Report on the Deliberation Results

March 8, 2018

Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau

Ministry of Health, Labour and Welfare

Brand Name	Signifor LAR Kit for i.m. injection 10 mg, Signifor LAR Kit for i.m. injection 20 mg, Signifor LAR Kit for i.m. injection 30 mg, and Signifor LAR Kit for i.m. injection 40 mg
Non-proprietary Name	Pasireotide Pamoate (JAN*)
Applicant	Novartis Pharma K.K.
Date of Application	June 30, 2017

Results of Deliberation

In its meeting held on March 1, 2018, the First Committee on New Drugs concluded that partial change applications for Signifor LAR Kit for i.m. injection 20 mg and 40 mg, and applications for Signifor LAR Kit for i.m. injection 10 mg and 30 mg may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

Signifor LAR Kit for i.m. injection 10 mg and 30 mg are not classified as a biological product or a specified biological product. The drug products are classified as powerful drugs. The re-examination period of Signifor LAR Kit for i.m. injection 10 mg, 20 mg, 30 mg, and 40 mg is 10 years for the indication and the dosage and administration proposed in the present application.

Conditions of Approval

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because of the very limited number of subjects included in Japanese clinical studies, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product until data are collected from the planned number of patients, thereby identifying the characteristics of treated patients, collecting data on the safety and efficacy of the product as early as possible, and taking necessary measures to ensure its proper use.

**Japanese Accepted Name (modified INN)*

Review Report

February 8, 2018
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	(a) Signifor LAR Kit for i.m. injection 10 mg, (b) Signifor LAR Kit for i.m. injection 20 mg, (c) Signifor LAR Kit for i.m. injection 30 mg, and (d) Signifor LAR Kit for i.m. injection 40 mg
Non-proprietary Name	Pasireotide Pamoate
Applicant	Novartis Pharma K.K.
Date of Application	June 30, 2017
Dosage Form/Strength	Powder for suspension for injection: Each vial contains 17.1, 32.9, 49.4, or 65.8 mg of Pasireotide Pamoate (equivalent to 12.5, 24, 36, or 48 mg of pasireotide)
Application Classification	(a) and (c): Prescription drug; (4) Drugs with new indications, (6) Drugs with a new dosage, and (8) Drugs in an additional dosage form (b) and (d): Prescription drug; (4) Drugs with new indications and (6) Drugs with a new dosage
Items Warranting Special Mention	Orphan drug (Orphan Drug Designation No. 262 of 2012 [*24 yaku*]; PFSB/ELD Notification No. 0215-1 dated February 15, 2012, issued by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare)
Reviewing Office	Office of New Drug I

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of Cushing's disease, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions.

Indication(s)

(a) and (c):

Treatment of patients with Cushing's disease (who have had an inadequate response to surgery or for whom surgery is not an option)

(b) and (d):

1. Improvement of hypersecretion of growth hormone and insulin-like growth factor 1 (IGF-1) (somatomedin-C) and related symptoms in patients with acromegaly or pituitary gigantism (who have had an inadequate response to surgery or for whom surgery is not an option)
2. Treatment of patients with Cushing's disease (who have had an inadequate response to surgery or for whom surgery is not an option)

(Underline denotes additions)

Dosage and Administration

(a) and (c):

The usual adult dosage is 10 mg of pasireotide administered by intramuscular injection into the gluteal muscle every 4 weeks. The dose may be increased to a maximum of 40 mg, depending on the patient's condition.

(b) and (d):

Acromegaly and pituitary gigantism:

The usual adult dosage is 40 mg of pasireotide administered by intramuscular injection into the gluteal muscle every 4 weeks for 3 months. Thereafter, doses of 20 mg, 40 mg, or 60 mg are administered every 4 weeks, depending on the patient's condition.

Cushing's disease:

The usual adult dosage is 10 mg of pasireotide administered by intramuscular injection into the gluteal muscle every 4 weeks. The dose may be increased to a maximum of 40 mg, depending on the patient's condition.

(Underline denotes additions/changes)

Conditions of Approval

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because of the very limited number of subjects included in Japanese clinical studies, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product until data are collected from the planned number of patients, thereby identifying the characteristics of treated patients, collecting data on the safety and efficacy of the product as early as possible, and taking necessary measures to ensure its proper use.

Attachment

Review Report (1)

December 28, 2017

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency.

Product Submitted for Approval

Brand Name	(a) Signifor LAR Kit for i.m. injection 10 mg, (b) Signifor LAR Kit for i.m. injection 20 mg, (c) Signifor LAR Kit for i.m. injection 30 mg, and (d) Signifor LAR Kit for i.m. injection 40 mg
Non-proprietary Name	Pasireotide Pamoate
Applicant	Novartis Pharma K.K.
Date of Application	June 30, 2017
Dosage Form/Strength	Powder for suspension for injection: Each vial contains 17.1, 32.9, 49.4, or 65.8 mg of Pasireotide Pamoate (equivalent to 12.5, 24, 36, or 48 mg of pasireotide)
Proposed Indication(s)	(a) and (c): <u>Treatment of Cushing's disease</u> (b) and (d): <u>1.</u> <u>Improvement of hypersecretion of growth hormone and insulin-like growth factor 1 (IGF-1) (somatomedin-C) and related symptoms in patients with acromegaly or pituitary gigantism (who have had an inadequate response to surgery or for whom surgery is not an option)</u> <u>2. Treatment of patients with Cushing's disease</u> (Underline denotes additions)

Proposed Dosage and Administration

(a) and (c):

<u>Cushing's disease</u>

<u>The usual adult dosage is 10 mg of pasireotide administered by intramuscular injection into the gluteus every 4 weeks. The dose may be increased to a maximum of 40 mg according to the clinical status of the patient.</u>

(b) and (d):

Acromegaly and pituitary gigantism:

The usual adult dosage is 40 mg of pasireotide administered by intramuscular injection into the gluteal muscle every 4 weeks for 3 months. Thereafter, doses of 20 mg, 40 mg, or 60 mg are administered every 4 weeks, depending on the clinical status of the patient.

Cushing's disease:

The usual adult dosage is 10 mg of pasireotide administered by intramuscular injection into the gluteal muscle every 4 weeks. The dose may be increased to a maximum of 40 mg according to the clinical status of the patient.

(Underline denotes additions)

Table of Contents

List of Abbreviations

See Appendix

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Signifor LAR is supplied as a powder for suspension for injection and its active ingredient is pasireotide pamoate, which is a somatostatin analog developed by Novartis Pharma (Switzerland). In Japan, Signifor LAR Kit for i.m. injection 20 mg, 40 mg, and 60 mg were approved in September 2016 for the following indications: "Improvement of hypersecretion of growth hormone and insulin-like growth factor-1 (IGF-1) (somatomedin-C) and related symptoms in patients with acromegaly or pituitary gigantism (who have had an inadequate response to surgery or for whom surgery is not an option)."

Cushing's disease is a condition where excessive secretion of adrenocorticotropic hormone (ACTH) by a benign pituitary adenoma leads to excess cortisol production from the adrenal glands, resulting in chronic hypercortisolemia. Cushing's syndrome is a collection of characteristic clinical signs and symptoms resulting from chronic excessive secretion of cortisol from the adrenal glands, and Cushing's disease is a form of Cushing's syndrome. Specific clinical signs and symptoms of chronic hypercortisolemia in patients with Cushing's disease include physical changes such as moon face, central obesity, and buffalo hump; reddish-purple striae distensae on the skin; thinning of the skin; ecchymosis; muscular weakness caused by proximal muscle atrophy; and growth retardation accompanied by obesity in pediatric patients. Nonspecific clinical signs and symptoms include hypertension, menstrual disorder, acne, hairiness, oedema, glucose tolerance abnormal, osteoporosis, pigmentation, and mental disorders (*Eur J Endocrinol*. 2015;172:R227-39, *Manual for the Treatment of Cushing's Syndrome*, rev. 2nd ed. Shindan-to-Chiryosha;2015). Further, chronic excessive secretion of cortisol potentially not only aggravate the complications, but also cause serious infections due to compromised immune function, and vascular disorders resulting from hypertension or dyslipidaemia, etc., leading to death. The mortality of patients with Cushing's disease is 0.98 to 9.3 times that of the age- and gender-matched normal population. According to overseas reports, the prevalence of Cushing's disease is 40 cases per million people, and the incidence rate of Cushing's disease is 1.2 to 2.4 per million per year (*Endocr Rev*. 2015;36:385-486). An estimated 450 individuals have Cushing's disease in Japan.[1)]

Pasireotide pamoate is a cyclohexapeptide somatostatin analog (SSA), and inhibits secretion of ACTH, GH, and other hormones, as with endogenous somatostatin, via binding to human somatostatin receptors (sstrs). The applicant has claimed that the results of the multi-regional phase III study demonstrated the efficacy and safety of pasireotide pamoate (hereinafter referred to also as "pasireotide long-acting release [LAR]") in the treatment of Cushing's disease, and has filed an application for partial change.

Outside Japan, pasireotide pamoate was approved for the treatment of Cushing's disease in Europe in September 2017. In the US, an application for pasireotide pamoate was submitted in August 2017, and

1) According to a nationwide epidemiological survey conducted in 1997 by the Ministry of Health and Welfare Research Committee on Specified Disease, "Disorders of adrenal hormone production," an estimated 1250 patients had Cushing's syndrome ("Nationwide epidemiological survey of disorders of adrenal hormone production in Japan": FY1998 research report reported by the Ministry of Health and Welfare Research Committee on Specified Disease, "Disorders of adrenal hormone production"). Of the 417 subjects studied, 35.8% had Cushing's disease. Based on the above findings, an estimated 450 patients have Cushing's disease in Japan.

is under review as of December 2017. In some countries and regions, a subcutaneous formulation[2)] containing the active ingredient pasireotide diaspartate, which is to be administered twice daily, has been approved for the treatment of Cushing's disease.

Pasireotide pamoate was designated as an orphan drug for the intended indication of Cushing's disease (Orphan Drug Designation No.262 of 2012 [*24 yaku*]; PFSB/ELD Notification No.0215-1 dated February 15, 2012, by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare).

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

Although the present application has been filed for a new indication and a new dosage, an application for Signifor LAR Kit for i.m. injection 10 mg and 30 mg was also filed for approval of an additional dosage form. Accordingly, data relating to quality were submitted. While this report only describes matters relating to the new indication and new dosage, the data submitted for approval of "drugs in an additional dosage form" were also reviewed by PMDA. No significant problems were found with the data.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

While the present application has been filed for a new indication, a new dosage, and an additional dosage form, no new data on "non-clinical pharmacology" were submitted.

3.R Outline of the review conducted by PMDA

3.R.1 Mechanism of action of pasireotide

The applicant's explanation about the mechanism of action of pasireotide:

Cushing's disease is a condition where excessive secretion of ACTH by a benign pituitary adenoma leads to excess cortisol production from the adrenal glands, resulting in chronic hypercortisolemia. The goal of therapy is therefore to normalize cortisol levels. As with naturally occurring somatostatin, pasireotide exerts its pharmacological activities such as inhibition of secretion of ACTH and GH from the pituitary gland via binding to sstrs. Five sstr subtypes, sstrs 1 to 5, are known. Pasireotide has the highest affinity for sstr 5 (*Eur J Endocrinol.* 2002;146:707-16).

While sstrs are distributed in various tissues, expression of sstr 5 is the highest compared with other subtypes (sstrs 1-4) in pituitary adenoma cells from patients with Cushing's disease (*Eur J Endocrinol.* 2005;152:645-54, and *J Clin Endocrinol Metab.* 2006;91:4482-8). Dexamethasone pretreatment was reported to lower the sstr 2 mRNA expression in AtT20 cells; whereas sstr 5 mRNA expression levels were not lowered (*Pituitary.* 2004;7:257-64, and *Am J Physiol Endocrinol Metab*. 2005;289:E278-87). The above findings suggest that sstr 5 is likely to play an important role in Cushing's disease that is

2) In Europe, pasireotide diaspartate was approved for the treatment of patients with Cushing's disease in April 2012. The recommended dose is 600 μg by subcutaneous injection twice daily, and the dose may be adjusted within the range from 300 μg to 900 μg, as necessary. In the US, pasireotide diaspartate was approved for the treatment of patients with Cushing's disease in December 2012. The recommended dose is 600 or 900 μg by subcutaneous injection twice daily, and the dose may be adjusted within the range of 300 μg to 900 μg, as necessary.

characterized by high blood cortisol levels; therefore, pasireotide, which has a high affinity for sstr 5, is expected to inhibit excessive ACTH secretion from the pituitary gland of a patient with Cushing's disease, thereby reducing excessive cortisol secretion from the adrenal glands in a secondary manner.

The actions of pasireotide on Cushing's disease are studied both *in vitro* and *in vivo*. Pasireotide has been reported to inhibit ACTH secretion in primary culture of pituitary adenoma cells from patients with Cushing's disease, and in AtT20 cells (*J Clin Endocrinol Metab*. 2006;91:4482-8, and *Eur J Endocrinol.* 2005;152:645-54). In normal rats, pasireotide inhibited the secretion of corticotropin releasing hormone (CRH)-induced plasma ACTH and corticosterone, whereas the inhibitory effect of octoreotide, an SSA having a high affinity for sstr 2, was reduced compared with that of pasireotide (*Eur J Endocrinol.* 2005;153:R7-10, and *J Endocrinol Invest.* 2005;28:28-35). Further, pasireotide is reported to reduce the tumor weight and plasma ACTH levels in mice transplanted with AtT20 cells, which are animal models of Cushing's disease (*Mol Cell Endocrinol.* 2014;394:37-46), and reduce the pituitary tumor size, plasma ACTH levels, and urinary cortisol levels compared to pre-treatment in dogs that developed ACTH-producing pituitary tumor in a spontaneous manner (*Neuroendocrinology.* 2011;94:124-36).

Based on the above, pasireotide, via binding to sstrs, inhibits excessive ACTH secretion from the pituitary gland of a patient with Cushing's disease, thereby reducing excessive cortisol secretion from the adrenal glands in a secondary manner.

PMDA accepted the applicant's explanation.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

While the present application has been filed for a new indication, a new dosage, and an additional dosage form, no new data were submitted because data on non-clinical pharmacokinetics have already been evaluated when the initial application was filed.

5. Toxicity and Outline of the Review Conducted by PMDA

The present application has been filed for a new indication, a new dosage, and an additional dosage form, and no data on toxicity were submitted.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

Plasma pasireotide concentrations were determined by radioimmunoassay (RIA), and the lower limit of quantitation (LLOQ) was 30 or 150 pg/mL.[3)]

[3)] In Studies B2208, B2208E1, B2305, and G2304, plasma pasireotide concentrations were determined by an analytical method with an LLOQ of 150 pg/mL. For some specimens in Studies B2208 and B2208E1, plasma pasireotide concentrations were determined by an analytical method with an LLOQ of 30 pg/mL.

6.2 Clinical pharmacology

The applicant submitted evaluation data in the form of results from a multi-regional phase III study (Study G2304), and reference data in the form of results from foreign clinical studies of the pasireotide subcutaneous formulation (Studies B2208, B2208E1, and B2305). The results of the main study are outlined below.

6.2.1 Multi-regional phase III study (CTD 5.3.5.2-1, Study G2304 [Since November 2011, data cut-off in November 2015])

A randomized, double-blind study was conducted in patients with Cushing's disease (target sample size, 148 subjects [74 subjects each in the pasireotide LAR 10 mg and 30 mg groups]) in Japan and other countries to investigate the efficacy and safety of pasireotide LAR [see Section "7.1 Multi-regional phase III study" for the details of the study design, and efficacy and safety results].

Table 1 shows pasireotide plasma trough concentrations in patients who received intramuscular doses of pasireotide LAR once every 4 weeks.

Table 1. Pasireotide plasma trough concentrations in patients who received intramuscular doses of pasireotide LAR once every 4 weeks

Sampling point	Pasireotide LAR 5 mg	Pasireotide LAR 10 mg	Pasireotide LAR 30 mg	Pasireotide LAR 40 mg
Day 29	–	2.03 ± 1.25 (65 subjects)	7.63 ± 4.58 (64 subjects)	–
Day 57	0.833 (1 subject)[a)]	2.35 ± 1.15 (57 subjects)	7.82 ± 4.22 (61 subjects)	–
Day 85	0.589, 1.48 (2 subjects)[a)]	2.39 ± 1.32 (59 subjects)	8.56 ± 4.26 (51 subjects)	–
Day 113	1.29 ± 0.237 (3 subjects)	2.40 ± 1.11 (51 subjects)	8.31 ± 3.87 (49 subjects)	–
Day 141	0.557, 1.52 (2 subjects)[a)]	2.47 ± 0.938 (25 subjects)	7.88 ± 4.00 (50 subjects)	10.7 ± 4.91 (20 subjects)
Day 169	1.85, 2.16 (2 subjects)[a)]	2.47 ± 0.946 (29 subjects)	8.46 ± 3.51 (51 subjects)	12.0 ± 5.08 (22 subjects)
Day 197	0.448, 0.993 (2 subjects)[a)]	2.88 ± 1.29 (35 subjects)	9.13 ± 4.25 (44 subjects)	11.9 ± 5.87 (21 subjects)
Day 225	1.19 ± 0.429 (3 subjects)	2.68 ± 0.975 (22 subjects)	8.57 ± 4.70 (28 subjects)	11.3 ± 5.18 (34 subjects)
Day 253	1.77 ± 0.881 (5 subjects)	2.87 ± 1.57 (17 subjects)	9.00 ± 4.93 (27 subjects)	12.1 ± 5.21 (33 subjects)
Day 281	1.24 ± 0.517 (3 subjects)	3.36 ± 1.48 (13 subjects)	8.18 ± 4.23 (16 subjects)	11.4 ± 5.85 (44 subjects)
Day 309	0.662 (1 subject)[a)]	2.50 ± 0.988 (23 subjects)	9.34 ± 5.61 (19 subjects)	12.0 ± 4.58 (43 subjects)
Day 337	1.91 ± 1.79 (3 subjects)	3.07 ± 1.62 (21 subjects)	8.90 ± 4.37 (15 subjects)	12.6 ± 6.21 (41 subjects)

Mean ± SD (number of subjects); unit, ng/mL; –, not applicable
a) individual values

6.2.2 Population Pharmacokinetics Analysis (CTD 5.3.3.5-2)

Population pharmacokinetics (PPK) analysis was performed using 1766 plasma pasireotide concentration data from 140 subjects (sex, 31 men and 109 women; race, 83 Caucasians, 2 Blacks, 41

Asians, and 14 other races) in the multi-regional phase III study (Study G2304), which was conducted in patients with Cushing's disease (software used, NONMEM ver.7.3.0).

The characteristics of subjects included in the PPK analysis were as follows (median [range]): age, 37.5 [18, 71] years; weight, 74.2 [46.5, 152.3] kg; and lean body weight (LBW), 47.4 [28.4, 84.4] kg.

A 2-compartment model with first-order elimination, in which the process of pasireotide LAR released from the administration site is described in 5 compartments, was constructed as the basic model. A full model was constructed with LBW, age, sex, race, estimated glomerular filtration rate (eGFR), alkaline phosphatase (ALP), gamma-glutamyl-transferase (GGT), and total bilirubin (TBIL) as covariates for apparent clearance (CL/F); LBW as a covariate for apparent volume of distribution (V/F); and dose as a covariate for bioavailability. The final model was constructed with the covariates examined by the backward elimination method, LBW as a covariate for CL/F and dose as a covariate for bioavailability.

The results of the examination of covariates obtained from the full model show that the subject with a baseline LBW of 40.0 kg (at 10th percentile) had a CL/F of 102 L/h; in contrast, the subject with a baseline LBW of 61.9 kg (at 90th percentile) had a CL/F of 154 L/h, which is 1.5 times that of the subject at 10th percentile. For other covariates, the ratio of CL/F at the 90th percentile to CL/F at the 10th percentile was less than 1.2. The change in pharmacokinetic parameters caused by inter-individual variation was analyzed, and the results showed that the ratio of CL/F at the 90th percentile to CL/F at the 10th percentile was 2.9.

6.R Outline of the review conducted by PMDA

6.R.1 Comparison of pharmacokinetics between Japanese and non-Japanese

PMDA asked the applicant to explain the similarity in the pharmacokinetics of pasireotide LAR between Japanese and non-Japanese.

The applicant's response:

Using the data from Study G2304, a study of pasireotide LAR in patients with Cushing's disease, the plasma trough concentrations of pasireotide in Japanese subjects were compared with those of non-Japanese subjects. Plasma trough concentration data are available only from 1 to 3 subjects treated with pasireotide LAR 5 mg, and therefore there are limited data for the comparison of trough concentrations between Japanese and non-Japanese subjects. Accordingly, trough concentrations in subjects receiving pasireotide LAR 10 to 40 mg were used for comparison. The plasma trough concentrations of pasireotide (the mean values at each sampling point) ranged from 1.98 to 4.74 ng/mL in Japanese subjects and from 2.03 to 3.29 ng/mL in non-Japanese subjects in the pasireotide LAR 10 mg group, from 5.64 to 10.8 ng/mL in Japanese subjects and from 7.46 to 9.20 ng/mL in non-Japanese subjects in the pasireotide LAR 30 mg group, and from 12.0 to 15.8 ng/mL in Japanese subjects and from 10.4 to 12.5 ng/mL in non-Japanese subjects in the pasireotide LAR 40 mg group, suggesting that trough concentrations tend to be slightly higher in Japanese subjects than in non-Japanese subjects.

A linear mixed-effect model was used to investigate the effect of covariate on steady-state trough concentration data from Study G2304. The results indicated that LBW, TBIL, and GGT were statistically significant covariates. The obtained covariate model suggested that a reduction in LBW by 20 kg increased trough concentrations by approximately 55%, and a two-fold increase in TBIL or in GGT resulted in an increase in trough concentration by approximately 16% and 9%, respectively. Based on the degree of effects of these covariates, as well as the differences in the characteristics of Japanese and non-Japanese subjects in Study G2304, the factor considered to be most likely to affect trough concentrations was LBW. The mean value of LBW of Japanese subjects was less than that of non-Japanese subjects by 3.6 kg (45.8 kg for Japanese subjects and 49.4 kg for non-Japanese subjects). The effect on trough concentrations was studied using a parameter estimated by the linear mixed-effect model, and the results showed that a reduction in LBW by 3.6 kg would increase steady-state trough concentrations by approximately 8%. In the linear mixed-effect model, ethnicity (Japanese subjects) was not considered to be a statistically significant covariate.

