the extension study were conducted from March 2004 to July 2007 (pegvisomant was approved in Japan in January 2007). In the present study, the raw data from the two clinical studies were re-analyzed using the integrated data and revised normative range for IGF-I.

Materials and Methods

Patients

Between March 2004 and November 2004, a total of 18 patients were recruited, who were 20 years old or older at the time of consent, with active acromegaly as determined by the presence of clinical signs and symptoms as well as elevated serum IGF-I levels at presentation (more than 1.3 times the upper limit of the gender- and age-specific normal [4]). Each patient was given written informed consent prior to the confirmation of eligibility. At the completion of the first 12 week treatment (initial pivotal study), patients were re-evaluated for eligibility in extension study. A total of 16 out of 18 patients were enrolled into the extension study and continued on the treatment with pegvisomant. Exclusion criteria from the study were: (I) patients who had undergone pituitary surgery within 3 months, radiotherapy within 2 years prior to the initial pivotal study, or medical therapy with other medications, (II) patients who had severe heart diseases needing a pacemaker, acute myocardial infarction within 6 months prior to the initial pivotal study, liver diseases (aspartate transaminase: serum glutamate oxaloacetate transaminase [AST: SGOT] or alanine aminotransferase: serum glutamate pyruvate transaminase [ALT: SGPT] 3-fold or more than the upper limit of normal range), renal diseases (blood urea nitrogen [BUN] ≥ 40 mg/dL or creatinine ≥ 2.0 mg/dL), suspected malignant tumors, and pituitary adenoma within 3 mm from the optic chiasm, and (III) patients with diseases except for acromegaly which was expected to increase serum GH level or serum IGF-I level.

Study design and efficacy assessment

The two phase III studies, consisting of the initial pivotal study and the extension study (ClinicalTrials.gov number, NCT00143416), were designed as multicenter, non-blinded, uncontrolled trial and performed at 9 clinical research centers in Japan. These studies were performed in accordance with the declaration of Helsinki and approved by ethical committees at each center. The treatment period of the initial pivotal study was 12 weeks. After the completion of the initial pivotal study, the extension study started seamlessly. The treatment period of the extension study was a maximum of 6 months after the regulatory approval of pegvisomant in Japan, which was performed as a postmarketing clinical trial after approval.

Pegvisomant was self-administered or given by a doctor or his/her assistant at home. On Day 1, patients subcutaneously received pegvisomant at a loading dose of 40 mg, followed by 10 mg once daily injection for 8 weeks (Day 2 - Day 56). Patients received either 10 or 15 mg once daily from 9 to 12 weeks (Day 57 - Day 84). Titration of daily dose was permitted 4 weeks after the initiation of the extension study. The daily dose was adjusted so that serum IGF-I levels could be maintained within the age- and gender-specific normal range [4]. The dose adjustment was made in increments or decrements of 5 mg at 8-week intervals (without any deviation from a daily dose range of 10-30 mg) for up to 6 months after the regulatory approval.

The primary endpoint of the initial pivotal study was the changes in serum levels of IGF-I. The secondary endpoints were the proportion of subjects who achieved normalized serum IGF-I levels, the ring size, clinical symptoms (headache, arthralgia, excessive perspiration, fatigue and swelling of soft-tissue) and endocrinological parameters (serum IGF-I and GH levels).

Serum IGF-I was measured with an immunoradiometric assay (IRMA) kit (FUJIFILM RI Pharma Co., Ltd., Tokyo, Japan [former Daiichi Radioisotope Laboratories, Ltd., Japan]) by LSI Medience Corporation (former Mitsubishi BCL), Inc., Japan. Serum GH was measured using immunofluorometric assay (IFMA) by Neuroendocrine Unit Laboratories, Medizinische Klinik Innenstadt der Ludwig-Maximilians University, Munich, Germany, which was specially designed to determine endogenous GH in the presence of an excess pegvisomant. The ring size of the fourth digit of the hand was measured using A-Z6 standardized European jeweler’s rings. The clinical symptoms was evaluated with scores ranging from
Pegvisomant in Japanese acromegaly

