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Efficacy and safety of long-acting pasireotide in Japanese patients with acromegaly or pituitary gigantism: results from a multicenter, open-label, randomized, phase 2 study

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Abstract. A multicenter, open-label, phase 2 study was conducted to investigate the efficacy and safety of long-acting pasireotide formulation in Japanese patients with acromegaly or pituitary gigantism. Medically naïve or inadequately controlled patients (on somatostatin analogues or dopamine agonists) were included. Primary end point was the proportion of all patients who achieved biochemical control (mean growth hormone [GH] levels<2.5μg/L and normalized insulin-like growth factor-1 [IGF-1]) at month 3. Thirty-three patients (acromegaly, n=32; pituitary gigantism, n=1) were enrolled and randomized 1:1:1 to receive open-label pasireotide 20mg, 40mg, or 60mg. The median age was 52 years (range, 31-79) and 20 patients were males. At month 3, 18.2% of patients (6/33; 90% confidence interval: 8.2%, 32.8%) had biochemical control (21.2% [7/33] when including a patient with mean GH<2.5μg/L and IGF-1< lower limit of normal). Reductions in the median GH and IGF-1 levels observed at month 3 were maintained up to month 12; the median percent change from baseline to month 12 in GH and IGF-1 levels were −74.71% and −59.33%, respectively. Twenty-nine patients completed the 12-month core phase, 1 withdrew consent, and 3 discontinued treatment due to adverse events (AEs; diabetes mellitus, hyperglycemia, liver function abnormality, n=1 each). Almost all patients (97%; 32/33) experienced AEs; the most common AEs were nasopharyngitis (48.5%), hyperglycemia (42.4%), diabetes mellitus (24.2%), constipation (18.2%), and hypoglycemia (15.2%). Serious AEs were reported in 7 patients with the most common being hyperglycemia (n=2). Long-acting pasireotide demonstrated clinically relevant efficacy and was well tolerated in Japanese patients with acromegaly or pituitary gigantism.

Key words: Pasireotide, Acromegaly, Growth hormone, Insulin-like growth factor-1, Japanese

ACROMEGALY AND PITUITARY GIGANTISM are rare conditions characterized by chronic hypersecretion of growth hormone (GH) from a pituitary adenoma leading to overproduction of insulin-like growth factor-1 (IGF-1) [1]. Elevated GH and IGF-1 levels lead to metabolic dysfunction and somatic overgrowth, resulting in significant morbidity and mortality. Therefore, the recommended treatment approach is to normalize GH and IGF-1 levels [2].

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The management options for acromegaly include surgery, medical treatment, and radiation therapy [2]. Transsphenoidal surgery is the primary treatment option for acromegaly. Medical treatment is usually used as a second-line treatment in patients with persistent or recurrent disease following surgery. Radiotherapy is generally reserved as a third-line treatment option and is usually indicated when surgery and/or medical therapy have failed to achieve disease control [3].

Currently, there are 3 drug classes available for the treatment of acromegaly, which are somatostatin analogues (SSAs), GH-receptor antagonist, and dopamine agonists. Somatostatin subtype receptors (SSTRs), especially 2 and 5, are found to be prevalent on GH-secreting pituitary adenomas [4]. Octreotide and lanreotide, the first-generation SSAs, which

preferentially bind to SSTR2 [3], are therefore an effective treatment option [5-8] and have been the mainstay of medical therapy for patients with acromegaly [2, 4, 9]. Recent guidelines suggest that long-acting octreotide and lanreotide Autogel can also be used as primary medical treatment after surgery or as first-line medical treatment in patients for whom surgery is not appropriate (due to contraindications or in patients who refuse to undergo surgery) [2]. Cabergoline and bromocriptine, the dopamine agonists, have lower efficacy than SSAs and are mainly reserved for patients with mild elevations of GH and IGF-1 levels [2]. Pegvisomant, a GH-receptor antagonist, is highly effective in reducing IGF-1 levels; however, has no effect in reducing GH levels [10, 11]. Despite these available medical treatment options, "real-life" studies have shown that approximately 50% of patients with acromegaly are not controlled [9, 12, 13].

Pasireotide (SOM230) is a multireceptor-targeted, next-generation SSA, which has a higher binding affinity for SSTR5 and similar affinity for SSTR2 compared to first-generation SSAs. Long-acting pasireotide has demonstrated superior efficacy in terms of biochemical control (mean GH levels, <2.5 μg/L and normalized IGF-1) over long-acting octreotide in medically naïve patients [14]; as well as over continued treatment with first-generation SSAs in inadequately controlled patients [15]. In both these phase 3 studies, long-acting pasireotide was well tolerated with a safety profile similar to other SSAs except for a higher frequency and degree of hyperglycemia [14-16]. Long-acting pasireotide is approved for the treatment of acromegaly by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) [17, 18], and in many other countries based on results of these 2 pivotal trials. Long-acting pasireotide 20 mg, 40 mg, and 60 mg has recently been approved as a treatment for acromegaly and/or pituitary gigantism in Japan.

The aim of the current phase 2 study was to evaluate the efficacy and safety of long-acting pasireotide in Japanese patients with acromegaly or pituitary gigantism. Here, we report the 12-month results from this open-label, randomized, ongoing, long-acting pasireotide dose-response, phase 2 study.