Although strict comparison is difficult due to the limited pharmacokinetic data from Japanese subjects, the above results suggested that the difference in the mean of trough concentrations between non-Japanese and Japanese subjects was attributable to the LBW difference between these subgroups. However, individual trough concentrations in Japanese subjects are primarily within the range of individual trough concentrations in non-Japanese subjects. Given that the inter-individual variation (variation coefficient of geometric means) of trough concentrations in the overall population including Japanese and non-Japanese subjects ranged from 38.7% to 73.9%, there are no clear differences in pharmacokinetics between Japanese and non-Japanese subjects.

PMDA accepted the applicant's response that there are no significant differences in pharmacokinetics between Japanese and non-Japanese subjects, taking into consideration the ranges of individual trough concentrations in Japanese and non-Japanese subjects and the inter-individual variation, while trough concentrations obtained in Study G2304 tended to be slightly higher in Japanese subjects than in non-Japanese subjects.

6.R.2 Recommended clinical dose of pasireotide LAR

The applicant's explanation about the recommended clinical dose of pasireotide LAR from the standpoint of pharmacokinetics:

The pasireotide subcutaneous formulation (hereinafter referred to also as "s.c. pasireotide") has already been approved in Europe and the US. The recommended dose of s.c. pasireotide is 600 μg twice daily in Europe and 600 or 900 μg twice daily in the US, and in both regimens, the dose may be adjusted as necessary in the range of 300 to 900 μg per dose. Using the plasma pasireotide concentration data from Study C2111,[4)] which was conducted in healthy non-Japanese adults who received a single dose of

4) A bioequivalence study conducted in non-Japanese healthy adult men who received a single dose of pasireotide LAR 60 mg by intramuscular injection. The results of the study were submitted when the initial application was filed.

pasireotide LAR 60 mg, a simulation was performed to estimate pharmacokinetic parameters following administration of 10 to 40 mg of pasireotide LAR to patients with Cushing's disease once every 4 weeks for a total of 6 doses. The results of the simulation[5)] were compared with the results of another simulation, which was performed to estimate pharmacokinetic parameters following administration of s.c. pasireotide 300 to 900 μg twice daily, using PPK analysis of plasma pasireotide concentration data from Studies B2208 and B2305,[6)] in which non-Japanese patients received s.c. pasireotide 600 or 900 μg twice daily. The results showed that the steady-state trough concentration and $AUC_{0\text{-}28\ day}$ following administration of pasireotide LAR 10 mg were similar to those following administration of s.c. pasireotide 300 μg twice daily, and the steady-state trough concentration following administration of pasireotide LAR 30 mg was slightly higher than that following administration of s.c. pasireotide 900 μg twice daily; however, $AUC_{0\text{-}28\ day}$ was estimated to be similar. In Study B2305, when the dose was decreased to s.c. pasireotide 300 μg twice daily, there were some responders who had a mean urinary free cortisol (mUFC) ≤1.0 × ULN,[7)] indicating that the pasireotide subcutaneous formulation is effective at lower dose levels. Further, the efficacy of s.c. pasireotide 900 μg twice daily has been demonstrated and the dose is defined as the starting dose. Based on these findings and taking into consideration the exposure at these dose levels, the starting dose levels of 10 and 30 mg were selected for Study G2304 conducted in patients with Cushing's disease. The steady-state trough concentrations and $AUC_{0\text{-}28\ day}$ following administration of pasireotide LAR 40 mg were higher than those following administration of s.c. pasireotide 900 μg twice daily, while C_{max} was similar to that following administration of s.c. pasireotide 600 μg twice daily. In Study G2304, the pasireotide LAR dose was allowed to be increased up to 40 mg in subjects who failed to respond to treatment with pasireotide LAR 30 mg.

The results of the pharmacokinetic parameter simulation using plasma pasireotide concentration data obtained in Study G2304 showed that the trough concentrations were similar to the results of the above-mentioned simulation,[5)] which was performed to estimate pharmacokinetic parameters in patients with Cushing's disease based on the plasma pasireotide concentration data from non-Japanese healthy adults that were used as the rationale for the regimen employed in Study G2304; in contrast, C_{max} and $AUC_{0\text{-}28\ day}$ estimated by the previous simulation[5)] were approximately 2 to 3 times the C_{max} and $AUC_{0\text{-}28\ day}$ estimated by the simulation using data from Study G2304. The data from various studies[8)] in which s.c. pasireotide or pasireotide LAR was administered to healthy adults or patients with Cushing's disease

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5) Based on the pharmacokinetic data from Studies B2113 and B2305, in which the pasireotide subcutaneous formulation was administered to non-Japanese healthy adults (Study B2113) and patients with Cushing's disease (Study B2305), trough concentrations in patients with Cushing's disease were approximately twice those in healthy adults; further, based on the results of PPK analysis using pharmacokinetic data following administration of the pasireotide subcutaneous formulation, the CL/F of patients with Cushing's disease was estimated to be approximately 50% of that of healthy adults. On the basis of these results, a simulation was performed using the superposition method assuming that the drug concentration in patients with Cushing's disease is twice that of healthy adults.

6) Study B2208 is a foreign phase II study in which non-Japanese patients with Cushing's disease received s.c. pasireotide 600 μg twice daily for 15 days.
Study B2305 is a foreign phase III study with a treatment duration of 12 months, in which non-Japanese patients with Cushing's disease received s.c. pasireotide 600 or 900 μg twice daily for 3 months, and thereafter, if the response was inadequate at Months 3 and 6, the dose was allowed to be increased to 900 or 1200 μg twice daily, and if there was any problem with tolerability, the dose was allowed to be decreased to 300 μg twice daily.

7) Using 24-hour urine samples from healthy subjects (n = 28), urinary free cortisol concentrations were determined by HPLC, and the upper limit of normal (ULN) was specified as 145 nmol/24 h based on the 95th percentile (*Clin Chem.* 1997;43:1386-91).

8) Data from or PPK analysis data for the following studies: 5 foreign phase I studies of the pasireotide subcutaneous formulation in healthy adults (Studies B2101, B2102, B2106, B2108, and C2101); foreign phase II and III studies of the pasireotide subcutaneous formulation in patients with Cushing's disease (Studies B2208 and B2305); foreign phase I studies of pasireotide LAR in healthy adults (Studies C2101 and C2111); and a multi-regional phase III study of pasireotide LAR in patients with Cushing's disease (Study G2304).

were analyzed, and CL/F was compared using the model equations of PPK analysis to investigate the difference. The ratio of CL/F of healthy adults to that of patients with Cushing's disease was 1.3 to 1.7 for pasireotide LAR, and 1.7 to 2.2 for s.c. pasireotide, indicating that the difference in CL/F between patients with Cushing's disease and healthy adults was greater with s.c. pasireotide than with pasireotide LAR. The reason for the difference remains unclear. Pasireotide exposure was estimated based on the difference in the pharmacokinetics of pasireotide between healthy adults and patients with Cushing's disease receiving the pasireotide subcutaneous formulation, and the simulation[5)] was performed assuming that pasireotide exposure in patients with Cushing's disease receiving pasireotide LAR would be twice that in healthy adults. This may have resulted in overestimation of the C_{max} and $AUC_{0\text{-}28\ day}$. In Study G2304, steady-state trough concentrations following the third dose or subsequent doses in the pasireotide LAR 10, 30, and 40 mg groups (the mean values in each sampling point; the same shall apply hereinafter in this paragraph) ranged from 2.39 to 3.36 ng/mL, from 7.88 to 9.34 ng/mL, and from 10.7 to 12.6 ng/mL, respectively. In Study B2305, steady-state trough concentrations on Day ≥15 in patients receiving s.c. pasireotide 300 or 900 μg twice daily ranged from 1.46 to 6.09 ng/mL, and from 7.97 to 9.06 ng/mL, respectively, indicating that the trough concentrations were similar between pasireotide LAR 10 mg and s.c. pasireotide 300 μg twice daily, and between pasireotide LAR 30 mg and s.c. pasireotide 900 μg twice daily.

The relationship between the plasma pasireotide concentrations and mUFC obtained from Study G2304 was investigated using the E_{max} model.[9)] The results showed that there was a positive correlation between the trough concentration and mUFC reduction, and that the EC_{50} (mean [± standard error]) was estimated to be 0.6 ng/mL (±0.28), and $C_{effective}$ (mean [± standard error]) of the plasma pasireotide concentration at which mUFC reaches ULN[10)] was estimated to be 12.6 ng/mL (±16.53). The median of steady-state trough concentrations in subjects in the pasireotide LAR 10, 30, and 40 mg groups in Study G2304 were 2.42, 7.89, and 11.20 ng/mL, respectively. While the $C_{effective}$ was similar to that following administration of pasireotide LAR 40 mg, the trough concentrations at <40 mg were lower than that of $C_{effective}$. In contrast, when the achievement rate to the maximum inhibitory effect on mUFC and its 95% confidence interval (CI) following administration of pasireotide LAR 10, 30, or 40 mg were estimated using the E_{max} model, the achievement rate [95% CI] was estimated to be 79.35 [64.99, 93.71]% for the 10 mg group, 92.70 [86.82, 98.57]% for the 30 mg, and 94.75 [90.45, 99.06]% for the 40 mg, suggesting that the maximum inhibitory effect on mUFC can almost be achieved at pasireotide LAR 10 mg. Furthermore, the trough concentrations, and achievement rate to the maximum inhibitory effect on mUFC, as well as its 95% CI at pasireotide LAR 20 mg, a dose level which was not studied in Study G2304, were estimated. The estimated trough concentration was 5.31 ng/mL, and the estimated maximum inhibitory effect and its 95% CI were 89.50 [81.32, 97.68]%, suggesting that trough concentrations that are sufficiently high to exert inhibitory effect on mUFC can be achieved at pasireotide LAR 20 mg.

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9) $E = E_0 - (E_0 - E_{max}) \times$ [plasma pasireotide concentration] / ([plasma pasireotide concentration] + EC_{50}); E, the absolute value of mUFC; E_0, baseline mUFC; E_{max}, mUFC when pasireotide LAR exerts its maximum effect; EC_{50}, half maximal effective concentration of pasireotide in plasma. Using the E_{max} model, the plasma pasireotide concentration at which mUFC reaches ULN ($C_{effective}$), and achievement rate to the maximum inhibitory effect on mUFC ($[E_0 - E] / [E_0 - E_{max}]$) were estimated.

10) Using 24-hour urine samples from healthy subjects (n = 150), urinary free cortisol concentrations were determined by LC-MS/MS, and the ULN was specified as 166.48 nmol/24 h based on the 97.5th percentile.

As shown above, while some of the pharmacokinetic parameters were overestimated in the simulations of pharmacokinetics following administration of pasireotide LAR based on pharmacokinetic data of s.c. pasireotide, the trough concentrations at pasireotide LAR 10 and 30 mg are similar to the dose range of the pasireotide subcutaneous formulation approved overseas. The relationship between the trough concentration and mUFC also supports the validity of dose levels selected in Study G2304 and the efficacy of pasireotide LAR at the dose levels.

PMDA's view:

Because some pharmacokinetic parameters were overestimated in the simulations of pharmacokinetics following administration of pasireotide LAR based on the pharmacokinetic data of the pasireotide subcutaneous formulation, it is difficult to judge the appropriateness of dose levels selected in Study G2304. However, based on the relationship between the trough concentration following administration of pasireotide LAR and mUFC, as well as efficacy and safety results in Study G2304, which is discussed later, the range for the recommended clinical dose of pasireotide LAR presented by the applicant does not seem to have any significant problems. The appropriateness of the regimen of pasireotide LAR is further discussed in the clinical section [see Section "7.R.5 Dosage and administration"].

6.R.3 Use in patients with hepatic impairment

The applicant's explanation about the recommended clinical dose of pasireotide LAR for patients with hepatic impairment:

Study B2114[11)] was conducted in patients with hepatic impairment, and the study results were presented for the initial regulatory submission. The pharmacokinetics of pasireotide LAR in patients with hepatic impairment were investigated in the study. The results showed that C_{max} was higher in subjects with mild, moderate, or severe hepatic impairment than in subjects with normal hepatic function by 7%, 67%, and 69%, respectively, and AUC_{inf} was higher in subjects with mild, moderate, or severe hepatic impairment than in subjects with normal hepatic function by 8%, 60%, and 79%, respectively. Based on the results of this study, as with patients with acromegaly or pituitary gigantism, no dose adjustment of pasireotide LAR is needed for patients with Cushing's disease who have mild hepatic impairment. To investigate the appropriateness of the dose level for patients with moderate hepatic impairment, pharmacokinetic parameters following administration of the 12th dose in patients receiving pasireotide LAR 10 to 40 mg by intramuscular injection once every 4 weeks were estimated using PPK analysis, based on the plasma pasireotide concentration data from Study G2304 which was conducted in patients with Cushing's disease. The results were assumed to be the pharmacokinetic parameters of patients with normal hepatic function, and the pharmacokinetic parameters of patients with moderate hepatic impairment were estimated by multiplying by the exposure ratio of a patient with moderate hepatic impairment to a patient with normal hepatic function, obtained from Study B2114 ($AUC_{0\text{-}28\ day}$, 1.60; $C_{22\ day}$ and $C_{trough\ 28\ day}$, 1.67) (Table 2). The results of estimation showed that pharmacokinetic

11) An open-label, parallel-group, comparative study was conducted in non-Japanese subjects with normal hepatic function, and non-Japanese subjects with hepatic impairment (classification of hepatic impairment by Child-Pugh score, Score 5 to 6 [mild], Score 7 to 9 [moderate], and Score 10 to 15 [severe]) who received a single dose of 600 μg of s.c. pasireotide.

parameters following administration of pasireotide LAR 10 or 20 mg to patients with moderate hepatic impairment were within the range of exposure levels in patients with normal hepatic function following administration of pasireotide LAR 10 to 40 mg. In contrast, the pharmacokinetic parameters following administration of pasireotide LAR 30 or 40 mg to patients with moderate hepatic impairment were higher than the exposure levels in patients with normal hepatic function following administration of pasireotide LAR 40 mg.

Table 2. Estimated pharmacokinetic parameters following administration of the 12th dose in patients receiving pasireotide LAR 10 to 40 mg by intramuscular injection once every 4 weeks

	Dose	$AUC_{0\text{-}28\ day}$ (ng•day/mL)	$C_{22\ day}$ (ng/mL)	$C_{trough\ 28\ day}$ (ng/mL)
Patients with normal hepatic function	Pasireotide LAR 10 mg	80.7	3.07	2.78
	Pasireotide LAR 20 mg	171.07	6.53	5.97
	Pasireotide LAR 30 mg	267.0	10.22	9.39
	Pasireotide LAR 40 mg	365.4	14.0	12.93
Patients with moderate hepatic function	Pasireotide LAR 10 mg	129.1	5.13	4.64
	Pasireotide LAR 20 mg	273.7	10.91	9.97
	Pasireotide LAR 30 mg	427.2	17.07	15.68
	Pasireotide LAR 40 mg	584.7	23.38	21.59

$AUC_{0\text{-}28\ day}$: Area under the plasma pasireotide concentration-time curve from 0 to 28 days after the 12th dose of pasireotide LAR
$C_{22\ day}$: Plasma pasireotide concentration at 22 days after the 12th dose of pasireotide LAR, which is assumed to be C_{max}
$C_{trough\ 28\ day}$: Pasireotide plasma trough concentration at 28 days after the 12th dose of pasireotide LAR

Based on the above, the appropriate dosage for patients with moderate hepatic impairment is a starting dose of 10 mg, and the dose may be increased to a maximum of 20 mg depending on the patient's condition. Taking into consideration the possibility that pasireotide LAR may exacerbate hepatic impairment, pasireotide LAR should be contraindicated for safety reasons in patients with Cushing's disease who have severe hepatic impairment, as with patients with acromegaly or pituitary gigantism, indications that have already been approved.

PMDA's view:
Although there are no particular problems in the dosage for patients with hepatic impairment from the standpoint of exposure levels, the safety of pasireotide LAR in patients with hepatic impairment will be further discussed in the clinical section [see Section "7.R.6.1 Patients with hepatic impairment"].

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted evaluation data in the form of results from the multi-regional phase III study (Study G2304) (Table 3), and reference data, in the form of results from foreign clinical studies of the pasireotide subcutaneous formulation (Studies B2208, B2208E1, and B2305).

Table 3. List of reference data on efficacy and safety

Data class	Location	Study identifier	Phase	Target population	Enrolled	Summary of dosage regimen	Primary endpoints
Evaluation data	Multi-regional	G2304	III	Patients with Cushing's disease	150 subjects	Pasireotide LAR 10 or 30 mg once every 4 weeks by intramuscular injection	Efficacy Safety

The results from the main study are outlined below.

7.1 Multi-regional phase III study (CTD 5.3.5.2-1, Study G2304 [Since November 2011, data cut-off in November 2015; end of the core phase[12)]])

A randomized, double-blind study was conducted in patients with Cushing's disease (target sample size, 148 subjects [74 subjects each in the pasireotide LAR 10 mg and 30 mg groups]) in Japan and other countries[13)] to investigate the efficacy and safety of pasireotide LAR [see Section "6.2.1 Multi-regional phase III study" for the details of pharmacokinetics].

Key inclusion criteria are patients aged ≥18 years who had a diagnosis of ACTH-dependent Cushing's disease meeting the criteria (a) through (d) shown below, and patients who had persistent or recurrent disease, or de novo patients who were not considered candidates for pituitary surgery.

(a) The mUFC levels of three 24-hour urine samples collected within 2 weeks before screening (30 to 7 days prior to the start of treatment with the study drug) are ≥1.5 × ULN and ≤5 × ULN[10)];

(b) morning plasma ACTH is within or above the normal range;

(c) pituitary origin of excessive ACTH secretion has been confirmed;[14)] and

(d) in the case of patients with mUFC ≤3 × ULN, such patients must undergo 3 tests (low-dose dexamethasone suppression test, dexamethasone-CRH test, and late night salivary cortisol or serum cortisol levels) to exclude the possibility of pseudo-Cushing's disease (anomalies in ≥2 test results), unless histopathological evidence of ACTH staining pituitary tumor is present.

This study consisted of a core phase (12 months) and an extension phase (12 months). In and after the extension phase, subjects, who were considered by the investigator or sub-investigator to have a clinical benefit, had the option to continue study treatment until the start of treatment in the rollover study (Study B2412),[15)] and thereafter, the subjects continued to receive pasireotide LAR in Study B2412.

During the core phase, subjects received pasireotide LAR 10 or 30 mg once every 4 weeks by intramuscular injection into the gluteal muscle as the starting dose. For subjects with uncontrolled mUFC, if there were no safety concerns, dose increases were allowed at Months 4, 7, and 9, either at 10,

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12) The time when all subjects completed the 12-month treatment period of the core phase, or the study discontinued before reaching 12 months were defined as the end of the core phase (data cut off on November 10, 2015), and data up to the end of the core phase include data for the extension phase and thereafter up to the cut-off date, in addition to the data during the 12-month core phase.

13) The US, Italy, Belgium, China, Canada, France, Germany, Poland, Turkey, Brazil, India, Peru, Spain, Argentina, the Netherlands, Russia, Thailand, and UK

14) Pituitary origin of excessive ACTH secretion has been confirmed by at least one of the following 3 items:
   (a) History of MRI confirmation of pituitary adenoma (>6 mm) with positive dynamic test (CRH or high-dose dexamethasone suppression test)
   (b) History of inferior petrosal sinus sampling in patients with a tumor (≤6 mm), and after CRH or DDAVP stimulation, any of the following criteria are met
      a. Pituitary to peripheral ACTH ratio ≥2 at baseline, or
      b. Pituitary to peripheral ACTH ratio ≥3 after CRH or DDAVP stimulation
   (c) Prior pituitary surgery with histopathological exam confirming an ACTH staining adenoma

15) Rollover study (Study B2412) was an open-label extension study in patients with Cushing's disease, acromegaly, and other diseases who received pasireotide LAR or s.c. pasireotide. Subjects were allowed to enter this study after database lock in the core phase (Month 12) of Study G2304, and subjects were to enter the rollover study when the assessment at Month 12 of the extension phase of G2304 Study was completed after the database lock of the core phase. As of the data cut-off date ([redacted], 20[redacted]), 303 subjects were enrolled. Of these subjects, 62 were subjects with Cushing's disease (40 subjects including 6 Japanese subjects received pasireotide LAR, and 22 subjects received s.c. pasireotide).

30, or 40 mg, by 1 level at a time,[16] up to a maximum dose of 40 mg. At the beginning, pasireotide LAR was administered under the double-blind condition. Starting at Month 7, it was administered under the open-label condition.[17] Subjects who had had a clinical benefit at the completion of the core phase (Month 12)[18] and who had showed acceptable tolerability were allowed to enter the extension phase. The assessment of mUFC was performed every 3 months in the extension phase. If the UFC remained uncontrolled despite ≥3 months of treatment at the dose level prior to dose increase, and if there were no safety concerns, the dose was permitted to be increased to a maximum of 40 mg.[19] If there was any safety problem during the core and/or extension phase, the dose was to be decreased by only 1 dose level at a time, from 30 to 10 mg, or 10 to 5 mg during the first 7 months of the core phase, and thereafter, the dose was permitted to be decreased to 5 mg, as necessary, both in the core and extension phases, and treatment was to be discontinued in subjects who could not tolerate 5 mg. Table 4 shows the dosage at each time point up to Month 12.

