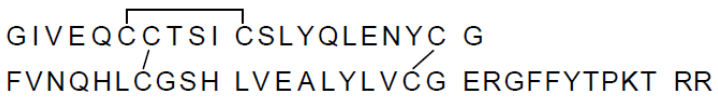
Review Report

October 10, 2014
The Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical products submitted for registration are as follows.

[Brand name]	Insulin Glargine BS Cartridge for Injection [Lilly], and Insulin Glargine BS Miriopen for Injection [Lilly]
[Non-proprietary name]	Insulin Glargine (Genetical Recombination) [Insulin Glargine Biosimilar 1] (JAN*)
[Applicant]	Eli Lilly Japan K.K.
[Date of application]	December 24, 2013
[Dosage form/Strength]	Solution for injection: One cartridge (3 mL) or kit (3 mL) contains 300 units of Insulin Glargine (Genetical Recombination) [Insulin Glargine Biosimilar 1].
[Application classification]	Prescription drug, (7) Biosimilar
[Definition]	Insulin Glargine [Insulin Glargine Biosimilar 1] is an analogue of human insulin, being substituted asparagine residue with glycine residue at 21st of A chain and added two arginine residues at C-terminal of B chain. It is a peptide composed with A chain consisting of 21 amino acid residues and B chain consisting of 32 amino acid residues.
[Structure]	 Disulfide bonds (shown as solid lines) Molecular formula, $C_{267}H_{404}N_{72}O_{78}S_6$ Molecular weight, 6,062.89
[Special features]	None
[Reviewing office]	Office of Cellular and Tissue-based Products

**Japanese Accepted Name (modified INN)*

Review Results

October 10, 2014

[Brand name]	Insulin Glargine BS Cartridge for Injection [Lilly], and Insulin Glargine BS Miriopen for Injection [Lilly]
[Non-proprietary name]	Insulin Glargine (Genetical Recombination) [Insulin Glargine Biosimilar 1]
[Applicant]	Eli Lilly Japan K.K.
[Date of application]	December 24, 2013

[Results of review]

Based on the submitted data, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that these proposed products are comparable to "Lantus cartridge for injection" and "Lantus Solostar for injection" (hereinafter collectively referred to as Lantus), and are classified as biosimilar products to Lantus.

As a result of its regulatory review, PMDA has concluded that these products may be approved for the following indication and dosage and administration.

[Indication]

Treatment of diabetes mellitus where treatment with insulin is required

[Dosage and administration]

The usual initial dosage for adults is 4 to 20 units of Insulin Glargine (Genetical Recombination) [Insulin Glargine Biosimilar 1] administered subcutaneously once daily. This drug may be used in combination with other insulin products. The drug may be administered either before breakfast or at bedtime but should be administered at the same time each day. The dose should be adjusted according to the patient's symptoms and test findings. The usual total insulin dose for maintenance therapy is 4 to 80 units/day if the drug is used with concomitant insulin products.

However, a higher dose than stated above may be used as needed.

[Conditions for approval]

The applicant is required to develop a risk management plan and implement it appropriately.

Review Report (1)

August 13, 2014

I. Product Submitted for Registration

[Brand name] Insulin Glargine BS Cartridge for Injection [Lilly], and Insulin Glargine BS Miriopen for Injection [Lilly]

[Non-proprietary name] Insulin Glargine (Genetical Recombination)

[Applicant] Eli Lilly Japan K.K.

[Date of application] December 24, 2013

[Dosage form/Strength] Solution for injection: One cartridge (3 mL) or kit (3 mL) contains 300 units of Insulin Glargine (Genetical Recombination)

[Proposed indication] Treatment of diabetes mellitus where treatment with insulin is required

[Proposed dosage and administration]

The usual initial dosage for adults is 4 to 20 units of Insulin Glargine (Genetical Recombination) [Insulin Glargine Biosimilar 1] administered subcutaneously once daily. This drug may be used in combination with other insulin products. The drug may be administered either before breakfast or at bedtime but should be administered at the same time each day. The dose should be adjusted according to the patient's symptoms and test findings. The usual total insulin dose for maintenance therapy is 4 to 80 units/day if the drug is used with concomitant insulin products.

However, a higher dose than stated above may be used as needed.

II. Summary of the Submitted Data and Outline of Review by the Pharmaceuticals and Medical Devices Agency

The data submitted in the application and the outline of review by the Pharmaceuticals and Medical Devices Agency (PMDA) are as shown below.

1. Origin or history of discovery and usage conditions in foreign countries etc.

Insulin and insulin analogs lower blood glucose levels by stimulating peripheral glucose uptake, especially by skeletal muscle and fat tissues, and by inhibiting hepatic glucose production. They are also known to enhance protein synthesis and inhibit proteolysis in the muscle, and enhance lipid synthesis and inhibit lipolysis.

Insulin Glargine (Genetical Recombination) (hereinafter referred to as “insulin glargine”) is a long-acting human insulin analog developed by Hoechst in Germany (currently Sanofi) to mimic a more physiological basal insulin secretion profile. Insulin glargine has a substitution of glycine for asparagine at the 21st amino residue of A chain and 2 arginines added to the carboxy terminal of B chain, and these

modifications result in a shift in the isoelectric point from a pH of 5.4 to 6.7. Once injected into the subcutaneous tissue, insulin glargine precipitates immediately at the physiological pH in subcutaneous tissues. The insulin glargine precipitate is slowly distributed into the systemic circulation, thereby providing a basal insulin profile. In Japan, insulin glargine is indicated for patients with diabetes mellitus where treatment with insulin is required.

Insulin Glargine BS Cartridge for Injection [Lilly] and Insulin Glargine BS Miriopen for Injection [Lilly] (hereinafter collectively referred to as IG-BS) were developed as biosimilar versions of their reference products, Lantus Cartridge for Injection and Lantus Solostar for Injection (Sanofi K.K.), respectively, both of which are insulin glargine products approved in Japan. IG-BS was developed with international collaboration in many countries, including Japan. IG-BS is under review in Europe, the United States, and other [redacted] countries as of July 2014. At present, no countries have approved IG-BS.

2. Data relating to quality

2.A Summary of the submitted data

2.A.(1) Drug substance

2.A.(1).1) Generation and control of the cell substrate

[redacted]

[redacted] Also, the results of purity tests of the MCB and WCB for bacteria, fungi, and bacteriophages demonstrated the absence of contaminants.

The MCB and WCB are stored in the vapor phase of liquid nitrogen. The MCB is expected to last the lifetime of the products. A new WCB is generated from the MCB as needed. The newly prepared WCB is qualified by the above-described characterization and purity tests.

2.A.(1).2) Manufacturing process

[redacted]

[redacted]

Process validation of the commercial-scale manufacturing process for the drug substance was carried out.

2.A.(1).3) Safety evaluation of adventitious agents

No ingredients or materials of biological origin are used during the manufacturing process of the drug substance.

2.A.(1).4) Manufacturing process development (Comparability)

The major changes made to the manufacturing process during the development of the drug substance are described below. Manufacturing Process C is the proposed manufacturing process.

- Change from Manufacturing Process A to B: Change from pilot scale to production scale (Scale-up of the fermentation and purification processes, and change of manufacturing sites)
- Change from Manufacturing Process B to C: Improvement of the production-scale manufacturing process (changes of process parameters in the fermentation and purification processes)

Assessment of the quality attributes of the drug substance revealed that the drug substance is comparable before and after these manufacturing process changes.

2.A.(1).5) Characterization

(a) Structure/Composition

i) Primary structure

- On the basis of the results of amino acid composition analysis, amino acid sequence analysis using Edman degradation, and peptide mapping, the amino acid sequence of IG-BS was assumed to be consistent with the theoretical sequence [see "2.B.(1) Primary structural analysis"].

ii) Higher-order structure

- [redacted]
- Infrared spectrophotometry revealed that IG-BS has alpha helix structures.
- [redacted] The position and strength of characteristic wavelength peaks of IG-BS were consistent with those reported with zinc-free human insulin.[1].

[1] *Biochemistry*. 1990;29:9289-93

(b) Physicochemical properties

i) Molecular weight

- The molecular weight of IG-BS measured by time-of-flight mass spectrometry and electrospray ionization was [redacted]Da, which was nearly identical to the theoretical molecular weight.
- The apparent weight-average molecular weight measured by static light scattering technique was [redacted]kDa, and the hydrodynamic radius measured by dynamic light scattering technique was [redacted]nm.

ii) Solubility

- [redacted]

iii) Electrophoretic patterns

- The isoelectric point of the major band was [redacted].

iv) Liquid chromatographic patterns

- [redacted]
- Size exclusion chromatography (SEC) revealed peaks of high molecular weight proteins in addition to the main peak.

v) Spectroscopic profiles

- The absorption coefficient was [redacted] $(mg/mL)^{-1}cm^{-1}$.

(c) Biological properties

- The binding affinity of IG-BS to the human insulin receptor isoform A (hIR-A), human insulin receptor isoform B (hIR-B), and human insulin-like growth factor-1 receptor (hIGF-1R) was determined.
- In an experiment using human embryonic kidney 293 (HEK293) cells that express hIR-A or hIR-B, IG-BS induced the autophosphorylation of the human insulin receptors.
- IG-BS promoted cell division of human and rat cell lines.
- IG-BS stimulated *de novo* lipid synthesis in mouse preadipocytes cell line 3T3L1. [see "3.(i).A.(1) *In vitro* studies"]
- A reporter gene assay was conducted on the basis of the fact that insulin inhibits the transcription of glucose-6-phosphatase in H4IIE rat hepatoma cells in a concentration-dependent manner. As a result, IG-BS inhibited the production of luciferase in these cells stimulated by dexamethasone, a glucocorticoid, in a concentration-dependent manner. A comparison of biological activity using the same assay showed that IG-BS possesses a biological activity equivalent to that of the reference biological product, and the specific activity of IG-BS is defined at 27.49 U/mg, which is similar to that of the reference biological product.
- In a study of the glucose lowering effect of IG-BS in rabbits, it decreased blood glucose levels in a dose-dependent manner.

(d) Product-related substances

No molecular entities were considered product-related substances.

(e) Impurities

i) Process-related impurities

[redacted] It has been confirmed that all of the process-related impurities are adequately removed in the manufacturing process. [redacted]

ii) Product-related impurities

[redacted] It has been confirmed that all of the product-related impurities are adequately removed in the manufacturing process. These impurities detected by reverse-phase chromatography (RPC) and size exclusion chromatography (SEC) are controlled by the specifications for the drug substance and drug product.

2.A.(1).6) Control of drug substance

[redacted]

2.A.(1).7) Stability of drug substance

Primary stability studies on the drug substance are as shown in Table 1.

Table 1. Overview of primary stability studies on the drug substance

Study	No. of batches*1	Storage condition	Storage period	Storage package
Long-term	3	-15°C to -5°C	30 months*2	Brown glass containers
Accelerated	3	2°C to 8°C	6 months	Brown glass containers
Stress testing (Photostability)	1	Ambient temperature, an overall illumination of 1,240,000 lux·hr and an integrated near ultraviolet energy of 576 W·h/m^2		Glass containers (with or without aluminum foil cover)

*1, The drug substance was manufactured through Manufacturing Process [redacted].
*2, The stability study is ongoing.

At the long-term and accelerated conditions, there were no major changes for all attributes tested throughout the study period.

In the stress testing (photostability studies), the contents of related substances and high molecular weight proteins increased in samples in non-covered containers, while no clear changes in these contents were observed in samples in containers covered with aluminum foil.

[redacted] The long-term stability study on the drug substance will continue for up to [redacted] months.

2.A.(2) Drug products

2.A.(2).1) Drug products and formulation development

The primary container is a 3 mL glass cartridge with a chlorobutyl rubber stopper. The drug products are a cartridge and a kit (a pen-type injector containing a cartridge) and each contains 300 units of IG-BS. The drug products contain concentrated glycerin, *m*-cresol, and zinc oxide as excipients. The secondary package is a paper carton.

2.A.(2).2) Manufacturing methods

[redacted]

Process validation of the commercial-scale manufacturing process has been conducted.

2.A.(2).3) Manufacturing process development

During the drug product development, changes in manufacturing scale, dosage form, and plunger were made [see “2.B.(2) The effect of the change of plunger on product stability”].

2.A.(2).4) Control of drug product

The proposed specifications for the drug product include content, description, identity (precipitation reaction and retention time), pH, purity (related substances [RPC], high molecular weight proteins [SEC]), foreign insoluble matter, insoluble particulate matter, sterility, zinc, *m*-cresol, and assay (RPC).

2.A.(2).5) Stability of drug product

Primary stability studies on the drug product are as shown in Table 2.

[2]For the kit only

Table 2. Overview of primary stability studies on the drug product

	No. of lots[*1]	Storage condition	Storage period	Storage package
Long-term	3	2 ºC - 8ºC, ambient humidity	24 months[*2]	Glass cartridge
Accelerated	3	28 ºC - 32ºC, 65%RH	6 months	
Stress testing (Photostability)	1	Ambient temperature, an overall illumination of 1,230,000 lux·hr and an integrated near ultraviolet energy of 568 W·h/m^2		Glass cartridge (with or without aluminum foil cover)

*1, Proposed commercial formulation
*2, The stability study is ongoing.

Under the long-term conditions, the contents of related substances and high molecular weight proteins tended to increase slightly, but there were no changes for other attributes tested throughout the study period.

[redacted]

Based on the above results, a shelf life of 24 months has been proposed for the drug product when stored at 2ºC to 8°C, protected from light. The long-term stability study on the drug product will continue for up to [redacted] months.

2.A.(3) Reference materials

[redacted] The stability of the primary reference material and the working reference material will be confirmed periodically.