Materials and Methods

Study design and patient population

This multicenter, open-label, randomized phase 2 study included a 12-month core treatment period followed by an optional extension period (Fig. 1). Patients were randomized 1:1:1 to receive long-acting pasireotide 20 mg, 40 mg, or 60 mg. Patients were stratified based on prior medication (SSA or dopamine agonist) received (yes or no). In patients who received long-acting pasireotide 20 mg or 40 mg, the dose could be increased up to 60 mg if mean GH was ≥ 2.5 μg/L and/or IGF-1 >ULN (upper limit of

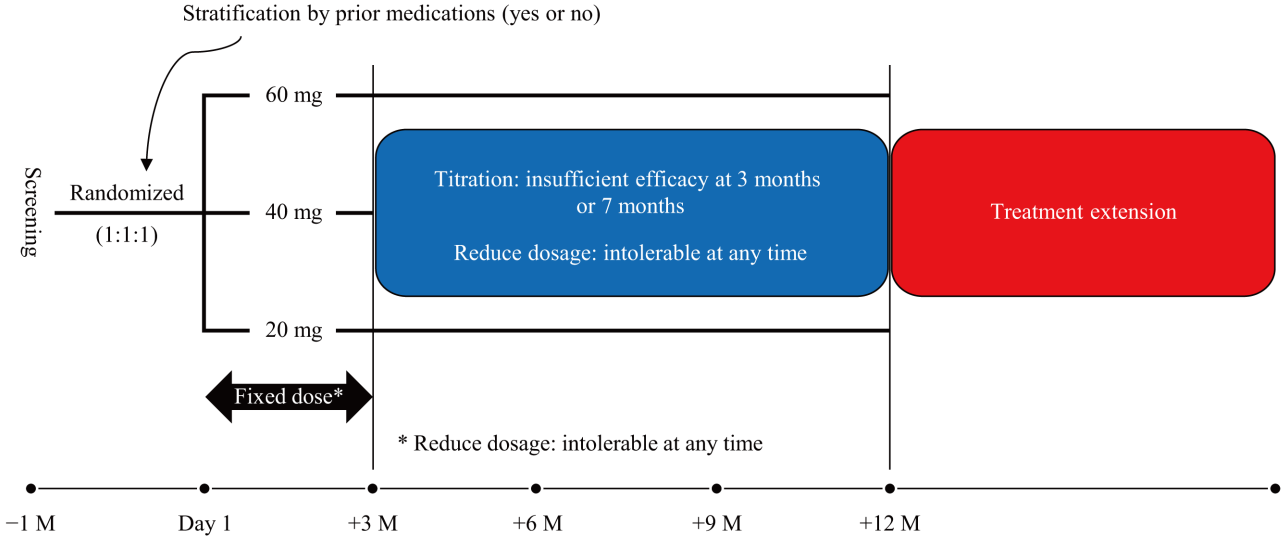

Fig. 1 Study design

normal), based on the GH and IGF-1 measurements at month 3 and month 7. The dose could be decreased anytime during the study for tolerability issues. Antidiabetic medications were permitted and could be initiated or adjusted at investigators' discretion for the management of hyperglycemia during the study. Recommended guidelines for prophylactic or supportive treatment for expected adverse events (AEs; including management of study-drug induced AEs) were provided in the study protocol as well as patient was educated on the signs and symptoms of hyperglycemia. The monitoring and the management of hyperglycemia in this study were based on the current recommendations from the American Diabetes Association and European Association for the Study of Diabetes. As part of the monitoring, patients were required to self-monitor their blood glucose at specified intervals and in addition, fasting plasma glucose was collected at each study visit. Appropriate management measures were to be taken by the investigator throughout the study based on the guidelines detailed in protocol including referral to a diabetes specialist or initiation/adjustment of the antidiabetic medication. The efficacy and safety data for 12 months of study treatment are presented based on the cutoff date of April 02, 2015.

Adult male and female patients (≥18 years of age) with acromegaly or pituitary gigantism who were medically naïve or inadequately controlled with current medications were included in the study. Inclusion criteria included a lack of GH nadir suppression to <1 μg/L after an oral glucose tolerance test (OGTT) or 2-hour 5-point mean GH >5 μg/L, elevated IGF-1 level (age and sex adjusted) in medically naïve patients. Patients with inadequately controlled acromegaly or pituitary gigantism who had a 2-hour 5-point mean GH >2.5 μg/L and age- and sex-adjusted IGF-1 >1.3 times ULN, even after ≥3 months of treatment with SSAs or dopamine agonists were also eligible. All patients who had received prior therapies underwent an appropriate washout before screening (≥4 weeks for long-acting SSA and ≥8 weeks for dopamine agonists or GH receptor antagonist). Patients with poorly controlled diabetes (glycosylated hemoglobin [HbA_{1c}] >8%) were excluded from the study.

This study was conducted in accordance with the Declaration of Helsinki, and an independent ethics committee or institutional review board for each study center approved the study protocol. The study was conducted to obtain approval from Ministry of Health, Labour and Welfare (MHLW) for use of pasireotide in Japanese patients with acromegaly or pituitary gigantism. The investigators adhered to Good Clinical Practice Guidelines. All patients provided written informed consent to participate in the study. The ClinicalTrials.gov identifier is NCT01673646.

End points

Primary end point was the proportion of all patients who achieved biochemical control, ie, mean GH <2.5 μg/L and age- and sex-adjusted normal IGF-1 at month 3. Key secondary end points included the proportion of patients who achieved GH <2.5 μg/L at month 3; proportion of patients who achieved normal IGF-1 at month 3; proportion of patients who achieved biochemical control at month 3 in each dose group (20 mg, 40 mg, and 60 mg); safety and tolerability throughout the study; pharmacokinetics and pharmacodynamics. Other end points included measurements of tumor volume at months 6 and 12; proportion of patients who achieved biochemical control at months 6, 9, and 12, proportion of patients who achieved GH <2.5 μg/L at months 6, 9, and 12; proportion of patients who achieved normal IGF-1 at months 6, 9, and 12. Changes from baseline in GH, ring size and symptoms (headache, fatigue, perspiration, paresthesia, osteoarthralgia) were also assessed.

Analyses methods

Full analysis set (FAS) includes all randomized patients, and patients were analyzed according to the study treatment that they were randomized to during the randomization process. Safety set includes all patients who received at least 1 dose of study treatment, and patients were analyzed according to the study treatment which they received.

Growth hormone (5-point mean level) was assessed from a 2-hour profile (120 minutes, 90 minutes, 60 minutes, 30 minutes, and 0 minutes) after resting for 1 hour and prior to treatment. All the GH 2-hour profiles were to be taken at the same time (around 8:00 AM to 10:00 AM). IGF-1 was assessed using a single sample taken prior to injection at the same visit. The samples for GH and IGF-1 were analyzed centrally (Quest Diagnostics).