The normalization rate were calculated and summarized with the actual value and percentage change from baseline by descriptive statistics for each visit and the end of the extension study. The percentage of IGF-I normalization was calculated as the proportion of subjects who achieved a serum IGF-I level within the revised reference range at least one time-point in these studies. Further, the number of subjects who achieved normalized IGF-I levels at each visit was summarized. Other secondary endpoints (serum GH levels, the ring size, the total and individual scores for clinical symptoms of acromegaly and the score for the overall health status of acromegaly) at each visit and at the end of the extension study were summarized with descriptive statistics for actual values and changes from baseline.

The safety data were summarized for all patients who received at least one dose of pegvisomant.

Results

Baseline characteristics of patients

A total of 18 subjects (10 men and 8 women) were enrolled in the initial pivotal study. Of 18 subjects, 16 subjects (9 men and 7 women) moved to the extension study with the last subject’s observation in July 2007 (max 168 weeks). The baseline characteristics of the initial 18 subjects are listed in Table 1. All 18 subjects had received the previous medical therapy and 16 received surgery. The mean serum IGF-I and GH concentrations at the baseline were 823.9 ng/mL and 20.6 ng/mL, respectively. Two subjects in the initial pivotal study and 2 subjects in the extension study were withdrawn from the study due to adverse events. The percentage of subjects in each daily dose vs time is shown in Fig. 1. Of 16 subjects who received pegvisomant, the daily dose was increased to 20 mg or more once daily in 5 subjects. Four of the 5 subjects received 30 mg once daily, and one of them received an overdose of 60 mg once daily at Week 152. Dose at the end of therapy was summarized in 4 levels (10 mg per day; n=7, 15 mg per day; n=4, 20 mg per day; n=2, 30 mg per day; n=3) in the extension study.

Statistical analysis

Efficacy was assessed in the Full Analysis Set (FAS) which included patients who received at least one dose of pegvisomant and who had baseline and at least one post-baseline efficacy assessment.

According to the revised reference intervals of serum IGF-I levels [6], the standard deviation (SD) score and the normalization rate were calculated and summarized with the actual value and percentage change from baseline by descriptive statistics for each visit and the end of the extension study. The percentage of IGF-I normalization was calculated as the proportion of subjects who achieved a serum IGF-I level within the revised reference range at least one time-point in these studies. Further, the number of subjects who achieved normalized IGF-I levels at each visit was summarized. Other secondary endpoints (serum GH levels, the ring size, the total and individual scores for clinical symptoms of acromegaly and the score for the overall health status of acromegaly) at each visit and at the end of the extension study were summarized with descriptive statistics for actual values and changes from baseline.

The safety data were summarized for all patients who received at least one dose of pegvisomant.

Efficacy

Serum IGF-I concentrations, IGF-I SD score and Percentage of IGF-I normalization

The serum IGF-I levels (actual value) and the percentage change from baseline (at the start of the treatment in the initial pivotal study) in serum IGF-I levels
are shown in Table 2. The serum IGF-I levels decreased over time until around Week 48 and the decreased level was maintained thereafter. The mean in serum IGF-I actual levels was 201.3 ± 87.1 ng/mL at Week 152 (14 subjects) and 255.5 ± 158.1 ng/mL at the time of the last observation (16 subjects) vs 826.4 ± 320.7 ng/mL at baseline. The mean percentage change in serum IGF-I levels was −76.5 ± 8.4% at Week 152 (14 subjects) and −64.7 ± 29.7% at the time of last observation (16 subjects).

The IGF-I SD score vs time is shown in Fig. 2. The IGF-I SD score decreased over time until around Week 48 and the decreased level was maintained thereafter. The mean in the SD score was 1.2 ± 2.0 at Week 152 (14 subjects) and 2.0 ± 2.5 at the time of the last observation (16 subjects) vs 8.8 ± 3.2 at baseline (Table 2).

