Review Report

November 10, 2015

Pharmaceuticals and Medical Devices Agency

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

[Brand name]	Suiny Tab. 100 mg
[Non-proprietary name]	Anagliptin (JAN*)
[Applicant]	Sanwa Kagaku Kenkyusho Co., Ltd.
[Date of application]	February 4, 2015
[Dosage form/Strength]	Each tablet contains 100 mg of Anagliptin.
[Application classification]	Prescription drug (4) Drug with a new indication
[Items warranting special mention]	None
[Reviewing office]	Office of New Drug I

**Japanese Accepted Name (modified INN)*

Review Results

November 10, 2015

[Brand name]	Suiny Tab. 100 mg
[Non-proprietary name]	Anagliptin
[Applicant]	Sanwa Kagaku Kenkyusho Co., Ltd.
[Date of application]	February 4, 2015

[Results of review]
Based on the submitted data, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the efficacy of the product in the treatment of patients with type 2 diabetes mellitus has been demonstrated and its safety is acceptable in view of its observed benefits.

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

[Indication]	Type 2 diabetes mellitus
[Dosage and administration]	The usual adult dosage is 100 mg of anagliptin orally administered twice daily (morning and evening). If the clinical response is not adequate, the dose may be increased up to 200 mg only when the patient's clinical course is closely monitored. (Not changed)
[Condition for approval]	The applicant is required to develop and appropriately implement a risk management plan.

Review Report (1)

October 2, 2015

I. Product Submitted for Registration

[Brand name]	Suiny Tab. 100 mg
[Non-proprietary name]	Anagliptin
[Name of applicant]	Sanwa Kagaku Kenkyusho Co., Ltd.
[Date of application]	February 4, 2015
[Dosage form/Strength]	Each tablet contains 100 mg of Anagliptin.
[Proposed indication]	Type 2 diabetes mellitus Anagliptin should be used only in patients who have not adequately responded to one of the following treatments: (a) Diet and/or exercise therapy alone (b) Use of α-glucosidase inhibitor in addition to diet and/or exercise therapy (c) Use of biguanide in addition to diet and/or exercise therapy (d) Use of sulfonylurea in addition to diet and/or exercise therapy (e) Use of thiazolidinediones in addition to diet and/or exercise therapy (Underline denotes deletion.[1])
[Proposed dosage and administration]	The usual adult dosage is 100 mg of anagliptin orally administered twice daily (morning and evening). If the clinical response is not adequate, the dose may be increased up to 200 mg only when the patient's clinical course is closely monitored. (Not changed)

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

The data submitted in this application and the outline of a review by the Pharmaceuticals and Medical Devices Agency (PMDA) are as shown below. Since this application has been filed for approval of the new indication, "Data relating to quality" have not been submitted. No new "Non-clinical data" have been submitted with the consideration that the data previously submitted to support the approved indications can be used for the review of the application.

1. Origin or history of discovery, use in foreign countries, and other information

Suiny Tab. 100 mg contains anagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, as the active ingredient. The product was approved in September 2012 for the indication of "Type 2 diabetes mellitus. The product should be used only in patients who have not adequately responded to one of the following treatments: (a) Diet and/or exercise therapy alone, (b) use of α-glucosidase inhibitor in addition to diet and/or exercise therapy, (c) use of biguanide in addition to diet and/or exercise therapy, (d) use of sulfonylurea in addition to diet and/or exercise therapy, or (e) use of thiazolidinediones in addition to diet and/or exercise therapy."

Based on the results from Japanese long-term studies of combination therapies, the applicant has now submitted a partial change approval application with the aim of changing the indication of the product to "type 2 diabetes mellitus."

[1] In light of the Guideline for Clinical Evaluation of Oral Hypoglycemic Agents (PFSB/ELD Notification No. 0709-1 dated July 9, 2010), the applicant conducted a long-term clinical study of the product in combination with the approved oral hypoglycemic agents (rapid-acting insulin secretagogues) expected to be concomitantly administered to patients in current clinical settings. The applicant has submitted a partial change approval application, considering that the data from this clinical study and from the studies conducted for the approved indication could support the proposed change of the indication of anagliptin to "type 2 diabetes mellitus."

[redacted].

2. Clinical data

2.(i) Summary of biopharmaceutic studies and associated analytical methods

No new data have been submitted.

2.(ii) Summary of clinical pharmacology studies

No new data have been submitted.

2.(iii) Summary of clinical efficacy and safety

2.(iii).A Summary of the submitted data

The evaluation data submitted by the applicant were the results from a phase III study of anagliptin in combination with a short-acting insulin secretagogue (glinide) (Study DP1007) and a phase III study of anagliptin in combination with insulin (Study DP1008) as well as data from Japanese clinical studies (Studies DP1001, DP1003, SK-0403-01, DP1002, and SK-0403-02) that had been subjected to the review for registration of the product. HbA1c is expressed as NGSP values for Studies DP1007 and DP1008, and as JDS values for Japanese clinical studies that had been subjected to the review for registration of the product.

2.(iii).A.(1) Phase III study of anagliptin in combination with glinide (5.3.5.2-1, Study DP1007 [[redacted] to [redacted]])

An open-label, uncontrolled study was conducted to evaluate the safety and efficacy of anagliptin in combination with glinide in Japanese patients with type 2 diabetes mellitus with inadequate glycemic control on glinide in addition to diet and exercise therapies[2] (target sample size, 60 subjects).

This study consisted of a run-in period (2-6 weeks) and a treatment period (52 weeks).

In the treatment period, anagliptin 100 mg was administered orally twice daily (200 mg/day) before morning and evening meals. Beginning at Week 28 of treatment, the dose escalation was allowed based on the HbA1c levels measured every 4 weeks from Week 24 to Week 36. The dose was increased to 200 mg twice daily (400 mg/day) in subjects who had HbA1c ≥6.9%. The dosing regimen of concomitant glinide had to remain unchanged for 8 weeks before the start of the run-in period and throughout the study period.

All of the 63 treated subjects were included in the safety analysis set and the Full Analysis Set (FAS). The FAS was used for the efficacy analysis. Two subjects discontinued the study (due to subject's request). A total of 46 subjects had their dose increased beginning at Week 28.

The primary efficacy endpoint was the change in HbA1c from baseline (Week 0) to the end of the study (Week 52 or discontinuation) in the FAS. The results are shown in Table 1. The secondary endpoint was the time-course changes in HbA1c from baseline to Week 52. The results are shown in Figure 1.

Table 1. Change in HbA1c from baseline to the end of the study (Study DP1007 [combination with glinide], FAS)

Baseline	At the end of the study	Change at the end of the study	95% confidence interval (CI) of the change at the end of the study
8.14 ± 0.93 (n = 63)	7.27 ± 0.75 (n = 63)	−0.87 ± 0.71 (n = 63)	[−1.05, −0.69]

Unit, %; mean ± standard deviation (SD); missing data were imputed with Last Observation Carried Forward (LOCF).

[2] Key inclusion criteria: Patients with type 2 diabetes mellitus aged ≥20 years on diet or diet/exercise therapy who had HbA1c of ≥6.9% and <10.5% in the run-in period (2-6 weeks prior to baseline), and who was on a stable regimen of glinide for 8 weeks prior to the start of the run-in period.

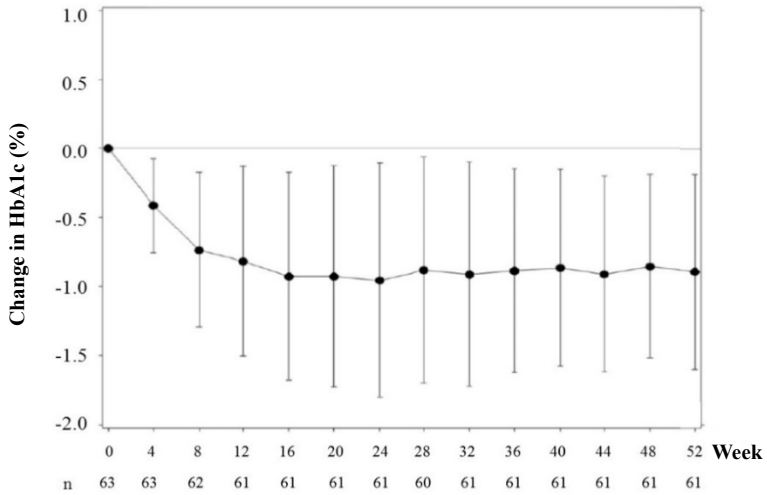

Figure 1. Time-course changes in HbA1c from the start of treatment with anagliptin to the end of the study
(Study DP1007 [combination with glinide], FAS) (mean ± SD)

Table 2 shows the analysis results of other secondary endpoints. The proportion of subjects who achieved HbA1c <7.0% at the end of the study was 42.9% (27 of 63 subjects).