The primary variable, ie, proportion of patients with biochemical control at month 3, was presented along with the corresponding Clopper-Pearson exact

2-sided 90% confidence interval (CI). The patients with missing values of mean GH levels and/or IGF-1 at 3 months of study treatment or who discontinue prior to the assessment at 3 months of study treatment will be considered as nonresponders. The proportion of patients with GH <2.5 μg/L and/or normal IGF-1 for all patients randomized at months 6, 9, 12, and those by dose group at month 3 were presented along with Clopper-Pearson exact 2-sided 95% CI.

For a subgroup analysis, SSA-uncontrolled group (n=20) was defined as patients who had received prior SSA treatment for ≥12 weeks. Other/SSA-naïve group (n=13) was defined as patients who had not received any treatment for acromegaly (n=8), or had received <12 weeks of a prior SSA and/or had taken other medication (dopamine agonists) for acromegaly (n=5) (Table 1). A total of 21 patients received prior SSA treatment. One patient who received prior SSA treatment (subcutaneous octreotide acetate) for one week was grouped under "other/SSA-naïve" group, as the treatment duration (<12 weeks) is deemed insufficient to evaluate the response to SSA.

Table 1 Demographics and baseline characteristics (full analysis set)

Variable	Pasireotide long-acting 20 mg n=11	Pasireotide long-acting 40 mg n=11	Pasireotide long-acting 60 mg n=11	Pasireotide long-acting all doses N=33
Median age, years (range)	64.0 (35.0-66.0)	50.0 (32.0-73.0)	46.0 (31.0-79.0)	52.0 (31.0-79.0)
<65, n (%)	8 (72.7)	9 (81.8)	10 (90.9)	27 (81.8)
≥65, n (%)	3 (27.3)	2 (18.2)	1 (9.1)	6 (18.2)
Sex, n				
Female/male	4/7	7/4	2/9	13/20
Median weight, kg (range)	67.5 (47.2-87.5)	64.6 (52.7-97.5)	84.9 (38.1-105.0)	70.4 (38.1-105.0)
Median BMI, kg/m^2 (range)	25.2 (17.3-33.8)	25.6 (20.3-31.9)	24.6 (15.1-32.6)	25.5 (15.1-33.8)
Indication, n				
Acromegaly/pituitary gigantism	11/0	11/0	10/1	32/1
Median time since initial diagnosis, months (range)	48.0 (2.3-282.8)	51.0 (7.7-210.7)	94.1 (3.3-300.8)	63.1 (2.3-300.8)
Prior surgery, n				
Yes/no	9/2	10/1	10/1	29/4
Use of prior SSA treatment for ≥12 weeks, n (%)	7 (63.6)	6 (54.5)	7 (63.6)	20 (60.6)
Subcutaneous octreotide acetate, n	7	6	7	20
Lanreotide, n	0	0	2	2
Bromocriptine mesilate, n	4	2	1	7
Cabergoline, n	5	4	3	12
Pegvisomant, n	0	1	1	2
Use of prior SSA treatment for < 12 weeks and/or other medication, n (%)	1 (9.1)	3 (27.3)	1 (9.1)	5 (15.2)
Octreotide acetate, n	1	0	0	1
Bromocriptine mesilate, n	0	1	1	2
Cabergoline, n	1	3	0	4
Terguride, n	0	0	1	1
No previous medication (medically naïve), n (%)	3 (27.3)	2 (18.2)	3 (27.3)	8 (24.2)
Baseline median GH, μg/L (range)	9.40 (5.0-160.7)	9.96 (2.1-38.1)	15.88 (6.0-172.4)	11.84 (2.1-172.4)
Baseline median standardized IGF-1 x ULN (range)	2.69 (1.6-5.2)	2.68 (1.7-4.3)	2.55 (0.9-4.7)	2.66 (0.9-5.2)

BMI, body mass index; GH, growth hormone; IGF-1, insulin-like growth factor-1; SD, standard deviation; ULN, upper limit of normal. In the analysis, corresponding subgroups are used as SSA-uncontrolled group (n=20) defined as patients who had received prior SSA treatment for ≥12 weeks and other/SSA-naïve group (n=13) defined as patients who had not received any treatment for acromegaly (n=8), or had received <12 weeks of a prior SSA and/or other medication for acromegaly (n=5).

Adverse events (AEs) were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 and consisted of monitoring and recording of all AEs. Safety monitoring also includes regular monitoring of hematology, blood chemistry, and urinalysis parameters, performance of physical examinations, and body weight measurements. Blood samples for laboratory tests, including plasma glucose measurements, were drawn at each visit under fasted conditions before the morning dose.

From previous data in patients uncontrolled on octreotide, proportion of patients who achieved biochemical control after treatment with long-acting pasireotide was 17.3% with lower limit of 2-sided 95% CI as 9.8% [19]. Since, it was anticipated that a large proportion of patients who will enroll in the current study would be inadequately controlled on their prior octreotide treatment, the study pursued the lower limit of response rate of CI as 10%. Sample size of 30 was expected to show the lower limit of Clopper-Pearson exact 2-sided 90% CI >10%.

Results

Patient population

Thirty-three patients who enrolled from 26 centers in Japan were randomized to long-acting pasireotide 20 mg (n=11), 40 mg (n=11), or 60 mg group (n=11). Thirty-two patients were diagnosed with acromegaly and 1 patient with pituitary gigantism; the patient with pituitary gigantism was randomized to the 60 mg group. The first patient was enrolled in the study on October 16, 2012, and the last patient had 12 months of study treatment visit on April 02, 2015, which was the data cutoff date for the analysis. Twenty-nine (87.9%) patients completed the 12-month core phase. Three patients discontinued due to AEs and 1 patient withdrew consent.

