Long-term safety and treatment outcomes of pegvisomant in Japanese patients with acromegaly: results from the post-marketing surveillance

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Abstract. This post-marketing surveillance is to investigate the long-term safety and effectiveness of the growth hormone receptor antagonist pegvisomant, which is used in patients with acromegaly in routine clinical practice. This surveillance included all cases treated with pegvisomant during the study period from the start of marketing (June 5, 2007) to December 2015. Data for 251 patients with acromegaly treated with pegvisomant were collected from 119 institutions nationwide in Japan. Eighty-five patients received pegvisomant monotherapy throughout their treatment, while 165 patients were treated with somatostatin analogue or dopamine agonist in combination with pegvisomant. Mean dose of pegvisomant was 10.6 ± 6.1 mg/day in the entire treatment period (except for initial loading dose). The incidence of adverse drug reactions was 35.6% (89/250). No new safety concerns related to long-term treatment were observed. The major investigation items of incidence of abnormal liver function and tumor enlargement were 16.0% (40/250), and 5.2% (13/250) respectively. Efficacy at the final evaluation point was 96.4% (217/225) based on the overall clinical judgement of attending physicians, and efficacy in each observation period was over 94%. Improvement in IGF-I levels and clinical symptoms scores were also observed by comparing the data at baseline with each observation point during treatment. IGF-I normalization rate was 68.2% at 5 years. Pegvisomant monotherapy showed similar improvement here as well. These results suggest that long-term treatment with pegvisomant is effective in clinical practice.

Key words: Post-marketing surveillance, Pegvisomant, Acromegaly, IGF-I (Insulin-like Growth Factor- I), Monotherapy, Combined therapy

ACROMEGALY is a disease caused by hypersecretion of growth hormone (GH) due to GH-secreting pituitary adenoma. The first choice of acromegaly treatment is transsphenoidal surgery (TSS). Medical therapy is conducted if acromegaly is not controllable after surgery or adenomectomy is imperfect. Three medical therapies are recommended by Guidelines [1]: somatostatin analogue, GH receptor antagonist, and dopamine agonist.

Pegvisomant (genetical recombinant) is a GH receptor antagonist which was approved in Europe in 2002 and in the United States in 2003. It was approved in Japan in January 2007 as a pharmacotherapy for acromegaly through a regulatory approval based on clinical data obtained both domestic and overseas.

A clinical trial has been conducted in Japan for the treatment of 18 active acromegalic patients. Sixteen out of these 18 patients were transferred to long-term treatment. The dosage level of pegvisomant during long-term treatment was adjusted to 10–30 mg per day based on IGF-I levels. The IGF-I normalization rate (proportion of normal IGF-I levels at any point after the start of treatment) was 81.3% (13/16 patients). Neither pituitary tumor size nor anti-GH antibody levels showed any clinically significant changes. Abnormal liver enzyme elevated was observed in 3 patients who recovered after the discontinuation of treatment. In conclusion, pegvisomant shows excellent efficacy and good tolerability [2]. However, as the sample size of patients with acromegaly in the Japanese clinical study was limited, post-marketing surveillance of all cases treated with pegvisomant was to be conducted per the conditions of the drug’s license approval.
The purpose of this surveillance is to confirm the long-term safety and effectiveness of pegvisomant in routine clinical practice, and (1) abnormal liver function (2) enlargement of tumor (3) hypoglycemia are to be studied as the major investigation items.

This post-marketing surveillance allowed the acquisition of long-term treatment outcomes for pegvisomant in a large number of acromegalic patients in a real world clinical practice setting in Japan. Here, we provide a summary of this surveillance, as we believe it can be useful in the proper use of pegvisomant.

**Subjects and Methods**

This post-marketing surveillance was conducted in Japan in compliance with the ministerial ordinance on Good Post-Marketing Study Practice for Drugs (GPSP) as a condition for the regulatory approval. It was planned to collect the clinical data of all cases with acromegaly treated with pegvisomant during the surveillance study period from the start of marketing (June 5, 2007) to December 31, 2015.

This surveillance (Clinical Trials.gov identifier: NCT00658879) was conducted using an all-case investigation (including the retrospective data collection) in routine clinical practice. The observation period was for up to 5 years (260 weeks) from the start of pegvisomant treatment. Follow-up was performed at 6 months (26 weeks), 1 year (52 weeks), and in subsequent yearly visits after pegvisomant start. All the data for the 251 registered patients were collected and fixed.