[redacted]

2.A.(4) Comparison between the drug product and the reference biological product

Comparability studies were conducted to compare the quality attributes of the proposed drug substance and drug product with those of a reference insulin glargine product approved in the United States and Europe (hereinafter referred to as “the foreign reference biological product”).

[redacted]

[redacted] For some attributes, comparison was made using published information on the reference biological product. The comparison revealed slight differences in the contents of related substances between the drug product and the reference biological product [see "2.B.(3) Comparison between the drug product and the reference biological product"], but no differences were observed for other attributes.

[redacted]

The submitted data include the results of quality comparison studies between the foreign reference biological product and the reference biological product approved in Japan as well as product information on the reference biological product distributed outside Japan. On the basis of the data and information, the applicant claims that the foreign reference biological product is identical to the reference biological product available in Japan.

2.B Outline of the review by PMDA

Based on the submitted data and the following review, PMDA concluded that the drug product is similar to the reference biological product in terms of quality attributes, and that the quality of the drug substance and drug product is adequately controlled.

2.B.(1) Primary structural analysis

For the characterization of the drug substance, amino acid composition analysis, 15 cycles of Edman degradation, and peptide mapping were performed. The applicant explained that the amino acid sequence of IG-BS is assumed to be identical to that of the active ingredient of the reference biological product on the basis of the analysis results. However, the applicant had not confirmed the amino acid sequence of each peptide after enzymatic digestion.

As the Guideline for the Quality, Safety, and Efficacy Assurance of Follow-on Biologics (PFSB/ELD Notification No. 0304007, dated March 4, 2009) specifies that the primary structure of the follow-on

biologic (or biosimilar) must be consistent with that of the reference biological product, PMDA asked the applicant to identify the amino acid sequence of IG-BS wherever possible to confirm whether the primary structure of IG-BS is identical to that of the reference biological product.

The applicant responded that analysis with 32 cycles of Edman degradation and liquid chromatography-tandem mass spectrometry of peptides after enzymatic digestion revealed that the primary structure of IG-BS is identical to that of the reference biological product. PMDA accepted the response.

2.B.(2) The effect of the change of plunger on product stability

[redacted]

PMDA considers that there is no specific problem with the stability of the drug product under the proposed storage condition for the following reasons: although the content of high molecular weight proteins increased substantially in the drug product stored with the post-change package under the accelerated condition, no new extractables that may pose problems were detected from the post-change plunger; and the rate of formation of high molecular weight proteins increases in a temperature-dependent manner, and no problems were observed in the results of long-term testing at a temperature range of 2°C to 8°C. However, the drug product is intended to be used in divided doses, and is not intended for storage in a refrigerator after opening. An in-use period of 28 days was therefore proposed (see the "Precautions" section of the proposed package insert). Since in an in-use stability test, conducted under in-use conditions at 30°C for 32 days, no substantial increase in high molecular weight proteins was observed throughout the study period, it was confirmed that the in-use stability of the drug product during the in-use period specified in the package insert is assured.

2.B.(3) Comparison between the drug product and the reference biological product

[redacted]

The increase in the content of high molecular weight proteins in the drug product stored under the accelerated condition at 30°C for 6 months was attributable to the use of the package with the post-change plunger [see "2.B.(2) The effect of the change of plunger on product stability"], and the content of high molecular weight proteins did not differ between the drug product and the reference biological product after 24 months of storage under the long-term storage condition.

[redacted]

There was no particular difference in degradation profile between the drug product and the reference biologic under the long-term storage condition, and degradation did not occur even under the stress condition when the iron content satisfied the acceptance criteria for the drug substance (not more than [redacted]). Based on these findings, no particular problems should occur due to the difference observed under the stress condition.

Based on the above, although there were slight differences between the drug product and the reference biological product, these differences are not considered to affect the efficacy and safety of the drug product. It is thus considered that the quality attributes of the drug product are similar to those of the reference biological product.

PMDA concluded that the following applicant's explanation is acceptable: the differences in some quality attributes between the drug product and the reference biological product do not affect the efficacy and safety of the drug product, and the quality attributes of these products are similar.

3. Non-clinical data

3.(i) Summary of pharmacology studies

3.(i).A *Summary of the submitted data*

As primary pharmacodynamic studies, IG-BS was analyzed for the binding affinity to human insulin receptor (hIR), and human insulin-like growth factor 1 receptor (IGF-1R); hIR activation property; mitogenic potency; lipogenesis potency; and glucose lowering effect in rats. No secondary pharmacodynamic studies, safety pharmacology studies, or pharmacodynamic drug interaction studies were conducted.

Unless otherwise specified, parameters are expressed as geometric mean ± standard error.

3.(i).A.(1) *In vitro* studies (4.2.1.1.1)

3.(i).A.(1).1) Receptor binding affinity

The binding affinity of IG-BS to 2 hIR isoforms (hIR-A and hIR-B) and IGF-1R was determined using the membrane of human embryonic kidney 293 cells (HEK293 cells) overexpressing hIR-A, hIR-B or

IGF-1R by examining competitive radioligand binding to (3-[^{125}I]-iodotyrosyl-A14)-insulin or [^{125}I]-human insulin-like growth factor 1. The values of inhibition constant (Ki) of IG-BS and the reference biological product[3] against hIR-A were 0.408 ± 0.012 nM (n = 6) and 0.399 ± 0.018 nM (n = 6), respectively, those against hIR-B were 0.453 ± 0.028 nM (n = 6) and 0.450 ± 0.037 nM (n = 6), respectively, and those against IGF-1R were 16.0 ± 0.4 nM (n = 6) and 15.5 ± 0.6 nM (n = 6), respectively.

3.(i).A.(1).2) Receptor activation activity

The receptor activation activity of IG-BS and the reference biological product on hIR-A and hIR-B was determined using extracts of HEK293 cells overexpressing hIR-A or hIR-B by an enzyme-linked immunosorbent assay with an anti-hIR antibody and a labeled antibody recognizing phosphorylated tyrosine residues. The receptor activation activity on hIR-A, which was expressed as the concentration producing 50% of the effect of human insulin 100 nM (the active control), was 3.70 ± 0.20 nM (n = 6) for IG-BS and 4.50 ± 0.20 nM (n = 6) for the reference biological product. The corresponding figures on hIR-B were 2.05 ± 0.07 nM (n = 6) for IG-BS and 2.52 ± 0.12 nM (n = 6) for the reference biological product.

3.(i).A.(1).3) Mitogenic potency

The mitogenic potency by IGF-1R- and IR-dependent mechanisms was determined in terms of DNA uptake of [^{3}H]-thymidine using human osteosarcoma SAOS2 cells[4] (SAOS2 cells) for IGF-1R dependent mitosis and rat hepatic carcinoma H4IIe cells[5] (H4IIe cells) for IR-dependent mitosis. The mitogenic potency in SAOS2 cells, expressed as the concentration producing 50% of the effect of human insulin 1μM (the active control), was 0.531 ± 0.034 nM (n = 6) for IG-BS and 0.530 ± 0.027 nM (n = 6) for the reference biological product[3]. The mitogenic potency in H4IIe cells, expressed as the concentration producing 50% of the effect of human insulin 100 nM (the active control), was 8.97 ± 0.26 nM (n = 6) for IG-BS and 8.39 ± 0.36 nM (n = 6) for the reference biological product.

3.(i).A.(1).4) Lipogenesis potency

The effects of IG-BS and the reference biological product on *de novo* lipogenesis were evaluated using adipocytes differentiated from mouse fibroblast 3T3L1 cells. Production of triglycerides in the presence of [U-^{14}C]-glucose was determined based on the radioactivity in the lipid fraction. The lipogenesis potency, expressed as the concentration producing 50% of the effect of human insulin 100 nM (the active control), was 0.973 ± 0.092 nM (n = 6) for IG-BS, and 0.874 ± 0.077 nM (n = 6) for the reference biological product[3].

3.(i).A.(2) *In vivo* studies

Blood glucose-lowering effect (4.2.3.2.1, 4.2.3.2.2)

[3]The original insulin glargine product approved in the United States and Europe

[4]As SAOS2 cells express about 10-fold more IGF-IR than IR, the mitogenic potency in these cells depends more on the signal transmission via IGF-1R than IR.

[5]H4IIe cells express IR but not IGF-1R. In the absence of serum, the proliferation and survival of H4IIe cells strongly depend on insulin signaling. These characteristics are suitable as test systems of mitogenic potency and apoptosis inhibition.

The blood glucose lowering effect of IG-BS was tested in SD rats in two studies. Specifically, a study was conducted in male and female SD rats receiving the vehicle,[6] IG-BS, or the reference biological product subcutaneously at doses of 0.3, 1, or 2 mg/kg once daily for 4 weeks, and another study was conducted in male and female SD rats receiving the vehicle,[6] IG-BS, or the reference biological product[3] subcutaneously at doses of 0.3, 1, or 3 mg/kg (the dose reduced to 2 mg/kg during the study) once daily for 4 weeks. In all dose groups of IG-BS and the reference biological product, blood glucose levels decreased immediately after the administration and were reduced in a dose-dependent manner. IG-BS was, thus, equivalent to the reference biological product in terms of blood glucose lowering effect.

3.(i).B *Outline of the review by PMDA*

Based on the submitted data, PMDA concluded that IG-BS is similar to the reference biological product in terms of pharmacological effect.

3.(ii) Summary of pharmacokinetic studies

3.(ii).A *Summary of the submitted data*

Toxicokinetics (TK) profiles of IG-BS and the reference biological product after subcutaneous administration were evaluated in rats. No studies on distribution, metabolism, excretion, or pharmacokinetic drug interactions have been conducted.

Serum insulin glargine concentration was determined by a radioimmunoassay.

Toxicokinetics study (4.2.3.2.2)

Table 3 lists TK parameters measured on days 1 and 29 in male and female SD rats receiving IG-BS or the reference biological product subcutaneously at doses of 0.3, 1, or 2 mg/kg once daily for 1 month.

Table 3. TK parameters in rats receiving subcutaneous IG-BS or the reference biological product once daily for 1 month

				Day 1			Day 29		
	Sex	Dose (mg/kg)	No. of animals*	C_{max} (pM)	AUC_{0-24} (pM·h)	T_{max} (h)	C_{max} (pM)	AUC_{0-24} (pM·h)	T_{max} (h)
IG-BS	Male	0.3	25	4440	15,961	1	11,227	58,558	4
		1	25	16,390	95,241	4	25,700	142,077	4
		2	25	26,800	223,386	4	106,733	688,670	4
	Female	0.3	25	7813	26,376	2	14,033	41,784	2
		1	25	20,133	98,567	4	17,967	116,315	2
		2	25	23,200	222,888	4	38,600	391,906	1
Reference biological product	Male	0.3	25	6947	19,216	2	12,230	44,819	1
		1	25	14,333	82,629	4	30,933	167,112	2
		2	25	17,567	174,405	8	38,800	313,244	8
	Female	0.3	25	6310	17,095	2	9537	31,585	1
		1	25	23,000	100,983	2	33,900	136,217	2
		2	25	41,500	239,692	4	47,433	478,785	2

Arithmetic mean

*, Back-up animals were included. A total of 3 animals were used at each time point.

Cmax, maximum serum concentration; Tmax, time to maximum serum concentration; AUC_{0-24}, area under the serum concentration-time curve from 0 to 24 hours

[6]Aqueous solution containing concentrated glycerin at 17 mg/mL, m-cresol at 2.7 mg/mL, and zinc oxide at [redacted] μg/mL (pH4.0 ± [redacted])

3.(ii).B *Outline of the review by PMDA*

In the toxicokinetics study, the TK parameters differed between the reference biological product groups and the IG-BS groups at some time points. The applicant explained that exposure to IG-BS did not markedly differ from that to the reference biological product for the following reasons: (i) the differences in the mean value of each TK parameter between the 2 products were within the range of variability of measurements; (ii) the number of animals used at each time point was small; and (iii) neither product showed consistently higher or lower TK parameters than the other.

Taking account of the fact that this toxicokinetics study had not been designed to conduct rigorous evaluation of the similarity of the 2 products in terms of TK parameters, PMDA accepted the applicant's explanation, and concluded on the basis of the submitted data that there is no specific problem with non-clinical pharmacokinetics of IG-BS.

3.(iii) Summary of toxicology studies

3.(iii).A *Summary of the submitted data*

Repeated-dose toxicity studies of IG-BS and the reference biological product were conducted. No single-dose toxicity studies, genotoxicity studies, carcinogenicity studies, reproduction toxicity studies, or local tolerance studies were conducted.

3.(iii).A.(1) Single dose toxicity studies

No single-dose toxicity studies were conducted. The acute toxicity of IG-BS was examined during 1-month subcutaneous toxicity studies in rats (4.2.3.2.1 and 4.2.3.2.2). No effects of treatment were observed after the first administration of the drug.

3.(iii).A.(2) Repeated-dose toxicity studies

In order to compare the toxicological profile of IG-BS to the reference biological product, 1-month subcutaneous toxicity studies of IG-BS were conducted to compare with the published results of toxicity studies of the reference biological product[7].

3.(iii).A.(2).1) One-month subcutaneous toxicity study in rats (4.2.3.2.1)

Male and female SD rats received 0 (vehicle[6]), 0.3, 1, or 3 mg/kg of IG-BS, or 0.3, 1, or 3 mg/kg of the reference biological product[8] once daily subcutaneously for 4 weeks. As death or moribund sacrifice was observed in the IG-BS 1 mg/kg group (1 of 10 males) and the reference biological product 3 mg/kg group (1 each of 10 males and 10 females), treatments for the 3 mg/kg groups of both products were suspended for 3 days from day 12, and restarted on day 15 with a reduced dose of 2 mg/kg (the highest dose groups are referred to as the 3/2 mg/kg groups). Findings in the IG-BS groups were increased adipose tissues at the administration site (subcutaneous tissues) in the 0.3 mg/kg and higher dose groups,

[7] *Int J Toxicol*.2002; 21: 171-9, Summary of the product application of the reference biological product (Approved on October 16, 2003).
[8] Insulin glargine product approved in the United States

islet cell atrophy in the 1 mg/kg or higher dose groups, and axonal degeneration of the sciatic nerve in the 3/2 mg/kg group. Similar changes were also observed in the reference biological product groups.