Table 2. Analysis results of other secondary endpoints
(Study DP1007 [combination with glinide], FAS)

Endpoint	Baseline	At the end of the study	Change at the end of the study	95% CI of the change at the end of the study
Fasting blood glucose (mg/dL)[a)]	168.2 ± 37.1 (n = 63)	150.3 ± 40.2 (n = 63)	−17.9 ± 28.9 (n = 63)	[−25.2, −10.7]
2-hour postprandial blood glucose (mg/dL)	222.5 ± 61.5 (n = 63)	197.3 ± 47.4 (n = 62)	−23.7 ± 41.2 (n = 62)	[−34.1, −13.2]
Postprandial blood glucose AUC (mg·h/dL)	419.2 ± 95.5 (n = 63)	359.9 ± 70.6 (n = 62)	−55.9 ± 66.8 (n = 62)	[−72.9, −38.9]

Mean ± SD
a) Missing data were imputed with LOCF.

Safety analysis was performed. The incidence of adverse events was 69.8% (44 of 63 subjects) and the incidence of adverse events for which a causal relationship to the study drug could not be ruled out (adverse drug reactions) was 27.0% (17 of 63 subjects). Table 3 shows adverse events and/or adverse drug reactions reported in ≥3% of subjects.

Table 3. Adverse events and/or adverse drug reactions reported in ≥3% of subjects
(Study DP1007 [combination with glinide], safety analysis set)

Adverse event term	Adverse event (n = 63)	Adverse drug reaction (n = 63)
Diabetic retinopathy	3.2 (2)	0.0 (0)
Constipation	3.2 (2)	1.6 (1)
Diarrhoea	3.2 (2)	3.2 (2)
Gastrooesophageal reflux disease	4.8 (3)	0.0 (0)
Large intestine polyp	3.2 (2)	1.6 (1)
Bronchitis	6.3 (4)	0.0 (0)
Herpes zoster	3.2 (2)	1.6 (1)
Nasopharyngitis	15.9 (10)	0.0 (0)
Pharyngitis	4.8 (3)	0.0 (0)
Oral herpes	3.2 (2)	0.0 (0)
Blood creatine phosphokinase increased	4.8 (3)	0.0 (0)
Blood creatinine increased	3.2 (2)	1.6 (1)
Hypoglycaemia	9.5 (6)	9.5 (6)
Back pain	4.8 (3)	0.0 (0)
Carpal tunnel syndrome	3.2 (2)	1.6 (1)
Diabetic neuropathy	3.2 (2)	0.0 (0)
Dizziness	3.2 (2)	1.6 (1)
Headache	4.8 (3)	0.0 (0)
Upper respiratory tract inflammation	7.9 (5)	0.0 (0)
Hyperkeratosis	3.2 (2)	1.6 (1)

Incidence % (number of subjects with events), MedDRA/J ver. 16.0

No deaths were reported. Four serious adverse events were reported in 4 subjects (bile duct stone in 1, pyelonephritis in 1, large intestine polyp in 1, and ankle fracture in 1), but a causal relationship to the study drug was ruled out for all events. There were no adverse events leading to study drug discontinuation. Six events of hypoglycaemia were reported in 6 subjects; all were considered adverse drug reactions, but were mild in severity. No clinically meaningful changes were observed in laboratory parameters, vital signs, body weight, or 12-lead electrocardiogram (ECG).

2.(iii).A.(2) Phase III study of anagliptin in combination with insulin (5.3.5.1-1, Study DP1008 [[redacted] to [redacted]])

A placebo-controlled, randomized, double-blind, parallel-group study (Treatment Period I) and an open-label study (Treatment Period II) were conducted to evaluate the efficacy and safety of anagliptin in combination with insulin in Japanese patients with type 2 diabetes mellitus with inadequate glycemic control on insulin in addition to diet and exercise therapies[3] (target sample size, 120 subjects [60 per group]).

This study consisted of a run-in period (2-6 weeks) and 2 treatment periods (Treatment Period I [12 weeks] and Treatment Period II [40 weeks]).

Anagliptin 100 mg or placebo was administered orally twice daily (200 mg/day) before morning and evening meals for 12 weeks in Treatment Period I. In Treatment Period II, anagliptin 100 mg was administered orally twice daily (200 mg/day) before morning and evening meals for 40 weeks (hereinafter, "continued anagliptin group" refers to the subjects who continued to receive anagliptin for 52 weeks and "placebo/anagliptin group" refers to the subjects who received placebo in the double-blind period and anagliptin in the open-label period). Beginning at Week 28 of treatment, the dose escalation was allowed based on the HbA1c levels measured every 4 weeks from Week 24 to Week 36. The dose was increased to 200 mg twice daily (400 mg/day) in subjects who had HbA1c ≥7.0%. The dose of concomitant insulin was not to be changed during the run-in period and unless the criteria for dose reduction[4] (rescue treatment) were met, but in Treatment Period II, dose reduction or increase was allowed at the discretion of the investigator or the sub-investigator.

All of the 123 subjects treated during Treatment Period I (61 in the placebo group, 62 in the anagliptin group) were included in the safety analysis set; of these, 1 in the placebo group (subject with no laboratory data) and 1 in the anagliptin group (subject with no laboratory data) were excluded from the analysis. The remaining 121 subjects were included in the FAS, which was used for the efficacy analysis. A total of 119 subjects (58 in the placebo group, 61 in the anagliptin group) completed Treatment Period I1. Of these, 112 subjects (56 in the placebo/anagliptin group, 56 in the continued anagliptin group) completed Treatment Period II. A total of 4 subjects discontinued the study during Treatment Period I; 3 were in the placebo group (all due to adverse events) and 1 was in the anagliptin group (due to adverse event). A total of 7 subjects discontinued the study during Treatment Period II, out of which 2 were in the placebo/anagliptin group (1 due to adverse event, 1 due to adverse event and meeting withdrawal criteria) and 5 were in the continued anagliptin group (4 due to adverse events, 1 due to adverse event and subject's request). A total of 82 subjects (37 in the placebo/anagliptin group, 45 in the continued anagliptin group) had their dose increased beginning at Week 28.

The primary efficacy endpoint was the change in HbA1c from baseline (Week 0) to the last assessment of Treatment Period I (Week 12 or discontinuation) in the FAS. The results are shown in Table 4, demonstrating the superiority of anagliptin over placebo.

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[3] Key inclusion criteria: Patients with type 2 diabetes mellitus aged ≥20 years who were on a stable regimen of insulin (≤40 units/day, ≤2 agents) for 8 weeks prior to the start of the run-in period and who had HbA1c of ≥7.0% and <11.0% and fasting serum C-peptide of ≥0.6 ng/mL in the run-in period (2-6 weeks prior to baseline). Only one α-glucosidase inhibitor or biguanide was permitted as concomitant oral hypoglycemic agent, and the type of the oral hypoglycemic agent and dosing regimen were expected to remain consistent throughout the run-in and treatment periods.

[4] Dose reduction criteria: In a subject meeting either 1) or 2) below, the dose of insulin for the run-in period and Treatment Period I was allowed to be reduced by 1 to 4 units/day until it was determined that the subject had no risk of developing hypoglycaemia. The dose was allowed to be increased for subjects whose glycemic control worsened after the dose reduction, as long as it did not exceed the initial dose.

(1) Exhibiting hypoglycaemic symptoms with self-measured blood glucose level of <70 mg/dL, or is considered hypoglycaemia by the investigator or sub-investigator.

(2) Having self-measured blood glucose level of <80 mg/dL on ≥2 consecutive measurements and considered to be at high risk of developing hypoglycaemia by the investigator or sub-investigator.

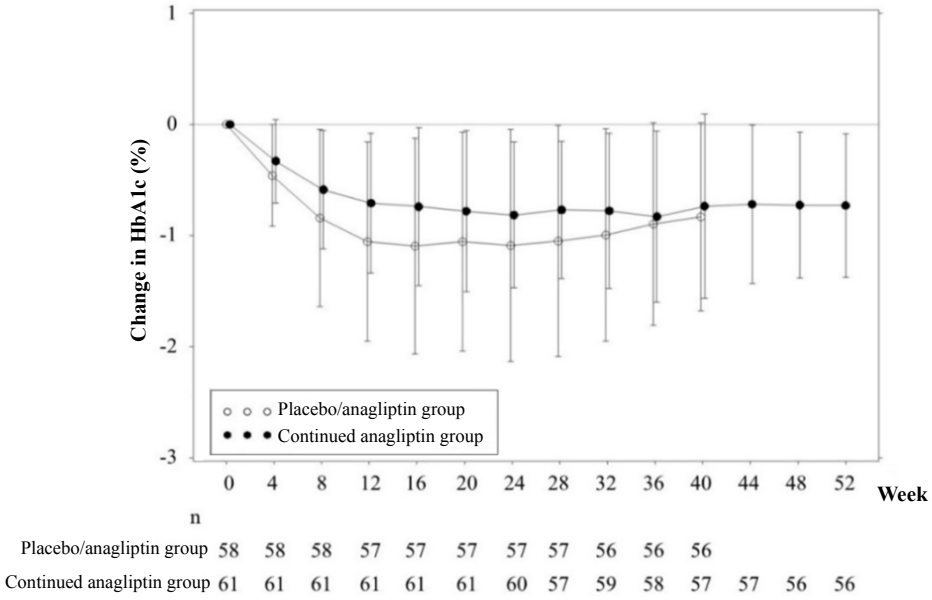
Table 4. Change in HbA1c from baseline to the last assessment of Treatment Period I (Study DP1008 [combination with insulin], FAS)

Treatment group	Baseline	At the last assessment	Change at the last assessment	Difference from placebo [95% CI][a)]
Placebo (n = 60)	8.21 ± 1.00	8.32 ± 1.29	0.11 ± 0.70	−0.82 [−1.06, −0.58]
Anagliptin (n = 61)	8.33 ± 0.90	7.62 ± 0.90	−0.71 ± 0.63	

Unit, %; mean ± SD; missing data were imputed with LOCF.

a) Adjusted mean calculated by analysis of variance (ANOVA) with the treatment group and presence/absence and type of oral hypoglycemic agents as explanatory variables and its 95% CI.