**Participants**

All cases treated with pegvisomant were the object of this survey. Of a total of 251 patients whose data were collected, 250 patients were included in the safety assessment and one patient was excluded because of the contract violation/incomplete. Of the 250 patients in the safety assessment, one patient (McCune-Albright Syndrome) was excluded due to ineligible disease, and 249 patients were included in the efficacy assessment.

**Safety assessment**

The safety of pegvisomant was investigated based on the results of adverse events, adverse drug reactions (treatment-related adverse events), and the major investigation items (abnormal liver function, enlargement of tumor, hypoglycemia). In this surveillance, “hepatic disorder including abnormal laboratory test value of liver function” was defined as reported by the attending physician’s judgement and then an event classified as “drug-related hepatic disorder-comprehensive search (SMQ)” excluding “liver-related coagulation and bleeding disturbances (SMQ)” in SMQ of MedDRA. Enlargement of tumor was classified as “neoplasms benign, malignant, and unspecified (including cysts and polyps)” in the System Organ Class (hereinafter SOC) and defined as events related to increase in pituitary tumor size specified by the comments made by attending physicians. Hypoglycemia was defined as events of “hypoglycemic conditions NEC” in the Highest Level Terms (HLT) of MedDRA.

Investigation of the major investigation items was performed through the use of clinical test values, including serum IGF-I, liver function related [AST(GOT), ALT(GOT), GGT, ALP, total bilirubin], sugar-related (fasting blood glucose, HbA1c). The shared reference intervals of the JAPANESE COMMITTEE FOR CLINICAL LABORATORY PRACTICE (JCCLS) was used in the evaluation for the purpose of comparison with the reference intervals [3].

**Efficacy assessment**

The evaluation of effectiveness was performed using clinical outcomes, serum IGF-I levels, clinical symptoms score related to acromegaly, and ring size. The IGF-I normalization was calculated by using the IGF-I standard value for the normal Japanese population by gender and age as categorized by Isojima et al. [4]. The clinical symptoms score for acromegaly comprises five clinical symptoms (headache, sweating, joint pain, tiredness, soft tissue enlargement), and the determination is based on the overall health conditions, including these five clinical symptoms. Five clinical symptoms were evaluated on a 0–8 point scale (symptom nonexistent = 0, mild = 2, moderate = 4, severe but bearable = 6, severe and unbearable = 8). The total score ranged from 0 to 40. The overall health condition was evaluated on a 0–10 point scale (poor = 0, good = 10) based on clinical symptoms (headache, sweating, joint pain, tiredness, soft tissue enlargement) [2]. Finger ring size was measured using Japanese ring size (size 1–30) or European ring size (size A-Z/2) and the change in ring size was evaluated using the corresponding value (score: 1–63) in the ring size conversion chart.

**Statistical method**

The safety analysis set comprised all cases treated with pegvisomant at least once, and the efficacy analysis set comprised all cases excluding cases with no efficacy evaluation and/or ineligible diseases from the safety analysis set.

Adverse event terms were based on the ICH MedDRA/J version 19.0. Adverse events in which a causal relationship could not be ruled out were regarded as adverse drug reactions and counted among the number of adverse drug reactions for each SOC, and every pre-
ferred term (hereinafter PT), and its incidence ( [%]: number of adverse drug reactions/safety population). In addition, the timing of the onset of adverse drug reactions (initial events) was recorded at each time point of occurrence.

The primary endpoint of efficacy was the clinical efficacy rate defined as follows, “number of effective subjects/(number of effective subjects + number of ineffective subjects) × 100”. The clinical efficacy was comprehensively evaluated every year from the start of the administration by the physician in charge in three categories of “effective”, “ineffective”, and “undecidable”, based on change of serum IGF-1 levels, clinical symptoms score related to acromegaly, and ring size. The change of the clinical efficacy was presented using the efficacy rate and its 95% confidence interval (CI) each year.

Serum IGF-I, clinical symptom score for acromegaly, and ring size were summarized descriptively for the actual values, changes from the baseline etc. Moreover, the normalization rate and its 95% CI were calculated for serum IGF-I. Since serum IGF-I has different reference ranges depending on gender and age, it was also summarized by Standard Deviation Score (SDS) as an evaluation method in which the effects of gender and age were adjusted.