Based on the above results, the no observed adverse effect level (NOAEL) of IG-BS was determined to be 0.3 mg/kg.

3.(iii).A.(2).2) One-month subcutaneous toxicity study in rats (4.2.3.2.2)

Male and female SD rats received 0 (vehicle[6]), 0.3, 1, or 2 mg/kg of IG-BS, or 0.3, 1, or 2 mg/kg of the reference biological product[9] once daily subcutaneously for 4 weeks. Death or moribund sacrifice was observed in the 1 mg/kg (1 of 10 females) and 2 mg/kg (1 of 10 females) groups of IG-BS, and in the 1 mg/kg (1 of 10 females) and 2 mg/kg (2 of 10 males) of the reference biological product. Findings in the IG-BS groups were islet cell atrophy and increased adipose tissues at the administration site (subcutaneous tissues) in the 1 mg/kg and higher dose groups, and axonal degeneration of the sciatic nerve in the 2 mg/kg group. According to published articles[10], the applicant discussed that all findings observed in this study were attributable to the pharmacological effects (blood glucose-lowering and lipid synthesis activities) or the continued high blood insulin levels. Similar findings were observed in the reference biological product groups.

Based on the above results, the NOAEL of IG-BS was determined to be 0.3 mg/kg.

3.(iii).A.(3) Local tolerance studies

Local tolerance studies were not performed. The local irritant effects of IG-BS was evaluated in 2 repeated dose toxicity studies [see "3.(iii).A.(2) Repeated-dose toxicity studies"]. In both studies, increased adipose tissues at the administration site (subcutaneous tissues) were observed both in the IG-BS groups and the reference biological product groups, but no clinical signs or histopathological findings suggestive of local irritant effects were observed.

3.(iii).B Outline of the review by PMDA

No carcinogenicity studies of IG-BS were conducted. The applicant explained the carcinogenic risk of IG-BS as follows:

Pharmacological properties possibly related to carcinogenicity are binding affinity to IGF-1R and mitogenic potency to cells dominantly expressing IGF-1R or hIR (e.g., SAOS2 cells and H4IIe cells). These properties are similar between IG-BS and the reference biological product [see "3.(i).A.(1) In vitro studies"]. It has been reported that insulin glargine exerts more potent mitogenic potency than human insulin does, but after subcutaneous administration it is rapidly metabolized into metabolites M1 and M2 that exert mitogenic activity similar to that of human insulin[11]. IG-BS is considered to be metabolized in a similar manner to the reference biological product as these products are similar in terms

[9]The original insulin glargine product approved in Europe

[10]*Brain Res.*1990;531: 8-15, *Am J Physiol.*1989;256: C190-6, *Endocrine J.* 2005; 52:623-8, *Diabetologia*.1988; 31:621-6, *J Clin Invest.*1992; 89: 432-6, *J Clin Invest.*1995;96: 2227-35, *Physiol Behav*.1995; 57:717-21

[11]*PLoS ONE.*2010; 5: e9540, *Diabetes Care.*2012; 35: 2626-30, *Diabetes Care*.2012; 35: 2647-9

of quality attributes. One-month subcutaneous toxicity studies in rats revealed no clear differences between the 2 products in TK profile, as well as the absence of local intolerance or proliferative changes at the site of injection in both product groups. Based on the above, carcinogenic risk of subcutaneous administration of IG-BS is similar to that of the reference biological product.

PMDA accepted the applicant's explanation, and concluded that the toxicological profile of IG-BS is similar to that of the reference biological product and that there is no specific problem in terms of the toxicity of IG-BS.

4. Clinical data

Clinical data package

As the evaluation data, the applicant submitted the results of a clinical pharmacology study that investigated the comparability of pharmacokinetics (PK) between IG-BS and the reference biological product in non-Japanese healthy volunteers (Study I4L-MC-ABEA), and a multi-regional phase III clinical study that evaluated the efficacy of IG-BS by investigating the non-inferiority of IG-BS to the reference biological product in Japanese and non-Japanese patients with type I diabetes mellitus (Study I4L-MC-ABEB). As reference data, the applicant submitted the results of clinical pharmacology studies in non-Japanese healthy volunteers and patients with type 1 diabetes mellitus (Studies I4L-MC-ABEO, I4L-MC-ABEN, I4L-MC-ABEI, I4L-MC-ABEM, and I4L-MC-ABEE) and a multi-regional phase III study in non-Japanese patients with type 2 diabetes mellitus (Study I4L-MC-ABEC).

PMDA considered the clinical data package for this application as follows, and reviewed the data.

Insulin and insulin analogs are administered to compensate for the lack of insulin in the body, and the necessary amount of extrinsic insulin may differ by the patient's disease condition and lifestyle. Therefore different patients need different doses of insulin, and they must adjust their insulin doses by themselves according to the physician's instructions. Multiple insulin products with different profiles may be often used in combination to achieve appropriate blood glucose control. In the development of biosimilars, it is essential to demonstrate the comparability with the reference biological product in terms of efficacy at the same dose. Insulin and insulin analogs require personalized dose adjustment and frequent dose changes, and may be given with other insulin products. Because of this characteristic of insulin and insulin analogs, the accurate assessment of comparability in efficacy between the reference biological product and a biosimilar should be based on direct and accurate indicators of blood glucose lowering effect, rather than on parameters of blood glucose control such as HbA1c and fasting blood glucose levels.

During the development process of IG-BS, the applicant conducted a study to verify the comparability in PK between IG-BS and the reference biological product (Study I4L-MC-ABEA), and a study to demonstrate the non-inferiority of IG-BS to the reference biological product using the change in HbA1c as an endpoint (Study I4L-MC-ABEB). For the above-described reasons, PMDA considered that pharmacodynamic (PD) comparability using glucose infusion rate (total glucose infused [G_{tot}] and

maximum glucose infusion rate [R_{max}]) in subjects using a glucose clamp in Study I4L-MC-ABEA is an appropriate method to confirm the comparability of IG-BS with the reference biological product in terms of efficacy. Accordingly, the data from Study I4L-MC-ABEA were assessed for the comparability in terms of PK and PD. The data from Study I4L-MC-ABEB were used as supplemental data on efficacy to confirm the comparability of IG-BS with the reference biological product in terms of blood glucose control, and used for safety evaluation including immunogenicity.

The main objective of Study I4L-MC-ABEA was to assess the comparability of PK. However, the protocol had pre-defined primary endpoints and bioequivalence acceptance ranges to demonstrate the comparability of PD, thus, the study was able to evaluate the comparability with a sufficient power. PMDA considered that the data from Study I4L-MC-ABEA may be used to evaluate PD comparability.

4.(i) Summary of biopharmaceutical studies and associated analytical methods

4.(i).A *Summary of the submitted data*

Serum insulin glargine concentration was determined using a radioimmunoassay (RIA) after polyethylene glycol separation to remove antibody-bound insulin glargine. As this RIA detects both insulin glargine and human insulin, Owen's formula[12] was used to calculate serum concentration of extrinsic insulin by subtracting that of intrinsic insulin through correction based on C-peptide concentration. Serum C-peptide concentration was determined using a chemiluminescent immunoassay.

Anti-drug antibodies were determined by RIA with a cut point for insulin glargine of 0.26% bound/total (B/T), and a cut point for the cross reaction with human insulin of 1.06% B/T. A result of >0.26% B/T was considered positive for anti-drug antibodies.

4.(ii) Summary of clinical pharmacology studies

4.(ii).A *Summary of the submitted data*

As the evaluation data, the results from a clinical pharmacology study in non-Japanese healthy volunteers conducted to investigate the comparability of PK between IG-BS and the reference biological product (Study I4L-MC-ABEA) was used.

Evaluation data

Clinical pharmacology study (5.3.1.2.1, Study I4L-MC-ABEA; November 2011 to July 2012)

A randomized, double-blind, 2-treatment, 4-period, repeated cross-over, 24-hour glucose clamp study was conducted in non-Japanese healthy volunteers aged ≥18 and ≤60 years with a maximum number of subjects of 98 (assumed that ≥78 subjects would complete the study). The subjects were to receive single subcutaneous doses of IG-BS and the reference biological product at a dose of 0.5 U/kg (with treatment periods separated by a washout period of ≥7 days).

[12]Human Insulin: Clinical Pharmacological Studies in Normal Man (MTP Press Limited, 1986)

A total of 80 subjects were randomized to receive the study drugs. All 80 subjects were included in the full analysis set (FAS) and were analyzed for PK, PD, and safety. After the end of the second period of the study by which time single doses of IG-BS and the reference biological product had been given, 2 subjects withdrew from the study at their own request.

Table 4 summarizes the results of the primary PK endpoints, i.e., the area under the serum concentration-time curve from 0 to 24 hours (AUC_{0-24}) and the maximum serum concentration (C_{max}) of IG-BS and the reference biological product. The IG-BS to the reference biological product ratios [90% confidence interval] of the least squares geometric means of AUC_{0-24} and C_{max} were 0.91 [0.87, 0.96] and 0.95 [0.90, 1.00], respectively. These ratios were within the pre-specified acceptable bioequivalence range of 0.80-1.25[13], which indicates the comparability of IG-BS to the reference biological product.

Table 4. AUC_{0-24} and C_{max} of IG-BS and the reference biological product (FAS)

	Study period	Least square geometric mean*1	Ratio between groups*1	90% CI of ratio
AUC_{0-24} (pmol·h/L)	IG-BS (n = 79*2)	1797.21	0.91	[0.87, 0.96]
	Reference biological product (n = 80)	1972.34		
C_{max} (pmol/L)	IG-BS (n=80)	112.17	0.95	[0.90, 1.00]
	Reference biological product (n = 80)	118.38		

*1, Parameters were converted into logarithmic values. Then the between-group difference of the logarithmic values were estimated with a linear mixed-effects model using treatment period, sequence of administration, and drug as the fixed effects and subjects as the random effect, and were reversely transformed.

*2, Data for analysis were not obtained in 1 subject.

Table 5 and Figure 1 show changes over time in PK parameters and serum drug concentrations of IG-BS and the reference biological product.

Table 5. Summary of PK parameters of IG-BS and the reference biological product (FAS)

Study period	C_{max} (pmol/L)	AUC_{0-24} (pmol·h/L)	$AUC_{0-\infty}$ (pmol·h/L)	T_{max} (h)	$t_{1/2}$ (h)
IG-BS (n = 80)	112 (39)	1810 (40)	2830 (39)	12.0	9.95 (66)
Reference biological product (n = 80)	119 (34)	1980 (36)	2930 (41)	12.0	9.76 (61)

Geometric mean (CV%)

$AUC_{0-\infty}$, area under serum concentration-time curve from zero to infinity; T_{max}, time to maximum serum concentration; $t_{1/2}$, elimination half life

[13]As the results obtained at 1 time point from 2 subjects receiving the dose of IG-BS in the 1st period and the result at 1 time point from 1 subject receiving the dose of the reference biological product in the 2nd period met the pre-specified criteria for outliers, these 3 measurements were excluded from the analysis.

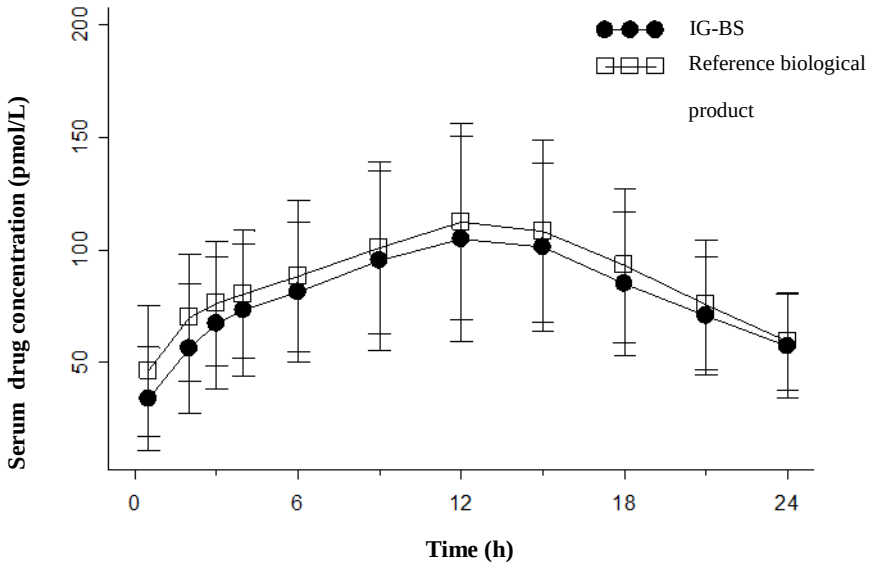


Figure 1. Changes over time in serum concentrations of IG-BS and the reference biological product (arithmetic mean ± standard deviation, FAS)

Table 6 summarizes the results of the primary PD endpoints, i.e., G_{tot} and R_{max} of IG-BS and the reference biological product. The IG-BS to the reference biological product ratios [90% confidence interval] of the least squares geometric means of G_{tot} and R_{max} were 0.95 [0.91, 1.00] and 0.99 [0.94, 1.04], respectively. These ratios were within the pre-specified acceptable bioequivalence range of 0.80-1.25.