The secondary endpoint was the time-course changes in HbA1c from baseline or the start of treatment with anagliptin (Week 0 for the continued anagliptin group, Week 12 for the placebo/anagliptin group) to Week 52. The results are shown in Figure 2. The change (mean ± standard deviation [SD]) [95% CI] in HbA1c from baseline or the start of treatment with anagliptin to the last assessment (Week 52 or discontinuation) was −0.80% ± 0.85% [−1.02, −0.58] in the placebo/anagliptin group and −0.72% ± 0.64% [−0.89, −0.56] in the continued anagliptin group, showing a decrease in HbA1c from baseline or the start of treatment with anagliptin in both groups.



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Placebo/anagliptin group	58	58	58	57	57	57	57	57	56	56	56		
Continued anagliptin group	61	61	61	61	61	61	60	57	59	58	57	57	56	56

Figure 2. Time-course changes in HbA1c from baseline or the start of treatment with anagliptin to Week 52 (Study DP1008 [combination with insulin], FAS) (mean ± SD)

Table 5 shows the analysis results of other secondary endpoints.

Table 5. Analysis results of other secondary endpoints
(Study DP1008 [combination with insulin], FAS) (overall treatment period [52 weeks])

Endpoint	Treatment group	Baseline or the start of treatment with anagliptin[c)]	Change at the last assessment	95% CI of the change at the last assessment
Fasting blood glucose[a)] (mg/dL)	Placebo/anagliptin group	165.9 ± 42.5 (n = 58)	−15.6 ± 40.1 (n = 58)	[−26.1, −5.0]
	Continued anagliptin group	159.5 ± 45.8 (n = 61)	−8.5 ± 36.2 (n = 61)	[−17.7, 0.8]
2-hour postprandial blood glucose (mg/dL)	Placebo/anagliptin group	240.7 ± 64.0 (n = 58)	−40.8 ± 56.7 (n = 56)	[−56.0, −25.6]
	Continued anagliptin group	239.4 ± 62.6 (n = 61)	−22.9 ± 59.5 (n = 61)	[−38.2, −7.7]
Postprandial blood glucose AUC (mg·h/dL)	Placebo/anagliptin group	432.3 ± 100.7 (n = 57)	−64.3 ± 88.9 (n = 56)	[−88.1, −40.5]
	Continued anagliptin group	431.8 ± 103.1 (n = 61)	−38.0 ± 96.5 (n = 61)	[−62.7, −13.3]

Proportion of subjects with HbA1c <7.0%[b)]	Treatment Period I (up to Week 12)	Placebo group	Anagliptin group
		8.3 (5/60)	21.3 (13/61)
	Overall treatment period (up to Week 52)	Placebo/anagliptin group	Continued anagliptin group
		27.6 (16/58)	29.5 (18/61)

Mean ± SD
a) Missing data were imputed with LOCF.
b) Number of subjects who achieved HbA1c <7.0% at the last assessment/number of assessed subjects
c) Week 0 (continued anagliptin group) or Week 12 (placebo/anagliptin group)

Safety analysis was performed. The incidence of adverse events during Treatment Period I was 49.2% (30 of 61 subjects) in the placebo group and 54.8% (34 of 62 subjects) in the anagliptin group, and the incidence of adverse drug reactions was 29.5% (18 of 61 subjects) in the placebo group and 32.3% (20 of 62 subjects) in the anagliptin group. Table 6 shows adverse events and/or adverse drug reactions reported in ≥3% of subjects in either group during Treatment Period I.

Table 6. Adverse events and/or adverse drug reactions reported in ≥3% of subjects in either group during Treatment Period I
(Study DP1008 [combination with insulin], safety analysis set)

Adverse event term	Adverse event		Adverse drug reaction	
	Placebo (n = 61)	Anagliptin (n = 62)	Placebo (n = 61)	Anagliptin (n = 62)
Abdominal distension	0.0 (0)	4.8 (3)	0.0 (0)	4.8 (3)
Constipation	1.6 (1)	3.2 (2)	1.6 (1)	3.2 (2)
Influenza	0.0 (0)	3.2 (2)	0.0 (0)	0.0 (0)
Nasopharyngitis	6.6 (4)	4.8 (3)	0.0 (0)	0.0 (0)
Blood creatine phosphokinase increased	3.3 (2)	0.0 (0)	3.3 (2)	0.0 (0)
White blood cell count increased	3.3 (2)	0.0 (0)	0.0 (0)	0.0 (0)
Hypoglycaemia	24.6 (15)	25.8 (16)	24.6 (15)	24.2 (15)
Upper respiratory tract inflammation	4.9 (3)	3.2 (2)	1.6 (1)	0.0 (0)

Incidence % (number of subjects with events), MedDRA/J ver. 16.0

For the overall treatment period (the duration of treatment with anagliptin, i.e., Week 12 to Week 52 for the placebo/anagliptin group and Week 0 to Week 52 for the continued anagliptin group), the incidence of adverse events was 79.3% (46 of 58 subjects) in the placebo/anagliptin group and 85.5% (53 of 62 subjects) in the continued anagliptin group, and the incidence of adverse drug reactions was 53.4% (31 of 58 subjects) in the placebo/anagliptin group and 58.1% (36 of 62 subjects) in the continued anagliptin group. Table 7 shows adverse events and/or adverse drug reactions reported in ≥3% of subjects during the overall treatment period.

Table 7. Adverse events and/or adverse drug reactions reported in ≥3% of subjects during the overall treatment period
(Study DP1008 [combination with insulin], safety analysis set[a])

Adverse event term	Adverse event (n = 120)	Adverse drug reaction (n = 120)
Overall adverse events	82.5 (99)	55.8 (67)
Constipation	6.7 (8)	5.0 (6)
Cystitis	3.3 (4)	0.8 (1)
Nasopharyngitis	17.5 (21)	0.0 (0)
Blood uric acid increased	3.3 (4)	0.8 (1)
Hypoglycaemia	44.2 (53)	44.2 (53)
Arthralgia	3.3 (4)	0.0 (0)
Upper respiratory tract inflammation	6.7 (8)	0.0 (0)

Incidence % (number of subjects with events), MedDRA/J ver. 16.0

a) Data from the overall treatment period (the duration of treatment with anagliptin, i.e., Week 12 to Week 52 for the placebo/anagliptin group and Week 0 to Week 52 for the continued anagliptin group). Data for both treatment groups include subjects who had their dose increased to 200 mg.