Table 4. Dose level at each time point up to Month 12 (Study G2304)

Time point	Number of subjects[a]	Pasireotide LAR 10 mg					Pasireotide LAR 30 mg				
		0 mg	5 mg	10 mg	30 mg	40 mg	0 mg	5 mg	10 mg	30 mg	40 mg
Baseline	74/76	–	–	74 (100)[b]	–	–	–	–	–	76 (100)[e]	–
Month 1	73/75	–	1 (1.4)	72 (98.6)[b]	–	–	1 (1.3)	–	3 (4.0)	71 (94.7)[e]	–
Month 4	65/69	–	2 (3.1)	32 (49.2)[c]	31 (47.7)[d]	–	–	–	8 (11.6)	33 (47.8)[d]	28 (40.6)[g]
Month 7	54/62	–	3 (5.6)[d]	22 (40.7)[e]	16 (29.6)[d]	13 (24.1)[d]	3 (4.8)	–	6 (9.7)	20 (32.3)[d]	33 (53.2)[g]
Month 9	52/60	2 (3.8)[d]	3 (5.8)[d]	18 (34.6)[f]	12 (23.1)[d]	17 (32.7)[f]	2 (3.3)	1 (1.7)	6 (10.0)	14 (23.3)	37 (61.7)[e]
Month 12	40/41	–	5 (12.5)[f]	11 (27.5)[f]	13 (32.5)[d]	11 (27.5)[f]	–	1 (2.4)	4 (9.8)	7 (17.1)	29 (70.7)[e]

Number of subjects at each dose level (%); –, no applicable subjects

a) Number of subjects in the pasireotide LAR 10 mg group/number of subjects in the pasireotide LAR 30 mg group at each time point;
b) 7 Japanese subjects; c) 6 Japanese subjects; d) 1 Japanese subject; and e) 4 Japanese subjects; f) 2 Japanese subjects; and
g) 3 Japanese subjects

Of the 150 subjects who were randomized to treatment groups (74 subjects including 7 Japanese subjects randomized to the 10 mg group, and 76 subjects including 4 Japanese subjects randomized to the 30 mg group), all subjects were included in the FAS and safety analysis set, and the FAS was the primary efficacy analysis set. Of the 150 subjects, 104 (50 subjects in the 10 mg and 54 subjects in the 30 mg groups) completed the core phase, and among these subjects, 81 (40 subjects including 7 Japanese subjects in the 10 mg group, and 41 subjects including 4 Japanese subjects in the 30 mg group) entered the extension phase. By the data cut-off date at the end of the core phase, 32 subjects (the 10 mg group) and 43 subjects (the 30 mg group) discontinued study treatment for the following reasons: insufficient therapeutic effect in 28 subjects (9 subjects including 1 Japanese subject in the 10 mg group and 19

16) To consider dose increase at Months 4, 7, and 9, mUFC was calculated based on the UFC levels of 24-hour urine samples measured 3 times approximately 7 to 19 days after administration at the previous time point. At Month 4, if the patient achieved mUFC ≤1.5 × ULN, the starting dose (10 or 30 mg) was continued; if the patient achieved mUFC >1.5 × ULN, the dose was increased to the next dose level (from 10 to 30 mg, or from 30 to 40 mg). At Months 7 and 9, if the patient achieved mUFC above ULN, the dose was increased to the next dose level; if the patient achieved mUFC at or below ULN, the treatment was continued at the same dose level. The dose could be increased to a maximum of 40 mg.

17) Patients and investigators/sub-investigators were unblinded after the analysis of Month 12; Sponsor and contract research organizations were unblinded at the time of analysis at Month 7.

18) If the patient achieved mUFC at or below ULN, or if the patient did not achieve mUFC at or below ULN but received a clinical benefit in the opinion of the primary or sub-investigator.

19) If the patient achieved mUFC ≤1.5 times ULN, the treatment was continued at the same dose level; if the patient achieved mUFC >1.5 times ULN, the dose was increased to the next dose level (for patients who had a starting dose of 30 mg in the extension phase, and treatment was continued at 30°mg because mUFC was ≤1.5 times ULN, the final criteria for dose increase was when mUFC was above ULN), the dose was allowed to be increased to a maximum of 40 mg.

subjects including 2 Japanese subjects in the 30 mg group), consent withdrawal in 19 subjects (12 subjects in the 10 mg group and 7 subjects in the 30 mg group), adverse events in 18 subjects (8 subjects including 1 Japanese subject in the 10 mg group and 10 subjects including 1 Japanese subject in the 30 mg group), protocol deviation in 4 subjects (2 subjects in the 10 mg group and 2 subjects in the 30 mg group), administrative problems in 3 subjects (1 subject in the 10 mg group and 2 subjects in the 30 mg group), death in 2 subjects (2 subjects in the 30 mg group), and abnormal laboratory test results in 1 subject (the 30 mg group).

Table 5 shows the response rates (proportion of subjects who achieved mUFC ≤1.0 × ULN; the same shall apply hereinafter) at Month 7 regardless of dose increase at Month 4, which was the primary endpoint. The lower limit of the 95% CI for the response rate exceeded the prescribed threshold (15%[20)]) in both dose groups.

Table 5. Results of primary endpoint (Study G2304 [core phase], FAS)

Endpoint	Overall population		Japanese subpopulation	
	Pasireotide LAR 10 mg	Pasireotide LAR 30 mg	Pasireotide LAR 10 mg	Pasireotide LAR 30 mg
Response rate at Month 7[a)]	31/74 41.9 [30.51, 53.94]	31/76 40.8 [29.65, 52.67]	4/7 57.1 [18.41, 90.10]	1/4 25.0 [0.63, 80.59]

Upper row, number of subjects (responders/evaluated subjects); lower row, proportion of responders [95% CI] (%); LOCF
a) Response rate regardless of dose increase at Month 4; multiplicity adjustment based on a closed testing procedure from the high dose group

Table 6 shows the results of the key secondary endpoint (response rates at Month 7, where subjects with dose increase at Month 4 were defined as non-responders) and other secondary endpoints (response rate, mUFC, trends in plasma ACTH and serum cortisol levels). Also, percent change from baseline in pituitary tumor volume at Month 12 (mean value ± standard deviation [SD]) was −22.4 ± 34.66% (35 subjects) in the pasireotide LAR 10 mg group, and −16.8 ± 36.32% (38 subjects) in the pasireotide LAR 30 mg group (−4.1 ± 39.86% [7 Japanese subjects] in the 10 mg group, and −0.6 ± 9.18% [3 Japanese subjects] in the 30 mg group).

20) To confirm if the efficacy of pasireotide LAR is similar to that of the pasireotide subcutaneous formulation, Study G2304 employed criteria similar to those used in the foreign phase III study (Study B2305) in which non-Japanese patients with Cushing's disease received s.c. pasireotide 600 μg or 900 μg, and the lower limit of 95% CI for response rate was set as 15% because there were no confirmatory study data used as a basis for the effect size for efficacy when Study B2305 was designed. Therefore, patients eligible for pharmacotherapy will not recover spontaneously without being treated, and if a response rate >15% can be attained by pharmacotherapy, it would be clinically meaningful, and thus a threshold of 15% was selected as the lower limit of 95% CI.

Table 6. Results of key and other secondary endpoints (Study G2304 [core phase], FAS)

Endpoint	Assessment time point	Overall population		Japanese subpopulation	
		Pasireotide LAR 10 mg (N = 74)	Pasireotide LAR 30 mg (N = 76)	Pasireotide LAR 10 mg (N = 7)	Pasireotide LAR 30 mg (N = 4)
Response rates at Month 7, where subjects with dose increase at Month 4 were defined as non-responders (LOCF)[a)c)]		21/74 28.4 [18.50, 40.05]	24/76 31.6 [21.39, 43.25]	4/7 57.1 [18.41, 90.10]	0/4 0 [0.00, 60.24]
Response rate[a)c)]	Month 1	22/74 29.7 [19.66, 41.48]	28/76 36.8 [26.06, 48.69]	4/7 57.1 [18.41, 90.10]	1/4 25.0 [0.63, 80.59]
	Month 4	23/74 31.1 [20.83, 42.90]	28/76 36.8 [26.06, 48.69]	4/7 57.1 [18.41, 90.10]	1/4 25.0 [0.63, 80.59]
	Month 7	29/74 39.2 [28.04, 51.23]	31/76 40.8 [29.65, 52.67]	4/7 57.1 [18.41, 90.10]	1/4 25.0 [0.63, 80.59]
	Month 12	26/74 35.1 [24.39, 47.11]	19/76 25.0 [15.77, 36.26]	6/7 85.7 [42.13, 99.64]	2/4 50.0 [6.76, 93.24]
mUFC[b)] (nmol/24 h)	Baseline	462.6 ± 256.41	477.1 ± 331.75	395.5 ± 248.76	389.2 ± 184.07
	Month 1	327.6 ± 241.42	322.1 ± 401.48[q)]	193.3 ± 99.62	313.6 ± 351.32
		−135.0 ± 290.67	−161.0 ± 440.73[q)]	−202.2 ± 285.30	−75.6 ± 385.85
	Month 4	392.9 ± 724.75[d)]	269.3 ± 206.60[t)]	167.9 ± 124.70	262.7 ± 104.93
		−70.6 ± 742.10[d)]	−218.9 ± 333.69[t)]	−227.6 ± 275.02	−126.5 ± 105.37
	Month 7	240.8 ± 231.14[e)]	239.7 ± 178.66[o)]	133.7 ± 74.48	277.1 ± 84.43
		−192.4 ± 271.59[e)]	−234.3 ± 362.86[o)]	−261.9 ± 257.16	−112.2 ± 155.26
	Month 12	232.7 ± 209.51[f)]	248.3 ± 206.45[r)]	121.4 ± 58.10	286.8 ± 184.18
		−195.1 ± 282.46[f)]	−247.6 ± 387.05[r)]	−274.1 ± 267.14	−102.4 ± 32.24
Plasma ACTH level[b)] (pmol/L)	Baseline	16.3 ± 32.23[g)]	15.6 ± 9.90	14.6 ± 15.90	24.5 ± 14.27
	Month 1	15.6 ± 25.74[g)]	12.4 ± 7.07[s)]	13.9 ± 11.96	17.0 ± 3.46
		−0.7 ± 8.93[h)]	−3.2 ± 6.96[s)]	−0.7 ± 4.89	−7.5 ± 11.24
	Month 4	14.5 ± 13.79[i)]	12.1 ± 7.17[t)]	12.7 ± 14.48	17.5 ± 3.79
		−2.5 ± 24.98[j)]	−3.6 ± 6.57[t)]	−1.9 ± 1.77	−7.0 ± 10.95
	Month 7	12.5 ± 10.60[k)]	12.9 ± 9.05[u)]	13.9 ± 12.69	15.8 ± 4.92
		−4.4 ± 29.94[l)]	−2.4 ± 9.92[u)]	−0.7 ± 5.38	−8.8 ± 16.68
	Month 12	11.7 ± 13.67[m)]	12.6 ± 8.81[r)]	13.6 ± 16.42	18.5 ± 7.85
		−6.4 ± 29.23[m)]	−2.8 ± 8.01[r)]	−1.0 ± 1.15	−6.0 ± 9.70
Serum cortisol level[b)] (nmol/L)	Baseline	574.3 ± 202.29[n)]	572.8 ± 194.66	551.6 ± 278.08	516.1 ± 151.19
	Month 1	527.5 ± 196.24[n)]	501.3 ± 267.75[s)]	509.8 ± 183.07	477.4 ± 119.61
		−41.3 ± 202.83[g)]	−71.7 ± 286.84[s)]	−41.7 ± 188.19	−38.7 ± 166.56
	Month 4	521.0 ± 218.47[o)]	491.2 ± 194.72[o)]	450.7 ± 160.28	532.0 ± 56.49
		−51.8 ± 240.88[d)]	−80.2 ± 240.72[o)]	−100.9 ± 148.37	15.9 ± 205.80
	Month 7	505.0 ± 219.70[k)]	494.7 ± 185.34[d)]	477.5 ± 206.58	547.4 ± 65.50
		−73.1 ± 194.43[l)]	−68.4 ± 255.07[d)]	−74.1 ± 203.12	31.3 ± 176.63
	Month 12	479.3 ± 194.20[p)]	528.7 ± 167.88[r)]	461.7 ± 214.53	529.2 ± 128.90
		−88.0 ± 173.31[p)]	−38.0 ± 236.50[r)]	−89.9 ± 129.16	13.1 ± 149.71

a) Upper row, number of subjects (responders/evaluated subjects); lower row, proportion of responders [95% CI] (%)
b) Upper row, mean value of actual measurements ± SD; lower row, mean value ± SD of the change from baseline
c) Response rate, proportion of subjects who achieved mUFC at or below ULN
d) N = 66, e) N = 57, f) N = 50, g) N = 72, h) N = 70, i) N = 64, j) N = 62, k) N = 56, l) N = 55, m) N = 45, n) N = 73, o) N = 67, p) N = 46, q) N = 74, r) N = 54, s) N = 75, t) N = 69, and u) N = 65

Table 7 shows the characteristics of individual subjects in the Japanese subpopulation, and Table 8 shows the trends in mUFC, plasma ACTH, and serum cortisol levels of these individual subjects.

Table 7. Characteristics of individual subjects
(Study G2304 [end of the core phase[a)]], Japanese subpopulation)

	Subject No.										
	4401/ 00002	4404/ 00001	4405/ 00002	4407/ 00002	4408/ 00001	4410/ 00001	4411/ 00001	4407/ 00001	4409/ 00001	4411/ 00003	4416/ 00001
Sex	F	F	F	M	M	F	F	M	F	F	M
Age (year)	62	41	42	34	36	28	62	34	39	39	39
Body weight (kg)	50.8	46.5	54.0	72.2	58.7	61.2	53.1	63.2	100.4	56.8	77.0
BMI (kg/m^2)	24.6	19.6	21.1	26.7	21.3	21.6	24.5	21.0	37.5	24.3	25.8
Prior pituitary adenoma surgery	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Disease duration (month)	9.49	108.29	7.66	62.49	15.44	102.77	21.45	68.96	55.69	64.36	93.14
Pasireotide LAR starting dose	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	30 mg	30 mg	30 mg	30 mg

a) In addition to the data for the core phase up to Month 12, data for the extension phase and thereafter up to the data cut-off date are included.

Table 8. Trends in mUFC, plasma ACTH, and serum cortisol levels in individual subjects
(Study G2304 [end of the core phase[a)]], Japanese subpopulation)

Endpoint	Assessment time point	Subject No.										
		4401/ 00002	4404/ 00001	4405/ 00002	4407/ 00002	4408/ 00001	4410/ 00001	4411/ 00001	4407/ 00001	4409/ 00001	4411/ 00003	4416/ 00001
Starting dose of pasireotide LAR		10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	30 mg	30 mg	30 mg	30 mg
mUFC (nmol/24 h)	Baseline	238.17	297.83	926.60	349.43	385.77	404.63	166.10	607.43	459.40	306.27	183.73
	Month 4	185.03	91.20	118.07	90.47	421.37	212.60	56.57	332.10	370.90	192.73	154.93
	Month 7	40.03	111.07	130.10	40.30	198.23	214.33	201.50	273.73	356.27	317.27	160.93
	Month 12	70.70	135.97	116.97	52.43	115.13	125.00	233.83	512.57	359.37	160.10	115.10
	Month 24	40.03	106.13	–	115.37	147.13	146.73	77.67	–	425.30	–	–
	Month 36	–	73.83	–	23.87	115.23	–	–	–	–	–	–
Plasma ACTH level (pmol/L)	Baseline	11.0	11.0	11.0	50.0	10.0	5.0	4.0	20.0	42.0	28.0	8.0
	Month 4	9.0	9.0	9.0	45.0	9.0	6.0	2.0	15.0	23.0	17.0	15.0
	Month 7	6.0	15.0	10.0	41.0	11.0	12.0	2.0	23.0	12.0	14.0	14.0
	Month 12	9.0	9.0	12.0	50.0	9.0	4.0	2.0	24.0	25.0	17.0	8.0
	Month 24	8.0	6.0	–	47.0	11.0	6.0	3.0	–	13.0	–	–
	Month 36	–	13.0	–	61.0	11.0	–	–	–	–	–	–
Serum cortisol level (nmol/L)	Baseline	325.0	676.0	997.7	815.6	313.4	326.1	407.2	401.2	575.5	702.4	385.2
	Month 4	256.3	518.7	642.8	632.6	249.1	425.2	429.9	574.7	533.9	451.6	567.8
	Month 7	110.9	715.4	648.9	552.4	315.6	537.5	461.6	495.5	499.1	559.8	635.1
	Month 12	181.3	688.1	773.9	524.8	314.8	311.2	437.9	630.2	558.1	587.4	341.0
	Month 24	204.2	396.5	–	570.8	263.5	387.9	552.1	–	569.2	–	–
	Month 36	–	642.6	–	677.1	392.6	–	–	–	–	–	–

–, not applicable
a) In addition to the data for the core phase up to Month 12, data for the extension phase and thereafter up to the data cut-off date are included.

Regarding safety, Table 9 shows the incidence of adverse events and adverse drug reactions reported in ≥10% subjects in any group at the end of the core phase in the overall population. Table 10 shows the incidence of adverse events and adverse drug reactions reported in ≥2 subjects in any group at the end of the core phase in the Japanese subpopulation.

Table 9. Incidence of adverse events and adverse drug reactions reported in ≥10% of subjects in any group (Study G2304 [end of the core phase[a)]] [overall population[b)]], safety analysis set)

Event	Pasireotide LAR 10 mg (N = 74)		Pasireotide LAR 30 mg (N = 76)	
	Adverse event	Adverse drug reaction	Adverse event	Adverse drug reaction
Events total	98.6 (73)	90.5 (67)	100 (76)	96.1 (73)
Hyperglycaemia	48.6 (36)	47.3 (35)	47.4 (36)	46.1 (35)
Diarrhoea	35.1 (26)	28.4 (21)	43.4 (33)	35.5 (27)
Cholelithiasis	20.3 (15)	18.9 (14)	44.7 (34)	43.4 (33)
Diabetes mellitus	18.9 (14)	17.6 (13)	23.7 (18)	23.7 (18)
Nausea	20.3 (15)	14.9 (11)	21.1 (16)	14.5 (11)
Headache	24.3 (18)	2.7 (2)	13.2 (10)	3.9 (3)
Nasopharyngitis	21.6 (16)	0 (0)	15.8 (12)	0 (0)
Fatigue	16.2 (12)	12.2 (9)	18.4 (14)	7.9 (6)
Hypertension	13.5 (10)	2.7 (2)	15.8 (12)	2.6 (2)
Abdominal pain	13.5 (10)	10.8 (8)	15.8 (12)	11.8 (9)
Hypoglycaemia	12.2 (9)	2.7 (2)	15.8 (12)	2.6 (2)
Oedema peripheral	12.2 (9)	1.4 (1)	15.8 (12)	1.3 (1)
Influenza	16.2 (12)	0 (0)	7.9 (6)	0 (0)
Dizziness	12.2 (9)	6.8 (5)	10.5 (8)	0 (0)
Urinary tract infection	10.8 (8)	0 (0)	11.8 (9)	0 (0)
Back pain	10.8 (8)	2.7 (2)	9.2 (7)	1.3 (1)
Decreased appetite	4.1 (3)	2.7 (2)	15.8 (12)	10.5 (8)
Asthenia	13.5 (10)	5.4 (4)	6.6 (5)	2.6 (2)
Blood glucose increased	8.1 (6)	8.1 (6)	10.5 (8)	9.2 (7)
Insomnia	10.8 (8)	2.7 (2)	6.6 (5)	0 (0)
Arthralgia	12.2 (9)	1.4 (1)	3.9 (3)	1.3 (1)
Abdominal pain upper	4.1 (3)	1.4 (1)	10.5 (8)	5.3 (4)

% incidence (n); MedDRA (ver.18.1)

a) In addition to the data for the core phase up to Month 12, data for the extension phase and thereafter up to the data cut-off date are included.

b) Study drug treatment period (median [range]): 449.0 [28.0, 1393.0] days in the pasireotide LAR 10 mg group; 380.5 [28.0, 1294.0] days in the pasireotide LAR 30 mg group
Number of doses of the study drug (median [range]): 16.5 [1.0, 50.0] doses in the pasireotide LAR 10 mg group; 13.5 [1.0, 47.0] doses in the pasireotide LAR 30 mg group

Table 10. Incidence of adverse events and adverse drug reactions reported in ≥2 subjects in any group (Study G2304 [end of the core phase[a)]] [Japanese subpopulation[b)]], safety analysis set)

Event	Pasireotide LAR 10 mg (N = 7)		Pasireotide LAR 30 mg (N = 4)	
	Adverse event	Adverse drug reaction	Adverse event	Adverse drug reaction
Events total	100 (7)	85.7 (6)	100 (4)	100 (4)
Hyperglycaemia	42.9 (3)	42.9 (3)	25.0 (1)	25.0 (1)
Diarrhoea	28.6 (2)	28.6 (2)	25.0 (1)	25.0 (1)
Diabetes mellitus	42.9 (3)	42.9 (3)	0 (0)	0 (0)
Nasopharyngitis	42.9 (3)	0 (0)	25.0 (1)	0 (0)
Fatigue	42.9 (3)	42.9 (3)	0 (0)	0 (0)
Hypercholesterolaemia	0 (0)	0 (0)	50.0 (2)	25.0 (1)
Glucose tolerance impaired	0 (0)	0 (0)	75.0 (3)	75.0 (3)
Constipation	28.6 (2)	28.6 (2)	0 (0)	0 (0)
Eczema	28.6 (2)	0 (0)	0 (0)	0 (0)
Haemorrhoids	28.6 (2)	14.3 (1)	0 (0)	0 (0)
Seborrhoeic dermatitis	28.6 (2)	0 (0)	0 (0)	0 (0)

% incidence (n); MedDRA (ver.18.1)

a) In addition to the data for the core phase up to Month 12, data for the extension phase and thereafter up to the data cut-off date are included.

b) Study drug treatment duration (median [range]): 981.0 [502.0, 1393.0] days in the pasireotide LAR 10 mg group; 490.0 [406.0, 700.0] days in the pasireotide LAR 30 mg group
Number of doses of the study drug (median [range]): 36.0 [18.0, 50.0] doses in the pasireotide LAR 10 mg group; 17.5 [15.0, 25.0] doses in the pasireotide LAR 30 mg group

Two deaths occurred in the pasireotide LAR 30 mg group (cardiopulmonary failure and pulmonary artery thrombosis in 1 subject each), and a causal relationship to the study drug was ruled out for both of the events. Serious adverse events occurred in 21 subjects in the pasireotide LAR 10 mg group (road traffic accident, diverticulitis, pneumonia, femoral neck fracture/stress fracture, anogenital dysplasia, blood cortisol increased, pituitary-dependent Cushing's syndrome, endometrial cancer/endometrial cancer, injection site pain, cholelithiasis, subcutaneous abscess, angina unstable/gamma-glutamyl-transferase [GGT] increased/pituitary-dependent Cushing's syndrome, haemorrhoids/dysphonia/hyperadrenocorticism, blood cortisol decreased, hypertensive crisis, hyperglycaemia, adrenal insufficiency/large intestine polyp/osteoarthritis [Japanese subject], diabetes mellitus [Japanese subject], ovarian cyst, cholecystitis acute/cholelithiasis/oedematous pancreatitis, and stress fracture in 1 subject each) and in 17 subjects in the pasireotide LAR 30 mg group (cellulitis/spondylolisthesis, pituitary-dependent Cushing's syndrome, cholelithiasis/abortion spontaneous, cardiac failure, anaemia, cholelithiasis, angina pectoris, acute kidney injury/blood cortisol decreased/malaise/blood cortisol decreased/gastric ulcer, coronary artery occlusion, sinus bradycardia, deep vein thrombosis, arthritis/cardiopulmonary failure/cardiac arrest/dyspnoea, pulmonary embolism, pulmonary embolism/sepsis/septic shock/pulmonary artery thrombosis, osteoporosis [Japanese subject], endometrial cancer [Japanese subject], and nephrolithiasis [Japanese subject] in 1 subject each). Among these, the events reported in 8 subjects in the pasireotide LAR 10 mg group were considered to be adverse drug reactions (injection site pain, cholelithiasis, GGT increased, blood cortisol decreased, hyperglycaemia, adrenal insufficiency [Japanese subject], diabetes mellitus [Japanese subject], and cholecystitis acute/cholelithiasis/oedematous pancreatitis in 1 subject each), and the events reported in 4 subjects in the pasireotide LAR 30 mg group were considered to be adverse drug reactions (cholelithiasis, anaemia, blood cortisol decreased/malaise/blood cortisol decreased, deep vein thrombosis in 1 subject each). Adverse events led to treatment discontinuation in 9 subjects in the pasireotide LAR 10 mg group (hyperglycaemia in 2 subjects; blood cortisol increased, coronary artery stenosis, pituitary-dependent Cushing's syndrome, alanine aminotransferase [ALT] increased, hypercorticoidism/blood glucose increased, diabetes mellitus [Japanese subject], and cholecystitis acute/hepatic enzyme increased/cholelithiasis/blood bilirubin increased/oedematous pancreatitis/ascites in 1 subject each) and in 10 subjects in the pasireotide LAR 30 mg group (diabetes mellitus in 3 subjects; cholecystitis/hyperglycaemia, hepatic function abnormal, cholelithiasis, hyperkalaemia, pulmonary embolism, endometrial cancer [Japanese subject], and ALT increased/cholelithiasis in 1 subject each). Among these, the events reported in 6 subjects in the pasireotide LAR 10 mg group were considered to be adverse drug reactions occurred (hyperglycaemia in 2 subjects; ALT increased, hypercorticoidism/blood glucose increased, diabetes mellitus [Japanese subject], and cholecystitis acute/hepatic enzyme increased/cholelithiasis/blood bilirubin increased/oedematous pancreatitis/ascites in 1 subject each) and the events reported in 7 subjects in the pasireotide LAR 30 mg group were considered to be adverse drug reactions (diabetes mellitus in 3 subjects; cholecystitis/hyperglycaemia, cholelithiasis, hyperkalaemia, and ALT increased/cholelithiasis in 1 subject each).