Table 1 Patient characteristics

| Characteristics                          | Safety analysis set (250 patients) |
|------------------------------------------|------------------------------------|
| Gender (Male/Female)                     | 109 (43.6%)/141 (56.4%)            |
| Age at PegV initiation                   | 49.4 ± 15.8 [49.5, 7–83]*           |
| Duration of acromegaly (yr)              | 11.8 ± 9.1 [10.0, 0.3–45.0]*        |
| Dose at PegV initiation (mg/day)         | 15.1 ± 13.4 [10.0, 1.4–40.0]*       |
| Co-morbidities**                         |                                    |
| Diabetes mellitus                        | 34.0%                              |
| Hypertension                             | 32.0%                              |
| Constipation                             | 12.4%                              |
| Dyslipidaemia                            | 11.6%                              |
| Previous treatment (other than medical therapy) | 195 (78.0%)                  |
| Pituitary adenomectomy                   | 143 (57.2%)                         |
| Radiation therapy in addition to pituitary surgery | 49 (19.6%)          |
| Radiation therapy only                   | 3 (1.2%)                            |
| Previous medical therapy***             | 214 (85.6%)                         |
| Octreotide, s.c. injection               | 32 (12.8%)                          |
| Octreotide LAR, i.m. injection           | 164 (65.6%)                         |
| Lanreotide autogel, s.c. injection       | 15 (6.0%)                           |
| Bromocriptine mesilate                   | 29 (11.6%)                          |
| Cabergoline                              | 72 (28.8%)                          |

* Mean ± S.D. [Median, Min–Max]  
** Observed in subjects of 10.0% or more (with duplicate)  
*** With duplicate

Results

Participants

The characteristics of the participants (safety analysis set) are shown in Table 1. The safety analysis set included 250 patients, of whom 109 patients (43.6%) were males and 141 patients (56.4%) were females. The mean age (median, Min–Max) was 49.4 years (49.5, 7–83). The average duration of acromegaly was 11.8 years. There were 16 patients (6.4%) with abnormal liver function. As to the treatments other than pharmacotherapy, 143 patients (57.2%) received pituitary adenomectomy only, while 49 patients (19.6%) received radiation therapy in addition to pituitary surgery, and 3 patients (1.2%) received radiation therapy only. Major co-morbidities (observed in at least 10% of the patients) were diabetes mellitus (34.0%), hypertension (32.0%), constipation (12.4%), and dyslipidaemia (11.6%). Of the 250 patients in the safety analysis set, 214 patients (85.6%) were received medical therapy for acromegaly at baseline, and 31 patients (12.4%) did not receive any medical therapy. Of these patients, 196 patients (78.4%) were treated using somatostatin analogue (with or without dopamine agonist).

Of the 250 patients in the safety analysis set, drug administration to 74 patients (29.6%) was discontinued.
The reasons for discontinuation were adverse events (21 patients [8.4%]), untraceable (20 patients [8.0%], insufficient efficacy (3 patients [1.2%]), death (2 patients) (cause of death: suffocation by accidental ingestion after acute subdural hematoma and multiple organ failure by multiple metastatic cancer [progression of malignant tumor], abnormal laboratory test results (1 patient), and other (27 patients [10.8%]). The timing of discontinuation after the start of treatment was within 26 weeks (32 patients: 12.8%), more than 1 year but less than 2 years (52 patients: 6.0%), and more than 26 weeks but less than 1 year (52 patients; 10 patients: 4.0%).

Of the 250 patients in the safety analysis set, the mean daily dosage (except initial loading dose and drug withdrawal) was 10.6 mg (median; 10.0 mg) [95 patients (38.0%) below 10 mg, 113 patients (45.2%) between 10–15 mg]. The mean treatment period (SD) was 3.1 years (1.9), and 76 patients (30.4%) were treated for over 5 years.

Table 2 shows the change in the percentage of subjects in each therapy during the treatment period.

| Therapy          | 12 weeks | 1 year | 3 years | 5 years | Last observation |
|------------------|----------|--------|---------|---------|-----------------|
| PegV-mono        | 42.2 (100)| 36.1 (75)| 40.9 (61)| 50.5 (51)| 34.1 (85)       |
| Combined*        | 57.8 (137)| 63.9 (133)| 59.1 (88)| 49.5 (50)| 65.9 (164)      |

* Summary of Combination therapy with pegvisomant throughout the entire treatment period is as follows (including the cases with duplicate usage or the cases switching drugs). Octreotide, s.c.: 3.2%, Octreotide LAR, i.m.: 42.8%, Lanreotide autogel, s.c.: 9.6%, Bromocriptine mesilate: 7.2%, and Cabergoline: 25.6%