No deaths were reported. During Treatment Period I, serious adverse events were reported in 3 subjects in the placebo group (4 events; angina pectoris in 1, radius fracture and pelvic fracture in 1, and gastric cancer in 1) and 2 subjects in the anagliptin group (2 events; acute myocardial infarction in 1 and coronary artery stenosis in 1). A causal relationship to the study drug was ruled out for all these events. During the overall treatment period, serious adverse events were reported in 5 subjects in the placebo/anagliptin group (5 events; hypoglycaemia in 1, mechanical ileus in 1, large intestine polyp in 1, limb injury in 1, and gastric cancer in 1) and 4 subjects in the continued anagliptin group (5 events; acute myocardial infarction in 1, coronary artery stenosis and lung neoplasm malignant in 1, foot fracture in 1, and subdural haematoma in 1). Hypoglycaemia in the placebo/anagliptin group was considered an adverse drug reaction. During Treatment Period I, adverse events leading to study drug discontinuation were reported in 3 subjects in the placebo group (8 events; radius fracture and pelvic fracture in 1, aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, blood alkaline phosphatase increased, and blood lactate dehydrogenase increased in 1, and gastric cancer in 1) and 2 subjects in the anagliptin group (3 events; acute myocardial infarction in 1 and abdominal distension and malaise in 1); of these, 5 events reported in 1 subject in the placebo group (aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, blood alkaline phosphatase increased, and blood lactate dehydrogenase increased) and 2 events reported in 1 subject in the anagliptin group (abdominal distension and malaise) were considered adverse drug reactions. During the overall treatment period, adverse events leading to study drug discontinuation were reported in 2 subjects in the placebo/anagliptin group (2 events; alanine aminotransferase increased in 1 and gastric cancer in 1) and 6 subjects in the continued anagliptin group (7 events; acute myocardial infarction in 1, foot fracture in 1, lung neoplasm malignant in 1, platelets decreased in 1, abdominal distension and malaise in 1, and abdominal discomfort in 1); of these, 3 events reported in 2 subjects in the continued anagliptin group (abdominal distension/malaise, abdominal discomfort) were considered adverse drug reactions. The incidence of hypoglycaemia during Treatment Period I was 24.6% (15 of 61 subjects) in the placebo group and 25.8% (16 of 62 subjects) in the anagliptin group; these events were considered adverse drug reactions, but all the events were mild in severity except for 1 event in the anagliptin group. The incidence of hypoglycaemia during the overall treatment period was 44.8% (26 of 58 subjects) in the placebo/anagliptin group and 43.5% (27 of 62 subjects) in the continued anagliptin group, and all the events were considered adverse drug reactions, but all the events were mild in severity except for 1 severe event in the placebo/anagliptin group. The subject who experienced severe hypoglycaemia was using both basal and bolus insulin; the event resolved following glucose ingestion and the subject completed the remaining treatment period without hypoglycaemia. No clinically meaningful changes were observed in laboratory parameters, vital signs, body weight, or 12-lead ECG.

2.(iii).A.(3) Phase II study (monotherapy) (5.3.5.1-2, Study DP1001 [[redacted] to [redacted]])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted to evaluate the efficacy and safety of anagliptin in Japanese patients with type 2 diabetes mellitus[5] (target sample size, 300 subjects [60 per group]).

This study consisted of a run-in period (2-6 weeks) and a treatment period (12 weeks).

During the treatment period, anagliptin at a dose of 25, 50, 100, or 200 mg or placebo was administered orally twice daily immediately before morning and evening meals for 12 weeks.

All of the 358 treated subjects (69 in the placebo group, 74 in the anagliptin 25 mg group, 72 in the anagliptin 50 mg group, 72 in the anagliptin 100 mg group, and 71 in the anagliptin 200 mg group) were included in the safety analysis set and the FAS. Of these, 343 subjects (66 in the placebo group, 69 in the anagliptin 25 mg group, 71 in the anagliptin 50 mg group, 69 in the anagliptin 100 mg group, and 68 in the anagliptin 200 mg group) were included in the Per Protocol Set (PPS), which was used for the primary efficacy analysis, and the remaining 15 subjects were excluded from analysis due to short treatment duration (<70 days), non-compliance with the protocol, ineligibility for participation in the study, etc. While a total of 342 subjects completed the study, 16 subjects discontinued, including 4 subjects in the placebo group (2 due to adverse event and worsening of glycemic control, 1 due to worsening of glycemic control, and 1 for other reasons), 5 subjects in the anagliptin 25 mg group (3 due to adverse event, 1 due to adverse event and worsening of glycemic control, and 1 due to subject's request), 3 subjects in the anagliptin 50 mg group (1 due to worsening of glycemic control, 1 due to worsening of glycemic control and other reasons, and 1 due to subject's request), 2 subjects in the anagliptin 100 mg group (2 due to adverse event), and 2 subjects in the anagliptin 200 mg group (1 due to adverse event and 1 due to subject's request).

Table 8 shows the change in HbA1c from baseline (Week 0) to the end of the study (Week 12 or discontinuation) in the PPS. A comparison based on an analysis of variance (ANOVA) model in a closed testing procedure, in which anagliptin 200 mg is tested against placebo first, revealed a significant decrease in HbA1c in all anagliptin groups compared with the placebo group. The results for the FAS, as with the results for the PPS, showed a significant decrease in HbA1c in all anagliptin groups compared with the placebo group.

Table 8. Change in HbA1c from baseline to the end of the study (Study DP1001, PPS)

	Placebo (n = 66)	Anagliptin 25 mg (n = 69)	Anagliptin 50 mg (n = 71)	Anagliptin 100 mg (n = 69)	Anagliptin 200 mg (n = 68)
Baseline	7.56 ± 0.92	7.57 ± 0.93	7.70 ± 0.97	7.47 ± 0.74	7.44 ± 0.85
At the end of the study	7.71 ± 1.21	7.04 ± 1.00	7.10 ± 1.19	6.73 ± 0.71	6.64 ± 0.58
Change at the end of the study	0.15 ± 0.67	−0.53 ± 0.56	−0.60 ± 0.78	−0.74 ± 0.49	−0.80 ± 0.45
Difference from placebo [95% CI]	-	−0.67 [−0.88, −0.47]	−0.75 [−0.95, −0.55]	−0.89 [−1.09, −0.68]	−0.95 [−1.16, −0.74]
Test result[a)]	-	$P < 0.0001$	$P < 0.0001$	$P < 0.0001$	$P < 0.0001$

Unit, %; mean ± SD; missing data were imputed with LOCF. -, Not applicable

a) *P* value obtained from pairwise comparison test using a closed procedure, in which anagliptin 200 mg, 100 mg, 50 mg, and 25 mg are tested against placebo in this order.

Table 9 shows the analysis results of key secondary endpoints.

[5] Key inclusion criteria: Patients with type 2 diabetes mellitus on diet or diet/exercise therapy aged ≥20 and <75 years who had HbA1c of ≥6.5% and <10.0% in the run-in period (2-6 weeks prior to baseline). Subjects receiving an oral hypoglycemic agent had to stop the oral agent at least 8 weeks prior to the start of the run-in period.

Table 9. Analysis results of key secondary endpoints[a] (Study DP1001, PPS)

Endpoint	Treatment group	Baseline	Change at the end of the study	Difference from placebo [95% CI]
Fasting blood glucose[a] (mg/dL)	Placebo	166.6 ± 40.3 (n = 66)	−2.2 ± 30.9 (n = 66)	-
	Anagliptin 25 mg	167.1 ± 35.1 (n = 69)	−16.8 ± 22.3 (n = 69)	−14.5 [−25.9, −3.2]
	Anagliptin 50 mg	169.7 ± 38.8 (n = 71)	−20.5 ± 26.3 (n = 71)	−18.3 [−29.6, −7.0]
	Anagliptin 100 mg	162.5 ± 30.8 (n = 69)	−19.5 ± 27.8 (n = 69)	−17.3 [−28.7, −5.9]
	Anagliptin 200 mg	162.3 ± 35.4 (n = 68)	−23.5 ± 27.1 (n = 68)	−21.3 [−32.8, −9.9]
2-hour postprandial blood glucose[b] (mg/dL)	Placebo	264.6 ± 65.8 (n = 66)	−11.7 ± 45.2 (n = 63)	-
	Anagliptin 25 mg	261.9 ± 73.7 (n = 69)	−42.7 ± 45.0 (n = 67)	−31.0 [−51.2, −10.8]
	Anagliptin 50 mg	262.7 ± 66.2 (n = 71)	−44.0 ± 45.1 (n = 68)	−32.3 [−52.5, −12.2]
	Anagliptin 100 mg	251.5 ± 59.6 (n = 69)	−41.3 ± 50.7 (n = 69)	−29.6 [−49.7, −9.6]
	Anagliptin 200 mg	260.0 ± 72.1 (n = 68)	−52.6 ± 48.8 (n = 68)	−40.9 [−61.1, −20.8]
Postprandial blood glucose AUC[b] (mg·h/dL)	Placebo	499.5 ± 93.1 (n = 66)	−18.3 ± 70.5 (n = 63)	-
	Anagliptin 25 mg	495.6 ± 101.3 (n = 69)	−68.4 ± 61.3 (n = 67)	−50.1 [−80.3, −19.9]
	Anagliptin 50 mg	495.1 ± 93.4 (n = 71)	−74.4 ± 67.8 (n = 68)	-56.1 [-86.2, -26.0]
	Anagliptin 100 mg	478.6 ± 82.0 (n = 69)	-68.4 ± 75.3 (n = 69)	-50.1 [-80.1, -20.1]
	Anagliptin 200 mg	488.8 ± 102.9 (n = 69)	-84.0 ± 75.4 (n = 68)	-65.7 [-95.8, -−35.6]

Mean ± SD; -, Not applicable

a) Missing data were imputed with LOCF.

b) Changes in the 2-hour postprandial blood glucose and AUC of postprandial blood glucose from baseline (Week 0) to Week 12

The proportion of subjects who achieved HbA1c <6.5% at Week 12 was 6.3% (4 of 63 subjects) in the placebo group, 28.4% (19 of 67 subjects) in the anagliptin 25 mg group, 35.3% (24 of 68 subjects) in the anagliptin 50 mg group, 40.6% (28 of 69 subjects) in the anagliptin 100 mg group, and 44.1% (30 of 68 subjects) in the anagliptin 200 mg group.