Table 6. G_{tot} and R_{max} of IG-BS and the reference biological product (FAS)

	Treatment period	Least square Geometric mean*	Ratio between groups*	90% CI of ratio
G_{tot} (mg/kg)	IG-BS (n = 80)	2571.49	0.95	[0.91, 1.00]
	Reference biological product (n = 80)	2697.32		
R_{max}(mg/kg/min)	IG-BS (n = 80)	2.84	0.99	[0.94, 1.04]
	Reference biological product (n = 80)	2.86		

*, Parameters were converted into logarithmic values. Then the between-group difference of the logarithmic values were estimated with a linear mixed-effects model using treatment period, sequence of administration, and drug as the fixed effects and subjects as the random effect, and were reversely transformed.

Table 7 and Figure 2 show changes over time in PD parameters and glucose infusion rate (GIR) of IG-BS and the reference biological product with glucose clamp.

Table 7. Summary of PD parameters of IG-BS and the reference biological product

	R_{max} (mg/kg/min)	G_{tot} (mg/kg)	TR_{max} (h)
IG-BS (n = 80)	2.85 (46)	2580 (45)	11.40
Reference biological product (n = 80)	2.88 (41)	2710 (40)	11.10

Geometric mean (CV%)
TR_{max}, time to maximum glucose infusion rate

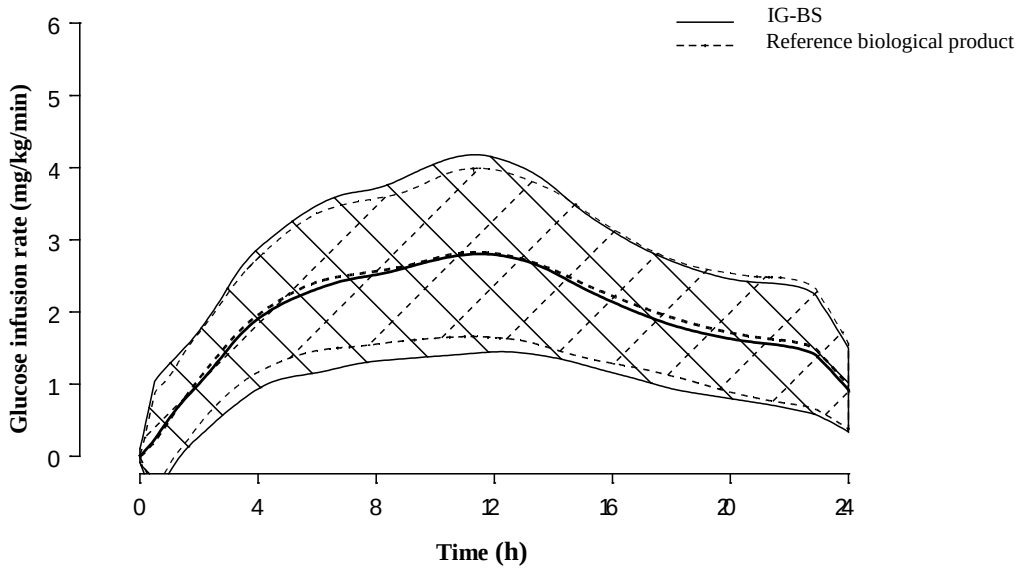


Figure 2. Glucose infusion rates of IG-BS and the reference biological product (arithmetic mean ± standard deviation, FAS)

Table 8 summarizes commonly observed adverse events. Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 11 of 80 subjects (13.8%) after the administration of IG-BS, and 14 of 80 subjects (17.5%) after the administration of the reference biological product. Of these, main adverse events were injection site pain (5 of 80 subjects [6.3%] for IG-BS vs. 6 of 80 subjects [7.5%] for the reference biological product), injection site erythema (4 of 80 subjects [5.0%] vs. 2 of 80 subjects [2.5%]), and hypoglycaemia (3 of 80 subjects [3.8%] vs. 3 of 80 subjects [3.8%]).

There were no cases of serious adverse events, adverse events resulting in discontinuation of study, or death in any study periods. No subjects had positive results for anti-drug antibodies.

Table 8. Common adverse events occurring in ≥2% of subjects (FAS)

	Study period	
	IG-BS (n = 80)	Reference biological product (n = 80)
All adverse events	50 (62.5)	54 (67.5)
Local reaction after treatment	17 (21.3)	17 (21.3)
Headache	15 (18.8)	25 (31.3)
Injection site pain	5 (6.3)	6 (7.5)
Nausea	4 (5.0)	5 (6.3)
Injection site erythema	4 (5.0)	2 (2.5)
Diarrhoea	4 (5.0)	1 (1.3)
Hypoglycaemia	3 (3.8)	3 (3.8)
Abdominal pain	2 (2.5)	2 (2.5)
Oropharyngeal pain	2 (2.5)	1 (1.3)
Influenza	2 (2.5)	0
Myalgia	2 (2.5)	0
Oral herpes	2 (2.5)	0
Vomiting	2 (2.5)	0
Influenza like illness	1 (1.3)	2 (2.5)
Muscle spasms	1 (1.3)	2 (2.5)
Infusion site swelling	0	3 (3.8)
Arthralgia	0	2 (2.5)
Pain in extremity	0	2 (2.5)

No. of subjects (%)

4.(ii).B *Outline of the review by PMDA*

4.(ii).B.(1) Pharmacokinetic comparability of IG-BS to the reference biological product

In Study I4L-MC-ABEA, 90% confidence intervals for the IG-BS to the reference biological product ratios of the least squares geometric means of AUC_{0-24} and C_{max}, which were the primary pharmacokinetic endpoints of the study, were within the pre-specified acceptable bioequivalence range. However, data at 1 time point each from 3 subjects were excluded as outliers. PMDA asked the applicant to provide a justification for the exclusion of these outliers.

The applicant explained as follows:

Measurements regarded as outliers were clearly deviated from the serum drug concentration curve before and after the time point of concern for each subject, and approximately 4- to 13-fold the mean serum drug concentration at the time point of concern. Since these measurements cannot be explained biologically with the known fluctuations in PK parameters after the administration of IG-BS or the reference biological product, the applicant classified these measurements at 3 different points into outliers and excluded them from analysis. When these outliers are included in the analysis, the IG-BS to the reference biological product ratios [90% confidence interval] of least square geometric means of AUC_{0-24} and C_{max} were 0.91 [0.87, 0.96] and 0.97 [0.91, 1.03], respectively, which were still within the pre-specified bioequivalence acceptable bioequivalence range (0.80 to 1.25).

PMDA considered that the applicant's explanation regarding these 3 measurements as outliers is understandable, and concluded that the results of Study I4L-MC-ABEA indicate pharmacokinetic

comparability of IG-BS with the reference biological product, taking also into account that the results of the analysis performed including these outliers were within the acceptable bioequivalence range.

4.(ii).B.(2) Pharmacodynamic comparability of IG-BS to the reference biological product

PMDA considers as follows:

In Study I4L-MC-ABEA, the IG-BS to the reference biological product ratios [90% confidence interval] of the least square geometric means of G_{tot} and R_{max}, which were the primary PD endpoints of the study, were within the pre-specified acceptable bioequivalence range. However, as G_{tot} and R_{max} are positioned as parameters of comparability in clinical efficacy, it is appropriate to assess these parameters on the basis of a 95% confidence interval. A pre-specified analysis with a confidence interval of 95%, which was specified in the statistical analysis plan, revealed that the IG-BS to the reference biological product ratios [95% confidence intervals] of G_{tot} and R_{max} were 0.95 [0.90, 1.01] and 0.99 [0.93, 1.05], respectively. On the basis of the fact that the study was sufficiently powered for the 95% confidence interval level, and the ratio was within the pre-specified acceptable bioequivalence range (0.80 to 1.25), and that changes over time in GIP were similar between IG-BS and the reference biological product (Figure 2), PMDA concluded that IG-BS is comparable with the reference biological product in terms of blood glucose lowering effect.

Accordingly, as mentioned in "Clinical data package" in "4. Clinical Data," PMDA determined that the pharmacodynamic comparability of IG-BS with the reference biological product supports the comparability of these two products in terms of efficacy. This conclusion will be finalized, taking account comments from the Expert Discussion.

4.(iii) Summary of clinical efficacy and safety

4.(iii).A *Summary of the submitted data*

As the evaluation data, the results of a multi-regional phase III clinical study (Study I4L-MC-ABEB) in patients with type 1 diabetes mellitus were submitted. As reference data, the results of a multi-regional phase III clinical study (Study I4L-MC-ABEC) in patients with type 2 diabetes mellitus were submitted.

PMDA used these clinical study results in safety evaluation and supplemental efficacy evaluation [see “Clinical data package” in “4. Clinical Data”].

Evaluation data

4.(iii).A.(1) Multi-regional phase III clinical study in patients with type 1 diabetes mellitus[14] **(5.3.5.1.1: Study I4L-MC-ABEB, September 2011 to March 2013)**

A randomized open-label, parallel group comparison study was conducted to compare the efficacy and safety of IG-BS and the reference biological product in concomitant therapy with insulin lispro

[14]Key inclusion criteria: Patients aged ≥18 years with type 1 diabetes mellitus for ≥ 12 months with BMI ≤35.0kg/m^2, HbA1c ≤11.0%, and on basal bolus insulin regimen for ≥ 12 months

(genetical recombination) in Japanese and non-Japanese[15] patients with type 1 diabetes mellitus aged ≥18 years (target sample size, 400 to 550 patients).

Subjects were to receive IG-BS or the reference biological product subcutaneously at the dose equivalent to the basal insulin[16] used before the initiation of the study at the same time of day (during the day or at evening or bedtime) once daily for up to 52 weeks. Insulin lispro was to be administered subcutaneously 3 times daily before meals at the dose equivalent to the pre-meal insulin[17] used before the initiation of the study. During the study, the doses of basal and bolus insulin were to be adjusted to achieve target blood glucose levels, i.e., HbA1c <7.0%, fasting blood glucose level ≤108 mg/dL (6.0 mmol/L), and pre-meal blood glucose level from 70 to 130 mg/dL while avoiding hypoglycaemia. Patients were stratified by country of study, HbA1c at visit 1 (<8.5% or ≥8.5%), and timing of basal insulin administration (during the day or at evening or bedtime) at randomization.

Among 536 patients[18] randomized, 535 patients consisting of 268 patients[19] in the IG-BS group (including 49 Japanese patients) and 267 patients[20] in the reference biological product group (including 51 Japanese patients) received the allocated study drugs. All of the 535 patients were included in the full analysis set (FAS) for the assessment of efficacy and safety.

The change in HbA1c from baseline to week 24 (least square mean ± standard error), which was assessed as the primary efficacy endpoint, was -0.352% ± 0.053% in the IG-BS group and -0.460% ± 0.054% in the reference biological product group, with a between-group difference [95% confidence interval] of 0.108% [-0.002%, 0.219%]. As the upper limit of the confidence interval was less than the pre-specified acceptable limit (0.4%), the non-inferiority of IG-BS over the reference biological product was demonstrated. The difference [95% confidence interval] between IG-BS and the reference biological product in the Japanese subpopulation was -0.028% [-0.296%, 0.239%] (Table 9).

[15]Belgium, Germany, Greece, Hungary, Mexico, Poland, Romania, and the United States
[16]Intermediate-acting insulin preparations, the reference biological product, or insulin detemir (genetical recombination)
[17]Human insulin (genetical recombination), insulin lispro, Insulin aspart (genetical recombination), or insulin glulisin (genetical recombination)
[18]One patient in the IG-BS group discontinued the study before the first dose of the allocated study drugs.
[19]Including 1 patient to whom the reference biological product was mistakenly administered.
[20]Including 1 patient to whom IG-BS was mistakenly administered.

Table 9. Change in HbA1c from baseline to week 24 (FAS, LOCF)

	Treatment group	Baseline	Week 24	Change	Least square mean of change*	Between-group difference in least square mean of change [95%CI]*
Entire study population	IG-BS (n = 267)	7.755 ± 0.070	7.439 ± 0.066	-0.315 ± 0.045	-0.352 (0.053)	0.108 [-0.002, 0.219]
	Reference biological product (n = 267)	7.788 ± 0.063	7.355 ± 0.056	-0.433 ± 0.043	-0.460 (0.054)	
Japanese subpopulation	IG-BS (n = 49)	7.614 ± 0.125	7.353 ± 0.132	-0.261 ± 0.107	-0.296 (0.131)	-0.028 [-0.296, 0.239]
	Reference biological product (n = 51)	7.667 ± 0.136	7.420 ± 0.135	-0.247 ± 0.095	-0.268 (0.131)	

Unit, %; arithmetic mean ± standard error, least square mean (standard error)
*, An analysis of covariance using country (not included in the analysis of the Japanese subpopulation), treatment group, timing of basal insulin administration (during daytime or at evening/bedtime), and baseline HbA1c value as explanatory variables.

Tables 10 and 11 summarize the results of analysis of main secondary endpoints from baseline to week 24 in the entire study population and the Japanese subpopulation.

Table 10. Results of analysis of main secondary endpoints in entire study population (FAS, LOCF)

Endpoint		IG-BS	Reference biological product
Basal insulin dose (U/kg/day)	Baseline	0.327 ± 0.009 (n = 268)	0.309 ± 0.008 (n = 266)
	Week 24	0.348 ± 0.010 (n = 268)	0.334 ± 0.009 (n = 266)
Total insulin dose (U/kg/day)	Baseline	0.717 ± 0.016 (n = 264)	0.706 ± 0.016 (n = 266)
	Week 24	0.733 ± 0.016 (n = 264)	0.715 ± 0.016 (n = 266)

Arithmetic mean ± standard error

Table 11. Results of analysis of main secondary endpoints in the Japanese subpopulation (FAS, LOCF)

Endpoint		IG-BS	Reference biological product
Basal insulin dose (U/kg/day)	Baseline	0.279 ± 0.015 (n = 49)	0.252 ± 0.014 (n = 51)
	Week 24	0.275 ± 0.014 (n = 49)	0.266 ± 0.014 (n = 51)
Total insulin dose (U/kg/day)	Baseline	0.746 ± 0.032 (n = 49)	0.766 ± 0.041 (n = 51)
	Week 24	0.724 ± 0.034 (n = 49)	0.805 ± 0.042 (n = 51)

Arithmetic mean ± standard error

Figures 3 and 4 illustrate changes over time in HbA1c from baseline to week 52 in the entire study population and the Japanese subpopulation.