Table 3 Mean dose of PegV (mg/day) on medical therapy.

| Therapy          | 12 weeks | 1 year | 3 years | 5 years | Last observation |
|------------------|----------|--------|---------|---------|-----------------|
| Entire population| 9.1 (231)| 10.9 (201)| 12.5 (148)| 13.8 (99)| 10.6 (248)      |
| PegV-mono        | 11.0 (97)| 13.1 (71)| 13.1 (60)| 15.6 (50)| 11.6 (84)       |

Mean (m)

The mean doses of pegvisomant for the monotherapy sub-group and the entire population group are shown in Table 3. Dose increases throughout the entire treatment period were observed both in the monotherapy sub-group and the entire population group. The mean dose of pegvisomant for the entire population group increased from 10.9 mg at year 1 to 13.8 mg at year 5, while in the monotherapy sub-group the increase was from 13.1 mg at year 1 to 15.6 mg at year 5. These results indicated that there was a higher mean dose in the monotherapy sub-group than entire population group throughout the treatment.

Safety

The summary of adverse drug reactions and those occurred in at least 5 patients (2%) is shown in Table 4. The incidence of adverse drug reactions (hereinafter incidence) was 35.6% (89/250). The number of patients with onset of adverse drug reactions and the incidence (occurred in at least 5 patients) were abnormal hepatic function (25 patients [10.0%]), liver disorder (9 patients [3.6%]), obesity (7 patients [2.8%]), disease progression (7 patients [2.8%]), pituitary tumor (6 patients [2.4%]), headache (6 patients [2.4%]), and weight gain (5 patients [2.0%]). A total of 29 serious adverse drug reactions were observed in 20 patients. These included liver disorder (5 patients [2.0%]), pituitary tumor (including disease progression; 5 patients [2.0%]), benign pituitary tumor (including disease progression; 3 patients [1.2%]).
and recurrent pituitary tumor (2 patients [0.8%]). The three major investigation items are described below.

**Abnormal liver function**

Forty-four events of adverse drug reactions corresponding to abnormal liver function were observed in 40 patients, indicating an incidence of 16% (40/250). Regarding adverse drug reactions classified according to the SOC (Fig. 1), “Hepatobiliary Disorders” was observed in 34 patients (13.6%) and “Investigations” in 6 patients (2.4%). The details of “Hepatobiliary Disorders” according to PT were abnormal hepatic function (25 patients), liver disorder (9 patients), hyperbilirubinemia (1 patient), and drug-induced liver injury (1 patient). The details of “Investigations” according to PT were AST increased (1 patient), ALT increased (2 patients), GGT increased (3 patients), liver function test abnormal (2 patients). Most of the adverse drug reactions related to abnormal liver function occurred within 26 weeks after the start of pegvisomant treatment (Fig. 1).

**Tumor size**

Of the 250 patients included in the safety analysis set, adverse events related to increase in tumor size were observed in 21 patients, and 13 patients (5.2%) were judged as having adverse drug reactions, while 10

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**Table 4** Summary of adverse drug reactions and those occurred in at least 5 patients (2%)

| Term Category | N (%) |
|---------------|-------|
| Number of patients included (Safety analysis set) | 250   |
| Number of ADRs | 137   |
| Number of patients with onset of ADRs (%) | 89 (35.6) |
| Hepatic function abnormal | 25 (10.0) |
| Liver disorder | 9 (3.6) |
| Obesity | 7 (2.8) |
| Disease progression | 7 (2.8) |
| Pituitary tumor | 6 (2.4) |
| Headache | 6 (2.4) |
| Weight increased | 5 (2.0) |

Terminology was categorized by MedDRA/J version 19.0.

Number of patients (%)

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**Fig. 1** Summary of abnormal liver function and number of adverse events of abnormal liver function according to the treatment duration

The summary of abnormal liver function and number of adverse events of abnormal liver function according to the treatment duration are shown. The summary of treatment-related adverse events of abnormal liver function was 34 patients (13.6%) in Hepatobiliary Disorders (SOC classified) and 6 patients (2.4%) in Investigations (SOC classified). Most of the adverse events of abnormal liver function occurred within 26 weeks after the start of pegvisomant treatment.