The percentage of IGF-I normalization is also shown in Table 2. The number of subjects whose IGF-I level became normal at anytime post-baseline were 13 and the percentage of IGF-I normalization was 81.3% (13/16 subjects) throughout the study. The serum IGF-I levels never reached the reference range in 3 subjects. Out of the 3 subjects, one subject discontinued the extension study due to adverse events and 2 subjects showed serum IGF-I levels drastically decreased but did not reach the reference range. In the 2 subjects, the minimum in the IGF-I SD score was 2.6
### Table 2: Serum insulin-like growth factor I (IGF-I) concentrations during pegvisomant monotherapy

| Visit       | N* | Actual value (ng/mL)† | Percentage change from Baseline (%)‡ | SD score§ | Normalization n¶ | % | 95% confidence interval |
|-------------|----|-----------------------|---------------------------------------|-----------|------------------|---|-------------------------|
| Baseline    | 16 | 826.4 ± 320.7†        | 8.8 ± 3.2 (8.8 ± 3.0)                |           |                  |   |                         |
| Week 1 || 18 | 523.1 ± 237.9         | −36.6 ± 16.7†                        | 5.9 ± 2.9 | 2                | 11.1 | (1.4, 34.7) |
| Week 2      | 18 | 465.6 ± 255.4         | −44.5 ± 18.6†                        | 5.1 ± 3.2 | 3                | 16.7 | (3.6, 41.4) |
| Week 4      | 18 | 397.8 ± 176.9         | −50.8 ± 18.1†                        | 4.2 ± 2.6 | 2                | 11.1 | (1.4, 34.7) |
| Week 8      | 16 | 423.0 ± 232.8         | −49.4 ± 20.2†                        | 4.5 ± 3.0 | 1                | 6.3  | (0.2, 30.2) |
| Week 12     | 16‡ | 316.1 ± 142.9†       | −59.5 ± 19.0†                        | 3.0 ± 2.4 | 6‡               | 37.5  | (15.2, 64.6) |
| Week 24     | 15 | 275.2 ± 114.6         | −63.8 ± 22.7                         | 2.4 ± 2.1 | 7                | 46.7  | (21.3, 73.4) |
| Week 48     | 13 | 204.1 ± 97.1          | −76.3 ± 9.9                          | 1.1 ± 2.0 | 8                | 61.5  | (31.6, 86.1) |
| Week 72     | 13 | 178.6 ± 68.9          | −79.3 ± 7.1                          | 0.6 ± 1.6 | 9                | 69.2  | (38.6, 90.9) |
| Week 96     | 12 | 176.1 ± 84.8          | −81.0 ± 5.0                          | 0.6 ± 1.9 | 8                | 66.7  | (34.9, 90.1) |
| Week 120    | 13 | 187.5 ± 76.7          | −77.7 ± 9.8                          | 0.9 ± 1.7 | 8                | 61.5  | (31.6, 86.1) |
| Week 152    | 14 | 201.3 ± 91.0          | −76.5 ± 8.4                          | 1.2 ± 2.0 | 8                | 57.1  | (28.9, 82.3) |
| Week 160    | 9  | 215.4 ± 75.4          | −74.8 ± 10.1                         | 1.8 ± 1.8 | 5                | 55.6  | (21.2, 86.3) |
| End of Treatment | 16 | 255.5 ± 158.1        | −64.7 ± 29.7                         | 2.0 ± 2.5 | 13               | 81.3  | (54.9, 96.0) |

* Number of treated subjects in the study period. † Mean ± SD. ‡ Number of subjects who achieved normal IGF-I at the visit. The criteria of normalization is SD score < +2. § Data from 16 subjects who were treated in the long-term extension study. ¶ For Weeks 1 to 8, changes were from the baseline value for 18 subjects who were treated in the initial pivotal study. ‿ Weeks 1 to 8, and 12, the initial pivotal study; Weeks 12 to 168 and the end of the treatment, the long-term extension study. # Data from the initial pivotal study.