Vital sign exhibited no clinically notable anomalies.

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

Cushing's disease is a rare disease[1)] and an estimated 450 people have been affected by this disease in Japan. In addition, only 11 Japanese patients participating in the multi-regional phase III study (Study G2304).[21)] Given these facts, PMDA decided to evaluate the efficacy in Japanese subjects also on an individual case basis.

The applicant's explanation about the efficacy of pasireotide LAR in the treatment of Cushing's disease: In Study G2304, subjects received pasireotide LAR 10 or 30 mg once every 4 weeks, and the dose was adjusted at Months 4, 7, and 9 depending on mUFC. Table 5 shows the response rate at Month 7 regardless of dose increase at Month 4, which is the primary endpoint. At both dose levels, the lower limit of 95% CI exceeded the pre-specified threshold (15%[20)]), demonstrating the efficacy of pasireotide LAR in the treatment of patients with Cushing's disease. Further, mUFC, plasma ACTH, and serum cortisol levels decreased at Month 1, and tended to be below baseline levels up to Month 12 (Table 6). Percent change from baseline in pituitary tumor volume at Month 12 indicated that, as discussed in Section "7.1 Multi-regional phase III study," the pituitary tumor volume was also reduced after treatment with pasireotide LAR.

To evaluate the long-term efficacy of pasireotide LAR until the end of the study,[22)] including the extension phase of Study G2304, the trends in mUFC, plasma ACTH, and serum cortisol levels at Months 12, 24, and 36 were studied. As shown in Table 11, reduced mUFC, plasma ACTH, and serum cortisol levels tended to be maintained at and after Month 12. Percent change from baseline in pituitary tumor volume (mean value ± SD) was −22.7 ± 40.10% (21 subjects) at Month 24 and −19.0 ± 43.15% (10 subjects) at Month 36 in the pasireotide LAR 10 mg group, and −30.7 ± 32.96% (17 subjects) at Month 24 and −34.9 ± 12.69% (4 subjects) at Month 36 in the pasireotide LAR 30 mg group.

21) "Basic Principles on Global Clinical Trials" (Notification No. 0928010, dated September 28, 2007, by the Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare) presents a guide for determining a sample size and proportion of Japanese subjects for a study conducted as a multi-regional clinical trial, and it specifies that approximately 15% to 20% of study subjects could be Japanese. However, because enrollment of patients with Cushing's disease (a rare disease) is difficult, patients were enrolled in the multi-regional phase III study (Study G2304) from the standpoint of feasibility. The sample size of Japanese subjects was not determined from the standpoint of maintaining consistency between the overall population and Japanese subpopulation.

22) The time point when all subjects had completed all of the assessment for the core and extension phases, or discontinued earlier (data cut-off date, December 21, 2016). The data up to the end of the study include data for the core and extension phases and thereafter up to the data cut-off date.

Table 11. Trends in mUFC, plasma ACTH, and serum cortisol levels at Months 12, 24, and 36
(Study G2304 [end of the study], FAS)

Endpoint	Assessment time point	Pasireotide LAR 10 mg (N = 74)	Pasireotide LAR 30 mg group (N = 76)
mUFC (nmol/24 h)	Baseline	462.6 ± 256.41	477.1 ± 331.75
	Month 12	232.7 ± 209.51[a)]	248.3 ± 206.45[i)]
		−195.1 ± 282.46[a)]	−247.6 ± 387.05[i)]
	Month 24	176.8 ± 241.92[b)]	177.2 ± 134.27[j)]
		−236.2 ± 292.91[b)]	−265.2 ± 313.47[j)]
	Month 36	105.0 ± 65.60[c)]	180.2 ± 81.83[k)]
		−298.4 ± 136.09[c)]	−164.6 ± 66.76[k)]
Plasma ACTH level (pmol/L)	Baseline	16.3 ± 32.23	15.6 ± 9.90
	Month 12	11.7 ± 13.67[d)]	12.6 ± 8.81[i)]
		−6.4 ± 29.23[d)]	−2.8 ± 8.01[i)]
	Month 24	12.5 ± 12.06[e)]	11.9 ± 8.56[j)]
		−8.2 ± 41.55[f)]	−1.2 ± 8.34[j)]
	Month 36	11.1 ± 15.34[c)]	7.2 ± 2.59[l)]
		−0.2 ± 4.38[g)]	−1.2 ± 3.56[l)]
Serum cortisol level (nmol/L)	Baseline	574.3 ± 202.29	572.8 ± 194.66
	Month 12	479.3 ± 194.20[h)]	528.7 ± 167.88[i)]
		−88.0 ± 173.31[h)]	−38.0 ± 236.50[i)]
	Month 24	412.3 ± 154.10[e)]	490.8 ± 158.27[j)]
		−93.8 ± 169.02[e)]	−87.4 ± 273.31[j)]
	Month 36	456.9 ± 222.26[c)]	386.1 ± 67.10[l)]
		−51.5 ± 275.21[c)]	−176.9 ± 250.55[l)]

Upper row, mean value of actual measurements ± SD;
lower row, mean value ± SD of the change from baseline
a) N = 50, b) N = 33, c) N = 14, d) N = 45, e) N = 32, f) N = 31, g) N = 13, h) N = 46
i) N = 54, j) N = 25, k) N = 4, and l) N = 5

PMDA asked the applicant to explain intrinsic and extrinsic ethnic factors and differences in characteristics between Japanese and non-Japanese patients, as well as efficacy in Japanese patients.

The applicant's response:

As for extrinsic ethnic factors, no ethnic differences in the pathological condition and symptoms of patients with Cushing's disease have been reported, and diagnostic criteria are similar between Japan and other countries (*J Clin Endocrinol Metab.* 2003;88:5593-602, and "Guide for the diagnosis of Cushing's disease [revised on FY2009]" FY2009 Research report by the Research group of diencephalohypophysial function disorder, Research Program of Intractable Diseases funded by Health and Labour Sciences Research Grants). In the treatment of Cushing's disease, hypercortisolemia has a serious impact on the clinical symptoms and prognosis of patients. The primary goal of therapy is therefore to normalize cortisol levels. If surgical resection of pituitary adenoma cannot be performed, or if surgical resection failed to result in remission of pituitary adenoma, radiation therapy (stereotactic radiation therapy or fractionated external beam radiation therapy), pharmacotherapy (drugs suppressing ACTH secretion, adrenocorticosteroid synthesis inhibitors, and glucocorticoid receptor antagonists), or bilateral adrenalectomy is performed both in and outside Japan (e.g., *J Clin Endocrinol Metab.* 2015;100:2807-31, *Manual for the Treatment of Cushing's Syndrome*, rev. 2nd ed. Shindan-to-Chiryosha;2015) [see Section "7.R.3 Clinical positioning"]. Further, no significant differences in the goal of therapy and treatment algorithm exist between Japan and other countries. As for intrinsic ethnic

factors, there seem to be no clear ethnic differences in the pharmacokinetics of pasireotide between Japanese and non-Japanese patients with Cushing's disease [see Section "6.R.1 Comparison of pharmacokinetics between Japanese and non-Japanese"].

Table 12 shows the results of assessment of similarity in intrinsic ethnic factors (e.g., age, sex, body weight, body mass index [BMI], and disease duration) for characteristics of the Japanese subpopulation and overall population in Study G2304. Although a strict comparison is limited because there were only 11 Japanese subjects, body weight was lower in the Japanese subpopulation than in the overall population (the mean for the Japanese subpopulation, 63.08 kg, and the mean for the overall population, 76.23 kg); the median duration (months) required to enroll a patient in this study after a diagnosis of Cushing's disease was longer in the Japanese subpopulation than in the overall population (Japanese subpopulation, 62.5 months, and the overall population, 22.3 months). However, there was no consistent trend between body weight and baseline mUFC, or between the duration required to enroll a person in this study after being diagnosed as having Cushing's disease and baseline mUFC. The difference in the median baseline mUFC (Japanese subpopulation, 349.4 nmol/24 h, and the overall population, 396.9 nmol/24 h) was approximately 50 nmol/24 h between the overall population and Japanese subpopulation; however, this is not considered to be a significant difference because there are large intra-individual variations in mUFC. There were no significant differences in other items between the overall population and Japanese subpopulation.

Table 12. Baseline subject characteristics in Study G2304
(Japanese subpopulation and overall population, FAS)

Item		Japanese subpopulation		Overall population	
		Pasireotide LAR 10 mg (N = 7)	Pasireotide LAR 30 mg (N = 4)	Pasireotide LAR 10 mg (N = 74)	Pasireotide LAR 30 mg (N = 76)
Age (year)		43.6 ± 13.41	37.8 ± 2.50	38.3 ± 12.52	38.6 ± 12.99
Sex[a)]	Male	2 (28.6)	2 (50.0)	16 (21.6)	16 (21.1)
	Female	5 (71.4)	2 (50.0)	58 (78.4)	60 (78.9)
Body weight (kg)		56.64 ± 8.402	74.35 ± 19.304	74.52 ± 18.616	77.90 ± 19.301
BMI (kg/m^2)		22.77 ± 2.522	27.15 ± 7.185	28.37 ± 6.560	29.53 ± 6.745
Duration required for patient enrollment in the clinical trial after a diagnosis of Cushing's disease (month)[b)]		21.5 [7.7, 108.3]	66.7 [55.7, 93.1]	22.3 [0.9, 394.7]	22.4 [0.7, 231.9]
Prior pituitary tumor removal[a)]		7 (100)	4 (100)	59 (79.7)	64 (84.2)
Baseline mUFC (nmol/24 h)[b)]		349.4 [166.1, 926.6]	382.8 [183.7, 607.4]	409.8 [44.7, 1432.9]	371.6 [50.8, 1670.0]
Subject's glucose tolerance status at baseline[a)]	Diabetes mellitus	5 (71.4)	2 (50.0)	27 (36.5)	33 (43.4)
	Pre-diabetes	0 (0)	0 (0)	12 (16.2)	12 (15.8)
	Normal glucose tolerance	2 (28.6)	2 (50.0)	35 (47.3)	31 (40.8)

Mean value ± SD
a) Number of subjects (% incidence), b) median [range]

In the Japanese subpopulation, the proportion of subjects who were responders at Month 7 regardless of dose increase at Month 4, which is the primary endpoint, was 4 of 7 subjects in the pasireotide LAR 10 mg group, and 1 of 4 subjects in the pasireotide LAR 30 mg group (Table 5). As shown in Tables 6 and 8, mUFC, plasma ACTH, and serum cortisol levels tended to be below baseline levels following administration of pasireotide LAR. The above findings demonstrated the efficacy of pasireotide LAR in the Japanese subpopulation and suggested no clear differences between the Japanese and non-Japanese subjects, although a strict comparison between the Japanese subpopulation and overall population is difficult because the study included only 11 Japanese subjects.

PMDA's view on the efficacy of pasireotide LAR:
In Study G2304, which included Japanese patients with Cushing's disease, pasireotide LAR was shown to have a certain degree of efficacy in the treatment of Cushing's disease, and there were no significant differences in the efficacy of pasireotide LAR between the Japanese subpopulation and the overall population even though efficacy evaluation is difficult due to the limited number of Japanese subjects. Based on the above, it can be concluded that the data submitted have demonstrated the efficacy of pasireotide LAR. Post-marketing information should be continuously collected because data from only the small number of Japanese patients with Cushing's disease have been studied so far, and information on the efficacy of pasireotide LAR is limited.

7.R.2 Safety

The applicant's explanation:
The incidences of adverse events at the end of the core phase[12)] and at the end of the study[22)] in Study G2304 are shown in Tables 13 and 14, respectively. There was no trend toward significantly increasing incidence with increasing treatment duration. Safety analysis was performed for the Japanese subpopulation. At the end of the core phase, serious adverse events were reported in 2 subjects in the pasireotide LAR 10 mg group (adrenal insufficiency/large intestine polyp/osteoarthritis and diabetes mellitus in 1 subject each) and in 3 subjects in the pasireotide LAR 30 mg group (osteoporosis, endometrial cancer, and nephrolithiasis in 1 subject each). Among these, serious adverse events in 2 subjects in the pasireotide LAR 10 mg group (adrenal insufficiency and diabetes mellitus in 1 subject each) were considered to be adverse drug reactions; however, these were controllable by dose interruption, dose reduction, or treatment of the events. Adverse events led to treatment discontinuation in 1 subject in the pasireotide LAR 10 mg group (diabetes mellitus) and in 1 subject in the pasireotide LAR 30 mg group (endometrial cancer); among these events, diabetes mellitus in the pasireotide LAR 10 mg group was considered to be an adverse drug reaction. Adverse events led to dose interruption or dose reduction in 3 subjects in the pasireotide LAR 10 mg group (adrenal insufficiency/decreased appetite, Addison's disease/fatigue/nasopharyngitis, and diabetes mellitus in 1 subject each) and in 1 subject in the pasireotide LAR 30 mg group (glucose tolerance abnormal). Among these, adverse events other than nasopharyngitis were considered to be adverse drug reactions. In the Japanese subpopulation, hyperglycaemia-related events were reported in 6 subjects in the pasireotide LAR 10 mg group (diabetes

mellitus in 3 subjects, hyperglycaemia in 2 subjects, and hyperglycaemia/blood insulin decreased in 1 subject) and in 4 subjects in the pasireotide LAR 30 mg group (glucose tolerance abnormal in 3 subjects and hyperglycaemia 1 subject). These were considered to be adverse drug reactions, and only the subject in the pasireotide LAR 10 mg group (diabetes mellitus) experienced a serious adverse event. A strict comparison of the incidence of adverse events between the Japanese subpopulation and overall population is difficult because there were only 11 Japanese subjects. The treatment duration up to the data cut-off date at the end of the core phase was longer in the Japanese subpopulation than in the overall population, and the Japanese subjects received more doses of the study drug. However, there was no significant difference in the incidence of adverse events only in the core phase up to Month 12 between the overall population and the Japanese subpopulation,[23)] and no safety concerns were noted in Japanese subjects. Furthermore, based on the incidences of adverse events in the Japanese subpopulation at the end of the core phase and at the end of the study (Tables 13 and 14), there was no trend toward significantly increasing incidence with increasing treatment duration. There were no new serious adverse events or adverse events leading to treatment discontinuation in the Japanese subpopulation after the end of the core phase.

23) In the total study population (150 subjects) and in the Japanese subpopulation (11 subjects), adverse events occurred in 98.7% (148 of 150) of subjects and in 100.0% (11 of 11) of subjects; adverse reactions in 90.0% (135 of 150) of subjects and in 90.9% (10 of 11) of subjects; serious adverse events in 17.3% (26 of 150) of subjects and in 18.2% (2 of 11) of subjects; adverse events leading to treatment discontinuation in 10.0% (15 of 150) of subjects and in 0% (0 of 11) of subjects; adverse events leading to dose interruption or reduction in 22.7% (34 of 150) of subjects and in 36.4% (4 of 11) of subjects.

Table 13. Incidence of major adverse events up to the end of the core phase[a)] in Study G2304
(overall population and Japanese subpopulation, safety analysis set)

	Overall population[b)]			Japanese subpopulation[c)]		
	Pasireotide LAR 10 mg (N = 74)	Pasireotide LAR 30 mg (N = 76)	Total (N = 150)	Pasireotide LAR 10 mg (N = 7)	Pasireotide LAR 30 mg (N = 4)	Total (N = 11)
Any adverse event	98.6 (73)	100 (76)	99.3 (149)	100 (7)	100 (4)	100 (11)
Adverse drug reaction	90.5 (67)	96.1 (73)	93.3 (140)	85.7 (6)	100 (4)	90.9 (10)
Serious adverse event	28.4 (21)	22.4 (17)	25.3 (38)	28.6 (2)	75.0 (3)	45.5 (5)
Adverse event leading to treatment discontinuation	12.2 (9)	13.2 (10)	12.7 (19)	14.3 (1)	25.0 (1)	18.2 (2)
Event leading to dose interruption or reduction	23.0 (17)	25.0 (19)	24.0 (36)	42.9 (3)	25.0 (1)	36.4 (4)
Hyperglycaemia-related event	71.6 (53)	81.6 (62)	76.7 (115)	85.7 (6)	100 (4)	90.9 (10)
Cholelithiasis-related event	24.3 (18)	44.7 (34)	34.7 (52)	14.3 (1)	0 (0)	9.1 (1)
Liver-related event	20.3 (15)	19.7 (15)	20.0 (30)	28.6 (2)	0 (0)	18.2 (2)
Bradycardia-related event	5.4 (4)	11.8 (9)	8.7 (13)	14.3 (1)	0 (0)	9.1 (1)
QT prolongation-related event	2.7 (2)	5.3 (4)	4.0 (6)	0 (0)	0 (0)	0 (0)
Coagulation-related event[d)]	1.4 (1)	0 (0)	0.7 (1)	0 (0)	0 (0)	0 (0)
Reduced GH/IGF-1-related event[e)]	2.7 (2)	0 (0)	1.3 (2)	14.3 (1)	0 (0)	9.1 (1)
Hypocortisolemia-related event	8.1 (6)	9.2 (7)	8.7 (13)	14.3 (1)	0 (0)	9.1 (1)
Hypotension-related event[f)]	5.4 (4)	6.6 (5)	6.0 (9)	14.3 (1)	0 (0)	9.1 (1)
Hypothyroidism-related event	1.4 (1)	5.3 (4)	3.3 (5)	0 (0)	0 (0)	0 (0)
Injection site reaction-related event[g)]	2.7 (2)	2.6 (2)	2.7 (4)	0 (0)	0 (0)	0 (0)
Low blood count-related event[h)]	8.1 (6)	9.2 (7)	8.7 (13)	14.3 (1)	0 (0)	9.1 (1)
Pancreatitis-related event[i)]	2.7 (2)	5.3 (4)	4.0 (6)	14.3 (1)	0 (0)	9.1 (1)
Gastrointestinal disorders (SOC)	63.5 (47)	61.8 (47)	62.7 (94)	85.7 (6)	50.0 (2)	72.7 (8)

% incidence (n);

a) In addition to the data for the core phase up to Month 12, data for the extension phase and thereafter up to the data cut-off date are included.

b) Study drug treatment duration (median [range]): 449.0 [28.0, 1393.0] days in the pasireotide LAR 10 mg group; 380.5 [28.0, 1294.0] days in the pasireotide LAR 30 mg group
Number of doses of the study drug (median [range]): 16.5 [1.0, 50.0] doses in the pasireotide LAR 10 mg group; 13.5 [1.0, 47.0] doses in the pasireotide LAR 30 mg group

c) Study drug treatment duration (median [range]): 981.0 [502.0, 1393.0] days in the pasireotide LAR 10 mg group; 490.0 [406.0, 700.0] days in the pasireotide LAR 30 mg group
Number of doses of the study drug (median [range]): 36.0 [18.0, 50.0] doses in the pasireotide LAR 10 mg group; 17.5 [15.0, 25.0] doses in the pasireotide LAR 30 mg group

d) Events coded to the following MedDRA Preferred terms (PTs): blood fibrinogen decreased, blood thrombin decreased blood thromboplastin abnormal, blood thromboplastin decreased, coagulation factor decreased, coagulation factor IX level decreased, coagulation factor V level decreased, coagulation factor VII level decreased, coagulation factor X level decreased, hypofibrinogenaemia, international normalised ratio abnormal, prothrombin level decreased, prothrombin time prolonged, prothrombin time ratio decreased, and thrombin time prolonged

e) Events coded to the following PTs: blood growth hormone decreased and insulin-like growth factor decreased

f) Events coded to the following PTs: blood pressure ambulatory decreased, blood pressure decreased, blood pressure diastolic decreased, blood pressure immeasurable, blood pressure orthostatic abnormal, blood pressure orthostatic decreased, blood pressure systolic decreased, hypotension, and mean arterial pressure decreased

g) Events coded to the following PTs: administration site abscess, immediate post-injection reaction, injection site atrophy, injection site bruising, injection site discolouration, injection site discomfort, injection site erosion, injection site erythema, injection site exfoliation, injection site granuloma, injection site haematoma, injection site haemorrhage, injection site hypersensitivity, injection site inflammation, injection site irritation, injection site necrosis, injection site nodule, injection site oedema, injection site pain, injection site rash, injection site pruritus, injection site reaction, injection site swelling, and injection site urticaria

h) Events coded to the following PTs: anaemia, febrile neutropenia, haematocrit decreased, haemoglobin decreased, leukopenia, lymphocyte count decreased, lymphopenia, neutropenia, platelet count decreased, red blood cell count decreased, and thrombocytopenia

i) Events coded to the following PTs: abdominal compartment syndrome, fat necrosis, hyperlipasaemia, pancreatitis, pancreatitis acute, pancreatitis haemorrhagic, pancreatitis necrotising, pancreatitis relapsing, peripancreatic fluid collection, blood trypsin increased, lipase abnormal, lipase increased, pancreatic enzyme abnormality, pancreatic enzymes abnormal, and pancreatic enzymes increased