Terminology was categorized by MedDRA/J version 19.0.
patients continued the medication without changing the dose, and 3 patients discontinued. The outcomes of 7 patients were not recovered [PTs of adverse drug reactions without recovery: pituitary tumor (3 patients), benign pituitary tumor (2 patients), and recurrent pituitary tumor (2 patients)]. Most of the adverse drug reactions related to increase in tumor size occurred within one year after the start of treatment. Of the 13 patients whose events were judged as adverse drug reactions, 12 patients received pituitary adenomectomy or radiation therapy before the start of pegvisomant treatment. Twelve out of 13 patients received therapy consisting of somatostatin analogue before the start of treatment. Of the 12 patients who received somatostatin analogue at baseline, 7 patients discontinued somatostatin analogue after the start of pegvisomant treatment, and 5 patients continued somatostatin analogue as combined therapy. One patient who had no medical history of somatostatin analogue continued pegvisomant treatment without somatostatin analogue.

**Hypoglycemia**

No adverse drug reactions corresponding to hypoglycemia were reported in this study.

**Effectiveness**

Of the 249 patients included in the efficacy analysis, data of 3 patients were not collected, and the assessment of clinical efficacy was performed by attending physicians through the use of an overall evaluation procedure in the cases of 246 patients. The summary of clinical efficacy at the last evaluation point was, effective (217 patients), not effective (8 patients), and indeterminable (21 patients). The overall efficacy rate was 96.4% (217/225). Efficacy rates exceeded over 94% at every observation point (year 1 [52 weeks], year 2 [104 weeks], year 3 [156 weeks], year 4 [208 weeks], year 5 [260 weeks]).

The change in IGF-I SDS for the pegvisomant monotherapy sub-group and the entire population group throughout the treatment is shown separately in Fig. 2. In the entire population group, the mean value at baseline of 5.0 (182 patients measured) decreased during treatment and IGF-I SDS maintained in the range of 1.4 to 3.2 throughout the treatment. Mean value at the last evaluation point was 2.0 (243 patients measured). The IGF-I normalization rates at baseline were 12.1% (22/182), and 44.4% (87/196) at year 1, 62.9% (88/140) at year 3, and 68.2% (58/85) at year 5. In the pegvisomant monotherapy sub-group, change in IGF-I SDS was observed similar trend throughout the treatment as well.

Table 5 shows the change in the total scores for clinical symptoms at baseline and at each observation period throughout the entire treatment period. The clinical symptoms score (headache, sweating, joint pain, tiredness, soft tissue enlargement) and the mean changes in the total scores for clinical symptoms were decreased at each evaluation point during treatment as compared to baseline, and improvements were observed. The mean value for overall health conditions increased at each evaluation point and improvements were also observed.

The mean value of converted finger ring size was 44.0 (28 patients measured) at baseline. This declined to 38.5–42.1 at each evaluation point, and improvements were observed.

**Discussion**

As the number of patients in the domestic clinical study was limited for the purpose of approval, this surveillance study was performed using an all-case investigation. Post-marketing surveillance was conducted by enrolling 251 patients in 119 institutions nationwide in Japan in order to assess the safety and effectiveness of pegvisomant throughout an entire treatment period lasting up to 5 years (mean 3.1 years).

ACROSTUDY is an international, non-interventional study, and has been conducted since 2004 in Europe and USA to evaluate the long-term safety and effectiveness of pegvisomant after post-marketing phase. The first interim analysis of the study was performed and reported by collecting the data of 1,288 patients (mean treatment period: 3.7 years), who were enrolled as of December 31, 2009 [5]. The most up-to-date interim report covers data for 2,090 patients (mean treatment period: 7.6 years) and was reported in 2018 [6]. In addition, sub-analysis results focusing on pegvisomant monotherapy [7] and combined therapy [8] were also reported. As post-marketing surveillance was required as a condition for the approval of pegvisomant in Japan, this surveillance study was conducted independently from ACROSTUDY.

Although patients with acromegaly enrolled in this study had a previous treatment history of either pituitary adenomectomy, radiation therapy, or medical therapy, the IGF-I normalization at baseline was low, with the rate at 12.1%. This surveillance was an observatory study conducted during routine clinical practice, and pegvisomant therapy was conducted without any protocol by attending physicians based on the indications, dosage and administration methods approved by the Ministry of Health, Labour and Welfare. The mean daily dosage of pegvisomant (except initial loading dose and drug withdrawal) was 10.9 mg at year 1, 12.5 mg at year 3, and 13.8 mg at year 5, showing increases in dosage during treatment. This reflected the improved IGF-I normalization from 44.4% at year 1, to 62.9% at year 3, and 68.2% at year 5.