Safety analysis was performed. The incidence of adverse events was 49.3% (34 of 69 subjects) in the placebo group, 55.4% (41 of 74 subjects) in the anagliptin 25 mg group, 51.4% (37 of 72 subjects) in the anagliptin 50 mg group, 56.9% (41 of 72 subjects) in the anagliptin 100 mg group, and 43.7% (31 of 71 subjects) in the anagliptin 200 mg group, and the incidence of adverse drug reactions was 10.1% (7 of 69 subjects) in the placebo group, 6.8% (5 of 74 subjects) in the anagliptin 25 mg group, 8.3% (6 of 72 subjects) in the anagliptin 50 mg group, 12.5% (9 of 72 subjects) in the anagliptin 100 mg group, and 7.0% (5 of 71 subjects) in the anagliptin 200 mg group. Table 10 shows adverse events reported in ≥3 subjects in any group. There was no adverse drug reaction reported in ≥3 subjects in any of the groups.

Table 10. Adverse events reported in ≥3 subjects in any group (Study DP1001, safety analysis set)

Adverse event term	Placebo (n = 69)	Anagliptin 25 mg (n = 74)	Anagliptin 50 mg (n = 72)	Anagliptin 100 mg (n = 72)	Anagliptin 200 mg (n = 71)
Constipation	1.4 (1)	1.4 (1)	4.2 (3)	1.4 (1)	2.8 (2)
Diarrhoea	4.3 (3)	1.4 (1)	0.0 (0)	4.2 (3)	2.8 (2)
Seasonal allergy	4.3 (3)	1.4 (1)	1.4 (1)	1.4 (1)	0.0 (0)
Nasopharyngitis	11.6 (8)	14.9 (11)	13.9 (10)	13.9 (10)	15.5 (11)
Back pain	2.9 (2)	4.1 (3)	0.0 (0)	2.8 (2)	1.4 (1)
Upper respiratory tract inflammation	1.4 (1)	4.1 (3)	2.8 (2)	4.2 (3)	1.4 (1)
Blood creatine phosphokinase increased	0.0 (0)	5.4 (4)	1.4 (1)	1.4 (1)	1.4 (1)
Occult blood positive	7.2 (5)	6.8 (5)	4.2 (3)	5.6 (4)	9.9 (7)

Incidence % (number of subjects with events), MedDRA/J ver. 10.1

No deaths were reported. Serious adverse events were reported in 2 subjects in the anagliptin 25 mg group (2 events; colon cancer in 1 and pneumonia in 1) and 1 event in 1 subject in the anagliptin 200 mg group (colonic polyp), but a causal relationship to the study drug was ruled out for all events. Adverse events leading to study drug discontinuation were reported in 2 subjects in the placebo group (4 events; glycosylated haemoglobin increased in 1 and headache, palpitations, and nausea in 1), 4 subjects in the anagliptin 25 mg group (4 events; dizziness in 1, colon cancer in 1, pneumonia in 1, and glycosylated haemoglobin increased in 1), 2 subjects in the anagliptin 100 mg group (4 events; alanine aminotransferase increased, gamma-glutamyltransferase increased, blood alkaline phosphatase increased in 1 and decreased appetite in 1), and 1 subject in the anagliptin 200 mg group (abdominal pain upper). Of these, 4 events in 2 subjects in the anagliptin 100 mg group and 1 event in 1 subject in the anagliptin 200 mg group were considered adverse drug reactions. One subject each in the placebo group, the anagliptin 50 mg group, and the anagliptin 100 mg group experienced 1 event of hypoglycaemia; all events were considered adverse drug reactions, but severity was mild. No clinically meaningful changes were observed in laboratory parameters, vital signs, body weight, or 12-lead ECG.

2.(iii).A.(4) Phase II/III study (monotherapy) (5.3.5.1-3, Study DP1003 [[redacted] to [redacted]])

A placebo-controlled, voglibose-referenced, randomized, double-blind, parallel-group study was conducted to evaluate the efficacy and safety of anagliptin in Japanese patients with type 2 diabetes mellitus[6] (target sample size, 240 subject [60 per group]).

This study consisted of a run-in period (2-6 weeks) and a treatment period (12 weeks).

During the treatment period, a double-dummy technique was employed. Subjects orally received anagliptin 100 or 200 mg or matching anagliptin placebo twice daily before morning and evening meals, and voglibose 0.2 mg or matching voglibose placebo 3 times daily immediately before every meal for 12 weeks.

All of the 244 treated subjects (58 in the placebo group, 63 in the anagliptin 100 mg group, 58 in the anagliptin 200 mg group, and 65 in the voglibose group) were included in the safety analysis set and the FAS. The efficacy analysis was performed on the FAS. A total of 232 subjects completed the study. The remaining 12 subjects discontinued the study, including 4 subjects in the placebo group (2 due to adverse events and worsening of glycemic control, 1 due to subject's request, and 1 due to lack of efficacy), 1 subject in the anagliptin 100 mg group (worsening of glycemic control), 1 subject in the anagliptin 200 mg group (subject's request), and 6 subjects in the voglibose group (5 due to adverse events, 1 due to adverse event and subject's request).

The change in HbA1c from baseline (Week 0) to the end of the study (Week 12 or discontinuation) in the FAS, the primary efficacy endpoint, was as shown in Table 11. A comparison based on an ANOVA model with a closed testing procedure, in which anagliptin 200 mg and 100 mg were tested against placebo, revealed a significant decrease in HbA1c in both anagliptin groups compared with the placebo group. The change (mean ± SD) in HbA1c from baseline (Week 0) to the end of the study (Week 12 or discontinuation) in the reference (voglibose) group was −0.32% ± 0.37%.

Table 11. Change in HbA1c from baseline to the end of the study (Study DP1003, FAS)

Treatment group	Baseline	At the end of the study	Change at the end of the study	Difference from placebo [95% CI]
Placebo (n = 58)	7.40 ± 0.99	7.46 ± 1.15	0.06 ± 0.57	-
Anagliptin 100 mg (n = 63)	7.31 ± 0.78	6.66 ± 0.71	−0.65 ± 0.49	−0.71 [−0.90, −0.52]
Anagliptin 200 mg (n = 58)	7.60 ± 0.87	6.86 ± 0.76	−0.74 ± 0.54	−0.80 [−0.99, −0.60]

Unit, %; mean ± SD; missing data were imputed with LOCF. -, Not applicable

Table 12 shows the analysis results of key secondary endpoints.

Table 12. Analysis results of key secondary endpoints (Study DP1003, FAS)

Endpoint	Treatment group	Baseline	Change at the end of the study	Difference from placebo [95% CI]
Fasting blood glucose[a] (mg/dL)	Placebo	161.4 ± 46.4 (n = 58)	−1.6 ± 40.6 (n = 58)	-
	Anagliptin 100 mg	153.2 ± 29.2 (n = 63)	−16.1 ± 18.2 (n = 63)	−14.5 [−25.8, −3.3]
	Anagliptin 200 mg	161.4 ± 33.9 (n = 58)	−21.5 ± 23.0 (n = 58)	−19.8 [−31.4, −8.3]
2-hour postprandial blood glucose[b] (mg/dL)	Placebo	225.1 ± 64.8 (n = 58)	−5.8 ± 37.3 (n = 54)	-
	Anagliptin 100 mg	221.0 ± 56.1 (n = 63)	−38.4 ± 39.3 (n = 62)	−32.6 [−50.0, −15.1]
	Anagliptin 200 mg	228.4 ± 60.5 (n = 58)	−37.5 ± 42.5 (n = 55)	−31.7 [−49.6, −13.8]
Postprandial blood glucose AUC[b] (mg·h/dL)	Placebo	434.2 ± 103.0 (n = 58)	−6.7 ± 59.7 (n = 54)	-
	Anagliptin 100 mg	423.7 ± 78.8 (n = 62)	−66.2 ± 52.0 (n = 61)	−59.5 [−84.0, −35.0]
	Anagliptin 200 mg	439.8 ± 88.5 (n = 58)	−67.2 ± 61.1 (n = 55)	−60.5 [−85.6, −35.3]
Proportion of subjects with HbA1c <6.5%[c]	Placebo	Anagliptin 100 mg	Anagliptin 200 mg	
	8.6 (5/58)	47.6 (30/63)	31.0 (18/58)	

Mean ± SD; -, Not applicable

a) Missing data were imputed with LOCF (1 subject in the 200 mg group was excluded from the analysis of the change because all post-treatment data were missing).

b) Change from baseline (Week 0) to Week 12

c) Number of subjects who achieved HbA1c <6.5% at the end of the study/number of evaluated subjects

Safety analysis was performed. The incidence of adverse events was 48.3% (28 of 58 subjects) in the placebo group, 47.6% (30 of 63 subjects) in the anagliptin 100 mg group, 55.2% (32 of 58 subjects) in

[6] Key inclusion criteria: Patients with type 2 diabetes mellitus on diet or diet/exercise therapy aged ≥20 and <75 years with HbA1c of ≥6.5% and <10.0% in the run-in period (2-6 weeks prior to baseline). Subjects receiving an oral hypoglycemic agent had to stop the oral agent at least 8 weeks prior to the start of the run-in period.

the anagliptin 200 mg group, and 56.9% (37 of 65 subjects) in the voglibose group. The incidence of adverse drug reactions was 20.7% (12 of 58 subjects) in the placebo group, 25.4% (16 of 63 subjects) in the anagliptin 100 mg group, 24.1% (14 of 58 subjects) in the anagliptin 200 mg group, and 35.4% (23 of 65 subjects) in the voglibose group. Table 13 shows adverse events and/or adverse drug reactions reported in ≥3 subjects in any group.