Of the 33 patients who were included, 20 were males; the median age of all patients was 52 years (range, 31-79). Overall mean (SD) duration of pasireotide exposure in the core phase was 310.8 days (73.0 days). The median number of injections during the core phase was 12 (range, 2-12). The majority of patients (87.9%; 29 of 33) who were enrolled had undergone prior surgery. Most of the patients (75.8%; 25 of 33) had received prior medical treatment; 20 patients received prior SSAs for ≥12 weeks, and 5 received treatment other than SSA (these patients are referred to as SSA naïve). Baseline median GH was higher in the 60 mg group compared to the 20 mg and 40 mg groups. Baseline median IGF-1 was similar across the groups. Values of baseline median GH and IGF-1 are shown in Table 1. The median time since initial diagnosis was higher in patients in the 60 mg group compared to 40 mg or 20 mg group. A total of 8 patients (male, n/N=7/20; female, n/N=1/13) received prior hormonal replacement therapy for associated hypopituitarism.

Efficacy

The proportion of patients who achieved biochemical control at month 3 (primary efficacy end point) was 18.2% (6 of 33 patients; 90% CI: 8.2%, 32.8%). The primary end point was not met, as the lower bound of the 90% CI was lower than the prespecified threshold of 10%. However, 1 patient had GH <2.5 μg/L and IGF-1 below lower limit of normal at month 3. The proportion of patients achieving biochemical control at month 3 was higher in the 40 mg group compared to the 20 mg and 60 mg groups (Table 2). The overall responses attained at month 3 were maintained up to month 12 (Fig. 2). The number of patients who achieved biochemical control, GH <2.5 μg/L, and normal IGF-1 with actual dose at baseline and at month 12 is presented in Fig. 3.

Table 2 Proportion of patients who achieved biochemical control, GH <2.5 μg/L, or normal IGF-1 at month 3 by randomized long-acting pasireotide groups (full analysis set)

n (%) [95% exact CI]	20 mg N=11	40 mg N=11	60 mg N=11	Overall N=33
GH <2.5 μg/L and normal IGF-1	1 (9.1%) [0.2, 41.3]	4 (36.4%) [10.9, 69.2]	1 (9.1%) [0.2, 41.3]	6 (18.2%) [7.0, 35.5]
GH <2.5 μg/L	3 (27.3%) [6.0, 61.0]	5 (45.5%) [16.7, 76.6]	2 (18.2%) [2.3, 51.8]	10 (30.3%) [15.6, 48.7]
Normalized IGF-1	2 (18.2%) [2.3, 51.8]	5 (45.5%) [16.7, 76.6]	1 (9.1%) [0.2, 41.3]	8 (24.2%) [11.1, 42.3]

GH, growth hormone; IGF-1, insulin-like growth factor-1.

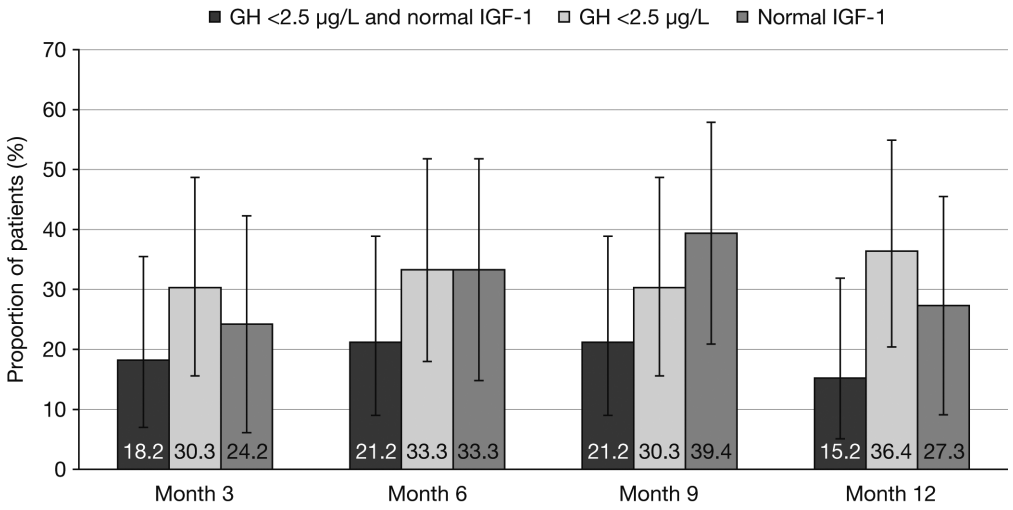

Fig. 2 Proportion of all patients who achieved biochemical control, GH <2.5 μg/L, or normal IGF-1 at months 3, 6, 9, and 12 (overall population, N=33; full analysis set)

GH, growth hormone; IGF-1, insulin-like growth factor 1. Patients who withdrew study prior to each time point were considered as nonresponders in the numerator and were included in the denominator (N=33) for this analysis. Number of patients who were on study at months 3, 6, 9, and 12 were 32, 30, 29 and 29, respectively. Error bars in the figure indicate the 95% confidence intervals.