These results coincided with ACROSTUDY (2018),
showing that mean daily dosage from 12.8 mg at year 1 to 18.9 mg at year 10, reflected the improved IGF-I normalization from 53% at year 1 to 73% at year 10.

The clinical efficacy rate determined entirely by attending physicians at the last evaluation point was 96.4% (217/225), while the IGF-I normalization was 53.5% at the last evaluation point. Data on the domestic clinical study including the continuous study at the completion were reported [2]. The data showed that the IGF-I normalization was 37.5% (95% CI: 15.2, 64.6) at 12 weeks, and 55.6% (95% CI: 21.2, 86.3) at 160 weeks (proportion of IGF-I levels within normal range at each evaluation point). Investigation of the daily dosage for combined therapy, and patient characteristics indicated
that there were differences between the domestic clinical study and this surveillance study, and as a result it is difficult to make a direct comparison of these two studies. Even so, this surveillance study also shows the effectiveness of pegvisomant and different tendencies from the results of the domestic clinical study were not observed. Investigation of the change in IGF-I SDS throughout the treatment period showed that it takes 3 years to achieve less than mean + 2SD (Fig. 2), and that proactive dose adjustment to achieve sooner reduction of IGF-I levels seems effective.

The incidence of adverse drug reactions in this surveillance study was 35.6% (89/250). Although it is difficult to compare this study directly with the domestic clinical study as the treatment duration and patient characteristics were different, the incidence of the surveillance study did not exceed 89.9% of the domestic clinical study.

Regarding major investigation items, the incidence of abnormal liver function (including liver disorder) was 16.0% (40/250, 44 events), which was comparable to the domestic clinical study (16.7%), and most of the outcomes improved to disappearance/recovery, or remission.

In the ACROSTUDY (2018) it was reported [5] that patients with at least one ALT or AST value > 3xULN (upper limit of normal) during follow up comprised 3% of the patients with a normal baseline and a transitory elevation of ALT or AST in most cases. A similar analysis was conducted in this surveillance study. Among the patients with normal baseline, elevation of liver function test > 3xULN at any observation point during treatment was 10.5% for ALT, and 7.5% for AST. This surveillance study is different from the ACROSTUDY in terms of observation periods and points, the medical management and access. Even so, the incidence of abnormal liver function test results of this surveillance was higher than in the ACROSTUDY (3%). Furthermore, it is difficult to directly compare the incidence of abnormal liver function between the pegvisomant monotherapy and combined therapy in this surveillance, and further investigation is needed.

Adverse events related to enlargement of tumor were reported in 21 patients, and 13 patients were judged as adverse drug reactions. In the ACROSTUDY, it was reported [6] that among 1,712 patients who had pituitary imaging results at baseline and during follow up, most patients (72.2%) had no change in tumor size relative to the prior scan, a decrease in tumor size (16.8%), an increase (6.8%), and both an increase and decrease (4.3%). Among 119 patients who had an increase in tumor size judged by attending physicians, the central reading under blinded conditions by masking other clinical data confirmed increases in 29 patients (24%), while there was no change in 23 patients (19%). On the other hand, in the ACROSTUDY [5], detailed comparison of determinations by attending physicians regarding the central reading was performed. Among 198 patients (21.2%) who had changes in tumor size, decrease (12.6%), increase (7.2%), and increase and decrease (1.4%) were confirmed by attending physicians, while patients with increase in tumor size (including increase and decrease) were confirmed in 3.2% at the central reading, suggesting that the determinations made by attending physicians has some tendency to overestimate the change in tumor size.

Objective evaluation of tumor size is not easy, as GH secreting tumors decrease and increase in size over the natural course of the disease. Although the tumor reducing effect of somatostatin analogue was reported in 20–50% of patients [9], this remains unclear, and discontinuation because of tumor enlargement was also reported in the clinical study of somatostatin analogue [10]. This surveillance is not a clinical study, but rather a study conducted during routine clinical practice. Therefore, start, stop, or restart of somatostatin analogue as combined therapy was freely determined by attending physicians without any protocol. Among the 13 patients with tumor enlargement reported as an adverse drug reaction, there were 7 patients who discontinued somatostatin analogue. There seems to be some possibility that somatostatin analogue may affect tumor size. Based on this surveillance study, it is not possible to conclude the relationship of pegvisomant on tumor enlargement. Attention is being drawn to the possibility of tumor enlargement via the information included in the “Impor-