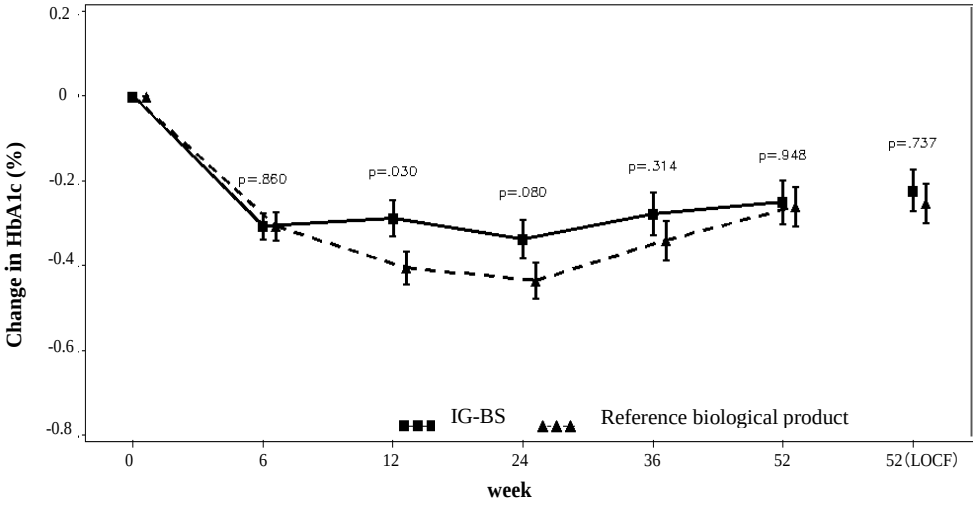


Figure 3. Change in HbA1c from baseline to Week 52 in the entire study population (arithmetic mean ± standard error, FAS)

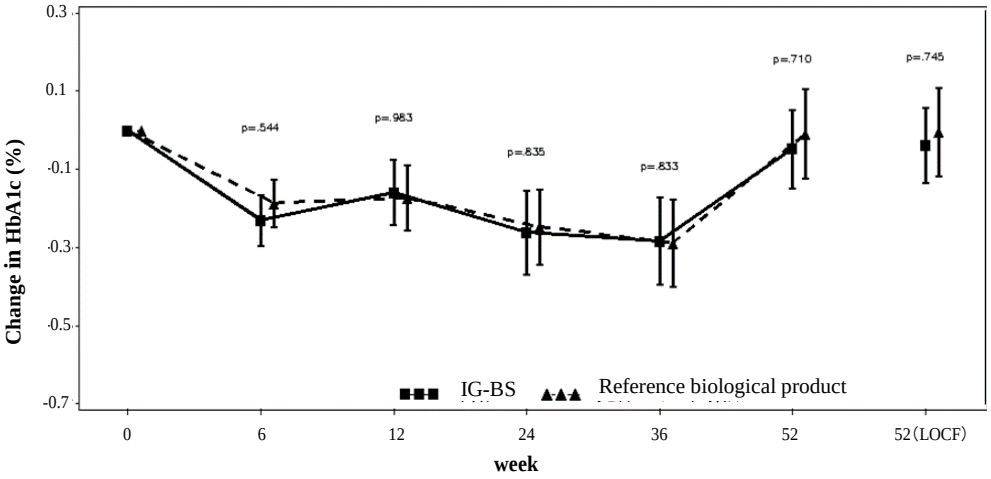


Figure 4. Change in HbA1c from baseline to Week 52 in the Japanese subpopulation (arithmetic mean ± standard error, FAS)

Table 12 summarizes commonly observed adverse events in the entire study population and the Japanese subpopulation. Adverse events for which a causal relationship to the study drug could not be ruled out in the entire study population were observed in 17 of 268 patients (6.3%) in the IG-BS group and 14 of 267 patients (5.2%) in the reference biological product group, and the corresponding figures in the Japanese subpopulation were 2 of 49 patients (4.1%) in the IG-BS group and 4 of 51 patients (7.8%) in the reference biological product group.

Table 12. Commonly observed adverse events (≥ 2%*) in the entire study population and the Japanese subpopulation in Study I4L-MC-ABEB (FAS)

	Entire study population		Japanese subpopulation	
	IG-BS (n = 268)	Reference biological product (n = 267)	IG-BS (n = 49)	Reference biological product (n = 51)
All adverse events	167 (62.3)	166 (62.2)	39 (79.6)	43 (84.3)
Nasopharyngitis	43 (16.0)	45 (16.9)	15 (30.6)	20 (39.2)
Upper respiratory tract infection	22 (8.2)	21 (7.9)	0	1 (2.0)
Hypoglycaemia	13 (4.9)	12 (4.5)	2 (4.1)	4 (7.8)
Diarrhoea	12 (4.5)	10 (3.7)	3 (6.1)	3 (5.9)
Back pain	10 (3.7)	9 (3.4)	3 (6.1)	3 (5.9)
Hypertension	9 (3.4)	5 (1.9)	1 (2.0)	2 (3.9)
Gastroenteritis	8 (3.0)	8 (3.0)	3 (6.1)	3 (5.9)
Sinusitis	7 (2.6)	8 (3.0)	0	0
Headache	7 (2.6)	7 (2.6)	2 (4.1)	1 (2.0)
Cough	6 (2.2)	8 (3.0)	0	2 (3.9)
Sinus congestion	6 (2.2)	5 (1.9)	0	0
Vomiting	6 (2.2)	2 (0.7)	1 (2.0)	0
Dizziness	6 (2.2)	0	1 (2.0)	0
Influenza	5 (1.9)	9 (3.4)	0	3 (5.9)
Bronchitis	4 (1.5)	8 (3.0)	0	0

No. of patients (%)

* Occurring in ≥2% of at least 1 of the groups in the entire study population

The incidence of serious adverse events observed in the entire study population was 7.5% (20 of 268 patients) in the IG-BS group and 9.0% (24 of 267 patients) in the reference biological product group. Serious adverse event occurring in 2 or more patients in the entire study population was hypoglycaemia, which developed in 13 of 268 patients (4.9%) in the IG-BS group and 12 of 267 patients (4.5%) in the reference biological product group. In the entire study population, serious adverse events for which a causal relationship to the study drug could not be ruled out was hypoglycaemia experienced by 10 of 268 patients (3.7%) in the IG-BS group and 9 of 267 patients (3.4%) in the reference biological product group. In the Japanese subpopulation, serious adverse events were reported in 3 of 49 patients (6.1%) in the IG-BS group and 6 of 51 patients (11.8%) in the reference biological product group. Serious adverse event occurring in 2 or more patients in the Japanese subpopulation was hypoglycaemia, observed in 2 of 49 patients (4.1%) in the IG-BS group and 4 of 51 patients (7.8%) in the reference biological product group. Serious adverse event for which a causal relationship to the study drug could not be ruled out was hypoglycaemia, which was observed in 3 of 267 patients (1.1%) in the reference biological product group.

Adverse events resulting in study discontinuation developed in 2 of 268 patients (0.7%) in the entire study population (maternal exposure during pregnancy and psychotic disorder [1 patient each]) in the IG-BS group, and 6 of 267 patients (2.2%) in the reference biological product group (maternal exposure during pregnancy, gliomatosis cerebri, hypertrophic cardiomyopathy, hypoglycaemia, refractory cytopenia with unilineage dysplasia, and suicide attempt [1 patient each]). The outcome of these adverse events was "recovered/resolved" in the case of psychotic disorder in the IG-BS group, and the cases of suicide attempt and hypoglycaemia in the reference biological product group (1 patient each); "not

recovered/not resolved" in the case of maternal exposure during pregnancy in the IG-BS group, and the cases of maternal exposure during pregnancy, gliomatosis cerebri, and refractory cytopenia with unilineage dysplasia in the reference biological product group (1 patient each); and "fatal" in the case of hypertrophic cardiomyopathy in the reference biological product group (1 patient). A causal relationship to the study drug could not be ruled out in the case of hypoglycaemia in the reference biological product group (1 patient). In the Japanese subpopulation, 3 of 51 patients (5.9%) discontinued the study due to gliomatosis cerebri, hypoglycaemia, and refractory cytopenia with unilineage dysplasia (1 patient each).

During the study period, 1 non-Japanese patient in the reference biological product group died due to hypertrophic cardiomyopathy, but a causal relationship between the event and the study drug was ruled out.

Table 13 summarizes the occurrence of anti-drug antibodies in the entire population and the Japanese subpopulation.

Table 13. Incidence of anti-drug antibodies in the entire study population and the Japanese subpopulation (FAS, LOCF)

	Entire study population		Japanese subpopulation	
	IG-BS (n = 268)	Reference biological product (n = 267)	IG-BS (n = 49)	Reference biological product (n = 51)
Baseline	45/265 (17.0)	55/267 (20.6)	8/49 (16.3)	9/51 (17.6)
Week 52 (LOCF)	73/265 (27.5)	59/267 (22.1)	13/49 (26.5)	7/51 (13.7)
Entire study period*	107/265 (40.4)	105/267 (39.3)	17/49 (34.7)	20/51 (39.2)

No. of patients (%)
*, Patients who had positive results for anti-drug antibodies at any time point after the administration of the study drug

Reference data

(1) Multi-regional phase III study in non-Japanese patients with type 2 diabetes mellitus (5.3.5.1.2: Study I4L-MC-ABEC, from September 2011 to September 2012)

A randomized, double-blind, parallel group comparison study was conducted to compare the efficacy and safety of IG-BS and the reference biological product in combination with oral antidiabetic drugs in Japanese and non-Japanese patients[21] with type 2 diabetes mellitus aged ≥18 years (target sample size, 606 to 792 patients). Insulin-naive patients were to start treatment with either IG-BS or the reference biological product subcutaneously at 10 U/day once daily, and patients who had used the reference biological product before participating in the study were to receive either of the 2 products at the same dose as the previous one of the reference biological product once daily subcutaneously. The dose was to be titrated by 1 unit per day to achieve a fasting blood glucose level of ≤100 mg/dL (5.6 mmol/L).

[21]Key inclusion criteria: Patients aged ≥18 years with type 2 diabetes mellitus; BMI ≤45 kg/m^2; receiving ≥2 different oral antidiabetic drugs at stable doses for 12 weeks before visit 1; and HbA1c 7.0% to 11.0% for those with no history of insulin therapy or ≤11.0% for those receiving the reference biological product.

Among 759 patients[22] randomized, 756 patients (376 patients in the IG-BS group and 380 patients in the reference biological product group) received the allocated study drugs. All of the 756 patients were included in the full analysis set (FAS) for safety assessment.

Table 14 lists commonly observed adverse events. Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 26 of 376 patients (6.9%) in the IG-BS group, and 23 of 380 patients (6.1%) in the reference biological product.

Table 14. Common adverse events occurring in ≥2% of patients (FAS)

Adverse events	Treatment group	
	IG-BS (n = 376)	Reference biological product (n = 380)
All adverse events	196 (52.1)	184 (48.4)
Nasopharyngitis	21 (5.6)	22 (5.8)
Upper respiratory tract infection	19 (5.1)	15 (3.9)
Abnormal weight gain	10 (2.7)	3 (0.8)
Diarrhoea	9 (2.4)	14 (3.7)
Back pain	9 (2.4)	10 (2.6)
Nausea	8 (2.1)	8 (2.1)
Cough	8 (2.1)	8 (2.1)
Headache	8 (2.1)	6 (1.6)
Sinusitis	8 (2.1)	3 (0.8)
Hypertension	8 (2.1)	3 (0.8)
Influenza	7 (1.9)	11 (2.9)
Arthralgia	7 (1.9)	8 (2.1)

No. of patients (%)

Serious adverse events were observed in 15 of 376 patients (4.0%) in the IG-BS group and 18 of 380 patients (4.7%) in the reference biological product group. Serious adverse events occurring in 2 or more patients in the entire patient population were hypoglycaemia (2 of 376 patients, 0.5%, in the IG-BS group vs. 3 of 380 patients, 0.8%, in the reference biological product group), coronary artery disease (1 of 376 patients, 0.3% vs. 3 of 380 patients, 0.8%), bronchitis (1 of 376 patients, 0.3% vs. 1 of 380 patients, 0.3%), and cellulitis (1 of 376 patients, 0.3% vs. 1 of 380 patients, 0.3%). Serious adverse events for which a causal relationship to the study drug could not be ruled out were hypoglycaemia, which developed in 2 of 376 patients (0.5%) in the IG-BS group, and 2 of 380 patients (0.5%) in the reference biological product group.