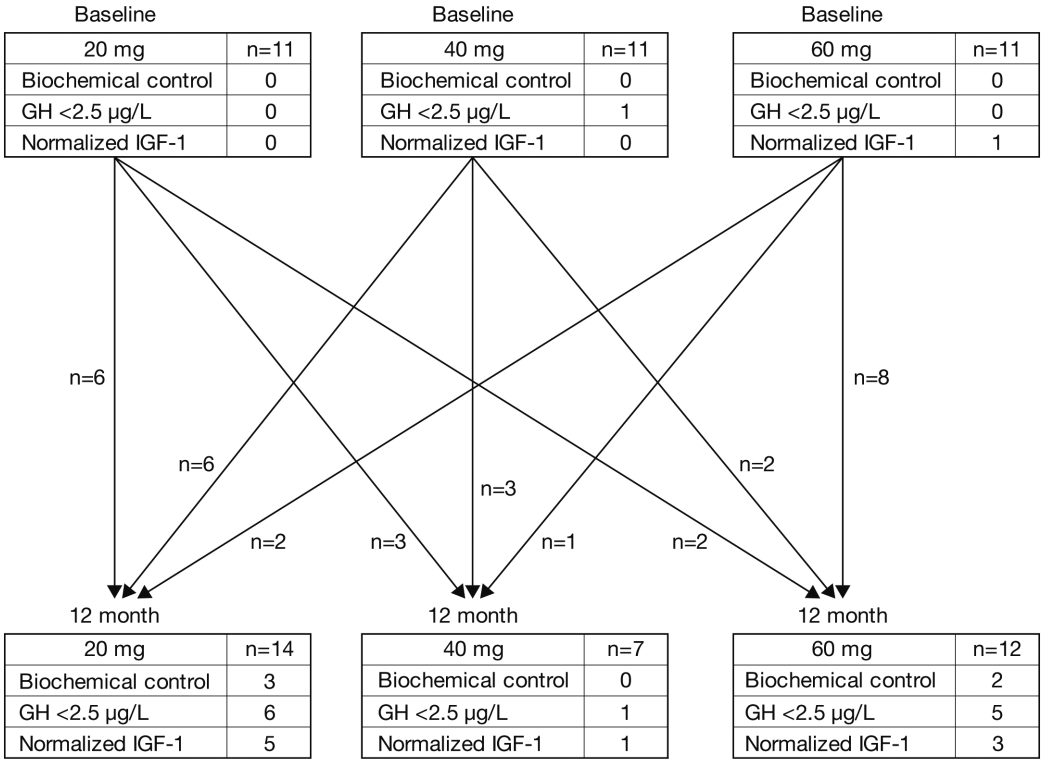

Fig. 3 Number of patients who achieved biochemical control, GH <2.5 μg/L, and normal IGF-1 with actual dose at baseline and at month 12[a] of study treatment

GH, growth hormone; IGF-1, insulin-like growth factor 1. The arrows depict the shift in dose levels from baseline to month 12 and "n" values on the arrow marks indicate the number of patients with the shift or who remained at the same dose level.
[a] Last available dose in case of patients who withdrew prior to month 12.

In the overall population, the median percent change in mean GH levels from baseline to month 12 was −74.71% (range, −94.7% to 1.9%). The median percent change in standardized IGF-1 levels from baseline to month 12 was −59.33% (range, −88.2% to −10.2%). Individual patient waterfall plots of mean GH and the corresponding standardized IGF-1 at month 12 relative to baseline are depicted in Fig. 4.

At month 12, the median percentage change in GH from baseline was similar in SSA-uncontrolled (−74.71%) and other/SSA-naïve (−75.59%) patient groups. The median percentage change in standardized IGF-1 from baseline in SSA-uncontrolled *vs* other/SSA-naïve patients was −47.97% *vs* −59.47% at month 12.

The proportion of patients with biochemical control at month 3 in the other/SSA-naïve group (30.8%; 4 of 13 patients, 95% CI: 9.1%, 61.4%) was higher than in the SSA-uncontrolled group (10%; 2 of 20 patients, 95% CI: 1.2%, 31.7%). At month 12, 15.4% (2 of 13 patients, 95% CI: 1.9%, 45.4%) and 15.0% (3 of 20 patients, 95% CI: 3.2%, 37.9%) of patients in the other/SSA-naïve and SSA-uncontrolled groups, respectively, achieved biochemical control.

Baseline MRI data were available for 29 patients. The median tumor volume (in mm^3, range) at baseline, months 6 and 12 were 386 (n=29; 19-44,272), 372 (n=27; 22-37,740), and 315 (n=26; 16-44,550), respectively. The median % change (range) in tumor volume from baseline was −6.6% (−87.4% to 124.8%) at month 6 and −0.36% (−89.7% to 80.4%) at month 12. There was 1 patient randomized to the 40 mg group with hemorrhage and cystic degeneration of the tumor during evaluations at months 6 and 12. Though this patient did not achieve biochemical control, mean GH and standardized IGF-1 values were lower than the baseline values throughout the core phase.

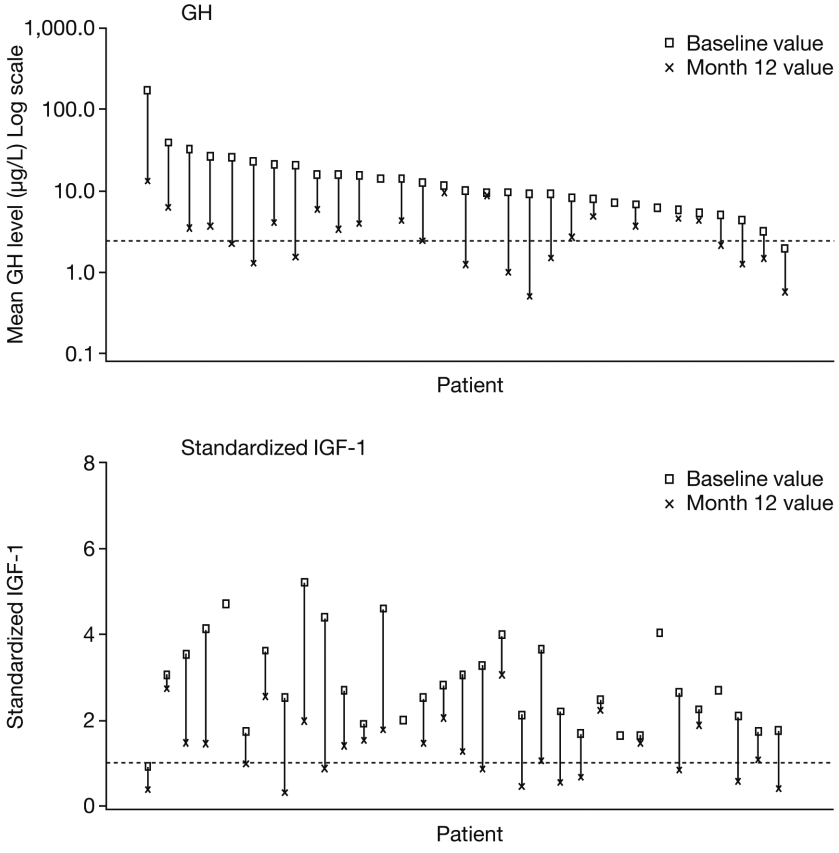

Fig. 4 Mean GH and the corresponding standardized IGF-1 at month 12 from baseline by individual patient (full analysis set)
Patient was considered a GH responder if the month 12 GH value was <2.5 µg/L (depicted by the reference line).
Patient was considered an IGF-1 responder, if the month 12 IGF-1 value was <1.0 x upper limit of normal (depicted by the reference line), but above lower limit of normal (not shown).