![Fig. 2](https://example.com/fig2.png)

**Fig. 2** Mean serum IGF-I SD score vs time in patients with acromegaly receiving pegvisomant monotherapy (mean, SD). Data for 18 subjects who were treated in the initial pivotal study, and 16 subjects at week 12 in the initial pivotal study include a subject who did not entered the long-term extension study and don’t include a subject who missed the observation within week 12 assessment window but entered in the long-term extension study (this subject’s last observation is included at week 12 of long-term extension study). The bottom, center and top line of the box show 25th, 50th and 75th percentiles respectively. The vertical lines extend to the most extreme value within 1.5 interquartiles ranges. Outlining values of this range are shown as asterisk. The arithmetic mean are shown as circle. EOT indicates end of treatment.
Serum concentration of GH levels

The mean serum concentration of GH vs time is shown in Fig. 3. The mean serum GH level increased until Week 24 (15 subjects, 38.5 ± 19.1 ng/mL); it was reduced and stable (values at baseline, 16.3 ± 12.2 ng/mL; at Week 152 [14 subjects], 21.0 ± 14.6 ng/mL; at the time of the last observation [16 subjects], 17.7 ± 13.6 ng/mL).

Clinical symptoms, ring size and glycohemoglobin

The categorical change from baseline in individual scores for symptoms and signs of acromegaly (headache, arthralgia, excessive perspiration, fatigue and soft-tissue swelling) and overall health status were mostly improved or unchanged and there were few subjects whose categorical change was worsened (Table 3).

The ring size was reduced over time until Week 12 and the reduction was maintained thereafter; the mean change from baseline was −2.9 ± 2.1 at Week 12 (16 subjects), −3.9 ± 2.7 at Week 152 (14 subjects) and −3.8 ± 2.8 at the time of the last observation (16 subjects) compared with the baseline of 40.8 ± 9.2 (16 subjects).

The glycohemoglobin (HbA1c: NGSP) levels were assessed at baseline and at the last observation. HbA1c were decreased by more than 0.5% in 4 subjects, unchanged (−0.5% ~ +0.5%) in 11 subjects, and increased by 0.5% in 1 subject.

Safety

Adverse events

Treatment-related adverse events (AEs) were observed in 16 (88.9%) subjects and are summarized in Table 4. Application/injection/incision/insertion site mass (local lipohypertrophy at the injection site) in 4 (22.2%) subjects, abdominal pain, headache, malaise, AST (SGOT) increased and ALT (SGPT) increased in 3 (16.7%) subjects each. In most cases, observed AEs were mild or moderate in severity, and there was one severe treatment-related AE (malaise). This subject reduced the dose and the severe malaise was resolved.

![Figure 3: Mean serum concentration of GH vs time in patients with acromegaly receiving pegvisomant monotherapy (mean, SD).](image-url)

Data for 18 subjects who were treated in the initial pivotal study, and 16 subjects at week 12 in the initial pivotal study include a subject who did not enter the long-term extension study and don’t include a subject who missed the observation within week 12 assessment window but entered in the long-term extension study (this subject’s last observation is included at week 12 of long-term extension study). The bottom, center and top line of the box show 25th, 50th and 75th percentiles respectively. The vertical lines extend to the most extreme value within 1.5 interquartiles ranges. Outlying values of this range are shown as asterisk. The arithmetic mean are shown as circle. EOT indicates end of treatment.
### Table 3  Clinical symptoms and overall health status