Table 14. Incidence of major adverse events up to the end of the study in Study G2304
(overall population and Japanese subpopulation, safety analysis set)

	Overall population[a)]			Japanese subpopulation[b)]		
	Pasireotide LAR 10 mg (N = 74)	Pasireotide LAR 30 mg (N = 76)	Total (N = 150)	Pasireotide LAR 10 mg (N = 7)	Pasireotide LAR 30 mg (N = 4)	Total (N = 11)
Any adverse event	98.6 (73)	100 (76)	99.3 (149)	100 (7)	100 (4)	100 (11)
Adverse drug reaction	90.5 (67)	96.1 (73)	93.3 (140)	85.7 (6)	100 (4)	90.9 (10)
Serious adverse event	29.7 (22)	25.0 (19)	27.3 (41)	28.6 (2)	75.0 (3)	45.5 (5)
Adverse event leading to treatment discontinuation	13.5 (10)	17.1 (13)	15.3 (23)	14.3 (1)	25.0 (1)	18.2 (2)
Event leading to dose interruption or reduction	23.0 (17)	25.0 (19)	24.0 (36)	42.9 (3)	25.0 (1)	36.4 (4)
Hyperglycaemia-related event	71.6 (53)	82.9 (63)	77.3 (116)	85.7 (6)	100 (4)	90.9 (10)
Cholelithiasis-related event	24.3 (18)	46.1 (35)	35.3 (53)	14.3 (1)	0 (0)	9.1 (1)
Liver-related event	20.3 (15)	21.1 (16)	20.7 (31)	28.6 (2)	0 (0)	18.2 (2)
Bradycardia-related event	5.4 (4)	11.8 (9)	8.7 (13)	14.3 (1)	0 (0)	9.1 (1)
QT prolongation-related event	2.7 (2)	5.3 (4)	4.0 (6)	0 (0)	0 (0)	0 (0)
Coagulation-related event[c)]	1.4 (1)	0 (0)	0.7 (1)	0 (0)	0 (0)	0 (0)
Reduced GH/IGF-1-related event[d)]	2.7 (2)	0 (0)	1.3 (2)	14.3 (1)	0 (0)	9.1 (1)
Hypocortisolemia-related event	10.8 (8)	10.5 (8)	10.7 (16)	28.6 (2)	0 (0)	18.2 (2)
Hypotension-related event[e)]	5.4 (4)	6.6 (5)	6.0 (9)	14.3 (1)	0 (0)	9.1 (1)
Hypothyroidism-related event	2.7 (2)	5.3 (4)	4.0 (6)	0 (0)	0 (0)	0 (0)
Injection site reaction-related event[f)]	2.7 (2)	2.6 (2)	2.7 (4)	0 (0)	0 (0)	0 (0)
Low blood count-related event[g)]	8.1 (6)	11.8 (9)	10.0 (15)	14.3 (1)	0 (0)	9.1 (1)
Pancreatitis-related event[h)]	2.7 (2)	5.3 (4)	4.0 (6)	14.3 (1)	0 (0)	9.1 (1)
Gastrointestinal disorders (SOC)	64.9 (48)	64.5 (49)	64.7 (97)	85.7 (6)	75.0 (3)	81.8 (9)

% incidence (n)

a) Study drug treatment duration (median [range]): 510.5 [28.0, 1682.0] days in the pasireotide LAR 10 mg group; 405.0 [28.0, 1595.0] days in the pasireotide LAR 30 mg group
Number of doses of the study drug (median [range]): 18.0 [1.0, 60.0] doses in the pasireotide LAR 10 mg group; 14.5 [1.0, 57.0] doses in the pasireotide LAR 30 mg group

b) Study drug treatment duration (median [range]): 1233.0 [502.0, 1682.0] days in the pasireotide LAR 10 mg group; 616.0 [448.0, 700.0] days in the pasireotide LAR 30 mg group
Number of doses of the study drug (median [range]): 42.0 [18.0, 60.0] doses in the pasireotide LAR 10 mg group; 22.0 [16.0, 25.0] doses in the pasireotide LAR 30 mg group

c) Events coded to the following PTs: blood fibrinogen decreased, blood thrombin decreased blood thromboplastin abnormal, blood thromboplastin decreased, coagulation factor decreased, coagulation factor IX level decreased, coagulation factor V level decreased, coagulation factor VII level decreased, coagulation factor X level decreased, hypofibrinogenaemia, international normalised ratio abnormal, prothrombin level decreased, prothrombin time prolonged, prothrombin time ratio decreased, and thrombin time prolonged

d) Events coded to the following PTs: blood growth hormone decreased and insulin-like growth factor decreased

e) Events coded to the following PTs: blood pressure ambulatory decreased, blood pressure decreased, blood pressure diastolic decreased, blood pressure immeasurable, blood pressure orthostatic abnormal, blood pressure orthostatic decreased, blood pressure systolic decreased, hypotension, and mean arterial pressure decreased

f) Events coded to the following PTs: administration site abscess, immediate post-injection reaction, injection site atrophy, injection site bruising, injection site discolouration, injection site discomfort, injection site erosion, injection site erythema, injection site exfoliation, injection site granuloma, injection site haematoma, injection site haemorrhage, injection site hypersensitivity, injection site inflammation, injection site irritation, injection site necrosis, injection site nodule, injection site oedema, injection site pain, injection site rash, injection site pruritus, injection site reaction, injection site swelling, and injection site urticaria

g) Events coded to the following PTs: anaemia, febrile neutropenia, haematocrit decreased, haemoglobin decreased, leukopenia, lymphocyte count decreased, lymphopenia, neutropenia, platelet count decreased, red blood cell count decreased, and thrombocytopenia

h) Events coded to the following PTs: abdominal compartment syndrome, fat necrosis, hyperlipasaemia, pancreatitis, pancreatitis acute, pancreatitis haemorrhagic, pancreatitis necrotising, pancreatitis relapsing, peripancreatic fluid collection, blood trypsin increased, lipase abnormal, lipase increased, pancreatic enzyme abnormality, pancreatic enzymes abnormal, and pancreatic enzymes increased

Table 15 shows the incidence of adverse events up to Month 12 by treatment duration in the core phase of Study G2304. Taking into consideration the timing of dose increase in Study G2304, the core phase was divided into 3 periods (0 to <4 months, 4 to <7 months, and 7 to ≤12 months), and the incidence of

adverse events was compared based on the period. Although the incidences of adverse events and adverse drug reactions were the highest in the period of 0 to <4 months, the incidence of serious adverse events and adverse events leading to treatment discontinuation did not differ significantly between the periods. The comparison of incidence by dose levels showed that, in the period of 0 to <4 months during which a fixed dose was administered, there were no significant differences in the incidence of adverse events between the pasireotide LAR 10 and 30 mg groups. In contrast, the incidences of adverse drug reactions and adverse events leading to dose interruption or dose reduction were higher in the pasireotide LAR 30 mg group than in the pasireotide LAR 10 mg group. The comparison of incidence by PT shows that the incidence of cholelithiasis-related events was the highest in the period of 7 to ≤12 months while the incidence of a majority of adverse events was the highest in the period of 0 to <4 months, and there was no trend toward increasing incidence associated with increasing treatment duration.

Table 15. Incidence of adverse events up to Month 12 by treatment duration
(Study G2304 [core phase], safety analysis set)

	0 to <4 months			4 to <7 months			7 to ≤12 months		
	Pasireotide LAR 10 mg (N = 74)	Pasireotide LAR 30 mg (N = 76)	Total (N = 150)	Pasireotide LAR 10 mg (N = 65)	Pasireotide LAR 30 mg (N = 69)	Total (N = 134)	Pasireotide LAR 10 mg (N = 54)	Pasireotide LAR 30 mg (N = 62)	Total (N = 116)
Any adverse event	93.2 (69)	97.4 (74)	95.3 (143)	76.9 (50)	71.0 (49)	73.9 (99)	85.2 (46)	85.5 (53)	85.3 (99)
Adverse drug reaction	74.3 (55)	89.5 (68)	82.0 (123)	44.6 (29)	43.5 (30)	44.0 (59)	55.6 (30)	62.9 (39)	59.5 (69)
Serious adverse event	10.8 (8)	3.9 (3)	7.3 (11)	6.2 (4)	5.8 (4)	6.0 (8)	7.4 (4)	9.7 (6)	8.6 (10)
Adverse event leading to treatment discontinuation	5.4 (4)	3.9 (3)	4.7 (7)	3.1 (2)	4.3 (3)	3.7 (5)	1.9 (1)	3.2 (2)	2.6 (3)
Event leading to dose interruption or reduction	6.8 (5)	18.4 (14)	12.7 (19)	4.6 (3)	5.8 (4)	5.2 (7)	14.8 (8)	12.9 (8)	13.8 (16)
Hyperglycaemia-related event	47.3 (35)	69.7 (53)	58.7 (88)	27.7 (18)	14.5 (10)	20.9 (28)	22.2 (12)	24.2 (15)	23.3 (27)
Cholelithiasis-related event	1.4 (1)	23.7 (18)	12.7 (19)	6.2 (4)	7.2 (5)	6.7 (9)	20.4 (11)	33.9 (21)	27.6 (32)
Liver-related event	13.5 (10)	9.2 (7)	11.3 (17)	3.1 (2)	5.8 (4)	4.5 (6)	7.4 (4)	6.5 (4)	6.9 (8)
Bradycardia-related event	2.7 (2)	7.9 (6)	5.3 (8)	0 (0)	2.9 (2)	1.5 (2)	5.6 (3)	3.2 (2)	4.3 (5)
QT prolongation-related event	2.7 (2)	2.6 (2)	2.7 (4)	0 (0)	0 (0)	0 (0)	0 (0)	1.6 (1)	0.9 (1)
Coagulation-related even[a)]	1.4 (1)	0 (0)	0.7 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Reduced GH/IGF-1-related event[b)]	2.7 (2)	0 (0)	1.3 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Hypocortisolemia-related event	2.7 (2)	6.6 (5)	4.7 (7)	3.1 (2)	0 (0)	1.5 (2)	5.6 (3)	4.8 (3)	5.2 (6)
Hypotension-related event[c)]	1.4 (1)	3.9 (3)	2.7 (4)	3.1 (2)	1.4 (1)	2.2 (3)	1.9 (1)	0 (0)	0.9 (1)
Hypothyroidism-related event	0 (0)	3.9 (3)	2.0 (3)	0 (0)	0 (0)	0 (0)	0 (0)	1.6 (1)	0.9 (1)
Injection site reaction-related event[d)]	1.4 (1)	1.3 (1)	1.3 (2)	0 (0)	1.4 (1)	0.7 (1)	0 (0)	0 (0)	0 (0)
Low blood count-related event[e)]	2.7 (2)	5.3 (4)	4.0 (6)	1.5 (1)	0 (0)	0.7 (1)	5.6 (3)	3.2 (2)	4.3 (5)
Pancreatitis-related event[f)]	0 (0)	0 (0)	0 (0)	1.5 (1)	2.9 (2)	2.2 (3)	0 (0)	3.2 (2)	1.7 (2)
Gastrointestinal disorders (SOC)	50.0 (37)	51.3 (39)	50.7 (76)	15.4 (10)	15.9 (11)	15.7 (21)	18.5 (10)	30.6 (19)	25.0 (29)

% incidence (n)

a) Events coded to the following PTs: blood fibrinogen decreased, blood thrombin decreased_blood thromboplastin abnormal, blood thromboplastin decreased, coagulation factor decreased, coagulation factor IX level decreased, coagulation factor V level decreased, coagulation factor VII level decreased, coagulation factor X level decreased, hypofibrinogenaemia, international normalised ratio abnormal, prothrombin level decreased, prothrombin time prolonged, prothrombin time ratio decreased, and thrombin time prolonged

b) Events coded to the following PTs: blood growth hormone decreased and insulin-like growth factor decreased

c) Events coded to the following PTs: blood pressure ambulatory decreased, blood pressure decreased, blood pressure diastolic decreased, blood pressure immeasurable, blood pressure orthostatic abnormal, blood pressure orthostatic decreased, blood pressure systolic decreased, hypotension, and mean arterial pressure decreased

d) Events coded to the following PTs: administration site abscess, immediate post-injection reaction, injection site atrophy, injection site bruising, injection site discolouration, injection site discomfort, injection site erosion, injection site erythema, injection site exfoliation, injection site granuloma, injection site haematoma, injection site haemorrhage, injection site hypersensitivity, injection site inflammation, injection site irritation, injection site necrosis, injection site nodule, injection site oedema, injection site pain, injection site rash, injection site pruritus, injection site reaction, injection site swelling, and injection site urticaria
e) Events coded to the following PTs: anaemia, febrile neutropenia, haematocrit decreased, haemoglobin decreased, leukopenia, lymphocyte count decreased, lymphopenia, neutropenia, platelet count decreased, red blood cell count decreased, and thrombocytopenia
f) Events coded to the following PTs: abdominal compartment syndrome, fat necrosis, hyperlipasaemia, pancreatitis, pancreatitis acute, pancreatitis haemorrhagic, pancreatitis necrotising, pancreatitis relapsing, peripancreatic fluid collection, blood trypsin increased, lipase abnormal, lipase increased, pancreatic enzyme abnormality, pancreatic enzymes abnormal, and pancreatic enzymes increased

PMDA's view:

Confirmation of the data during the core phase and at the end of the core phase in Study G2304 and data at the end of the study, as well as the safety data in the Japanese subpopulation of Study G2304, indicates that the observed events are known events. The safety of pasireotide LAR in the treatment of patients with Cushing's disease is acceptable provided that appropriate precautions are provided as with the approved indications. Events that require particular attention when using pasireotide LAR are the subject of additional discussion in the following sections.

7.R.2.1 Glycemic events (hyperglycaemia and hypoglycaemia)

The applicant's explanation:

The incidence of hyperglycaemia-related events[24)] at the end of the core phase of Study G2304 was 71.6% (53 of 74 subjects) in the pasireotide LAR 10 mg group, and 81.6% (62 of 76 subjects) in the pasireotide LAR 30 mg group (Table 16). The comparison of incidence by PT shows that the incidence of hyperglycaemia was the highest (48.6% [36 of 74 subjects] in the 10 mg group and 47.4% [36 of 76 subjects] in the 30 mg group), followed by diabetes mellitus (18.9% [14 of 74 subjects] in the 10 mg group and 23.7% [18 of 76 subjects] in the 30 mg group). Serious adverse events were reported in 2 subjects in the pasireotide LAR 10 mg group, 1 of the subjects was a Japanese subject who had developed moderate diabetes mellitus, and the other subject had developed severe hyperglycaemia. In the former subject, diabetes mellitus resolved following inpatient treatment, while in the latter subject, treatment with the study drug was discontinued following inpatient treatment, and severe hyperglycaemia remained unresolved on the final report day. Adverse events leading to treatment discontinuation were reported in 8 subjects. These events were diabetes mellitus in 4 subjects (1 subject [Japanese subject] in the 10 mg group and 3 subjects in the 30 mg group), hyperglycaemia in 3 subjects (2 subjects in the 10 mg group and 1 subject in the 30 mg group), and blood glucose increased in 1 subject (the 10 mg group). Most events were controllable by dose interruption, dose reduction, or appropriate action. Hyperglycaemia-related events requiring immediate medical care, such as diabetic ketoacidosis, hyperglycaemic coma, or hyperosmolar state, were not reported. The incidence of hyperglycaemia-related events in the overall population at the end of the study was 77.3% (116 of 150 subjects), which does not differ significantly from that at the end of the core phase indicating that there was no trend toward increasing incidence associated with prolonged treatment duration.

24) Events coded to the following MedDRA PTs: blood glucose increased, diabetes mellitus, diabetes mellitus inadequate control, diabetes with hyperosmolarity, diabetic coma, diabetic hyperglycaemic coma, diabetic hyperosmolar coma, diabetic ketoacidosis, diabetic ketoacidotic hyperglycaemic coma, fructosamine increased, glucose tolerance impaired, glucose tolerance decreased, glucose urine present, glycosuria, glycosylated haemoglobin increased, hyperglycaemia, impaired fasting glucose, ketoacidosis, ketonuria, ketosis, type 1 diabetes mellitus, type 2 diabetes mellitus, blood insulin decreased, glucose tolerance test abnormal, increased insulin requirement, hyperosmolar hyperglycaemic state, and insulin-requiring type 2 diabetes mellitus.

The data for hyperglycaemia-related events at the end of the core phase of Study G2304 by the subject's glucose tolerance status at baseline[25)] showed that the incidence of those events tended to be higher in subjects who had "diabetes mellitus" or "pre-diabetes" at baseline than in subjects who had "normal glucose tolerance." The baseline status of the 2 subjects who developed serious hyperglycaemia-related events was "diabetes mellitus." Of the 8 subjects whose treatment resulted in discontinuation, 6 subjects had "diabetes mellitus" at baseline and 2 subjects had "pre-diabetes" at baseline. The incidence of adverse events requiring dose interruption or discontinuation was higher in subjects with "diabetes mellitus" at baseline.

Table 16. Incidence of hyperglycaemia-related events (including data by subject's glucose tolerance status at baseline) (Study G2304 [end of the core phase[a)]], safety analysis set)

	Subject's glucose tolerance status at baseline	Pasireotide LAR 10 mg (N = 74)	Pasireotide LAR 30 mg (N = 76)	Total (N = 150)
Hyperglycaemia-related events	Total	71.6 (53/74)	81.6 (62/76)	76.7 (115/150)
	Diabetes mellitus	85.2 (23/27)	90.9 (30/33)	88.3 (53/60)
	Pre-diabetes	75.0 (9/12)	91.7 (11/12)	83.3 (20/24)
	Normal glucose tolerance	60.0 (21/35)	67.7 (21/31)	63.6 (42/66)
Serious adverse events	Total	2.7 (2/74)	0 (0/76)	1.3 (2/150)
	Diabetes mellitus	7.4 (2/27)	0 (0/33)	3.3 (2/60)
	Pre-diabetes	0 (0/12)	0 (0/12)	0 (0/24)
	Normal glucose tolerance	0 (0/35)	0 (0/31)	0 (0/66)
Adverse events leading to treatment discontinuation	Total	5.4 (4/74)	5.3 (4/76)	5.3 (8/150)
	Diabetes mellitus	7.4 (2/27)	12.1 (4/33)	10.0 (6/60)
	Pre-diabetes	16.7 (2/12)	0 (0/12)	8.3 (2/24)
	Normal glucose tolerance	0 (0/35)	0 (0/31)	0 (0/66)
Adverse events requiring dose interruption or reduction	Total	8.1 (6/74)	9.2 (7/76)	8.7 (13/150)
	Diabetes mellitus	14.8 (4/27)	18.2 (6/33)	16.7 (10/60)
	Pre-diabetes	0 (0/12)	8.3 (1/12)	4.2 (1/24)
	Normal glucose tolerance	5.7 (2/35)	0 (0/31)	3.0 (2/66)

% incidence (number of subjects with events/number of subjects analyzed)

a) In addition to the data for the core phase up to Month 12, data for the extension phase and thereafter up to the data cut-off date are included

In the core phase of Study G2304, the comparison of incidence of hyperglycaemia-related events up to Month 12 by treatment duration shows that the events tended to occur more frequently in the period of 0 to 4 months, during which the dose level was fixed (Table 15). In contrast, the incidence of hyperglycaemia-related events at the end of the study was not significantly higher than the incidence at the end of the core phase (Tables 13 and 14), indicating that there was no trend toward significantly increasing incidence associated with increasing treatment duration.

Table 17 shows the incidence of hyperglycaemia-related events by treatment duration after dose increase of pasireotide LAR in Study G2304. In this analysis, hyperglycaemia-related events that occurred

25) The following subjects were classified as having diabetes mellitus: subjects who were on antidiabetic drug medication, subjects with HbA1c ≥6.5%, or a fasting blood glucose level ≥126 mg/dL, or subjects who had a history of diabetes mellitus. The following subjects were classified as having pre-diabetes: subjects who had not been diagnosed as having diabetes mellitus but had a fasting blood glucose level ≥100 mg/dL and <126 mg/dL, or HbA1c ≥5.7% and <6.5%. The following subjects were classified as having no impaired glucose tolerance: subjects who had not been diagnosed as having diabetes mellitus and were not classified as pre-diabetes, and who also had a fasting blood glucose level <100 mg/dL, or HbA1c <5.7%.

following the first dose increase up to the next dose increase or dose decrease were tabulated. The observation period differed from one subject to another, which makes it difficult to interpret the results. However, results showed that hyperglycaemia-related events occurred following dose increase in 55.3% (57 of 103) of the subjects who had their dose increased. Overall, hyperglycaemia-related events occurred as early as within 1 week after dose increase, and approximately half of the subjects with hyperglycaemia-related events after dose increase experienced the events within 8 weeks after dose increase; however, there was no consistent trend in the time to onset of events over the 8-week period after dose increase.