### Table 5  Change in total scores for clinical symptoms

|                      | Pre-treatment | 1 year (52 weeks) | 2 years (104 weeks) | 3 years (156 weeks) | 4 years (208 weeks) | 5 years (260 weeks) | Last evaluation |
|----------------------|---------------|-------------------|---------------------|--------------------|---------------------|---------------------|-----------------|
| Number of patients   | 96            | 112               | 72                  | 63                 | 51                  | 43                  | 126             |
| Mean (S.D.)          | 9.1 (5.9)     | 6.3 (4.9)         | 5.2 (4.6)           | 5.5 (4.8)          | 5.1 (4.2)           | 4.8 (4.0)          | 5.4 (4.7)       |
| Median               | 9.0           | 6.0               | 5.0                 | 4.0                | 4.0                 | 4.0                 | 4.0             |

The total scores for clinical symptoms are summing up of score of headache, sweating, joint pain, tiredness and soft tissue enlargement = from 0 to 40.
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1. (2019) Diagnosis and treatment of hypothalamic pituitary dysfunction. Nihon Naibunpi Gakkai Zasshi 95 Suppl: 1–60. https://www.jstage.jst.go.jp/article/endocrine/95/S. May/95_1_article-char/ja/ (in Japanese).
2. Shimatsu A, Nagashima M, Hashigaki S, Ohki N, Chihara K (2016) Efficacy and safety of monotherapy by pegvisomant, a growth hormone receptor antagonist, in Japanese patients with acromegaly. Endocr J 63: 337–347.
3. Nonprofit Organization JAPANESE COMMITTEE FOR CLINICAL LABORATORY PRACTICE (2014) Shared Reference Intervals Available from URL: http://jccls.org/techreport/public_comment_201406.pdf. (in Japanese)
4. Isojima T, Shimatsu A, Yokoya S, Chihara K, Tanaka T, et al. (2012) Standardized centile curves and reference intervals of serum insulin-like growth factor-I (IGF-I) levels in a normal Japanese population using the LMS method. Endocr J 59: 771–780.
5. van der Lely AJ, Biller BM, Brue T, Buchfelder M, Ghigo E, et al. (2012) Long-term safety of pegvisomant in patients with acromegaly: comprehensive review of 1,288 subjects in ACROSTUDY. J Clin Endocrinol Metab 97: 1589–1597.
6. Buchfelder M, van der Lely AJ, Biller BMK, Webb SM, Brue T, et al. (2018) Long-term treatment with pegvisomant in routine clinical practice conducted in Japan during an observation period of up to 5 years reports that no new safety concerns were observed in patients with acromegaly throughout the long-term treatment. Overall clinical determinations by attending physicians showed that at the last evaluation point, clinical efficacy was 96.4% (217/225), and the IGF-I normalization was 53.5% (130/243) at the last observation.

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AS participated in this surveillance as a physician, and critically reviewed the manuscript and supervised the manuscript development. HY were responsible for the management of this surveillance. AO conducted the statistical analysis of this surveillance. HY, AO, and TS were responsible for the preparation of the draft manuscript and revision checked by AS.

All authors reviewed and approved the final manuscript.
ant: observations from 2,090 acromegaly patients in ACROSTUDY. *Eur J Endocrinol* 179: 419–427.

7. Tritos NA, Chanson P, Jimenez C, King D, Jönsson PJ, *et al.* (2017) Effectiveness of first-line pegvisomant monotherapy in acromegaly; an ACROSTUDY analysis. *Eur J Endocrinol* 176: 213–220.

8. Strasburger CJ, Mattsson A, Wilton P, Aydin F, Hey-Hadavi J, *et al.* (2018) Increasing frequency of combination medical therapy in the treatment of acromegaly with the GH receptor antagonist pegvisomant. *Eur J Endocrinol* 178: 321–329.

9. Takahashi Y (2014) Endocrine disease; progress in the diagnosis and treatment of acromegaly. *Nihon Naika Gakkai Zasshi* 103: 825–831 (In Japanese).

10. Product Evaluation Report (lanreotide acetate) [June 6, 2012 Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau] http://www.pmda.go.jp/drugs/2012/P201200095/47030000_22400AMX00734_A100_1.pdf (In Japanese).