| Scores for variables     | N* | Actual score†   | Change from baseline†   | Categorical change‡ |
|--------------------------|----|----------------|------------------------|---------------------|
|                          |    |                |                        | Improved | Unchanged | Worsened |
| **Headache**             |    |                |                        |          |           |          |
| Baseline                 | 16 | 0.9 ± 1.8      | −0.1 ± 1.0             | 2        | 12        | 2        |
| Week 12                  | 16 | 0.8 ± 1.7      | −0.2 ± 1.0             | 3        | 9         | 2        |
| Week 152                 | 14 | 0.8 ± 1.5      | −0.3 ± 1.2             | 3        | 12        | 1        |
| End of treatment         | 16 | 0.6 ± 1.4      | −0.4 ± 3.0             | 4        | 8         | 4        |
| **Arthralgia**           |    |                |                        |          |           |          |
| Baseline                 | 16 | 1.6 ± 2.6      | −0.5 ± 1.5             | 3        | 11        | 2        |
| Week 12                  | 16 | 1.1 ± 1.8      | −0.6 ± 3.2             | 4        | 7         | 3        |
| Week 152                 | 14 | 1.1 ± 2.1      | −0.4 ± 3.0             | 4        | 8         | 4        |
| End of treatment         | 16 | 1.2 ± 2.1      | −0.4 ± 3.0             | 4        | 8         | 4        |
| **Excess perspiration**  |    |                |                        |          |           |          |
| Baseline                 | 16 | 3.0 ± 2.5      | −0.5 ± 0.9             | 5        | 11        | 0        |
| Week 12                  | 16 | 2.5 ± 2.3      | −2.1 ± 1.9             | 9        | 5         | 0        |
| Week 152                 | 14 | 1.0 ± 1.9      | −1.9 ± 1.8             | 10       | 6         | 0        |
| End of treatment         | 16 | 0.6 ± 1.0      | −1.1 ± 1.8             | 10       | 6         | 0        |
| **Fatigue**              |    |                |                        |          |           |          |
| Baseline                 | 16 | 1.7 ± 1.8      | −0.3 ± 1.0             | 4        | 11        | 1        |
| Week 12                  | 16 | 1.4 ± 1.6      | −1.3 ± 1.9             | 7        | 6         | 1        |
| Week 152                 | 14 | 0.6 ± 1.0      | −1.1 ± 1.8             | 7        | 8         | 1        |
| End of treatment         | 16 | 0.6 ± 1.0      | −1.1 ± 1.8             | 7        | 8         | 1        |
| **Soft-tissue swelling** |    |                |                        |          |           |          |
| Baseline                 | 16 | 3.7 ± 2.3      | −0.8 ± 1.4             | 6        | 9         | 1        |
| Week 12                  | 16 | 2.9 ± 2.1      | −1.7 ± 2.0             | 9        | 5         | 0        |
| Week 152                 | 14 | 2.2 ± 1.8      | −1.6 ± 1.9             | 10       | 6         | 0        |
| End of treatment         | 16 | 2.1 ± 1.8      | −1.6 ± 1.9             | 10       | 6         | 0        |
| **Overall health status**|    |                |                        |          |           |          |
| Baseline                 | 16 | 6.2 ± 2.1      |                        |          |           |          |
| Week 12                  | 16 | 7.1 ± 2.2      | 0.9 ± 1.2              | 10       | 4         | 2        |
| Week 152                 | 14 | 7.1 ± 1.6      | 1.4 ± 1.9              | 9        | 4         | 1        |
| End of treatment         | 16 | 7.5 ± 1.5      | 1.3 ± 1.8              | 10       | 5         | 1        |

* Number of treated subjects in the study period (the long-term extension study). † Mean ± SD. The clinical symptoms was evaluated with scores ranging from 0 (no symptoms) to 8 (severe symptoms), and overall health status were determined based upon scores from 0 (poor) to 10 (good). ‡ The number of subjects in each category.