Table 17. Incidence of hyperglycaemia-related events by treatment duration after dose increase of pasireotide LAR[a)] (Study G2304 [end of the study period], safety analysis set)

	<1 week	≥1 week and <2 weeks	≥2 weeks and <4 weeks	≥4 weeks and <6 weeks	≥6 weeks and <8 weeks	≥8 weeks	Total
Pasireotide LAR 10 mg →30 mg (N = 50)	8.0 (4)	2.0 (1)	14.0 (7)	0 (0)	8.0 (4)	14.0 (7)	46.0 (23)
Pasireotide LAR 30 mg →40 mg (N = 80)	5.0 (4)	2.5 (2)	6.3 (5)	0 (0)	5.0 (4)	27.5 (22)	46.3 (37)
Study total (N = 103)[b)]	7.8 (8)	1.9 (2)	11.7 (12)	0 (0)	7.8 (8)	26.2 (27)	55.3 (57)

% incidence (n)

a) The incidence of the first hyperglycaemia-related events that occurred or were exacerbated following the first dose increase after the start of treatment, to 30 mg or 40 mg, up to the next dose increase/decrease. A dose re-escalation to the dose level prior to dose reduction was not included in the dose increase data.

b) In this study, a total of 103 subjects had their dose increased. In the study, the dose was to be increased by 1 level at a time in the order of 5 mg, 10 mg, 30 mg, and 40 mg; however, doses were increased by 2 levels at a time in 2 subjects (from 5 mg to 30 mg in 1 subject, and from 10 mg to 40 mg in another subject), and hyperglycaemia-related events did not occur following the first dose increase in either of these subjects.

The incidence of serious hyperglycaemia-related events or hyperglycaemia-related events leading to treatment discontinuation in Study G2304 is shown in Table 18. Many subjects were classified as having “diabetes mellitus” at baseline. A relatively high proportion of subjects developed the first hyperglycaemia-related events within 8 weeks of treatment with pasireotide LAR.

Table 18. Incidence of hyperglycaemia-related events in subjects who developed serious hyperglycaemia-related events or hyperglycaemia-related events leading to treatment discontinuation
(Study G2304 [end of the core phase[a)]], safety analysis set)

	Age and sex	Subject's glucose tolerance status at baseline	HbA1c at baseline (%)	Adverse event	Dose level of pasireotide LAR at onset of event	Time to onset of serious adverse event/adverse event leading to treatment discontinuation from the start of pasireotide LAR treatment (days)	Time to first onset of hyperglycaemia-related event including non-serious event from the start of pasireotide LAR treatment (days)
Serious adverse events	64 years/female[b)]	Diabetes mellitus	6.8	Hyperglycaemia	10mg	23 days	16 days
	34 years/male[c)]	Diabetes mellitus	6.5	Diabetes mellitus	5mg	596 days	22 days
Adverse events leading to treatment discontinuation	43 years/male	Pre-diabetes	6.3	Hyperglycaemia	10mg	21 days	21 days
	71 years/female	Pre-diabetes	6.2	Blood glucose increased	30mg	141 days	57 days
	37 years/female	Diabetes mellitus	5.7	Diabetes mellitus	40mg	142 days	21 days
	24 years/female	Diabetes mellitus	5.9	Hyperglycaemia	40mg	282 days	11 days
	45 years/female	Diabetes mellitus	6.7	Diabetes mellitus	30mg	22 days	22 days
	28 years/female	Diabetes mellitus	6.8	Diabetes mellitus	30mg	32 days	32 days
	64 years/female [b)]	Diabetes mellitus	6.8	Hyperglycaemia	10mg	23 days	16 days
	34 years/male[c)]	Diabetes mellitus	6.5	Diabetes mellitus	5mg	1121 days	22 days

a) In addition to the data for the core phase up to Month 12, data for the extension phase and thereafter up to the data cut-off date are included
b) Identical subject/event
c) Identical subject

Table 19 shows the trend of fasting plasma glucose (FPG) levels up to Month 12 of the core phase in Study G2304. The FPG levels reached a peak at Month 0.75 in both dose groups, with the FPG level of the pasireotide LAR 30 mg group being higher than that of the pasireotide LAR 10 mg group. Then, FPG levels tended to decrease in both groups up to Month 4. The FPG levels increased slightly in the pasireotide LAR 10 mg group at Month 5, and thereafter remained almost constant, while in the pasireotide LAR 30 mg group, the levels remained almost constant after Month 4. At Month 12, there was no significant difference between the dose groups. When analyzed by the subject's glucose tolerance status at baseline, FPG levels at Month 1 were higher than baseline for all statuses, with the mean change from baseline in FPG levels being the greatest for subjects with "diabetes mellitus," followed by those with "pre-diabetes" and those with "normal glucose tolerance." The mean FPG levels and the mean change from baseline in FPG levels at Month 12 did not show significant differences depending on the difference in the subject's glucose tolerance status. The mean FPG levels up to Month 4 were higher in the pasireotide LAR 30 mg group than in the pasireotide LAR 10 mg group in subjects with any form of glucose tolerance status, with the difference being the greatest in subjects with "diabetes mellitus" at baseline.

Table 19. Trend of fasting plasma glucose levels by subject's glucose tolerance status at baseline
(Study G2304 [core phase], safety analysis set)

Treatment group	Subject's glucose tolerance status at baseline	N	Baseline	Month 0.75	Month 1	Month 3	Month 4	Month 5	Month 7	Month 12
Pasireotide LAR 10 mg	Total	74	93.9±16.69 (N = 74)	128.8±44.69 (N = 72)	113.5±33.92 (N = 73)	110.3±27.22 (N = 67)	113.1±27.79 (N = 66)	125.2±41.17 (N = 61)	115.5±36.50 (N = 56)	125.6±50.22 (N = 49)
	Diabetes mellitus	27	105.5±20.99 (N = 27)	167.5±51.79 (N = 26)	132.4±44.46 (N = 26)	122.4±35.18 (N = 25)	128.7±31.09 (N = 23)	138.2±43.43 (N = 22)	126.8±39.95 (N = 21)	141.3±54.63 (N = 18)
	Pre-diabetes	12	92.2±9.59 (N = 12)	118.1±21.57 (N = 12)	116.1±23.93 (N = 12)	113±17.3 (N = 11)	115.3±27.88 (N = 12)	130.5±52.38 (N = 10)	124.1±33.35 (N = 8)	136.8±54.09 (N = 8)
	Normal glucose tolerance	35	85.5±7.17 (N = 35)	103±14.36 (N = 34)	98.7±17.2 (N = 35)	99.5±17.19 (N = 31)	100.7±18.18 (N = 31)	113.4±32.39 (N = 29)	104.1±32.11 (N = 27)	109.4±41.78 (N = 23)
Pasireotide LAR 30 mg	Total	76	95.8±20.37 (N = 74)	147.6±57.72 (N = 73)	138.5±50.01 (N = 75)	132.8±50.91 (N = 73)	121.2±29.89 (N = 68)	127.8±34.62 (N = 65)	124.4±31.79 (N = 65)	128.7±44.12 N = 53)
	Diabetes mellitus	33	106.1±24.99 (N = 33)	184±67.28 (N = 33)	167.1±60.95 (N = 32)	157.3±68.2 (N = 31)	128.7±38.14 (N = 29)	141.2±44.55 (N = 26)	130.6±37.35 (N = 27)	121.8±41.08 (N = 21)
	Pre-diabetes	12	95.1±12.82 (N = 11)	135.6±22.62 (N = 9)	135.4±28.25 (N = 12)	118.3±21.61 (N = 12)	119.6±16.3 (N = 10)	119.2±19.21 (N = 9)	120.6±23.03 (N = 9)	146.3±64.87 (N = 9)
	Normal glucose tolerance	31	84.7±7.22 (N = 30)	112.5±16.05 (N = 31)	110.2±18.4 (N = 31)	113.2±17.95 (N = 30)	114.4±22.14 (N = 29)	118.6±23.68 (N = 30)	119.9±28.29 (N = 29)	128.2±36.92 (N = 23)
Total	Total	150	94.8±18.58 (N = 148)	138.3±52.34 (N = 145)	126.2±44.49 (N = 148)	122.0±42.69 (N = 140)	117.2±29.05 (N = 134)	126.5±37.80 (N = 126)	120.3±34.20 (N = 121)	127.2±46.94 (N = 102)
	Diabetes mellitus	60	105.8±23.08 (N = 60)	176.7±61 (N = 59)	151.5±56.48 (N = 58)	141.7±58.17 (N = 56)	128.7±34.87 (N = 52)	139.9±43.6 (N = 48)	128.9±38.14 (N = 48)	130.8±48.18 (N = 39)
	Pre-diabetes	24	93.6±11.09 (N = 23)	125.6±23.22 (N = 21)	125.8±27.44 (N = 24)	115.8±19.42 (N = 23)	117.2±22.93 (N = 22)	125.2±39.61 (N = 19)	122.2±27.48 (N = 17)	141.8±58.38 (N = 17)
	Normal glucose tolerance	66	85.2±7.15 (N = 65)	107.5±15.8 (N = 65)	104.1±18.57 (N = 66)	106.3±18.74 (N = 61)	107.3±21.18 (N = 60)	116.1±28.17 (N = 59)	112.3±30.95 (N = 56)	118.8±40.12 (N = 46)

Unit, mg/dL; mean value ± SD

Table 20 shows the trend of HbA1c levels up to Month 12 of the core phase in Study G2304. At Month 2, HbA1c levels were higher than baseline in all dose groups, with the HbA1c in the pasireotide LAR 30 mg group being higher than that in the pasireotide LAR 10 mg group. Thereafter up to Month 12, HbA1c levels increased gradually in all dose groups, and there was no significant difference between the dose groups after Month 7. When analyzed by the subject's glucose tolerance status at baseline, HbA1c levels were higher than baseline for all the statuses at Month 2, with the mean change from baseline being the greatest in subjects with "diabetes mellitus," followed by those with "pre-diabetes" and those with "normal glucose tolerance." The mean HbA1c levels and the mean change in HbA1c levels from baseline at Month 12 did not show significant differences depending on the subject's glucose tolerance status. The mean HbA1c levels up to Month 4 were higher in the pasireotide LAR 30 mg than in the pasireotide LAR 10 mg group for all the statuses, with the difference being the greatest in subjects with "diabetes mellitus" at baseline.

Table 20. Trend of HbA1c levels by subject's glucose tolerance status at baseline
(Study G2304 [core phase], safety analysis set)

Treatment group	Subject's glucose tolerance status at baseline	N	Baseline	Month 2	Month 4	Month 7	Month 12
Pasireotide LAR 10 mg	Total	74	5.7 ± 0.62 (N = 74)	6.4 ± 1.05 (N = 69)	6.4 ± 0.94 (N = 64)	6.6 ± 1.14 (N = 56)	6.9 ± 1.38 (N = 48)
	Diabetes mellitus	27	6.1 ± 0.67 (N = 27)	7.2 ± 1.21 (N = 26)	7.1 ± 0.96 (N = 22)	7.4 ± 1.10 (N = 21)	7.4 ± 1.40 (N = 18)
	Pre-diabetes	12	5.8 ± 0.33 (N = 12)	6.4 ± 0.86 (N = 11)	6.4 ± 0.89 (N = 11)	6.4 ± 0.55 (N = 8)	6.9 ± 1.14 (N = 8)
	Normal glucose tolerance	35	5.3 ± 0.28 (N = 35)	5.8 ± 0.40 (N = 32)	5.9 ± 0.54 (N = 31)	6.1 ± 0.95 (N = 27)	6.4 ± 1.31 (N = 22)
Pasireotide LAR 30 mg	Total	76	5.7 ± 0.69 (N = 76)	6.8 ± 1.26 (N = 72)	6.8 ± 1.34 (N = 69)	6.8 ± 1.09 (N = 67)	7.0 ± 1.37 (N = 53)
	Diabetes mellitus	33	6.2 ± 0.69 (N = 33)	7.7 ± 1.37 (N = 30)	7.6 ± 1.63 (N = 29)	7.3 ± 0.99 (N = 27)	7.6 ± 1.41 (N = 21)
	Pre-diabetes	12	5.7 ± 0.25 (N = 12)	6.6 ± 0.49 (N = 12)	6.6 ± 0.52 (N = 11)	6.9 ± 1.39 (N = 10)	7.1 ± 1.54 (N = 9)
	Normal glucose tolerance	31	5.1 ± 0.29 (N = 31)	5.9 ± 0.57 (N = 30)	6.1 ± 0.65 (N = 29)	6.3 ± 0.87 (N = 30)	6.5 ± 1.07 (N = 23)
Total	Total	150	5.7 ± 0.66 (N = 150)	6.6 ± 1.17 (N = 141)	6.6 ± 1.18 (N = 133)	6.7 ± 1.11 (N = 123)	7.0 ± 1.37 (N = 101)
	Diabetes mellitus	60	6.2 ± 0.68 (N = 60)	7.4 ± 1.31 (N = 56)	7.4 ± 1.40 (N = 51)	7.4 ± 1.03 (N = 48)	7.5 ± 1.39 (N = 39)
	Pre-diabetes	24	5.8 ± 0.29 (N = 24)	6.5 ± 0.68 (N = 23)	6.5 ± 0.72 (N = 22)	6.6 ± 1.10 (N = 18)	7.0 ± 1.33 (N = 17)
	Normal glucose tolerance	66	5.2 ± 0.29 (N = 66)	5.9 ± 0.49 (N = 62)	6.0 ± 0.61 (N = 60)	6.2 ± 0.91 (N = 57)	6.4 ± 1.18 (N = 45)

Unit,%; mean value ± SD

Time to the first onset of hyperglycaemia (defined as HbA1c ≥6.5% or FPG level ≥126 mg/dL) from the start of study drug treatment in subjects with "pre-diabetes" or "normal glucose tolerance" at baseline was examined. Of the 90 subjects with "pre-diabetes" or "normal glucose tolerance" at baseline (47 subjects in the 10 mg group and 43 subjects in the 30 mg group), 45 subjects (19 subjects in the 10 mg group and 26 subjects in the 30 mg group) developed hyperglycaemia. Time to the first onset of hyperglycaemia from the start of study drug treatment (median [range]) was 84.0 [21, 1149] days in the overall population, 141.0 [21, 1149] days in the pasireotide LAR 10 mg group, and 57.0 [21, 469] days in the pasireotide LAR 30 mg group, indicating that the time to onset of hyperglycaemia was shorter in the pasireotide LAR 30 mg group than in the pasireotide LAR 10 mg group.

As for hypoglycaemia, 22 subjects (10 subjects in the 10 mg group [including 1 Japanese subject] and 12 subjects in the 30 mg group) developed hypoglycaemia by the end of Study G2304. While the majority of the hypoglycaemic events were either mild or moderate in severity, severe hypoglycaemia occurred in 4 subjects; however, a causal relationship to the study drug was ruled out for these events, and all these events resolved within a day. Hypoglycaemic events that were considered to be adverse drug reactions occurred in 4 subjects, and all of these events were mild in severity. No adverse events led to dose reduction, dose interruption, or treatment discontinuation of the study drug. According to analysis by glucose tolerance status at baseline, hypoglycaemia occurred in 4 subjects with "normal glucose tolerance" at baseline, in 2 subjects with "pre-diabetes" at baseline, and in 16 subjects with "diabetes mellitus" at baseline, indicating that the event frequently occurred in subjects with "diabetes mellitus" at baseline. Of the 22 subjects who developed hypoglycaemia, 20 subjects also developed hyperglycaemia-related events, and many of the subjects received medication for hyperglycaemia.

The above findings show that in the clinical study, many hyperglycaemia-related events occurred following administration of pasireotide LAR. The analysis of data from the core phase and other data indicated the incidence of hyperglycaemia-related events tended to be higher in the pasireotide LAR 30 mg group than in the pasireotide LAR 10 mg group. However, events such as diabetic ketoacidosis or hyperglycaemic coma did not occur, and hyperglycaemia-related events in the majority of subjects were manageable by dose reduction, dose interruption, or using a concomitant antidiabetic drug. Many subjects who developed hypoglycaemia in the clinical study had been receiving an antidiabetic drug for the treatment of hyperglycaemia; therefore, the enhanced hypoglycemic effect of antidiabetic drugs may have caused hypoglycemic symptoms. However, this does not seem to pose significant problems in terms of the safety of pasireotide LAR. In the package insert of pasireotide pamoate for the approved indications, precautions such as the following have been provided: blood glucose levels should be monitored on a regular basis; and if patients develop hyperglycaemia, the dose of pasireotide pamoate should be interrupted or reduced, or appropriate action should be taken. It is necessary to provide similar advice for management of hyperglycaemia in patients with Cushing's disease.

PMDA's view:

In Study G2304, hyperglycaemia-related events frequently occurred soon after the start of pasireotide LAR treatment. The analysis of the events on the basis of the subject's glucose tolerance status at baseline showed that the incidence of hyperglycaemia-related events tended to be higher in subjects with "diabetes mellitus" than in subjects with "pre-diabetes" or "normal glucose tolerance." Furthermore, FPG and HbA1c levels tended to increase soon after the start of treatment in all subjects regardless of their glucose tolerance status at baseline. Many cases of hypoglycaemia occurred associated with medications used to treat hyperglycaemia-related events. Severe cases of hypoglycaemia were confirmed to resolve on the same day as its onset, and no events led to treatment discontinuation. Based on the above findings, Advice should be provided on hyperglycaemia and hypoglycaemia as with the approved indications, and there is no particular problem with the applicant's explanation. Because of the limited number of Japanese patients included in clinical studies conducted in patients with Cushing's disease, the applicant should continue to collect post-marketing information on glycemic events and should inform healthcare professionals of any findings on time to onset or other aspects of hyperglycaemia-related events obtained from the results of Study G2304 using information materials, etc.

7.R.2.2 Bradycardia and QT prolongation

The applicant's explanation:

The incidence of bradycardia-related events[26)] at the end of the core phase of Study G2304 was 5.4% (4 of 74 subjects) in the pasireotide LAR 10 mg group and 11.8% (9 of 76 subjects) in the pasireotide LAR

[26)] Events coded to the following MedDRA PTs: atrial conduction time prolongation, atrioventricular block, atrioventricular block complete, atrioventricular block second degree, atrioventricular dissociation, bradycardia, conduction disorder, defect conduction intraventricular, electrocardiogram PQ interval prolonged, electrocardiogram PR prolongation, electrocardiogram QRS complex prolonged, electrocardiogram QT prolonged, long QT syndrome, sinoatrial block, and sinus bradycardia.

30 mg group, with all events being mild or moderate in severity. The comparison of incidence of events by PT shows that the incidence of sinus bradycardia was the highest (4.1% [3 of 74 subjects] in the 10 mg group and 7.9% [6 of 76 subjects] in the 30 mg group). Mild sinus bradycardia reported in 1 subject in the pasireotide LAR 30 mg group was a serious adverse event, but the event resolved without treatment after hospitalization of the subject for examinations. No adverse events led to treatment discontinuation. All events resolved without treatment, with the exception of 1 subject in the pasireotide LAR 30 mg group (sinus bradycardia) whose condition required dose reduction.

The incidence of QT prolongation-related events[27)] at the end of the core phase of Study G2304 was 2.7% (2 of 74 subjects) in the pasireotide LAR 10 mg group and 5.3% (4 of 76 subjects) in the pasireotide LAR 30 mg group. The comparison of incidence of events by PT shows that the events reported in ≥2 subjects were electrocardiogram QT prolonged (1 subject in the 10 mg group and 2 subjects in the 30 mg group). Cardiac arrest reported in 1 subject in the pasireotide LAR 30 mg group was a serious adverse event. This subject developed dyspnoea and was hospitalized on the same day. Subsequently, the subject had cardiopulmonary failure and cardiac arrest and died from cardiopulmonary failure on the same day. A causal relationship between the study drug and the event was ruled out by the investigator. No adverse events led to treatment discontinuation. All events resolved without treatment except for the case of cardiac arrest.

Based on the incidence of bradycardia- and QT prolongation-related events by treatment duration of the core phase (Table 15), at the end of the core phase (Table 13), and at the end of the study period (Table 14) in Study G2304, there was no trend toward significantly increasing incidence with increasing treatment duration.

Table 21 shows the results of the categorical analysis of QTcF interval data. While 3.3% (5 of 150) of subjects had a QTcF prolongation from baseline of >60 ms, no subjects had a QTcF >500 ms newly after baseline.

Table 21. Incidence of adverse events in subjects who had anomalities in QTcF interval
(Study G2304 [end of the core phase[a)]], safety analysis set)

QTcF interval	Pasireotide LAR 10 mg (N = 74)	Pasireotide LAR 30 mg (N = 76)
>450 ms	12.3 (9)[b)]	11.8 (9)
>480 ms	0 (0)	2.6 (2)
>500 ms	0 (0)	0 (0)
Change from baseline >30 ms	35.1 (26)	42.1 (32)
Change from baseline >60 ms	2.7 (2)	3.9 (3)

% incidence (n)

a) In addition to the data for the core phase up to Month 12, data for the extension phase and thereafter up to the data cut-off date are included.

b) N = 73

27) Events coded to the following MedDRA PTs: cardiac arrest, cardiac death, cardiac fibrillation, cardio-respiratory arrest, electrocardiogram QT interval abnormal, electrocardiogram QT prolonged, electrocardiogram repolarisation abnormality, electrocardiogram U-wave abnormality, long QT syndrome, loss of consciousness, sudden cardiac death, sudden death, syncope, torsade de pointes, ventricular arrhythmia, ventricular fibrillation, ventricular flutter, ventricular tachyarrhythmia, and ventricular tachycardia.

Based on the above-mentioned incidence of events in Study G2304, there was no trend toward increasing risks in subjects with Cushing's disease compared with the approved indications. Therefore, as with the precautions provided in the approved indications, careful administration is required in patients with QT prolongation or cardiac disease, and precautionary statements should be provided to the effect that electrocardiogram assessment should be performed before administration and 3 weeks after the start of pasireotide LAR treatment (the time when the plasma concentration of pasireotide reaches its maximum) as a rule, and that the patient's condition during treatment should be closely monitored and appropriate action should be taken if any abnormalities are noted.

PMDA's view:

Because bradycardia- and QT prolongation-related events occurred following administration of pasireotide LAR in the clinical studies, it is appropriate to provide precautions, as they have been for the approved indications. Because of the limited number of Japanese patients included in clinical studies conducted in patients with Cushing's disease, the applicant should continue to collect post-marketing information on bradycardia- and QT prolongation-related events.