A slight improvement in the signs of acromegaly or pituitary gigantism (headache, fatigue, perspiration, osteoarthralgia, and paresthesia) from baseline was seen throughout the study (data not shown). Among patients with a shift in symptom severity, the majority of those patients had a shift to less severe symptom than a shift in the opposite direction and the shifts to more severe signs were infrequent. The median ring size decreased from baseline (23.00; range, 12.0-30.0) to month 12 (21.50; range, 12.0-29.0), with a median percentage change of −2.0% (range, −6.0% to 1.0%).

Patient with pituitary gigantism

There was 1 patient with pituitary gigantism inadequately controlled on SSAs and dopamine agonists enrolled in the study. The patient was randomized to the 60 mg group at study entry and down-titrated to 40 mg following an adverse event of bacterial meningitis. Baseline mean GH and standardized IGF-1 values in this patient were 14.5 μg/L and 2.5, respectively. At month 12, mean GH was 4.4 μg/L and standardized IGF-1 was 1.4. This patient was not considered as a responder; however, mean GH and standardized IGF-1 values for this patient were lower than baseline values throughout the core phase. The percent change in tumor volume from baseline was −87.7% at month 12.

Safety

Overall, 87.9% (29 of 33) of patients were on treatment at the end of month 12. Three patients (9.1%) discontinued the study due to AEs (hyperglycemia, diabetes mellitus, and abnormal liver function test results, n=1 each) during the core phase. No deaths occurred during the core phase of the study.

Adverse events were reported in almost all patients (97%, 32 of 33 patients; Table 3). The most common AEs regardless of study drug relationship (by preferred term >10% of patients) were nasopharyngitis (48.5%), hyperglycemia (42.4%), diabetes mellitus (24.2%), constipation (18.2%), hypoglycemia (15.2%); cholelithiasis, glucose tolerance impaired, and nausea (each, 12.1%).

Most patients experienced at least 1 AE suspected to be related to study drug during the core phase; most of these AEs were mild to moderate in nature (Table 4). All the serious AEs (21.2%; 7 of 33) reported during the core phase of the study were suspected to be study drug related; with the most common being hyperglycemia (n=2) followed by bile duct stone, diabetes mellitus, meningitis bacterial, pulmonary embolism, and sudden hearing loss (n=1, each). Among these, bile duct stone, diabetes mellitus, meningitis bacterial, and pulmonary embolism were grade 3 or 4 serious AEs (overall: 12.1%, 4 of 33). None of the patients discontinued the study due to a serious AE.

Elevated glucose and glycosylated hemoglobin (HbA_{1c}) levels were seen soon after the initiation of pasireotide, but stabilized thereafter (Fig. 5). The mean fasting plasma glucose (FPG) at baseline, month 3, and month 12 were 109.2 mg/dL, 136.0 mg/dL, and 135.0 mg/dL, respectively. The mean glycosylated hemoglobin (HbA_{1c}) at baseline, month 3, and month 12 were 6.1%, 7.1%, and 7.0%, respectively. Most of the patients had a shift in FPG (19 of 33 patients) and HbA_{1c} (21 of 33 patients) levels to the higher category from baseline (Table 5). Among 31 patients who had

Table 3 Summary of adverse events at month 12

	All doses (N=33) n (%)
Any AEs	32 (97.0)
Suspected to be drug related	28 (84.8)
Grade 3 or 4 AEs	10 (30.3)
Serious AEs	7 (21.2)
Grade 3 or 4 serious AEs	4 (12.1)
AEs leading to discontinuation*	3 (9.1)
Death	0

* One patient each reported hyperglycemia, diabetes mellitus, and abnormal liver function test results; AE, adverse event.

Table 4 Adverse events suspected to be related to the study drug at month 12 (occurring in >5% of patients)

	All grades, overall population n (%)	Grade 3 or 4, overall population n (%)
Total	28 (84.8)	10 (30.3)
Hyperglycemia	14 (42.4)	3 (9.1)
Diabetes mellitus	8 (24.2)	2 (6.1)
Cholelithiasis	4 (12.1)	0
Glucose tolerance impaired	4 (12.1)	1 (3.0)
Alopecia	2 (6.1)	0
Biliary dilatation	2 (6.1)	0
Diarrhea	2 (6.1)	0
Electrocardiogram QT prolonged	2 (6.1)	0