Adverse events resulting in discontinuation of study developed in 6 of 376 patients (1.6%), which were tension headache, injection site pain, lung adenocarcinoma, lung carcinoma cell type unspecified recurrent, intestinal obstruction, and suicide ideation (1 patient each), and in 11 of 380 patients (2.9%) in the reference biological product group, which were injection site pain, injection site mass, paraesthesia oral, fluid retention, cardiac operation, pregnancy, anxiety, myocardial infarction, fatigue, coronary artery disease, and hypotension (1 patient each). The outcome of these adverse events was "recovering/resolving" for the case of coronary artery disease in the reference biological product group, "recovered/resolved with sequelae" for the case of intestinal obstruction in the IG-BS group; "not

[22]Three patients in the IG-BS group discontinued the study before receiving the allocated study drugs.

recovered/not resolved" for the case of lung carcinoma cell type unspecified recurrent in the IG-BS group, and the cases of fluid retention, injection site mass, pregnancy, and fatigue in the reference biological product group; "fatal" for the case of lung adenocarcinoma in the IG-BS group, and the case of myocardial infarction in the reference biological product group; and "recovered/resolved" for other adverse events. Of these, adverse events for which a causal relationship to the study drug could not be ruled out were injection site pain observed in 1 patient each of the IG-BS group and the reference biological product group, and injection site mass, paraesthesia oral, and fatigue (1 patient each) in the reference biological product group.

During the study period, 1 patient in the IG-BS group died from lung adenocarcinoma, and 1 patient in the reference biological product group died from myocardial infarction. A causal relationship between the event and the study drug was ruled out in these cases.

Table 15 summarizes the occurrence of anti-drug antibodies in study participants.

Table 15. Incidence of anti-drug antibodies in study participants (FAS, LOCF)

	Treatment group	
	IG-BS (n = 376)	Reference biological product (n = 380)
Baseline	20/365 (5.5)	13/365 (3.6)
Week 24	30/365 (8.2)	22/365 (6.0)
Entire study period*	56/365 (15.3)	40/365 (11.0)

No. of patients (%)
*, Patients who had positive results for anti-drug antibodies at any time point after the administration of the study drug

4.(iii).B *Outline of the review by PMDA*

4.(iii).B.(1) Efficacy

PMDA confirmed that IG-BS is comparable to the reference biological product in terms of blood glucose lowering effect on the basis of the results of Study I4L-MC-ABEA [see "4.(ii).B. Outline of the review by PMDA"], and that the comparability shown by Study I4L-MC-ABEA is consistent with efficacy results from Study I4L-MC-ABEB (i.e., long-term efficacy of IG-BS and the efficacy of IG-BS in the Japanese subpopulation), as described below.

4.(iii).B.(1).1) Long-term efficacy

PMDA considers that there are no particular differences between IG-BS and the reference biological product in the long-term efficacy, because the change in HbA1c from baseline to week 24 and the results of secondary efficacy endpoints were similar between the 2 products (Tables 9 and 10), and the change over time in HbA1c from baseline to week 52 was also similar between the 2 products (Figure 3) in Study I4L-MC-ABEB in patients with type 1 diabetes mellitus.

4.(iii).B.(1).2) Efficacy in the Japanese subpopulation

The applicant explained the consistency between the entire study population and the Japanese subpopulation in terms of efficacy on the basis of the findings of Study I4L-MC-ABEB as follows:

The upper limit of the 95% confidence interval of the difference between the IG-BS and the reference biological product groups in the least square mean change in HbA1c from baseline to week 24, the primary endpoint, was smaller than the pre-defined acceptable limit (0.4%) both in the entire study population and the Japanese subpopulation. The dose of basal insulin, one of the other efficacy endpoints, showed some different trends between the entire study population and the Japanese subpopulation, but showed similar profiles over time between the IG-BS group and the reference biological product group in both patient populations. These findings indicate that the trend of the results of efficacy evaluation do not differ substantially between the Japanese subpopulation and the entire study population.

PMDA confirmed that the changes in HbA1c at week 24, the primary endpoint in Study I4L-MC-ABEB, in the IG-BS group and the reference biological product group were similar between the Japanese subpopulation and the entire study population, and that no substantial differences between the IG-BS group and the reference biological product group were observed for other efficacy endpoints, and considered that there are no particular differences in efficacy between IG-BS and the reference biological product in the Japanese subpopulation as well as those in the entire study population.

4.(iii).B.(2) Safety

PMDA assessed the safety profile of IG-BS such as the occurrence of hypoglycaemia and allergy-related adverse events, anti-drug antibodies, and neoplasms. The percentage of patients with an increase in antibody binding rate tended to be higher in the IG-BS group than that in the reference biological product group in Study I4L-MC-ABEB [see "4.(iii).B.(2).5) Anti-drug antibodies"], but there were no substantial differences in occurrence of adverse events between the IG-BS group and the reference biological product group. IG-BS is thus considered tolerable. However, as currently available information is limited, surveillance should be continued after the market launch, and the obtained information should be appropriately provided to healthcare professionals. This conclusion will be finalized, taking account of comments from the Expert Discussion.

4.(iii).B.(2).1) Safety profile

Table 16 lists the incidence of adverse events and adverse drug reactions in Study I4L-MC-ABEB (52-week treatment) and Study I4L-MC-ABEC (24-week treatment). The applicant explained that the incidence of adverse events, adverse drug reactions, death, serious adverse events, and adverse events resulting in discontinuation of study did not differ substantially between the IG-BS group and the reference biological product group.

Table 16. Incidence of adverse events in Studies I4L-MC-ABEB and I4L-MC-ABEC (FAS)

	I4L-MC-ABEB 52-week treatment		I4L-MC-ABEC 24-week treatment	
	IG-BS (n = 268)	Reference biological product (n = 267)	IG-BS (n = 376)	Reference biological product (n = 380)
All adverse events	167 (62.3)	166 (62.2)	196 (52.1)	184 (48.4)
Adverse drug reactions	17 (6.3)	14 (5.2)	26 (6.9)	23 (6.1)
Death	0	1 (0.4)	1 (0.3)	1 (0.3)
Serious adverse events	20 (7.5)	24 (9.0)	15 (4.0)	18 (4.7)
Adverse events resulting in study discontinuation	2 (0.7)	6 (2.2)	6 (1.6)	11 (2.9)

The applicant explained about the safety of IG-BS in Japanese patients that the incidence of adverse events, adverse drug reactions, death, serious adverse events, and adverse events resulting in study discontinuation did not differ between the Japanese subpopulation and the entire study population in Study I4L-MC-ABEB [see "4.(iii).A.(1) Multi-regional phase III clinical study in type 1 diabetes mellitus"].

PMDA confirmed that the results of Studies I4L-MC-ABEB and I4L-MC-ABEC do not indicate any substantial difference in the incidence of adverse events between IG-BS and the reference biological product, and concluded that there is no substantial difference between the 2 products in terms of safety profile.

The number of Japanese patients who were assessed for the safety of IG-BS was small, therefore limiting the comparison of the safety profile of IG-BS between Japanese and non-Japanese patients. Nevertheless, no substantial difference was observed in terms of safety profile of IG-BS between the Japanese subpopulation and the entire study population. PMDA decided that IG-BS would be tolerable in Japanese patients.

4.(iii).B.(2).2) Hypoglycaemia

(a) Patients with type 1 diabetes mellitus

The applicant explained about the occurrence of hypoglycaemia associated with the use of IG-BS in patients with type 1 diabetes mellitus as follows:

During the entire treatment period in Study I4L-MC-ABEB, hypoglycaemia (overall hypoglycaemic events)[23] was reported by 256 of 268 patients (95.5%) in the IG-BS group and by 259 of 267 patients (97.0%) in the reference biological product group in the entire study population. The corresponding figures for severe hypoglycaemia[24] were 10 of 268 patients (3.7%) in the IG-BS group and 11 of 267 patients (4.1%) in the reference biological product group. Of the severe hypoglycaemia, those observed

[23]Severe hypoglycaemia, symptomatic hypoglycaemia with a blood glucose level of ≤70 mg/dL, asymptomatic hypoglycaemia with a blood glucose level of ≤70 mg/dL, symptomatic hypoglycaemia without blood glucose measurement, and other hypoglycaemia with a blood glucose level of ≤70 mg/dL. [24]Hypoglycaemia that requires another person for assistance during the administration of carbohydrate, glucagon, or other resuscitative actions.

[24]Hypoglycaemia that requires another person for assistance during the administration of carbohydrate, glucagon, or other resuscitative actions.

in 5 of 268 patients (1.9%) in the IG-BS group and 6 of 267 patients (2.2%) in the reference biological product group were major hypoglycaemia (blood glucose level, <54/mg/dL). More than half of the cases of severe hypoglycaemia developed during the day[25] (8 patients in the IG-BS group and 8 patients in the reference biological product group).

In the Japanese subpopulation, hypoglycaemia (overall hypoglycaemic events) developed in 48 of 49 patients (98.0%) in the IG-BS group and 49 of 51 patients (96.1%) in the reference biological product group, and severe hypoglycaemia developed in 2 of 49 patients (4.1%) in the IG-BS group and 4 of 51 patients (7.8%) in the reference biological product group. Of them, severe hypoglycaemia observed in 2 patients (3.9%) in the reference biological product group were major hypoglycaemia with a blood glucose level of <54 mg/dL. In the IG-BS group, severe hypoglycaemia developed in 1 patient at night[26], and in 1 patient during the day.

Table 17 lists the mean number of hypoglycaemic events per patient-year by category of hypoglycaemia occurring during the treatment period in Study I4L-MC-ABEB*.

The incidence and mean number of events of any categories of hypoglycaemia did not differ clearly between the IG-BS and the reference biological product group in the entire study population or the Japanese subpopulation.

[25]From waking up to bedtime
[26]From bedtime to waking up
*Added when preparing Review Report (2): The GCP inspection revealed that a case of hypoglycaemia had not been included in the case report form for the relevant patient. Although the omission of this case affects the mean number of events (37.05 events/year) of symptomatic hypoglycaemia with a blood glucose level of ≤70 mg/dL in Japanese patients in the IG-BS group, PMDA determined that the final efficacy and safety assessment is not affected by this discrepancy. When this case is included, the mean number of events increases by approximately 0.02 events/year (See "II.5. Others" of the Review Report (2)).

Table 17. Mean number of hypoglycaemic events per patient-year in Study I4L-MC-ABEB (FAS)

Category	Entire study population		Japanese subpopulation	
	IG-BS (n = 268)	Reference biological product (n = 267)	IG-BS (n = 49)	Reference biological product (n = 51)
Severe hypoglycaemia				
BG ≤70mg/dL	0.02 (0.15)	0.04 (0.26)	0.02 (0.14)	0.05 (0.28)
BG <54mg/dL	0.02 (0.14)	0.04 (0.26)	0	0.05 (0.28)
No BG measurements	0.05 (0.44)	0.04 (0.32)	0.04 (0.29)	0.08 (0.33)
Severe symptoms and BG >70 mg/dL*1	0	0	0	0
Nocturnal hypoglycaemia				
BG ≤70mg/dL	16.08 (20.18)	17.25 (19.53)	14.40 (23.38)	10.43 (17.91)
BG <54mg/dL	6.21 (10.68)	6.07 (8.66)	4.60 (10.05)	2.67 (4.20)
Symptomatic hypoglycaemia*2				
BG ≤70mg/dL	46.74 (51.34)	51.98 (62.13)	37.05 (51.83)	48.11 (73.33)
BG <54mg/dL	17.08 (22.97)	18.54 (27.82)	11.58 (19.85)	17.34 (32.73)
Asymptomatic hypoglycaemia*3				
BG ≤70mg/dL	27.49 (42.96)	24.98 (38.44)	36.04 (47.51)	33.10 (53.60)
BG <54mg/dL	5.90 (16.12)	4.95 (14.33)	6.53 (11.27)	6.87 (21.24)

Mean number of events/year (standard deviation)
BG, blood glucose
*1, Cases of severe symptoms with a blood glucose level of >70 mg/dL, which does not explain the severe symptoms.
*2, Events with typical hypoglycaemic symptoms
*3, Events without typical hypoglycaemic symptoms

(b) Patients with type 2 diabetes mellitus

The applicant explained about the occurrence of hypoglycaemia associated with the use of IG-BS in patients with type 2 diabetes mellitus as follows:

The number of patients reported hypoglycaemia (overall hypoglycaemic events) during the treatment period in Study I4L-MC-ABEC was 296 of 373 patients (79.4%) in the IG-BS group and 292 of 376 patients (77.7%) in the reference biological product group in the entire study population. The corresponding figures for severe hypoglycaemia were 2 of 373 patients (0.5%) in the IG-BS group and 2 of 376 patients (0.5%) in the reference biological product group. Among patients with severe hypoglycaemia, those observed in 1 of 373 patients (0.3%) in the IG-BS group and 1 of 376 patients (0.3%) in the reference biological product group were major hypoglycaemia (blood glucose level, <54/mg/dL). Severe hypoglycaemia developed at night in 1 patient in the IG-BS group, and during the day in 1 patient in the IG-BS group and 2 patients in the reference biological product group.

Table 18 lists the mean number of hypoglycaemic events per patient-year by category of hypoglycaemia during the treatment period in Study I4L-MC-ABEC.

The incidence and mean number of events of any categories of hypoglycaemia did not differ clearly between the IG-BS group and the reference biological product group.

Table 18. Mean number of hypoglycaemic events per patient-year in Study I4L-MC-ABEC (FAS)

Category	IG-BS (n = 373)	Reference biological product (n = 376)
Severe hypoglycaemia		
BG ≤70mg/dL	0.03 (0.66)	0.01 (0.16)
BG < 54mg/dL	0.01 (0.22)	0.01 (0.11)
No BG measurements	0.01 (0.11)	0
Severe symptoms and BG >70 mg/dL	0	0
Nocturnal hypoglycaemia		
BG ≤70 mg/dL	7.46 (11.73)	8.08 (14.62)
BG <54 mg/dL	1.48 (3.53)	1.57 (4.39)
Symptomatic hypoglycaemia		
BG ≤70 mg/dL	10.63 (17.71)	10.52 (17.12)
BG <54 mg/dL	2.29 (5.27)	2.32 (5.36)
Asymptomatic hypoglycaemia		
BG ≤70 mg/dL	9.76 (14.65)	10.86 (17.20)
BG <54 mg/dL	0.78 (2.69)	1.13 (4.72)

Mean number of events/year (standard deviation)

On the basis of the profile of hypoglycaemic events in Studies I4L-MC-ABEB and I4L-MC-ABEC, PMDA concluded that IG-BS and the reference biological product do not differ substantially in terms of hypoglycaemic risk in patients with type 1 and type 2 diabetes mellitus.