### Table 4  Treatment-related adverse events (AEs) that occurred in at least 2 subjects

| Treatment-related AEs (COSTART Preferred Term) | Severity | Total |
|------------------------------------------------|----------|-------|
|                                                | Mild     | Moderate | Severe | n (%) | n (%) | n (%) | n (%) |
| Total                                          | 11 (61.1) | 4 (22.2) | 1 (5.6) | 16 (88.9) |       |       |       |
| Abdominal pain                                 | 3 (16.7)  | 0        | 0       | 3 (16.7)  |       |       |       |
| Application/injection/incision/site mass       | 4 (22.2)  | 0        | 0       | 4 (22.2)  |       |       |       |
| Application/injection/de-vice complication      | 2 (11.1)  | 0        | 0       | 2 (11.1)  |       |       |       |
| Headache                                       | 1 (5.6)   | 2 (11.1) | 0       | 3 (16.7)  |       |       |       |
| Malaise                                        | 2 (11.1)  | 0        | 1 (5.6) | 3 (16.7)  |       |       |       |
| Diarrhea                                       | 2 (11.1)  | 0        | 0       | 2 (11.1)  |       |       |       |
| Hypercholesteremia                             | 2 (11.1)  | 0        | 0       | 2 (11.1)  |       |       |       |
| Hyperlipemia                                   | 2 (11.1)  | 1 (5.6)  | 0       | 2 (11.1)  |       |       |       |
| SGOT increased                                 | 2 (11.1)  | 1 (5.6)  | 0       | 3 (16.7)  |       |       |       |
| SGPT increased                                 | 2 (11.1)  | 1 (5.6)  | 0       | 3 (16.7)  |       |       |       |
| Arthralgia                                     | 1 (5.6)   | 1 (5.6)  | 0       | 2 (11.1)  |       |       |       |
| Respiratory tract infection                    | 1 (5.6)   | 1 (5.6)  | 0       | 2 (11.1)  |       |       |       |
| Abnormal vision                                | 2 (11.1)  | 0        | 0       | 2 (11.1)  |       |       |       |
| Eye pain                                       | 1 (5.6)   | 1 (5.6)  | 0       | 2 (11.1)  |       |       |       |

COSTART, Coding Symbols for a Thesaurus of Adverse Reaction Terms; SGOT, serum glutamate oxaloacetate transaminase; SGPT, serum glutamate pyruvate transaminase.
within 71 days after the onset. The long-term use of pegvisomant showed no increasing trend in the incidence of any AEs.

There was no death throughout the study. Four serious AEs were observed in 3 subjects (facial paralysis, chest pain, anemia and oedema). These events were all considered to be unrelated to treatment by the investigators and all were resolved.

Four subjects were withdrawn from the study due to AEs. Increases in AST and in ALT, which were related to pegvisomant, were reported in 3 subjects. The events were one moderate and two mild in severity. Moderate facial paralysis was reported in one subject and considered to be unrelated to pegvisomant. All these AEs resolved after discontinuation.

**Pituitary tumor size**

Central evaluation of MRI was performed to detect the changes in the pituitary tumor volume at 12 and 24 weeks, and subsequently every 8 weeks or 16 weeks until 168 weeks. The mean changes from baseline are $-0.14$ to $0.20$ cm$^3$ for the pituitary tumors volume, $-1.07$ to $0.50$ mm for the pituitary tumors maximum diameter. These changes were not considered to be clinically significant.

Percentage changes from baseline in pituitary tumors volume vs time in individual cases are shown in Fig. 4. There were some fluctuations in pituitary tumor size during observational period which were considered within the variations in measuring the volume. None of the patients demonstrated an obvious increase in pituitary tumor size throughout the study.

**Anti-GH antibody**

The anti-GH antibody was positive in 2 subjects among 16 subjects who moved to the extension study; the titers in one subject were 1:2 (Week 12) and 1:4 (Week 16); and 1:16 (Week 12) in the other subject. These values were low in titer and considered to have no significant influence on clinical outcome.

**Discussion**

The normalization of serum IGF-I is a useful predictor of clinical outcome, as well as morbidity and mortality, in patients with active acromegaly [7-9]. The high IGF-I level is indeed adapted as one of the diagnosis criteria for acromegaly and a sole biomarker to assess the efficacy of the GH receptor antagonist [3]. In addition, a U-shaped relationship was shown between IGF-I con-
centrations and mortality in the general population [10]. Mortality in acromegaly was significantly increased with elevated serum IGF-I. On the other hand, those with normal IGF-I was not different from general population. Meta-analysis had shown that normalization of IGF-I levels is crucially important to decrease the mortality in acromegaly [11]. The reference values of serum IGF-I level used in this study are currently the most accurate and practical data that are based on age- and gender-specific normative serum IGF-I range in Japanese [6], which is probably the most superb yardstick in the world. Therefore, assessment of the results in this study is presumed to be much reliable.