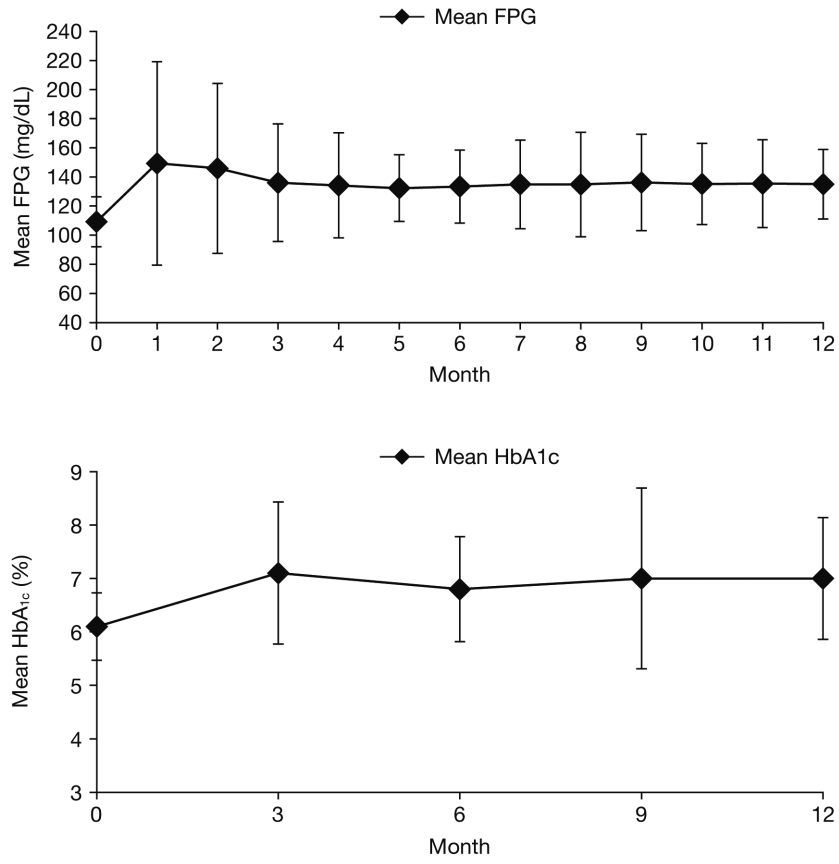

Fig. 5 Change in mean (**A**) FPG and (**B**) HbA_{1c} values from baseline at different time points (safety set)
Error bars in the figure indicate standard deviation. FPG, fasting plasma glucose; HbA_{1c}, glycosylated hemoglobin.

Table 5 Shift table for (**A**) FPG and (**B**) HbA_{1c} (N=33) (safety set)

(A)

FPG, n (%)	Baseline value	Last available value		
		<100 mg/dL	100 to <126 mg/dL	≥126 mg/dL
<100 mg/dL	11 (33.3)	0	9 (27.3)	2 (6.1)
100 to <126 mg/dL	17 (51.5)	0	9 (27.3)	8 (24.2)
≥126 mg/dL	5 (15.2)	0	2 (6.1)	3 (9.1)
Total	33 (100.0)	0	20 (60.6)	13 (39.4)

(B)

HbA_{1c}, n (%)	Baseline value	Last available value			
		<5.7%	5.7% to <6.5%	6.5% to <8%	≥8%
<5.7%	9 (27.3)	1 (3.0)	5 (15.2)	3 (9.1)	0
5.7% to <6.5%	15 (45.5)	0	6 (18.2)	6 (18.2)	3 (9.1)
6.5% to <8%	9 (27.3)	0	1 (3.0)	4 (12.1)	4 (12.1)
Total	33 (100.0)	1 (3.0)	12 (36.4)	13 (39.4)	7 (21.2)

Dark shade indicates shift to higher category; light shade indicates no shift; lighter shade indicate shift to lower category; FPG, fasting plasma glucose; HbA_{1c}, glycosylated hemoglobin. Diabetic: patients taking any antidiabetic medication, or with a history of diabetic medication, or HbA_{1c} ≥6.5% or fasting plasma glucose (FPG) ≥126 mg/dL; prediabetic: patients not qualifying as diabetic and with FPG ≥100 mg/dL and <126 mg/dL or HbA_{1c} ≥5.7% and <6.5%; normal glucose tolerance: patients not qualifying as diabetic or prediabetic and with FPG <100 mg/dL and/ or HbA_{1c} <5.7%.

HbA_{1c} value <7% at baseline, 9 patients had a shift in HbA_{1c} value ≥7% at last available value At month 12, nine patients received insulin, 4 received dipeptidyl (DPP-4) inhibitors alone, 12 received other oral hypoglycemic agents (OHA) with or without DPP-4 inhibitors, and 8 were not being treated with any antidiabetic medications.

No clinically meaningful changes were observed in systolic and diastolic blood pressure, and pulse rate. Two patients (6.1%) had a QTcF value >480 ms but no patients reported QTcF value >500 ms. No patients reported an increase from baseline in QT interval of >60 ms.

Discussion

This study aimed to evaluate the efficacy and safety of long-acting pasireotide in Japanese patients with acromegaly or pituitary gigantism. The primary efficacy end point (ie, proportion of patients with biochemical control at month 3, which was 18.2%; 90% CI: 8.2%, 32.8%) was not met, as the lower bound of the 90% CI was lower than the prespecified threshold of 10%. It should be noted that in this analysis, patients, whose IGF-1 was below lower limit of normal (over response), which is a clinically meaningful response, are not considered as responders. Including one such patient who had over response, the response rate was 21.2%. Of note, the heterogeneous nature of the patient population (medically naïve and inadequately controlled) and inclusion of the patient with pituitary gigantism may have contributed to the lower response than anticipated. Although the study did not meet the primary end point at month 3 as defined in the protocol, the results of this study demonstrate that the long-acting pasireotide has clinically relevant efficacy in Japanese patients with acromegaly, based on the decrease in GH and IGF-1 levels observed at month 3 and through the end of the core phase (12 months of study treatment). It should also be noted that a stringent criterion for response was chosen for this study in terms of excluding patients with IGF-1 < lower limit of normal who are considered responders from the clinical perspective.

One patient who had pituitary gigantism was included in the study due to the common etiology and the similar treatment approach as that of acromegaly; this patient had decreases in mean GH and standardized IGF-1 values from baseline through the end of the core phase, and tolerated pasireotide treatment well.

Almost all patients had a decrease from baseline in IGF-1 and GH levels at month 12. There was a relatively higher variability in baseline GH levels (median [range], 11.84 μg/L [2.1-172.4 μg/L]) than in standardized IGF-1 levels (2.66 [0.9-5.2]) in the overall population. Patients with baseline GH ≤10 μg/L (n=15) had higher response rate at month 3 (40% *vs* 5.6%) and month 12 (26.7% *vs* 16.7%) when compared to patients with baseline GH >10 μg/L (n=18). All patients who had reduction in mean GH levels had shown reduction in standardized IGF-1 levels (Fig. 4). As determined *post hoc*, the percent change from baseline in mean GH and standardized IGF-1 was robust in each dose group (data not shown), and overall population and was maintained throughout the study.