Table 13. Adverse events and/or adverse drug reactions reported in ≥3 subjects in any group (Study DP1003, safety analysis set)

Adverse event term	Adverse event				Adverse drug reaction			
	Placebo (n = 58)	Anagliptin 100 mg (n = 63)	Anagliptin 200 mg (n = 58)	Voglibose (n = 65)	Placebo (n = 58)	Anagliptin 100 mg (n = 63)	Anagliptin 200 mg (n = 58)	Voglibose (n = 65)
Abdominal distension	0.0 (0)	0.0 (0)	1.7 (1)	4.6 (3)	0.0 (0)	0.0 (0)	1.7 (1)	4.6 (3)
Constipation	5.2 (3)	1.6 (1)	3.4 (2)	1.5 (1)	5.2 (3)	1.6 (1)	1.7 (1)	1.5 (1)
Diarrhoea	1.7 (1)	3.2 (2)	5.2 (3)	7.7 (5)	1.7 (1)	3.2 (2)	5.2 (3)	6.2 (4)
Nasopharyngitis	12.1 (7)	3.2 (2)	10.3 (6)	7.7 (5)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Alanine aminotransferase increased	0.0 (0)	3.2 (2)	0.0 (0)	4.6 (3)	0.0 (0)	1.6 (1)	0.0 (0)	3.1 (2)
Aspartate aminotransferase increased	0.0 (0)	4.8 (3)	0.0 (0)	3.1 (2)	0.0 (0)	3.2 (2)	0.0 (0)	3.1 (2)
Occult blood positive	3.4 (2)	6.3 (4)	10.3 (6)	7.7 (5)	0.0 (0)	3.2 (2)	5.2 (3)	1.5 (1)
Upper respiratory tract inflammation	0.0 (0)	1.6 (1)	5.2 (3)	4.6 (3)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)

Incidence % (number of subjects with events), MedDRA/J ver. 12.1

No deaths were reported. Serious adverse events were reported in 1 subject in the anagliptin 100 mg group (1 event, putamen haemorrhage) and 2 subjects in the voglibose group (2 events, thyroid neoplasm in 1 and gastric cancer in 1). A causal relationship to the study drug was ruled out for all events. Adverse events leading to study drug discontinuation were reported in 2 subjects in the placebo group (3 events; glycosylated haemoglobin increased and blood glucose increased in 1 and glycosylated haemoglobin increased in 1), 6 subjects in the voglibose group (6 events; diarrhoea in 2, urticaria in 1, thyroid neoplasm in 1, gastric cancer in 1, and haematochezia in 1). Of these, 4 events reported in 4 subjects in the voglibose group (diarrhoea in 2, urticaria in 1, and haematochezia in 1) were considered adverse drug reactions. No adverse drug reactions occurred in the 100 mg and 200 mg groups. Two events of hypoglycaemia occurred in 2 subjects in the 200 mg group and 1 event of hypoglycaemia occurred in 1 subject in the voglibose group; all events were considered adverse drug reactions, but severity was mild. No clinically meaningful changes were observed in laboratory parameters, vital signs, body weight, or 12-lead ECG.

2.(iii).A.(5) Phase III long-term study (monotherapy) (5.3.5.1-4, Study SK-0403-01 [[redacted] to [redacted]])

An open-label, randomized, parallel-group study was conducted to evaluate the long-term efficacy and safety of anagliptin administered before or after a meal in Japanese patients with type 2 diabetes mellitus[7] (target sample size, 140 subjects [70 per group]).

This study consisted of a run-in period (2-6 weeks), Treatment Period I (12 weeks), and Treatment Period II (40 weeks).

During Treatment Period I, anagliptin 100 mg was administered orally twice daily before or after morning and evening meals for 12 weeks. During Treatment Period II, anagliptin 100 mg was administered orally twice daily before or after morning and evening meals for 40 weeks. Beginning at Week 16 of treatment, dose escalation was allowed based on HbA1c levels measured every 4 weeks from Week 12 to Week 36. The dose was increased to 200 mg twice daily for subjects who had HbA1c ≥6.5%

Of the 152 treated subjects, 151 subjects (81 in the preprandial group, 70 in the postprandial group) were included in the safety analysis set, and the remaining 1 subject in the postprandial group was excluded

[7] Key inclusion criteria: Patients with type 2 diabetes mellitus on diet or diet/exercise therapy aged ≥20 and <75 years who had HbA1c of ≥6.5% and <10.0% in the run-in period (2-6 weeks prior to baseline). Subjects receiving an oral hypoglycemic agent had to stop the oral agent at least 8 weeks prior to the start of the run-in period.

from analysis due to GCP non-compliance (medical records lost). Another subject in the preprandial group who requested for withdrawal from the study was excluded, and thus 150 subjects (80 in the preprandial group, 70 in the postprandial group) were included in the FAS, which was used for the efficacy analysis. A total of 146 subjects (78 in the preprandial group, 68 in the postprandial group) completed Treatment Period I, and 129 subjects (72 in the preprandial group, 57 in the postprandial group) completed Treatment Period II. A total of 23 subjects discontinued the study, including 6 subjects who discontinued in Treatment Period I (3 subjects in the preprandial group [1 due to adverse event and subject's request, 1 due to worsening of glycemic control, and 1 due to subject's request], 3 subjects in the postprandial group [2 due to adverse event, 1 due to adverse event and subject's request]) and 17 subjects who discontinued in Treatment Period II (6 subjects in the preprandial group [2 due to adverse event, 1 each due to adverse event and subject's request, 1 due to worsening of glycemic control, 1 due to aspartate aminotransferase or alanine aminotransferase ≥150 IU/L, and 1 due to medical judgment of the investigator or sub-investigator], 11 subjects in the postprandial group [5 due to adverse event, 2 due to adverse event and aspartate aminotransferase or alanine aminotransferase ≥150 IU/L, 2 due to medical judgment of the investigator or sub-investigator, 1 due to adverse event and worsening of glycemic control, and 1 due to adverse event and subject's request]). A total of 127 subjects (70 in the preprandial group, 57 in the postprandial group) had their anagliptin dose increased to 200 mg twice daily during Treatment Period II.

The primary efficacy endpoint was the change in HbA1c from baseline (Week 0) to the last assessment of Treatment Period I (Week 12 or discontinuation) in the FAS. The results are shown in Table 14. A significant decrease in HbA1c from baseline was observed in each treatment group as well as in the overall study population.

Table 14. Change in HbA1c from baseline to the last assessment of Treatment Period I (Study SK-0403-01 [monotherapy], FAS)

Treatment group	Baseline	At the last assessment	Change at the last assessment	95% CI of the change at the last assessment
Preprandial (n = 80)	7.92 ± 1.11	7.30 ± 1.03	−0.62 ± 0.66	[−0.76, −0.47]
Postprandial (n = 70)	7.68 ± 0.96	7.13 ± 0.98	−0.55 ± 0.55	[−0.68, −0.42]
Overall (n = 150)	7.81 ± 1.04	7.22 ± 1.01	−0.59 ± 0.61	[−0.68, −0.49]

Unit, %; mean ± SD; missing data were imputed with LOCF.

The secondary endpoint was the time-course changes in HbA1c from baseline (Week 0) to Week 52. The results are shown in Figure 3. The change (mean ± SD) in HbA1c from baseline (Week 0) to the last assessment (Week 52 or discontinuation) was −0.66% ± 0.85% (n = 80) in the preprandial group, −0.58% ± 0.81% in the postprandial group (n = 70), and −0.62% ± 0.83% for overall (n = 150).