In the present study, normalization of IGF-I by pegvisomant monotherapy was observed in 81.3% of patients (13/16 subjects) and the mean percentage change from baseline was −64.7% at the time of last observation. The effectiveness of pegvisomant was almost similar to that in previous overseas clinical trials [12, 13], in which serum IGF-I percentage change from baseline at 12 week by pegvisomant 20 mg daily was −62.5%, and IGF-I normalization was observed in 97% (87/90 subjects) for 12 months or more. However, the efficacy in normalizing IGF-I in a global safety surveillance study, ACROSTUDY, has been reported to be as low as 63.2% after 5 years of treatment [14] possibly due to inadequate dose adjustment.

The serum GH level measured by a specific assay not cross-reacting pegvisomant increased until Week 24 but was reduced and stable thereafter. In the previous studies, however, it has been reported that serum GH was sustained during 18 months [13]. Recent experimental data showed exogenous GH augment GH secretion from somatotroph adenoma via STAT3 [15]. Pegvisomant may block this positive feedback mechanism, which could explain the balanced GH levels during the therapy. Since GH receptors will be saturated with pegvisomant and GH actions totally blocked, GH rises will be not clinically relevant, and also probably independent of tumor characteristics [16]. Therefore, GH levels are not recommended as a marker of disease activity in acromegaly treated with pegvisomant because of persistent GH hypersecretion and interference of pegvisomant in commercially available GH assays [17].

In the present study, treatment-related adverse events were observed in 16 subjects. However, these events were all mild to moderate in severity, except for severe malaise in one subject. In safety issues, none of the treated patients showed an obvious increase in pituitary tumor size in accordance with the previously reported long-term clinical study [13] nor production of high titer antibody which might influence clinical outcome.

Three subjects were withdrawn from the present study due to abnormal elevation in serum AST and ALT levels; which were treatment-related and resolved after discontinuation. The similar findings have been reported in previous overseas studies [12, 13]. ACROSTUDY revealed that 30 out of 1178 patients (2.5%) showed serum AST or ALT levels above three times the upper limit of normal (ULN) range [14], indicating that hepatotoxicity of pegvisomant is not a rare adverse effect. Although the precise mechanisms of hepatotoxicity remain unclear, an idiosyncratic reaction is likely to be the cause [18, 19].

Local lipohypertrophy at the injection site [20] occurred in 4 patients although subjects were instructed to avoid repeated injections to the same area in the present study. To alleviate local lipohypertrophy, it is recommended to disperse injections within the same area and rotate areas for subcutaneous injection. There was no discontinuation throughout the study regarding these events.

The present study has clearly shown the efficacy and safety profiles of pegvisomant monotherapy in active Japanese acromegaly. Based on these observations and clinical experiences in other countries, pegvisomant has been approved for the treatment of IGF-I hypersecretion in active acromegaly who failed to cure after surgery or resisted other medication therapies, or for whom surgical indication was not allowed due to a variety of reasons. In Japan, pegvisomant is allowed to use in either monotherapy or combination with somatostatin analogues for active acromegaly, which are somewhat different from the clinical practice guidelines in EU and US, where the combination therapy with somatostatin analogues and pegvisomant is not regarded as the first-line medical treatment option.

A postmarketing surveillance is currently being conducted (ClinicalTrials.gov number, NCT00658879) to further confirm the safety and effectiveness by collecting information in Japanese clinical practice. Although the usefulness of pegvisomant as monotherapy were investigated in the present study, pegvisomant is used as a combination therapy with somatostatin analogues in many cases in the latter study which shall reveal the optimal usage of pegvisomant for managing acromegaly.
In conclusion, pegvisomant could be positioned the effective and useful medical therapy for Japanese active acromegaly with sustained high normalization rate of the serum IGF-I levels and with little concern for the safety, although these interpretation may be limited because of the small number of subjects.

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Disclosure

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