4.(iii).B.(2).3) Allergy-related adverse events

The applicant explained about the occurrence of allergy-related adverse events associated with the use of IG-BS as follows:

In the entire study population of Study I4L-MC-ABEB, allergy-related adverse events were observed in 20 of 268 patients (7.5%) in the IG-BS group (arthralgia, injection site reaction, and pruritus [3 patients each], rash [2 patients], injection site injuration, allergic respiratory symptom, arthritis, dermatitis allergic, photosensitivity reaction, injection site nodule, local swelling, drug hypersensitivity, and asthma [1 patient each]); and in 11 of 267 patients (4.1%) in the reference biological product group (arthralgia [5 patients], rash and injection-site reaction [2 patients each], and pruritus, urticaria, and hypersensitivity [1 patient each]). In the Japanese subpopulation, allergy-related adverse events developed in 7 of 49 patients (14.3%) in the IG-BS group (rash [2 patients], and arthralgia, injection-site reaction, pruritus, injection site induration, and allergic respiratory symptom [1 patient each]), and in 2 of 51 patients (3.9%) in the reference biological product group, both of whom experienced arthralgia. Although the incidence of allergy-related adverse events was higher in the IG-BS group than in the reference biological product group both in the entire study population and the Japanese subpopulation, the differences were not substantial. Although 1 patient in the IG-BS group experienced severe injection-site reaction, and a causal relationship between the study drug and the event was not ruled out, other events were mild or moderate in severity. None were severe adverse events or those resulting in study discontinuation.

In Study I4L-MC-ABEC, allergy-related adverse events developed in 21 of 376 patients (5.6%) in the IG-BS group, consisting of arthralgia (7 patients), pruritus (4 patients), rash and injection-site reaction (3 patients each), asthma (2 patients), and angioedema, injection site pruritus, injection site induration,

and nasal oedema (1 patient each); and in 27 of 380 patients (7.1%) in the reference biological product group, consisting of arthralgia (8 patients), asthma (5 patients), pruritus (4 patients), rash and injection-site reaction (3 patients each), dermatitis (2 patients), and rash macular, rash papular, rash pruritic, rash vesicular, periarthritis, and injection site pruritus (1 patient each). No substantial difference in the incidence of allergy-related adverse events was observed between the IG-BS and the reference biological product group. Most adverse events were mild or moderate in severity, and no adverse events resulted in study discontinuation. Serious adverse events observed in this study was severe asthma experienced by 1 patient in the IG-BS group, but a causal relationship of the event to the study drug was ruled out.

The applicant explained that these findings do not suggest any difference in safety in terms of allergic-related events between IG-BS and the reference biological product.

PMDA considers as follows:
There is no substantial difference in the incidence of allergy-related adverse events between IG-BS and the reference biological product in clinical studies. The risk of shock and anaphylactoid reactions has been advised in the package insert for the reference biological product, and the similar precautions will also be included in the package insert for IG-BS. Therefore no additional precautions for the occurrence of allergic-related adverse events are considered necessary.

4.(iii).B.(2).4) Injection site reactions

The applicant explained about the occurrence of injection site-related adverse events associated with the use of IG-BS as follows:
In the entire study population of Study I4L-MC-ABEB, injection site-related adverse events[27] developed in 7 of 268 patients (2.6%) in the IG-BS group and in 3 of 267 patients (1.1%) in the reference biological product group. In the Japanese subpopulation, the corresponding adverse events developed in 2 of 49 patients (4.1%) in the IG-BS group, and none in the reference biological product group. One patient in the Japanese subpopulation experienced injection-related pain, pruritus, and rash, and the severity of these events were mild or moderate for pain and rash, and severe for pruritus. This patient is also described as the patient of severe injection-site reaction in the section of allergy-related adverse events. Another Japanese patient with injection-related adverse events experienced injection site induration, but did not have injection-related pain, pruritus, or rash. None of these patients experienced injection site abscess, nodule, lipoatrophy, lipohypertrophy, or induration.

In Study I4L-MC-ABEC, injection site-related adverse events[27] were observed in 13 of 376 patients (3.5%) in the IG-BS group, and 11 of 380 patients (2.9%) in the reference biological product group. The incidence of the events was similar between the 2 groups.

[27]For patients in whom injection site-related adverse events developed, a questionnaire was used to assess for pain, pruritus, and rash associated with injection, as well as the nature of injection-site adverse events (e.g., abscess, nodule, lipoatrophy, lipohypertrophy, and induration).

Based on the above results, it is considered that the incidence of injection site-related adverse events is low, and does not differ clearly between IG-BS and the reference biological product. Additionally, the nature and incidence of the events observed in the Japanese subpopulation in Study I4L-MC-ABEB are not considered clinically relevant.

PMDA confirmed that the incidence of injection site-related adverse events did not differ between the IG-BS group and the reference biological product group in clinical studies. However, since injection site reactions are 1 of the most important adverse events associated with the use of insulin products, PMDA considers that information on injection site reactions should continue to be collected via post-marketing surveillance.

4.(iii).B.(2).5) Anti-drug antibodies

The applicant explained the development of anti-drug antibodies associated with the use of IG-BS as follows:

As Tables 13 and 15 summarize the incidence of anti-drug antibodies in Studies I4L-MC-ABEB and I4L-MC-ABEC, respectively, the incidence did not differ substantially between IG-BS and the reference biological product, or between the Japanese subpopulation and the entire study population.

In order to investigate the effect of an increase in anti-drug antibody binding rate on the efficacy and safety of IG-BS, the applicant conducted the following study using treatment-emergent antibody response (TEAR)[28] and modified TEAR[29].

Table 19 summarizes the occurrence of TEAR and modified TEAR in the entire study population and the Japanese subpopulation in Study I4L-MC-ABEB. In the Japanese subpopulation, TEAR and modified TEAR tended to be observed more commonly in the IG-BS group than in the reference biological product group. In Study I4L-MC-ABEC, the incidence of TEAR and modified TEAR did not differ substantially between the IG-BS and the reference biological product groups: The number of patients with TEAR by week 24 was 22 of 365 (6.0%) in the IG-BS group vs. 20 of 365 (5.5%) in the reference biological product group and that throughout the treatment period was 45 of 365 (12.3%) vs. 34 of 365 (9.3%); the number of patients with modified TEAR by week 24 was 12 of 365 (3.3%) vs. 7 of 365 (1.9%), and that throughout the treatment period was 14 of 365 (3.8%) vs. 14 of 365 (3.8%).

An analysis was conducted to investigate relationships of the presence or absence of TEAR or modified TEAR at the time of final assessment[30] and throughout the treatment period with the profile of adverse events, incidence of hypoglycaemia, changes in Hb1Ac, basal insulin dose from baseline, and other

[28]TEAR was defined as a positive result for anti-drug antibodies during the study after the administration of the study drug in a patient with a negative result at baseline, or as an absolute increase by ≥1 percent point and a relative increase by ≥30% in antibody binding rate from baseline in a patient with a positive result at baseline.

[29]The definition of TEAR was modified by considering the variation of measurements around the quantification limit (antibody binding rate ≥0.26%). The modified TEAR is defined as an antibody binding rate of ≥1.26% during the study after the administration of the study drug in a patient with a negative result at baseline, or as an absolute increase by ≥1 percent point and a relative increase by ≥30% in antibody binding rate from baseline in a patient with a positive result at baseline.

[30]Week 52 in Study I4L-MC-ABEB and week 24 in Study I4L-MC-ABEC.

factors. As a result, no clear relationships with these factors were seen for Studies I4L-MC-ABEB and I4L-MC-ABEC.

Table 19. Occurrence of TEAR and modified TEAR in Study I4L-MC-ABEB (FAS, LOCF)

	Entire study population				Japanese subpopulation			
	TEAR		Modified TEAR		TEAR		Modified TEAR	
	IG-BS (n = 268)	Reference biological product (n = 267)	IG-BS (n = 268)	Reference biological product (n = 267)	IG-BS (n = 49)	Reference biological product (n = 51)	IG-BS (n = 49)	Reference biological product (n = 51)
Week 52	53/265 (20.0)	32/267 (12.0)	18/265 (6.8)	12/267 (4.5)	11/49 (22.4)	3/51 (5.9)	5/49 (10.2)	1/51 (2.0)
During treatment period*	82/265 (30.9)	69/267 (25.8)	29/265 (10.9)	25/267 (9.4)	13/49 (26.5)	12/51 (23.5)	8/49 (16.3)	1/51 (2.0)

No. of patients (%)
* Patients with occurrence of TEAR or modified TEAR at any time point after the administration of the study drug.

Among the Japanese subpopulation, 25 patients, i.e., 13 patients in the IG-BS group and 12 patients in the reference biological product group, experienced TEAR during Study I4L-MC-ABEB. Investigation of clinical laboratory results in these 25 patients revealed that 9 patients (5 patients in the IG-BS and 4 patients in the reference biological product group) had at least 1 laboratory abnormality, but these changes were not clinically relevant. Some of these 25 patients already had laboratory abnormality at baseline. In 14 patients who had TEAR at week 52 (11 patients in the IG-BS group and 3 patients in the reference biological product group), the occurrence of TEAR did not change substantially from baseline to week 52 in HbA1c, the number of hypoglycaemic events, or insulin doses (basal insulin, pre-meal insulin, and total insulin).

In the Japanese subpopulation, of the 25 patients who had experienced TEAR during the 52-week treatment period, 9 (8 in the IG-BS group and 1 in the reference biological product group) met the criteria of modified TEAR. None of the 9 patients had clinically significant adverse events, or changes in HbA1c and insulin doses.

PMDA considers as follows:
In the Japanese subpopulation, the incidence of TEAR and modified TEAR tended to be higher in the IG-BS group than in the reference biological product group, but findings do not suggest any relationships of TEAR or modified TEAR with the occurrence of adverse events or the efficacy of IG-BS. The currently available data do not indicate that the immunogenicity risk of IG-BS is higher than that of the reference biological product. However, as currently available information is limited, data on the immunogenicity of IG-BS should continue to be collected during the post-marketing surveillance. When new data on the immunogenicity of IG-BS become available, the applicant should investigate the effect of the new findings on the efficacy and safety of the drug, and appropriately provide relevant information to healthcare professionals, among other measures.

4.(iii).B.(2).6) Neoplasms
The applicant explained the risk of development of neoplasms among patients receiving IG-BS as follows:

A possible relationship between the use of insulin glargine products and the occurrence of malignant tumors has attracted attention since the results of a retrospective analysis of medical records of a German statutory health insurance fund were published.[31] In risk management plans for foreign insulin glargine products, neoplasms are classified as an "important potential risk", and clinical studies have been conducted to investigate the occurrence of neoplasms in patients using insulin glargine. However, the European Medicines Agency's Committee for Proprietary Medicinal Products (CHMP) has concluded that there is no clear evidence on a causal relationship between insulin glargine products and an increase in neoplasms. The U.S. Food and Drug Administration (FDA) has not concluded that insulin glargine may increase cancer risk.

In Studies I4L-MC-ABEB and I4L-MC-ABEC, adverse events related to neoplasms were experienced by 6 of 644 patients (0.9%) in the IG-BS group, who had squamous cell carcinoma, skin papilloma, adrenal adenoma, fibroadenoma of breast, lung adenocarcinoma, or lung carcinoma cell type unspecified recurrent (1 patient each), and by 8 of 647 patients (1.2%) in the reference biological product group, who had squamous cell carcinoma (2 patients), skin papilloma, bladder cancer, gliomatosis cerebri, refractory cytopenia with unilineage dysplasia, thyroid neoplasm, or uterine leiomyoma (1 patient each). A relationship between the event and the study drug was ruled out for all these events. Cases of bladder cancer, gliomatosis cerebri, lung adenocarcinoma, and lung carcinoma cell type unspecified recurrent were serious adverse events, and the outcome of lung adenocarcinoma was fatal. All cases other than bladder cancer resulted in study discontinuation.

The applicant will collect information on regulatory measures in and outside Japan, and the progress of clinical studies of the reference biological product and other insulin products.

PMDA considered as follows:
The non-clinical studies [see "3.(iii).B Outline of the review by PMDA")] and clinical studies of IG-BS revealed no findings suggesting a higher risk of neoplasms associated with IG-BS compared with the reference biological product. However, careful attention should be paid to further findings on neoplasms associated with the use of IG-BS, the reference biological product, and other insulin products.

4.(iii).B.(3) Indication and Dosage and Administration

The indication and the dosage and administration of the reference biological product are as follows:

[Indication]

Diabetes mellitus where treatment with insulin is required

[Dosage and administration]

Lantus cartridge for injection

The usual initial dosage for adults is 4 to 20 units of Insulin Glargine (Genetical Recombination) [Insulin Glargine Biosimilar 1] administered subcutaneously once daily using the dedicated pen-type injection

[31] *Diabetologia* 2009; 52: 1732-44

device. This drug may be used in combination with other insulin products. The drug may be administered either before breakfast or at bedtime but should be administered at the same time each day. The dose should be adjusted according to the patient's symptoms and test findings. The usual total insulin dose for maintenance therapy is 4 to 80 units/day if the drug is used with concomitant insulin products.
However, a higher dose than stated above may be used as needed.