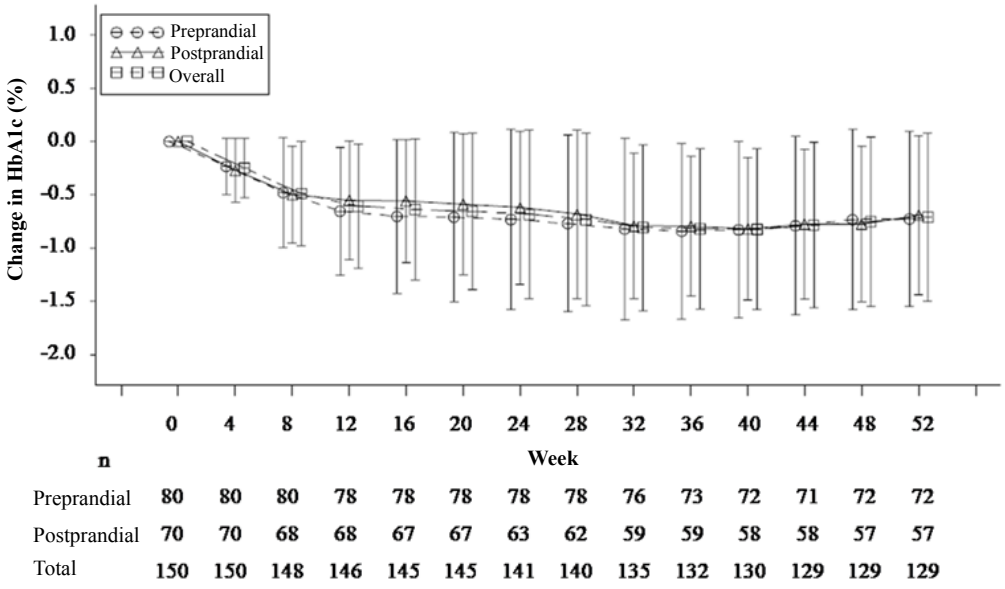

Figure 3. Time-course changes in HbA1c from baseline to Week 52 (Study SK-0403-01 [monotherapy], FAS) (mean ± SD)

Table 15 shows the analysis results of other secondary endpoints.

Table 15. Analysis results of other secondary endpoints (Study SK-0403-01 [monotherapy], FAS)

Endpoint	Treatment group	Baseline	Change at the last assessment	95% CI of the change at the last assessment
Fasting blood glucose[a] (mg/dL)	Preprandial	166.8 ± 40.1 (n = 80)	−10.7 ± 37.2 (n = 80)	[−18.9, −2.4]
	Postprandial	165.4 ± 36.6 (n = 70)	−14.7 ± 25.3 (n = 70)	[−20.7, −8.7]
	Overall	166.1 ± 38.4 (n = 150)	−12.5 ± 32.2 (n = 150)	[−17.7, −7.4]
2-hour postprandial blood glucose (mg/dL)	Preprandial	258.2 ± 60.2 (n = 80)	−35.9 ± 49.7 (n = 75)	[−47.4, −24.5]
	Postprandial	251.6 ± 60.6 (n = 70)	−25.1 ± 45.3 (n = 64)	[−36.4, −13.8]
	Overall	255.1 ± 60.3 (n = 150)	−31.0 ± 47.8 (n = 139)	[−39.0, −22.9]
Postprandial blood glucose AUC (mg·h/dL)	Preprandial	468.4 ± 95.1 (n = 80)	−57.2 ± 81.0 (n = 75)	[−75.9, −38.6]
	Postprandial	461.4 ± 97.8 (n = 70)	−42.3 ± 63.4 (n = 64)	[−58.1, −26.4]
	Overall	465.1 ± 96.1 (n = 150)	−50.4 ± 73.5 (n = 139)	[−62.7, −38.0]
Proportion of subjects with HbA1c <6.5%[b]	Treatment Period I (up to Week 12)	Preprandial	Postprandial	Overall
		20.0 (16/80)	25.7 (18/70)	22.7 (34/150)
	Overall treatment period (up to Week 52)	Preprandial	Postprandial	Overall
		26.3 (21/80)	22.9 (16/70)	24.7 (37/150)

Mean ± SD.
a) Missing data were imputed with LOCF.
b) Number of subjects who achieved HbA1c <6.5% at the last assessment/number of assessed subjects

Safety analysis was performed. The incidence of adverse events during Treatment Period I and the overall treatment period was 46.9% (38 of 81 subjects) and 84.0% (68 of 81 subjects), respectively, in the preprandial group, and 60.0% (42 of 70 subjects) and 91.4% (64 of 70 subjects), respectively, in the postprandial group. The incidence of adverse drug reactions during Treatment Period I and the overall treatment period were 12.3% (10 of 81 subjects) and 23.5% (19 of 81 subjects), respectively, in the preprandial group, and 7.1% (5 of 70 subjects) and 15.7% (11 of 70 subjects), respectively, in the postprandial group. Table 16 shows adverse events and/or adverse drug reactions reported in ≥3% of subjects in either group during the overall treatment period.

Table 16. Adverse events and/or adverse drug reactions reported in ≥3% of subjects in either group during the overall treatment period
(Study SK-0403-01 [monotherapy], safety analysis set)

Adverse event term	Adverse event			Adverse drug reaction		
	Preprandial group (n = 81)	Postprandial group (n = 70)	Overall (n = 151)	Preprandial group (n = 81)	Postprandial group (n = 70)	Overall (n = 151)
Cataract	3.7 (3)	1.4 (1)	2.6 (4)	0.0 (0)	0.0 (0)	0.0 (0)
Diabetic retinopathy	2.5 (2)	4.3 (3)	3.3 (5)	0.0 (0)	0.0 (0)	0.0 (0)
Abdominal pain upper	3.7 (3)	2.9 (2)	3.3 (5)	1.2 (1)	0.0 (0)	0.7 (1)
Colonic polyp	8.6 (7)	4.3 (3)	6.6 (10)	0.0 (0)	0.0 (0)	0.0 (0)
Constipation	8.6 (7)	5.7 (4)	7.3 (11)	4.9 (4)	1.4 (1)	3.3 (5)
Dental caries	4.9 (4)	1.4 (1)	3.3 (5)	0.0 (0)	0.0 (0)	0.0 (0)
Faeces hard	3.7 (3)	0.0 (0)	2.0 (3)	0.0 (0)	0.0 (0)	0.0 (0)
Gastritis	6.2 (5)	2.9 (2)	4.6 (7)	4.9 (4)	0.0 (0)	2.6 (4)
Reflux oesophagitis	1.2 (1)	4.3 (3)	2.6 (4)	0.0 (0)	1.4 (1)	0.7 (1)
Seasonal allergy	6.2 (5)	10.0 (7)	7.9 (12)	0.0 (0)	0.0 (0)	0.0 (0)
Herpes zoster	1.2 (1)	5.7 (4)	3.3 (5)	0.0 (0)	0.0 (0)	0.0 (0)
Nasopharyngitis	29.6 (24)	27.1 (19)	28.5 (43)	0.0 (0)	0.0 (0)	0.0 (0)
Pharyngitis	7.4 (6)	4.3 (3)	6.0 (9)	0.0 (0)	0.0 (0)	0.0 (0)
Alanine aminotransferase increased	2.5 (2)	4.3 (3)	3.3 (5)	0.0 (0)	0.0 (0)	0.0 (0)
Aspartate aminotransferase increased	1.2 (1)	4.3 (3)	2.6 (4)	0.0 (0)	0.0 (0)	0.0 (0)
Blood creatine phosphokinase increased	9.9 (8)	7.1 (5)	8.6 (13)	1.2 (1)	0.0 (0)	0.7 (1)
Haemoglobin decreased	0.0 (0)	4.3 (3)	2.0 (3)	0.0 (0)	1.4 (1)	0.7 (1)
White blood cell count increased	3.7 (3)	8.6 (6)	6.0 (9)	0.0 (0)	0.0 (0)	0.0 (0)
Protein urine present	3.7 (3)	1.4 (1)	2.6 (4)	0.0 (0)	0.0 (0)	0.0 (0)
Occult blood positive	16.0 (13)	14.3 (10)	15.2 (23)	1.2 (1)	1.4 (1)	1.3 (2)
Arthritis	3.7 (3)	0.0 (0)	2.0 (3)	0.0 (0)	0.0 (0)	0.0 (0)
Back pain	4.9 (4)	5.7 (4)	5.3 (8)	1.2 (1)	0.0 (0)	0.7 (1)
Headache	3.7 (3)	2.9 (2)	3.3 (5)	1.2 (1)	0.0 (0)	0.7 (1)
Rhinitis allergic	3.7 (3)	0.0 (0)	2.0 (3)	0.0 (0)	0.0 (0)	0.0 (0)
Upper respiratory tract inflammation	4.9 (4)	5.7 (4)	5.3 (8)	0.0 (0)	0.0 (0)	0.0 (0)
Eczema	2.5 (2)	5.7 (4)	4.0 (6)	0.0 (0)	1.4 (1)	0.7 (1)
Urticaria	3.7 (3)	0.0 (0)	2.0 (3)	0.0 (0)	0.0 (0)	0.0 (0)