7.R.2.3 Hepatic dysfunction

The applicant's explanation:

The incidence of liver-related events[28)] at the end of the core phase of Study G2304 was 20.3% (15 of 74 subjects) in the pasireotide LAR 10 mg group and 19.7% (15 of 76 subjects) in the pasireotide LAR 30 mg group. The comparison of incidence of events by PT shows that the incidence of GGT increased (9.5% [7 of 74 subjects] in the 10 mg group and 7.9% [6 of 76 subjects] in the 30 mg group) was the highest, followed by ALT increased (8.1% [6 of 74 subjects] in the 10 mg group and 6.6% [5 of 76 subjects] in the 30 mg group). GGT increased reported in 1 subject in the pasireotide LAR 10 mg group was the only serious adverse event. This subject, a woman aged 48 years, had ALT high on Day 50, and developed severe GGT increased on Day 86, leading to dose reduction. Treatment with the study drug was discontinued on Day 113 due to insufficient therapeutic effect, and the event resolved on Day 141. This subject had dyslipidaemia and hepatic steatosis at baseline; however, the liver function test results were within the normal range. Adverse events leading to treatment discontinuation occurred in 4 subjects. These events were ALT increased in 2 subjects (1 subject each in the 10 mg and 30 mg groups), hepatic enzyme increased in 1 subject (the 10 mg group), and hepatic function abnormal in 1 subject (the 30 mg group). The subject experiencing ALT increased in the pasireotide LAR 10 mg group was a woman aged 36 years. This subject developed aspartate aminotransferase (AST) high and severe ALT increased on Day 297, which led to treatment discontinuation. The subject had hepatic steatosis at baseline; however, the liver function test results were within the normal range. Similarly, the subject experiencing ALT increased in the pasireotide LAR 30 mg group was a woman aged 26 years. This subject developed AST high and severe ALT increased on Day 22, which led to dose interruption, and then treatment

28) Events coded to the following MedDRA PTs: ALT abnormal, ALT increased, ammonia increased, AST abnormal, AST increased, blood cholinesterase abnormal, blood cholinesterase decreased, GGT abnormal, GGT increased, guanase increased, hepatic enzyme abnormal, hepatic enzyme decreased, hepatic enzyme increased, hepatic function abnormal, hepatobiliary scan abnormal, hyperammonaemia, hypertransaminasaemia, liver function test abnormal, transaminases abnormal, transaminases increased, ultrasound liver abnormal, and urine bilirubin increased.

discontinuation on Day 57. This subject did not have liver disease at baseline, and the liver function test results were within the normal range. The subject who had hepatic enzyme increased was a woman aged 34 years. This subject developed severe hepatic enzyme increased on Day 499, which led to treatment discontinuation. The subject did not have liver disease at baseline, and the liver function test results were within the normal range. The subject who had hepatic function abnormal was a woman aged 29 years, who presented with AST high and ALT high on Day 198, and then developed severe hepatic function abnormal, which led to treatment discontinuation. While the subject had hepatic steatosis at baseline, her liver function test results were within the normal range.

Based on the incidence of liver-related events by the treatment period of the core phase (Table 15), at the end of the core phase (Table 13), and at the end of the study period (Table 14) in Study G2304, there was no trend toward significantly increasing incidence with increasing treatment duration.

Table 22 shows the results of the incidence of abnormal liver function test results at the end of the core phase of Study G2304. The mean AST and mean ALT reached a peak between Month 0.75 and Month 1.75 in both dose groups, with the value of the pasireotide LAR 30 mg group being slightly higher than that of the pasireotide LAR 10 mg group. From Month 3 to Month 12, the mean AST and mean ALT did not change significantly from the baseline values for both dose groups. Although AST and ALT levels increased after the start of study drug treatment, the increases were transient. No subjects had concurrent ALT or AST >3 × ULN and TBIL >2 × ULN. Furthermore, no subjects had results meeting the Hy's law (ALT or AST >3 × ULN, TBIL ≥2 × ULN, and ALP <2 × ULN).

Table 22. Incidence of abnormal liver function test
(Study G2304 [end of the core phase[a)]], safety analysis set)

		Pasireotide LAR 10 mg (N = 74)	Pasireotide LAR 30 mg (N = 76)	Total (N = 150)
ALT or AST	> ULN and ≤3 × ULN	50.0 (37)	57.9 (44)	54.0 (81)
	> 3 × ULN	13.5 (10)	14.5 (11)	14.0 (21)
	> 5 × ULN	5.4 (4)	3.9 (3)	4.7 (7)
	> 8 × ULN	0 (0)	1.3 (1)	0.7 (1)
TBIL	> 2 × ULN	0 (0)	2.6 (2)	1.3 (2)
	> 3 × ULN	0 (0)	1.3 (1)	0.7 (1)

% incidence (n); ULN, upper limit of normal
a) In addition to the data for the core phase up to Month 12, data for the extension phase and thereafter up to the data cut-off date are included.

Based on the above, there was no trend toward increasing risks of hepatic dysfunction compared with the approved indications. However, given liver-related events reported in the clinical studies, including serious adverse events and adverse events leading to treatment discontinuation, the applicant intends to provide precautionary statements to the effect that liver function tests should be performed at an early stage after the start of pasireotide LAR treatment and thereafter on a regular basis, similarly to that for the approved indications.

PMDA's view:

There are no particular problems with the applicant's opinion. However, because of the limited number of Japanese subjects evaluated in clinical studies involving patients with Cushing's disease, the applicant should continue to collect post-marketing information on hepatic dysfunction-related events.

7.R.2.4 Cholelithiasis

The applicant's explanation:

The incidence of cholelithiasis-related events[29)] at the end of the core phase of Study G2304 was 24.3% (18 of 74 subjects) in the pasireotide LAR 10 mg group and 44.7% (34 of 76 subjects) in the pasireotide LAR 30 mg group. The comparison of incidence of events by PT shows that the incidence of cholelithiasis was the highest (20.3% [15 of 74 subjects] in the 10 mg group and 44.7% [34 of 76 subjects] in the 30 mg group), indicating that the incidence of cholelithiasis is higher in the pasireotide LAR 30 mg group than in the pasireotide LAR 10 mg group. Serious adverse events occurred in 4 subjects, and these events were cholelithiasis in 3 subjects (1 subject in the 10 mg group and 2 subjects in the 30 mg group) and cholelithiasis/cholecystitis acute in 1 subject (the 10 mg group). The 3 subjects who developed cholelithiasis received inpatient treatment, and cholelithiasis resolved in all of the subjects. The subject who developed cholelithiasis/cholecystitis acute received inpatient treatment, and these events resolved after treatment with the study drug was discontinued. Adverse events leading to treatment discontinuation occurred in 4 subjects, and these events were cholelithiasis in 2 subjects (the 30 mg group), cholelithiasis/cholecystitis acute/blood bilirubin increased in 1 subject (the 10 mg group), cholecystitis in 1 subject (the 30 mg group). Most of the events were controllable without any treatment, dose interruption or dose reduction of pasireotide LAR.

The comparison of incidence of events by treatment period of the core phase of Study G2304 shows that the incidence of the events was highest in the period of 7 to ≤12 months (Table 15), while the incidence did not significantly increase at the end of the study period compared with that at the end of the core phase (Tables 13 and 14). There was no trend toward increasing incidence with increasing treatment duration.

According to the results of gallbladder ultrasonography, 8 of 64 subjects in the pasireotide LAR 10 mg group and 24 of 67 subjects in the pasireotide LAR 30 mg group had normal findings at baseline but were found to have new gallstones or biliary sludge at the final evaluation at the end of the core phase, indicating that cholelithiasis-related events tended to be more common in the pasireotide LAR 30 mg group.

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29) Events coded to the following MedDRA PTs: bile output abnormal, bile output decreased, bile output increased, bilirubin conjugated abnormal, bilirubin conjugated increased, blood bilirubin abnormal, blood bilirubin increased, cholangiogram abnormal, endoscopy biliary tract abnormal, hyperbilirubinaemia, jaundice, jaundice cholestatic, jaundice extrahepatic obstructive, ultrasound biliary tract abnormal, x-ray hepatobiliary abnormal, bilirubinuria, blood alkaline phosphatase abnormal, blood alkaline phosphatase increased, blood bilirubin unconjugated increased, deficiency of bile secretion, urine bilirubin increased, bile duct necrosis, bile duct stenosis, bile duct stone, biliary cirrhosis, bile duct obstruction, biliary colic, biliary dilatation, biliary fibrosis, biliary fistula, biliary ischaemia, biliary tract disorder, cholestasis, haemobilia, hepatitis cholestatic, hepatobiliary disease, perforation bile duct, biliary dyskinesia, cholecystectomy, cholecystitis, cholecystitis acute, cholecystitis chronic, cholelithiasis, cholelithiasis obstructive, gallbladder disorder, gallbladder enlargement, gallbladder fistula, gallbladder necrosis, gallbladder non-functioning, gallbladder obstruction, gallbladder oedema, gallbladder operation, gallbladder pain, gallbladder palpable, gallbladder perforation, cholelithiasis migration, cholecystogram intravenous abnormal, cholecystogram oral abnormal, and bilirubin excretion disorder.

Based on the above, while the analysis of data from the core phase of Study G2304 and other data indicated that cholelithiasis-related events tended to be more common in the pasireotide LAR 30 mg group than in the pasireotide LAR 10 mg group, with this trend being consistent with the results of gallbladder ultrasonography, there was no trend toward increasing incidence of cholelithiasis-related events with increasing treatment duration. Further, there was no trend toward increasing risks compared with the approved indications. The applicant is therefore to provide precautionary statements to the effect that testing of the gallbladder and bile duct should be performed on a regular basis before and during the pasireotide LAR treatment, similarly to that of the approved indications.

PMDA's view:
There are no particular problems with the applicant's opinion. However, because of the limited number of Japanese subjects evaluated in clinical studies involving patients with Cushing's disease, the applicant should continue to collect post-marketing information on cholelithiasis-related events.

7.R.2.5 Effects on pituitary function

The applicant's explanation:
The incidence of hypocortisolemia-related events[30)] at the end of the core phase of Study G2304 was 8.1% (6 of 74 subjects) in the pasireotide LAR 10 mg group and 9.2% (7 of 76 subjects) in the pasireotide LAR 30 mg group. The comparison of incidence of events by PT shows that adrenal insufficiency occurred in 10 subjects (4 subjects in the 10 mg group and 6 subjects in the 30 mg group) and blood cortisol decreased occurred in 4 subjects (2 subjects each in the 10 and 30 mg groups). Serious adverse events were blood cortisol decreased in 2 subjects (1 subject each in the 10 and 30 mg groups) and adrenal insufficiency in 1 subject (the 10 mg group [Japanese]), and all of these events resolved with dose interruption or reduction of pasireotide LAR, glucocorticoid treatment and other measures. There were no adverse events leading to treatment discontinuation. The incidence of hypothyroidism-related events[31)] at the end of the core phase of Study G2304 was 1.4% (1 of 74 subjects) in the pasireotide LAR 10 mg group and 5.3% (4 of 76 subjects) in the pasireotide LAR 30 mg group, and there were no serious events or adverse events leading to treatment discontinuation.

Based on the incidence of hypocortisolemia- or hypothyroidism-related events by the treatment duration of the core phase (Table 15), at the end of the core phase (Table 13), and at the end of the study period (Table 14) in Study G2304, there was no trend toward significantly increasing incidence with increasing treatment duration.

30) Events coded to the following MedDRA PTs: adrenal insufficiency, adrenal suppression, adrenocortical insufficiency acute, blood cortisol decreased, cortisol free urine decreased, glucocorticoids decreased, secondary adrenocortical insufficiency, and steroid withdrawal syndrome.

31) Events coded to the following MedDRA PTs: Blood thyroid stimulating hormone decreased, hypothyroidism, myxoedema, myxoedema coma, secondary hypothyroidism, thyroid dermatopathy, thyroxine free decreased, tri-iodothyronine decreased, and tri-iodothyronine free decreased.

Based on the above, while hypocortisolemia and hypothyroidism occurred in the clinical studies, there was no trend toward increasing incidence with increasing treatment duration. Furthermore, there was no trend toward increasing risks compared with the approved indications. The applicant therefore intends to provide precautionary statements to the effect that regular pituitary function tests should be performed before and during the pasireotide LAR treatment, and if hypocortisolemia is suspected, dose reduction or interruption of pasireotide LAR should be considered and appropriate action should be taken, and if thyroid-related anomalies are noted, thyroid function tests should be performed.

PMDA's view:
There are no particular problems with the applicant's opinion. However, because of the limited number of Japanese subjects evaluated in clinical studies involving patients with Cushing's disease, the applicant should continue to collect post-marketing information on the effects of the pasireotide LAR treatment on pituitary function.

7.R.3 Clinical positioning

The applicant's explanation:
The primary goal of treatment of Cushing's disease is to normalize cortisol levels, because hypercortisolemia has a serious impact on the clinical symptoms and prognosis of patients. In and outside Japan, surgical resection of pituitary adenoma which causes hypercortisolemia is the first-line therapy. However, pituitary adenomas are very small, and their identification is often difficult. Even if surgical resection of pituitary adenoma is possible, some patients fail to achieve remission after surgery or experience tumor recurrence after surgery. If remission is not achieved, reoperation is considered; however, the rate of remission is lower than that after the first surgery. Furthermore, in some cases, removal of pituitary adenomas requires total or partial resection of the pituitary gland, which increases the risk of developing panhypopituitarism. Once a patient have panhypopituitarism, the patient will require hormone replacement therapy throughout his/her lifetime (*Eur J Endocrinol.* 2015;172:R227-39, and *Manual for the Treatment of Cushing's Syndrome*, rev. 2nd ed. Shindan-to-Chiryosha;2015). If surgical resection of pituitary adenoma cannot be performed for any reason, or surgical resection did not result in remission, radiation therapy (stereotactic radiation therapy or fractionated external beam radiation therapy), pharmacotherapy, or bilateral adrenalectomy is selected both in Japan and other countries. However, radiation therapy takes time to have a therapeutic effect, and the remission rate varies significantly, from 28% to 86% depending on the report. Furthermore, as with surgical resection, radiation therapy also involves the risk of panhypopituitarism. As for pharmacotherapy, 3 adrenocorticosteroid synthesis inhibitors (mitotane, trilostane, and metyrapone) have been approved in Japan for the treatment of Cushing's disease; however, these drugs do not have a tumor reducing effect on pituitary adenoma, or a normalizing effect on the dynamics of the hypothalamic-pituitary-adrenal axis. Mitotane and trilostane take time to exert a therapeutic effect, and further, mitotane carries the risk of adrenal failure due to irreversible damage to the adrenal cortex. The effectiveness of trilostane is low, and virilism associated with increased adrenal androgens is a concern. Metyrapone requires a frequent, large daily dose, and there are problems that dose increase is not possible in some poorly controlled

patients. Bilateral adrenalectomy is a reliable treatment option for Cushing's disease; however, it causes irreversible primary adrenal insufficiency, requiring hormone replacement therapy throughout the patient's lifetime. Furthermore, after total adrenalectomy, there is an increased risk of developing Nelson's syndrome, in which ACTH-producing pituitary adenomas emerge and the tumors grow (e.g., *J Clin Endocrinol Metab.* 2015;100:2807-31, and *Manual for the Treatment of Cushing's Syndrome*, rev. 2nd ed. Shindan-to-Chiryosha;2015). Based on the above, the treatment options for Cushing's disease are very limited; therefore, a new treatment option is needed. There is a strong medical need for the development of a drug which not only normalizes cortisol levels but also has an antitumor effect on pituitary adenoma (a cause of hypercortisolemia) and which causes fewer serious adverse drug reactions and is highly convenient for patients.

Pasireotide LAR is an SSA that has a high affinity for 4 of the 5 sstrs subtypes (sstrs 1-5), namely, sstr 1, sstr 2, sstr 3, and sstr 5. Especially, pasireotide shows the highest affinity for sstr 5. Findings have suggested that sstr 5 is likely to play an important role as a therapeutic target for Cushing's disease. Pasireotide LAR, which has a high affinity for sstr 5, is expected to inhibit excessive ACTH secretion from the patient's pituitary gland, which is the cause of Cushing's disease, thereby reducing excessive cortisol secretion from the adrenal glands. The results from Study G2304 involving patients with Cushing's disease showed that some subjects had normalized mUFC after treatment with pasireotide LAR, and that mUFC, plasma ACTH, and serum cortisol levels as well as pituitary tumor volume following the administration of pasireotide LAR tended to be below baseline levels. Safety analysis showed no new risks other than events that were also of concern for the approved indications, acromegaly and pituitary gigantism. It is possible to control the risks through careful monitoring and, if necessary, by dose interruption, dose reduction, or appropriate action, in an approach similar to that adopted for patients with acromegaly or pituitary gigantism.

The above findings indicate that pasireotide LAR can be beneficial for the treatment of patients with Cushing's disease.

PMDA's view:
Pasireotide LAR has been shown to be effective in the treatment of patients with Cushing's disease [see Section "7.R.1 Efficacy"] and its safety is acceptable on the condition that appropriate precautions are provided [see Section "7.R.2 Safety"]. Therefore, pasireotide LAR can be an option for treating Cushing's disease.

7.R.4 Indications

PMDA's view:
Although data from only the limited number of Japanese patients have been studied, it can be concluded that the efficacy of pasireotide LAR in the treatment of Cushing's disease has been demonstrated [see Section "7.R.1 Efficacy"], and the safety is generally acceptable [see Section "7.R.2 Safety"]; therefore, there are no particular problems with adding Cushing's disease to the indications for pasireotide pamoate.

Based on the positioning of pharmacotherapy in the treatment of Cushing's disease [see Section "7.R.3 Clinical positioning"], together with the study population of Study G2304, the target population of pasireotide LAR is patients who have had an inadequate response to surgery or for whom surgery is not an option. Taking the above into account, a final decision on the appropriateness of the indications will be made based on comments from the Expert Discussion.

7.R.5 Dosage and administration

The applicant's explanation:

To determine the dosage regimen for Study G2304, simulation was performed using plasma pasireotide concentrations. As the result of the simulation, it was estimated that the steady-state trough concentrations and $AUC_{0\text{-}28\ day}$ following administration of pasireotide LAR 10 mg would be similar to those following administration of s.c. pasireotide 300 μg twice daily. In contrast, the steady-state trough concentrations following administration of pasireotide LAR 30 mg would be slightly higher than those following administration of s.c. pasireotide 900 μg twice daily, while $AUC_{0\text{-}28\ day}$ would be similar. Accordingly, pasireotide LAR 10 mg and 30 mg were selected as the starting dose levels. Further, C_{max} following administration of pasireotide LAR 40 mg was similar to that following administration of s.c. pasireotide 600 μg twice daily; therefore, the dose was allowed to be increased up to 40 m in patients who failed to respond to a dose of pasireotide LAR 30 mg [see Section "6.R.2 Recommended clinical dose of pasireotide LAR"]. If there were safety concerns, the dose was allowed to be decreased to a minimum of 5 mg, and the dose was to be adjusted, as necessary, within the range of 5 to 40 mg depending on the patient's condition.

The results of Study G2304 demonstrated the efficacy of pasireotide LAR at 10 mg and 30 mg for both the primary and key secondary endpoints, and no significant differences were noted between the 2 groups (Tables 5 and 6). On the other hand, up to Month 4, the period during which dose increase was not allowed, the results of efficacy by dose level indicate that the response rate was higher, and the change in mUFC from baseline was greater in the pasireotide LAR 30 mg group than in the pasireotide LAR 10 mg group (Table 6). After Month 4, the doses were increased in 31 subjects in the pasireotide LAR 10 mg group (increased to 30 mg from 10 mg) and 28 subjects in the pasireotide LAR 30 mg group (increased to 40 mg from 30 mg). Among these subjects, 10 subjects treated with pasireotide LAR 10/30 mg and 7 subjects treated with pasireotide LAR 30/40 mg were responders at Month 7. Furthermore, the response rate at Month 7 in subjects who were not a controlled responder or partially-controlled responder[32)] at Month 4 and thus resulted in dose increase was 35.3% (6 of 17 subjects) in the pasireotide LAR 10 mg group and 16.7% (2 of 12 subjects) in the pasireotide LAR 30 mg group, demonstrating that the dose increase was effective. The steady-state trough concentrations at pasireotide LAR 10 mg and 30 mg are comparable to those at the dose range of the pasireotide subcutaneous formulation approved in other countries, and a positive correlation was observed between plasma pasireotide concentrations and mUFC reduction [see Section "6.R.2 Recommended clinical dose of pasireotide LAR"].

32) Partially controlled responder: proportion of subjects who had ≥50% reduction in mUFC from baseline and mUFC >1.0 × ULN.

The incidence of adverse events in Study G2304 did not differ significantly from that found in the clinical studies conducted in patients with acromegaly and pituitary gigantism (both of which are the approved indications), suggesting that there are no safety concerns specific to patients with Cushing's disease. A comparison of safety between dose levels up to Month 4 (dose increase was not allowed) showed that the overall incidence of adverse events was similar between the pasireotide LAR 10 and 30 mg groups. However, the incidence of the following events was higher in the pasireotide LAR 30 mg group than in the pasireotide LAR 10 mg group (Table 15): adverse drug reactions (74.3% [55 of 74 subjects] in the 10 mg group and 89.5% [68 of 76 subjects] in the 30 mg group); adverse events leading to dose interruption or dose reduction (6.8% [5 of 74 subjects] in the 10 mg group and 18.4% [14 of 76 subjects] in the 30 mg group); and adverse events of special interest, i.e., hyperglycaemia-related events (47.3% [35 of 74 subjects] in the 10 mg group and 69.7% [53 of 76 subjects] in the 30 mg group) and cholelithiasis-related events (1.4% [1 of 74 subjects] in the 10 mg group and 27.3% [18 of 76 subjects] in the 30 mg group). Also, the results of analysis using a logistic regression model or a linear mixed effect model showed a positive correlation between pasireotide exposure and the incidence of hyperglycaemia.

Based on the above discussions, a starting dose of 10 mg was selected taking into account the results of the primary endpoint and key secondary endpoints, which indicated that the response rate was similar between the pasireotide LAR 10 and 30 mg groups, as well as the higher incidences of hyperglycaemia-related events and cholelithiasis-related events up to Month 4 in the pasireotide LAR 30 mg group. Further, it was decided that depending on the patient's condition, the dose can be increased to a maximum dose of pasireotide LAR 40 mg, at which tolerability was confirmed in Study G2304. This is because (1) reduction in mUFC up to Month 4 was slightly greater in the 30 mg group than in the 10 mg group, (2) some subjects achieved a response after dose increase(s), and (3) a positive correlation was observed between plasma pasireotide concentrations and mUFC reduction. While the dose level of pasireotide LAR 20 mg was not evaluated in Study G2304, the predicted PK/PD parameters theoretically suggest that reduction in mUFC is greater at 20 mg than at 10 mg, and the incidence of hyperglycaemia is lower at 20 mg than at 30 mg. The applicant therefore decided to use the 20 mg dose for dose adjustment so that the dose can be increased in 10 mg increments from the starting dose of 10 mg to the maximum dose of 40 mg depending on the patient's condition [see Section "6.R.2. Recommended clinical dose of pasireotide LAR"].