Lantus Solostar for injection
The usual initial dosage for adults is 4 to 20 units of Insulin Glargine (Genetical Recombination) [Insulin Glargine Biosimilar 1] administered subcutaneously once daily. This drug may be used in combination with other insulin products. The drug may be administered either before breakfast or at bedtime but should be administered at the same time each day. The dose should be adjusted according to the patient's symptoms and test findings. The usual total insulin dose for maintenance therapy is 4 to 80 units/day if the drug is used with concomitant insulin products.
However, a higher dose than stated above may be used as needed.

PMDA's view on the indication and dosage and administration is as follows:
In this application, the comparability of IG-BS to the reference biological product in terms of blood glucose lowering effect was confirmed in the clinical pharmacology study where glucose infusion rate in subjects with a glucose clamp was used as the PD marker, and the mechanism of action by which insulin decreases blood glucose levels does not differ between the type 1 and type 2 diabetes mellitus. Accordingly, IG-BS is considered to be comparable in efficacy to the reference biological product when used at the same doses for the same indication.

The submitted clinical study data do not suggest any new safety problems as compared with the safety profile of the reference biological product. PMDA therefore determined that IG-BS is as tolerable as the reference biological product when used with proper procedures, such as adjusting the dose according to the symptoms and laboratory findings of the patient.

In the “Dosage and Administration” section of the package insert for the reference insulin glargine cartridge (Lantus Cartridge for Injection), it is stated that the dedicated pen-type injection device should be used to administer the drug. However, this information may be included in the “Precautions” section rather than the “Dosage and Administration” section for the IG-BS cartridge.

As a result of its regulatory review, PMDA has concluded that IG-BS may be approved for the same indication and dosage and administration as the reference biological product (Lantus Solostar For Injection). However, since only a limited number of Japanese subjects have received IG-BS, information on the safety and efficacy of IG-BS should continue to be collected in post-marketing surveillance and other opportunities. A final decision on the approval of IG-BS with the indication and dosage and administration identical to the reference biological product will be made, taking account of comments raised in the Expert Discussion.

4.(iii).B.(4) Post-marketing investigations

The applicant is planning to conduct a specified use-results survey on long-term treatment to assess the safety and efficacy of IG-BS in clinical settings. The survey will be conducted with an observation period of 1 year, a survey period of 3 years, and a target number of patients of 1000. The applicant intends to collect information from at least 100 patients with type 1 diabetes mellitus and at least 500 patients with type 2 diabetes mellitus. The applicant considers that the safety profile of IG-BS can be assessed in a total of 1000 patients in terms of hypoglycaemia and hypersensitivity reaction, which are specified as priority survey items, on the basis of the incidences the two events reported in the clinical studies. The safety and efficacy of IG-BS in pediatric patients will be assessed by analyzing a subgroup of pediatric patients to be enrolled in this survey.

PMDA considers as follows:

Since only a limited number of Japanese patients have received IG-BS, information on the safety and efficacy of IG-BS should continue to be collected after the market launch. Data on immunogenicity of IG-BS should be collected because the drug is a therapeutic protein. In particular, if a patient has experienced an adverse drug reaction or loss of efficacy suspected to be due to the development of anti-drug antibodies, the following should be performed: (i) collect detailed information regarding the patient; (ii) test the patient for anti-drug antibodies whenever possible; (iii) and appropriately provide the collected information to healthcare professionals [see “4.(iii).B.(2).5) Anti-drug antibodies”].

A final decision will be made on the detailed plan for the post-marketing surveillance (e.g., methods, target number of patients, and items to be investigated), taking account of comments raised in the Expert Discussion.

III. Results of Compliance Assessment Concerning the Data Submitted in the Regulatory Application and Conclusion by PMDA

1. PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

A document-based compliance inspection and data integrity assessment were conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the regulatory application. As a result, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

2. PMDA's conclusion on the results of GCP on-site inspection

GCP on-site inspection was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the regulatory application (5.3.5.1.1). As a result, PMDA concluded that the clinical studies were generally performed in compliance with GCP and there should be no problem with conducting a regulatory review based on the submitted application documents. In some of the medical institutions conducting clinical studies of IG-BS, the following point for improvement was

identified and communicated to the head of the relevant medical institutions, although it would not affect the assessment of the clinical studies as a whole.

Point for improvement

Medical institutions

- Protocol violation (some tests were not proven to have been conducted).

IV. Overall evaluation

Based on the submitted data, PMDA has concluded that the comparability between IG-BS and the reference biological product has been demonstrated, for the following reasons: (i) IG-BS and the reference biological product showed marked similarity in quality attributes; (ii) the non-clinical studies showed similar physiological activity for IG-BS and the reference biological product, suggesting similar toxicological profile for both products; (iii) the clinical pharmacology studies demonstrated pharmacokinetic comparability of IG-BS to the reference biological product; (iv) IG-BS and the reference biological product were confirmed to be comparable in terms of blood glucose lowering effect, which indicates comparable clinical efficacy of both products; (v) and the clinical studies in patients with type 1 and type 2 diabetes mellitus showed that the safety profile of IG-BS did not particularly differ from that of the reference biological product.

If the Expert Discussion concludes that there are no particular problems, IG-BS may be approved as a biosimilar to Lantus Cartridge for Injection and Lantus Solostar for injection.

Review Report (2)

October 7, 2014

I. Product Submitted for Registration

[Brand name]	Insulin Glargine BS Cartridge for Injection [Lilly], and Insulin Glargine BS Miriopen for Injection [Lilly]
[Non-proprietary name]	Insulin Glargine (Genetical Recombination) [Insulin Glargine Biosimilar 1][32]
[Applicant]	Eli Lilly Japan K.K.
[Date of application]	December 24, 2013

II. Content of the Review

The outline of the comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) is described in the following sections. The expert advisors for the Expert Discussion were nominated based on their declarations or other relevant information concerning the product submitted for registration, 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. Comparability of IG-BS to the reference biological product in terms of efficacy

Based on the data of pharmacodynamic comparability in a clinical pharmacology study (Study I4L-MC-ABEA) in healthy non-Japanese volunteers, the comparability of IG-BS to the reference biological product in terms of efficacy was evaluated. The results of Study I4L-MC-ABEA indicated that the IG-BS to the reference biological product ratios [95% confidence interval] of the least squares geometric means of the total glucose infused and maximum glucose infusion rate, the primary endpoints for pharmacodynamics, were within the pre-specified acceptable bioequivalence range. Changes over time in maximum glucose infusion rate after administration were similar between IG-BS and the reference biological product. PMDA concluded that IG-BS is comparable in efficacy to the reference biological product because both products were confirmed to be comparable in blood glucose lowering effect. PMDA also confirmed that the results of Study I4L-MC-ABEA are consistent with the efficacy results of a multi-regional phase III clinical study (Study I4L-MC-ABEB) in Japanese and non-Japanese patients with type 1 diabetes mellitus.

The above conclusion of PMDA was supported by the expert advisors.

[32]The non-proprietary name was defined according to "Notification on Non-proprietary Names of Drugs" (PFSB/ELD Notification No. 0930-1, dated September 30, 2014).

2. Safety

PMDA confirmed that adverse event profiles do not differ substantially between IG-BS and the reference biological product based on the results of Study I4L-MC-ABEB and a multi-regional phase III clinical study (Study I4L-MC-ABEC) in non-Japanese patients with type 2 diabetes mellitus. In addition, adverse event profiles did not differ substantially between the entire patient population and the Japanese subpopulation in Study I4L-MC-ABEB. Based on these findings, PMDA concluded that IG-BS is tolerable regarding safety.

In the Japanese subpopulation of Study I4L-MC-ABEB, an increase in anti-drug antibody binding rate was observed more commonly in the IG-BS group than in the reference biological product group [see "4.(iii).B.(2).5) Anti-drug antibodies"]. However, there were no findings suggesting a relationship of this result and adverse event profiles or efficacy. Therefore, at present, IG-BS is not considered to have a higher immunogenicity risk than the reference biological product. Since currently available information is limited, surveillance should be continued after the market launch, appropriate measures should be taken based on newly available information, and the information should be appropriately provided to healthcare professionals.

The above conclusion of PMDA was supported by the expert advisors.

3. Indication and dosage and administrations

The comparability of IG-BS to the reference biological product in terms of blood glucose lowering effect was confirmed in a clinical pharmacology study, and the mechanism of action by which insulin reduces blood glucose levels dose not differ between type 1 and type 2 diabetes mellitus. IG-BS was therefore judged to be comparable in efficacy to the reference biological product when used at the same doses for the same indication. The clinical studies of IG-BS showed that the safety profile of IG-BS did not differ substantially from that of the reference biological product, revealing no new findings requiring attention. PMDA thus determined that IG-BS is as tolerable as the reference biological product in terms of safety when used with proper procedures, such as adjusting the dose according to the symptoms and laboratory findings of the patient.

Based on these results, PMDA determined that IG-BS may be approved for the same indication and the dosage and administration as the reference biological product (Lantus Solostar for injection).

The above conclusion of PMDA was supported by the expert advisors.

4. Risk management plan (draft)

At the Expert Discussion over the draft risk management plan submitted by the applicant, it was concluded that injection site reactions should be added as an important identified risk, and should be investigated as a priority survey item during the post-marketing surveillance, since injection site

reactions are one of the most important adverse events associated with insulin products and some of these events may not be assessed within the category of hypersensitivity reactions.

PMDA requested the applicant to take appropriate measures for the above points. The applicant revised the risk management plan (draft) and the specified drug use-results survey plan (draft), then submitted the outlines of the revised plans (Tables 20, 21, and 22), which were judged by PMDA to be appropriate.

Table 20. Safety and efficacy specifications in the risk management plan (draft)

Safety Specifications		
Important identified risks	Important potential risks	Important missing information
・ Hypoglycaemia ・ Hypersensitivity reactions ・ Injection site reactions	・ Errors in administration (using a wrong insulin product) ・ Neoplasms ・ Effects of the production of anti-insulin glargine antibodies	・ None
Efficacy Specifications		
・ Efficacy in clinical settings		

Table 21. Outline of additional pharmacovigilance activities and additional risk minimization activities in the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
・ Drug use-results survey*	・ Preparation and provision of patient guide

* See Table 22.

Table 22. Outline of post-marketing surveillance plan (draft)

Survey	Specified drug use-results survey
Purpose	Assess the long-term safety profile of IG-BS in diabetic patients in Japan, including those with type 1 diabetes and type 2 diabetes, in the clinical setting.
Method	Central registry system
Observation period	3 years (registration period, 2 years)
Population	Patients with diabetes mellitus
Target sample size	1000 patients (including at least 100 patients with type 1 diabetes and at least 500 patients with type 2 diabetes)
Priority survey items	Hypoglycaemia, hypersensitivity reactions, injection site reactions

5. Others

The GCP on-site inspection for the data submitted in the regulatory application (5.3.5.1.1) revealed inconsistencies[33] between the source document (patient diary) and case report forms in 3 patients. One of these inconsistencies was the omission of an event of “hypoglycaemia” occurring in a patient from the patient’s case report form. This causes a discrepancy in the mean number of symptomatic hypoglycaemia with a blood glucose level of ≤70 mg/dL reported in patients receiving IG-BS, as shown in Table 17 of the Review Report (1)[34]. However, the event of hypoglycaemia was not severe and this inconsistency has only a limited impact on the calculation of the mean number of hypoglycaemia.

[33]In the first patient, a result of 7-point blood glucose monitoring reported at the 7th visit were wrongly recorded in the case report form (the value was 151 mg/dL in the case report form but 131 mg/dL in the source document). In the second patient, an episode of hypoglycaemia, which was not severe, reported by a patient at the 5th visit was not recorded in the case report form. In the third patient, some results of 7-point blood glucose monitoring reported at the 9th visit were not recorded in the case report form (data for 1 day among the data for 3 days) and the dose of basal insulin reported at the 10th visit was inconsistent between the case report form (34 units) and the source document (8 units).

[34]In Table 17 of the Review Report (1), when this case of omission is included, the mean number of symptomatic hypoglycaemia with a blood glucose level of ≤70 mg/dL in the IG-BS group in the Japanese subpopulation increases by approximately 0.02 events/year from 37.05 events/year.

PMDA therefore concluded that the final efficacy and safety assessment is not affected by this inconsistency.

In one patient, the results of 7-point blood glucose monitoring were inconsistent between the case report form and the source documents. In another patient, the results of 7-point blood glucose monitoring were omitted from the case report form. In another patient, inconsistencies were found in the records of basal insulin doses. Nevertheless, these inconsistencies do not affect the final evaluation of the efficacy and safety of IG-BS, because these were inconsistencies or omissions at limited time points, and do not significantly affect overall results.

The mean numbers of hypoglycaemic events in Table 17 of the Review Report (1) reflect the data submitted at the time of application.

III. Overall Evaluation

As a result of its review, PMDA has concluded that IG-BS may be approved for the indication and the dosage and administration as shown below, with the following conditions. The drug substance and the drug product are both classified as powerful drugs, and the product is not classified as a biological product.

[Indication]
Treatment of diabetes mellitus where treatment with insulin is required

[Dosage and administration]
The usual initial dosage for adults is 4 to 20 units of Insulin Glargine (Genetical Recombination) [Insulin Glargine Biosimilar 1] administered subcutaneously once daily. This drug may be used in combination with other insulin products. The drug may be administered either before breakfast or at bedtime but should be administered at the same time each day. The dose should be adjusted according to the patient's symptoms and test findings. The usual total insulin dose for maintenance therapy is 4 to 80 units/day if the drug is used with concomitant insulin products.
However, a higher dose than stated above may be used as needed.

[Conditions for approval]
The applicant is required to develop a risk management plan and implement it appropriately.