Dose proportional response could not be observed among the patients in the 20 mg, 40 mg, and 60 mg group. It should be noted that the dose titrations were allowed and 18.2% of the patients at month 3 and 50% of the patients at month 12 did not remain at the same dose level assigned at the baseline (as shown in Fig. 3 for month 12). As described in methods section, dose down-titration due to AE was allowed at any time and dose up-titration was prohibited prior to month 3. Thus, the dose modifications may have played a major role in affecting the dose proportional relationship in this study. In addition, the following differences in baseline characteristics such as median age, male/female ratio [20], median GH, and time since initial diagnosis may have contributed to the variations in dose proportional response. The median age was higher in the 20 mg group than other groups. The median GH, male/female ratio, and the time since initial diagnosis were higher in the 60 mg group than in other groups, however, the median BMI and ratio of SSA naïve and SSA uncontrolled groups were balanced.

The goals of acromegaly treatment include biochemical and tumor mass control, the reversal or attenuation of signs and symptoms, and the maintenance of normal pituitary function, with the ultimate goal of decrease in morbidity and mortality. There are a number of drugs available for the treatment of acromegaly such as SSAs, dopamine agonists, and growth hormone receptor antagonist [2]. Clinical data supporting efficacy and safety of first-generation SSAs, long-acting octreotide [21] and lanreotide Autogel [22], in Japanese patients with acromegaly have previously been reported. In most of the studies, the response rate

in patients treated with first-generation SSAs ranges from 17% to 41% [2, 23-25]. In a retrospective study, pegvisomant monotherapy showed efficacy with sustained IGF-1 normalization in Japanese patients with acromegaly; however, there was no effect on GH reduction and tumor shrinkage, and safety concerns like liver toxicity were observed [26], which is consistent with the known profile of pegvisomant. Until now, no publications evaluating dopamine agonist monotherapy in Japanese population with acromegaly/pituitary gigantism are available. Cabergoline has effect on both GH and IGF-1 reduction [27], and the response rate with cabergoline monotherapy was found to be <10% [3]. Despite current available medical therapies, many patients are still uncontrolled. Recent results from the German Acromegaly Register and the Belgian registry in acromegaly patients treated with different therapies have shown that ~50% of the patients still had active disease [12, 13]. In a recently published meta-analysis with almost a total of 4,500 patients enrolled in the analyzed trials, the control rates were 56% for mean GH and 55% for IGF-1 normalization with the first-generation SSAs [9].

Although there were differences between the current study design and the 2 multinational phase 3 studies, the response rates in the subgroups: SSA uncontrolled, n=20: ~10.0% to 20.0% and others/SSA naïve, n=13: ~15.4% to 30.8% (range based on values at different time points) were consistent with the response rates observed in these 2 phase 3 studies for patients with inadequately controlled acromegaly [16] and patients with treatment-naïve acromegaly [14], respectively. A more pronounced reduction of median percentage change from baseline in standardized IGF-1 was observed in others/SSA-naïve group when compared to SSA-uncontrolled group at month 12, whereas median percentage change from baseline in mean GH was similar in both the groups. However, the findings from this subgroup analysis should be interpreted with caution due to the small number of patients in each group and the large variation observed in the data in these results.

The safety profile of long-acting pasireotide in the current study was similar to the known safety profile of first-generation SSAs except for the higher frequency and degree of hyperglycemia. None of the patients with normal HbA_{1c} levels (ie, HbA_{1c} <5.7%) at baseline had a shift to >8% in HbA_{1c} at the last available value. Hyperglycemia was controlled with glucose monitoring and by the initiation or treatment adjustment of the antidiabetic medication as needed. Pasireotide has a higher binding affinity for SSTR5 compared to first-generation SSAs which preferentially bind to SSTR2 [28]. Pasireotide causes reduction in insulin secretion by binding to SSTR5 receptors on the beta cells of the pancreatic islets [29]. Insulin secretion has been reported to be lower in East Asian population compared to Caucasian population [30]. Considering the mechanism of pasireotide associated hyperglycemia [31], plasma glucose levels should be carefully monitored in Japanese patients, and insulin-secreted therapy such as sulfonyl urea, rapid-acting insulin secretagogues (glinides), DPP4 inhibitors or glucagon-like peptide-1 (GLP-1) could be effective. The safety profile of pasireotide observed in this study was consistent with findings of previous studies [5-7] and with the 2 large phase 3 studies in acromegaly [14-16]. No new or unexpected safety signals were reported.

This phase 2 study had some limitations such as the broader inclusion criteria, ie, patients included in the study could be either medically naïve or inadequately controlled (on first-generation SSAs) and the open-label study design with no active label comparator.

In conclusion, in patients with acromegaly, the reduction in mean GH and standardized IGF-1 levels observed with long-acting pasireotide treatment was maintained through the end of core phase at month 12 in both medically naïve and in patients who were inadequately controlled on SSAs or dopamine agonists. In addition, the patient with pituitary gigantism who was a nonresponder had lower GH and IGF-1 levels compared to baseline values throughout the core phase. The safety profile of long-acting pasireotide was similar to first-generation SSAs except for the frequency and degree of hyperglycemia. Hyperglycemia was controllable with adequate glucose monitoring and antidiabetic treatment. No new safety signals were observed. Thus, long-acting pasireotide has clinically relevant efficacy and was well tolerated in Japanese patients with acromegaly or pituitary gigantism.

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Conflict of Interest

ST and AS have nothing to declare. MM and TK are employees of Novartis pharm K.K. This study was sponsored by Novartis. Financial support for medical editorial assistance was provided by Novartis Pharmaceuticals Corporation.

Appendix

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