Because some subjects continued to receive pasireotide LAR 5 mg in Study G2304, PMDA asked the applicant to explain whether a dose level of pasireotide LAR 5 mg should be included in the dosage regimen.

The applicant's response:
In Study G2304, 15 subjects received at least 1 dose of pasireotide LAR 5 mg (12 subjects in the 10 mg group and 3 subjects in the 30 mg group). The most common reason for dose reduction to 5 mg was "adverse events" in 11 subjects (blood cortisol decreased in 4 subjects; adrenal insufficiency and

hyperglycaemia in 2 subjects each; diabetes mellitus, nausea, osteoarthritis, GGT increased, and decreased appetite in 1 subject each[33]), followed by "protocol specification" in 4 subjects (from Month 12 onward, dose adjustment was allowed at the discretion of the investigators based on mUFC levels), and "dosing errors" in 2 subjects. Ten subjects received at least 3 doses of pasireotide LAR 5 mg, and the most common reason for dose reduction to 5 mg was "adverse events" in 8 subjects[33] (blood cortisol decreased in 4 subjects; adrenal insufficiency in 2subjects; diabetes mellitus, hyperglycaemia, and decreased appetite in 1 subject each), followed by "protocol specification" in 4 subjects (from Month 12 onward, dose adjustment was allowed at the discretion of the investigators based on mUFC levels). As shown above, the main reasons for dose reduction to 5 mg were decreased cortisol levels or hyperglycaemia-related events, which are considered to be pasireotide concentration-dependent, reversible responses; therefore, if the dose is interrupted to decrease plasma pasireotide concentrations until the resolution of such an event, treatment may be resumed at 10 mg depending on the patient's condition. Therefore, there is no need to add a dose level of 5 mg at present, and a starting dose of 10 mg is appropriate.

PMDA's view:

Based on the results from Study G2304 and other findings, there are no particular problems in specifying the dosage regimen as follows: the starting dose is 10 mg, as an intramuscular injection every 4 weeks, and the dose can be adjusted within the range of 10 to 40 mg depending on the patient's condition. As for the minimum dose level of 10 mg, while a considerable number of subjects underwent dose reduction to 5 mg and remained at 5 mg in Study G2304, the applicant explained that based on the main reasons for dose reduction, situations requiring dose reduction in patients on treatment with pasireotide LAR10 mg can be managed by taking measures such as dose interruption. This explanation is acceptable. However, healthcare professionals' view on the minimum dose level should be continuously collected, and development of a 5 mg formulation should be considered as necessary. A final decision on the appropriateness of the dosage regimen shown above will be made based on comments from the Expert Discussion [see Section "6.R.3 Use in patients with hepatic impairment" for the dose levels of pasireotide LAR in patients with moderate hepatic impairment].

7.R.6 Special patient populations

7.R.6.1 Patients with hepatic impairment

The applicant's explanation:

To assess safety in patients with hepatic impairment, the degree of hepatic impairment was classified according to the criteria of the National Cancer Institute-Cancer Therapy Evaluation Program (NCI-CTEP) (normal hepatic function [Group A], TBIL and AST at or below ULN; mild hepatic impairment [Group B1], TBIL at or below ULN and AST above ULN; mild hepatic impairment [Group B2], TBIL >1 to 1.5 × ULN; moderate hepatic impairment [Group C], TBIL >1.5 to 3 × ULN; and severe hepatic impairment [Group D], TBIL >3 × ULN). Study G2304, in which pasireotide LAR was administered to patients with Cushing's disease, including Japanese patients, and Studies B2305, B2208[6] and

33) Some patients had dose reduction due to more than one adverse event.

B2208E1,[34)] in which the pasireotide subcutaneous formulation was administered to non-Japanese patients with Cushing's disease, excluded the following patients: patients with a medical history of liver diseases such as hepatic cirrhosis, chronic active hepatitis B and chronic active hepatitis C, patients with ALT or AST >2 × ULN, and patients with TBIL >1.5 × ULN. Study G2304 included only 2 subjects with mild hepatic impairment (B1) at baseline (1 subject each in the 10 and 30 mg groups) and 1 subject with moderate hepatic impairment at baseline (the 30 mg group). These 3 subjects were classified based on the criteria of NCI-CTEP. By the end of the core phase,[12)] all these 3 subjects experienced adverse events and adverse drug reactions, the majority of which were mild or moderate in severity. Severe adverse events occurred in 2 subjects with mild hepatic impairment (GGT increased [the 10 mg group] and GGT increased/ulvovaginal candidiasis/hepatic function abnormal [the 30 mg group]) and 1 subject with moderate hepatic impairment (blood bilirubin increased/cholelithiasis/blood cortisol decreased). Among these events, cholelithiasis in 1 subject with moderate hepatic impairment was classified as a serious adverse event, which resolved following inpatient treatment, and its causal relationship to the study drug was ruled out. No adverse events led to treatment discontinuation. Among these 3 subjects with hepatic impairment, 1 subject with mild hepatic impairment and 1 subject with moderate hepatic impairment in the pasireotide LAR 30 mg group entered the extension phase. Safety data were analyzed for the subjects who entered the extension phase. The 1 subject with moderate hepatic impairment developed blood bilirubin increased during the core phase and this event continued until the last reporting time point; however, the severity of the event was either mild or moderate, and a causal relationship between the event and the study drug was ruled out.

In Studies B2305, B2208, and B2208E1, in which the pasireotide subcutaneous formulation was administered to non-Japanese patients with Cushing's disease, 2 subjects had mild hepatic impairment (B1) (1 subject each in Studies B2305 and B2208/B2208E1), 3 subjects had mild hepatic impairment (B2) (2 subjects in Studies B2305 and 1 subject in Study B2208/B2208E1), and 1 subject had moderate hepatic impairment (Study B2305). Safety data were analyzed for subjects with hepatic impairment at baseline in Studies B2305 and B2208/B2208E1. All the subjects developed adverse events or adverse drug reactions, the majority of which were mild or moderate in severity. Serious adverse events occurred in 1 subject with mild hepatic impairment (B1) (hypercorticoidism/hyperglycaemia/cholelithiasis) and 1 subject with moderate hepatic impairment (diabetes mellitus) in Study B2305, and events other than hypercorticoidism were considered to be adverse drug reactions. There were no cases of adverse events leading to treatment discontinuation or requiring dose reduction or interruption of the study drug.

In Study B2305, moderate to severe liver-related events (GGT increased in 3 subjects; hepatic enzyme increased, ALT increased/AST increased/GGT increased, and ALT increased/GGT increased in 1 subject each) occurred in 6 subjects without concurrent liver diseases at the start of the study, which resulted in treatment discontinuation. Also, the pasireotide subcutaneous formulation and pasireotide LAR have already been contraindicated in patients with severe hepatic impairment. Based on the above,

34) In Study B2208E1, an extension study of B2208, non-Japanese patients with Cushing's disease received s.c. pasireotide 600 μg twice daily, and for subjects who had an inadequate response, the dose was allowed to be increased to 900 μg twice daily or 600 μg 3 times daily (the treatment duration was not specified). The median (range) of the treatment duration was 9.7 (2, 107) months.

pasireotide LAR should be contraindicated in patients with Cushing's disease who have severe hepatic impairment.

Based on the above, in the 4 studies (Studies G2304, B2305, and B2208/B2208E1) in which pasireotide LAR or the pasireotide subcutaneous formulation was administered to patients with Cushing's disease, a very small number of subjects had hepatic impairment at baseline. Therefore, it is difficult to evaluate whether the safety of pasireotide LAR is likely to differ depending on the severity of hepatic impairment. However, no adverse events led to treatment discontinuation in these subjects, and the only adverse event requiring dose interruption or reduction was blood cortisol decreased, which occurred in 1 subject with moderate hepatic impairment in the core phase of Study G2304. All the rest of the adverse events were manageable with or without treatment. Based on the above findings, the data obtained so far have not suggested that the safety of pasireotide LAR is likely to differ depending on the severity of hepatic impairment within the mild to moderate range.

PMDA's view:
In the applicant's opinion, the available clinical data do not suggest that the safety of pasireotide LAR is likely to differ depending on the severity of hepatic impairment within the mild to moderate range. There are no particular problems with the applicant's opinion. However, given the risk of developing hepatic dysfunction in patients treated with pasireotide LAR [see Section "7.R.2.3 Hepatic dysfunction"], limited clinical experience with pasireotide LAR in patients with hepatic impairment, and pasireotide exposure in patients with hepatic impairment [see Section "6.R.3 Administration to patients with hepatic impairment"], it is appropriate to provide precautions regarding the need for careful administration to patients with non-severe hepatic impairment in a similar manner to those provided in the approved indications, and to contraindicate pasireotide LAR in patients with severe hepatic impairment. Post-marketing information on the safety of pasireotide LAR in patients with hepatic impairment should be continuously collected because information in patients with hepatic impairment have been very limited.

7.R.7 Post-marketing investigations

The applicant's explanation:
Because of the very limited number of Japanese patients with Cushing's disease, for which pasireotide LAR is indicated, the applicant has planned a specified use-results survey covering all patients with Cushing's disease who will receive pasireotide LAR for a follow-up period of 1 year (maximum of 3 years) to collect data to evaluate the long-term safety and efficacy of the drug in patients with Cushing's disease in clinical practice. Information on the incidence of hyperglycaemia, bradycardia, QT prolongation, hepatic dysfunction, gallstone formation, cholelithiasis aggravated (cholecystitis acute and pancreatitis), gastrointestinal disorders, hypocortisolemia, and other events will be collected.

PMDA's view:
Cushing's disease, for which pasireotide LAR is indicated, is also a rare disease in Japan, and data from the very limited number of Japanese patients with Cushing's disease who received pasireotide LAR

have been evaluated. Therefore, there are no particular problems with the applicant's plan to conduct post-marketing surveillance covering all patients with Cushing's disease who will receive pasireotide LAR and thereby to collect data on the safety of pasireotide LAR. The details of the survey method and items will be decided based on comments from the Expert Discussion.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The inspection and assessment are ongoing. The results and PMDA's conclusion will be reported in Review Report (2).

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The inspection is ongoing. The results and PMDA's conclusion will be reported in Review Report (2).

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that pasireotide LAR has efficacy in the treatment of Cushing's disease, and that pasireotide LAR has acceptable safety in view of its benefits. Pasireotide LAR has clinically significance because it offers a new treatment option for patients with Cushing's disease. The safety information on pasireotide LAR, including the following adverse events, should be further evaluated in post-marketing surveillance: hyperglycaemia, bradycardia, QT prolongation, hepatic dysfunction, gallstone formation, and cholelithiasis aggravated (cholecystitis acute and pancreatitis).

PMDA has concluded that Signifor LAR (pasireotide LAR) may be approved if the drug is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

February 8, 2018

Product Submitted for Approval

Brand Name	(a) Signifor LAR Kit for i.m. injection 10 mg, (b) Signifor LAR Kit for i.m. injection 20 mg, (c) Signifor LAR Kit for i.m. injection 30 mg, and (d) Signifor LAR Kit for i.m. injection 40 mg
Non-proprietary Name	Pasireotide Pamoate
Applicant	Novartis Pharma K.K.
Date of Application	June 30, 2017

List of Abbreviations See appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy

PMDA's view:

In Study G2304, which included Japanese patients with Cushing's disease, a certain number of subjects with Cushing's disease achieved a response to treatment with pasireotide pamoate ("pasireotide LAR"), and mUFC, plasma ACTH, and serum cortisol levels following administration of pasireotide LAR tended to be below baseline levels. No significant difference in the efficacy of pasireotide LAR has been observed between the Japanese subpopulation and the overall population, although a strict comparison is difficult due to the limited number of Japanese subjects. The discussion above has demonstrated the efficacy of pasireotide LAR. Post-marketing information on the efficacy of pasireotide LAR should be continuously collected because data from only the limited number of Japanese patients with Cushing's disease have been evaluated so far.

This conclusion by PMDA was supported by the expert advisors.

1.2 Safety

PMDA's view:

Confirmation of the data obtained during the core phase, at the end of the core phase,[12)] and the end of the study[22)] in Study G2304, as well as the safety data in the Japanese subpopulation of Study G2304, indicate that the events noted are previously known events, i.e., almost the same as those that have reported for the approved indications, acromegaly and pituitary gigantism. Thus, the safety of pasireotide LAR in the treatment of patients with Cushing's disease is acceptable on the condition that appropriate precautions are provided in a similar manner to those for the approved indications. Post-marketing data on the safety of pasireotide LAR should be continuously collected because data from only the limited number of Japanese patients have been evaluated in the clinical studies conducted in patients with Cushing's disease.

This conclusion by PMDA was supported by the expert advisors.

1.3 Indications

PMDA's view:

Despite the limited number of Japanese patients included in clinical studies, the efficacy of pasireotide LAR in the treatment of Cushing's disease has been demonstrated by the data submitted [see Section "7.R.1 Efficacy" of the Review Report (1)], and the safety of pasireotide LAR is generally acceptable [see Section"7.R.2 Safety" of the Review Report (1)]. Therefore, there are no particular problems in adding Cushing's disease to the indications of pasireotide LAR. Based on the positioning of pharmacotherapy in the treatment of Cushing's disease [see Section "7.R.3 Clinical positioning" of the Review Report (1)], together with the study population of G2304, the target population of pasireotide LAR is patients who have had an inadequate response to surgery or for whom surgery is not an option.

This conclusion by PMDA was supported by the expert advisors.

Based on the above discussion, PMDA asked the applicant to revise the "Indication" statement as shown below and confirmed that the revision was made appropriately.

Indication

Treatment of Cushing's disease (who have had an inadequate response to surgery or for whom surgery is not an option)

1.4 Dosage and administration

PMDA's view:

Based on the results from Study G2304 and other findings, there are no particular problems in specifying the dosage regimen as follows: the starting dose is 10 mg by intramuscular injection every 4 weeks, and the dose can be adjusted within the range of 10 to 40 mg depending on the patient's condition.

The minimum dose level of 10 mg was selected, although a considerable number of subjects underwent dose reduction to 5 mg and remained at 5 mg in Study G2304. The applicant explained that based on the main reasons for dose reduction, situations requiring dose reduction in patients treated with pasireotide LAR 10 mg can be managed by taking measures such as dose interruption. This explanation is acceptable. However, healthcare professionals' views on the minimum dose level should be continuously collected, and development of a 5 mg formulation should be considered as necessary.

This conclusion by PMDA was supported by the expert advisors.

PMDA asked the applicant to modify the "Dosage and Administration" and the "Precautions for Dosage and Administration" statements as shown below, and confirmed that modification and revision were made appropriately.

Dosage and administration
The usual adult dosage is 10 mg of pasireotide administered by intramuscular injection into the gluteal muscle every 4 weeks. The dose may be increased to a maximum of 40 mg, depending on the patient's condition.

Precautions for dosage and administration
(1) The maximum dose should be 40 mg. The dose may be adjusted within the range of 10 to 40 mg as necessary, based on the blood or urinary cortisol levels, clinical condition, and other factors. If no improvement is observed despite dose increase to 40 mg, switching to other therapies should be considered.
(2) The starting dose for patients with moderate hepatic impairment (Child-Pugh class B) is 10 mg administered by intramuscular injection into the gluteal muscle every 4 weeks. The dose may be increased to a maximum of 20 mg, as necessary, depending on the patient's condition.

1.5 Special populations

1.5.1 Patients with hepatic impairment

PMDA's view:
According to the applicant' explanation, data from Study G2304, as well as those from Studies B2305, B2208[6)] and B2208E1,[34)] in which the pasireotide subcutaneous formulation was administered to non-Japanese patients with Cushing's disease, do not indicate that the safety of pasireotide LAR is likely to differ depending on the severity of mild to moderate hepatic impairment. There are no particular problems with this viewpoint. However, given the risk of developing hepatic dysfunction in patients treated with pasireotide LAR [see Section "7.R.2.3 Hepatic dysfunction" in the Review Report (1)], limited clinical experience with pasireotide LAR in patients with hepatic impairment, and pasireotide exposure in patients with hepatic impairment [see Section "6.R.3 Use in patients with hepatic impairment" of the Review Report (1)], it is appropriate to provide precautions regarding the need for careful administration to patients with non-severe hepatic impairment in a similar manner to those

provided for the approved indications, and to contraindicate pasireotide LAR in patients with severe hepatic impairment. Post-marketing information on the safety of pasireotide LAR in patients with hepatic impairment should be continuously collected because data from patients with hepatic impairment have been very limited.

This conclusion by PMDA was supported by the expert advisors.

1.6 Risk management plan (draft)

In view of the discussions presented in Section "7.R.7 Post-marketing investigations" of the Review Report (1) and comments from the expert advisers at the Expert Discussion, PMDA has concluded that the current draft of the risk management plan for pasireotide LAR should include the safety and efficacy specifications presented in Table 23, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Tables 24 and 25.

Table 23. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Hyperglycaemia • Bradycardia • QT prolongation • Hepatic dysfunction • Gallstone formation, cholelithiasis aggravated (cholecystitis acute and pancreatitis) • Gastrointestinal disorders • Hypocortisolemia	• Haematological abnormalities (haematopoiesis suppressed) • Effects of the excessive suppression of pituitary hormone production • Hypothyroidism • Tumor enlargement	• Safety of pasireotide LAR in patients with hepatic impairment • Long-term safety
Efficacy specification		
• Long-term efficacy of pasireotide in patients with Cushing's disease in clinical practice		

Table 24. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Specified use-results survey (all-case surveillance) • Post-marketing clinical study[a)]	• Preparation and distribution of information materials for healthcare professionals • Preparation and distribution of information materials for patients

a) The ongoing rollover study (Study B2412, ongoing), which was an extension of Study G2304, will be switched to a post-marketing clinical study once the partial change application for new the indications has been approved.

Table 25. Outline of specified use-results survey (draft)

Objective	To evaluate the long-term safety and efficacy of pasireotide LAR in patients with Cushing's disease in clinical practice.
Survey method	Central registry system
Population	All patients with Cushing's disease who received pasireotide LAR
Observation period	1 year after the start of pasireotide LAR treatment (up to a maximum of 3 years)
Planned sample size	50 patients
Main survey items	Patient characteristics, status of treatment with pasireotide LAR, concomitant medications, safety evaluation (e.g., hyperglycaemia, bradycardia, QT prolongation, and hepatic dysfunction), efficacy evaluation (cortisol [in urine, saliva, blood] and plasma ACTH)

2. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

2.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

2.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.2-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. The results showed that clinical studies were conducted in compliance with GCP as a whole. PMDA therefore concluded that there should be no obstacles in conducting its review based on the application documents submitted. However, the following issue was found at the sponsor site, albeit with no major impact on the overall study evaluation, and was notified to the sponsor as a finding requiring corrective action.

Finding requiring corrective action

Sponsor

- Due to a flaw in the treatment assignment system, the study drug was not administered to some subjects as prescribed in the protocol.

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the proposed indications and dosage and administration as follows, with the conditions for approval shown below. Since the present application involves the indications of the product designated as an orphan drug, the re-examination period of the product is 10 years for the indications and dosage and administration proposed in the present application.

Indications

(a) and (c):

Treatment of Cushing's disease (who have had an inadequate response to surgery or for whom surgery is not an option)

(b) and (d):

1. Improvement of hypersecretion of growth hormone and insulin-like growth factor 1 (IGF-1) (somatomedin-C) and related symptoms in patients with acromegaly or pituitary gigantism (who have had an inadequate response to surgery or for whom surgery is not an option).

2. Treatment of Cushing's disease (who have had an inadequate response to surgery or for whom surgery is not an option)

(Underline denotes additions to the proposed indications)

Dosage and Administration

(a) and (c):

The usual adult dosage is 10 mg of pasireotide administered by intramuscular injection into the gluteal muscle every 4 weeks. The dose may be increased to a maximum of 40 mg, depending on the patient's condition.

(b) and (d):

Acromegaly and pituitary gigantism:

The usual adult dosage is 40 mg of pasireotide administered by intramuscular injection into the gluteal muscle every 4 weeks for 3 months. Thereafter, doses of 20 mg, 40 mg, or 60 mg are administered every 4 weeks, depending on the patient's condition.

Cushing's disease:

The usual adult dosage is 10 mg of pasireotide administered by intramuscular injection into the gluteal muscle every 4 weeks. The dose may be increased to a maximum of 40 mg, depending on the patient's condition.

(Underline denotes changes to the proposed dosage and administration)

Conditions of Approval

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because of the very limited number of subjects included in Japanese clinical studies, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product until data are collected from the planned number of patients, thereby identifying the characteristics of treated patients, collecting data on the safety and efficacy of the product as early as possible, and taking necessary measures to ensure its proper use.

Appendix

List of Abbreviations

ACTH	Adrenocorticotropic hormone
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AtT20	AtT-20 cells (clone D16-16)
AST	Aspartate aminotransferase
AUC	Area under the drug plasma concentration-time curve
Adverse drug reaction	An adverse event for which a causal relationship to the study drug cannot be ruled out
BMI	Body mass index
CL/F	Apparent clearance
C_{max}	Maximum plasma concentration
CRH	Corticotropin releasing hormone
DDAVP	1-Deamino-8-D-arginine-vasopressin acetate trihydrate
EC_{50}	Effective concentration resulting in 50%
eGFR	Estimated glomerular filtration rate
E_{max}	Maximum effect
FAS	Full Analysis Set
GGT	Gamma-glutamyl-transferase
GH	Growth hormone
GIP	Glucose dependent insulinotropic polypeptide
GLP-1	Glucagon-like peptide 1
HbA1c	Hemoglobin A1c
HPLC	High performance liquid chromatography
GH•IGF-1	Growth hormone insulin-like growth factor-1
LBW	Lean body weight
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
MRI	Magnetic resonance imaging
mUFC	Mean urinary free cortisol
NCI-CTEP	National Cancer Institute-Cancer Therapy Evaluation Program
PPK	Population pharmacokinetics
PSUR	Periodic safety update report
PT	Preferred term
PMDA	Pharmaceuticals and Medical Devices Agency
Pasireotide	pasireotide
Pasireotide LAR	Singnifor LAR for i.m.
QTcF	QT interval corrected for heart rate according to Fridericia's formula
RIA	Radioimmunoassay
SOC	System organ class
SSA	Somatostatin Analogue
sstr	Somatostatin receptor
Subcutaneous pasireotide formulation	Subcutaneous formulation containing pasireotide diaspartate as its active ingredient
TBIL	Total bilirubin
UFC	Urinary free cortisol

ULN	Upper limit of normal
V/F	Apparent volume of distribution