Incidence % (number of subjects with events), MedDRA/J ver. 14.0

No deaths were reported. A total of 14 serious adverse events were reported in 13 subjects (6 subjects in the preprandial group [colonic polyp in 2, gastric cancer in 1, atrioventricular block second degree and pneumonia chlamydial in 1, coronary artery stenosis in 1, and large intestine carcinoma in 1], and 7 subjects in the postprandial group [oesophageal carcinoma in 1, colon cancer in 1, fractured ischium in 1, rectal cancer in 1, cholelithiasis in 1, gastric cancer in 1, and large intestine carcinoma in 1]), but a causal relationship to the study drug was ruled out for all events. Adverse events leading to study drug discontinuation were reported in 4 subjects in the preprandial group (4 events; gastric cancer in 1, neurodermatitis in 1, gastritis in 1, and coronary artery stenosis in 1) and 12 subjects in the postprandial group (16 events; glycosylated haemoglobin increased in 1, oesophageal carcinoma in 1, colon cancer in 1, aspartate aminotransferase increased and alanine aminotransferase increased in 1, fractured ischium in 1, rectal cancer in 1, cholelithiasis, aspartate aminotransferase increased, alanine aminotransferase increased and gamma-glutamyltransferase increased in 1, discomfort in 1, gastric cancer in 1, large intestine carcinoma in 1, faeces discoloured in 1, and pruritus in 1). Of these, 2 events in 2 subjects in the preprandial group (neurodermatitis in 1 and gastritis in 1) and 3 events in 3 subjects in the postprandial group (discomfort in 1, faeces discoloured in 1, and pruritus in 1) were considered adverse drug reactions. Hypoglycaemia was reported in 2 subjects (1 in each group); both events were mild in severity, but the event in 1 subject in the preprandial group was considered an adverse drug reaction. No clinically meaningful changes were observed in laboratory parameters, vital signs, body weight, or 12-lead ECG.

2.(iii).A.(6) Phase III long-term study (combination with α-glucosidase inhibitor or pioglitazone) (5.3.5.1-5, Study DP1002 [[redacted] to [redacted]])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted to evaluate the efficacy and safety of anagliptin in Japanese patients with type 2 diabetes mellitus with inadequate glycemic control on α-glucosidase inhibitor (α-GI) or thiazolidinediones (TZD) (pioglitazone)[8] (target

[8] Key inclusion criteria: Patients with type 2 diabetes mellitus aged ≥20 and <75 years on diet or diet/exercise therapy with HbA1c of ≥6.5% and <10.0% in the run-in period (2-6 weeks prior to baseline) who were receiving α-GI or pioglitazone from at least 8 weeks before the start of the run-in period (2-6 weeks prior to baseline). The type and dosing regimen of the α-GI or pioglitazone had to remain unchanged for at least 8 weeks before the start of the run-in period.

sample size, 180 subjects; 90 subjects for each combination therapy [30 in the placebo group, 60 in the anagliptin group]).

This study consisted of a run-in period (2-6 weeks), Treatment Period I (12 weeks), and Treatment Period II (40 weeks).

During Treatment Period I, placebo or anagliptin 100 mg was administered orally twice daily before morning and evening meals for 12 weeks. During Treatment Period II, anagliptin 100 mg was administered orally twice daily before morning and evening meals for 40 weeks. Beginning at Week 28 of treatment, the dose escalation was allowed based on HbA1c levels measured every 4 weeks from Week 24 to Week 36. The dose was increased to 200 mg twice daily in subjects who had HbA1c ≥6.5%. The dosing regimen of concomitant α-GI or pioglitazone had to remain unchanged for 8 weeks before the start of the run-in period and throughout the study period. Data are presented below separately for the combination therapy with α-GI and for the combination therapy with pioglitazone.

(a) Combination therapy with α-GI

All of the 94 treated subjects (32 in the placebo group, 62 in the anagliptin group) were included in the safety analysis set and the FAS. The efficacy analysis was performed on the FAS. All the subjects completed Treatment Period I. Then, 85 subjects (27 in the placebo/anagliptin group, 58 in the continued anagliptin group) completed Treatment Period II. A total of 9 subjects discontinued the study, including 5 subjects in the placebo/anagliptin group who discontinued in Treatment Period II (3 due to adverse event, 1 each due to subject's request and inadequate efficacy) and 4 subjects in the continued anagliptin group (2 due to adverse event, 1 each due to subject's request and prioritization of treatment of complications). A total of 57 subjects (19 in the placebo/anagliptin group, 38 in the continued anagliptin group) had their anagliptin dose increased to 200 mg twice daily during Treatment Period II.

The primary efficacy endpoint was the change in HbA1c from baseline (Week 0) to the last assessment of Treatment Period I (Week 12 or discontinuation) in the FAS. The results are shown in Table 17, demonstrating the superiority of anagliptin over placebo.

Table 17. Changes in HbA1c from baseline to the last assessment of Treatment Period I (Study DP1002 [combination with α-GI], FAS)

Treatment group	Baseline	At the last assessment	Change at the last assessment	Difference from placebo [95% CI]
Placebo (n = 32)	7.59 ± 0.82	7.72 ± 0.97	0.12 ± 0.57	−0.93 [−1.17, −0.69]
Anagliptin (n = 62)	7.70 ± 0.96	6.89 ± 0.70	−0.81 ± 0.55	

Unit, %; mean ± SD; missing data were imputed with LOCF.

The secondary endpoint was the time-course changes in HbA1c from baseline (Week 0 for the placebo and continued anagliptin groups, Week 12 [the start of treatment with anagliptin] for the placebo/anagliptin group) to Week 52. The results are shown in Figure 4. The change (mean ± SD) [95% CI] in HbA1c from baseline or the start of treatment with anagliptin to the last assessment (Week 52 or discontinuation) was −0.84% ± 0.76% [−1.11, −0.56] in the placebo/anagliptin group and −0.85% ± 0.80% [−1.06, −0.65] in the continued anagliptin group, showing a decrease in HbA1c from baseline or the start of treatment with anagliptin treatment in both groups.

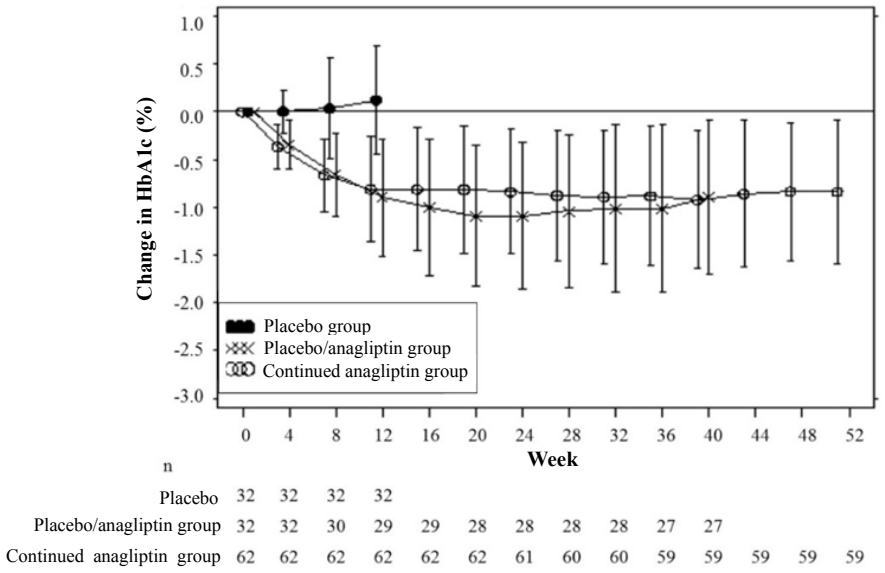

Figure 4. Time-course changes in HbA1c from baseline to Week 52 (Study DP1002 [combination with α-GI], FAS) (mean ± SD)

Table 18 shows the analysis results of other secondary endpoints.

Table 18. Analysis results of other secondary endpoints (Study DP1002 [combination with α-GI], FAS)

Endpoint	Treatment group	Baseline or before the start of treatment with anagliptin[c)]	Change at the last assessment	95% CI of the change at the last assessment
Fasting blood glucose[a)] (mg/dL)	Placebo/anagliptin group	168.8 ± 39.4 (n = 32)	−19.4 ± 32.6 (n = 32)	[−31.2, −7.7]
	Continued anagliptin group	161.2 ± 36.1 (n = 62)	−13.6 ± 27.5 (n = 62)	[−20.6, −6.7]
2-hour postprandial blood glucose (mg/dL)	Placebo/anagliptin group	233.8 ± 49.2 (n = 32)	−40.9 ± 45.1 (n = 30)	[−57.7, −24.1]
	Continued anagliptin group	229.1 ± 51.5 (n = 62)	−37.4 ± 50.9 (n = 62)	[−50.3, −24.4]
Postprandial blood glucose AUC (mg·h/dL)	Placebo/anagliptin group	415.4 ± 88.5 (n = 32)	−63.8 ± 76.0 (n = 30)	[−92.1, −35.4]
	Continued anagliptin group	403.8 ± 85.2 (n = 62)	−54.3 ± 70.5 (n = 62)	[−72.2, −36.4]
Proportion of subjects with HbA1c <6.5%[b)]	Treatment Period I (up to Week 12)	Placebo group	Anagliptin group	
		6.3 (2/32)	32.3 (20/62)	
	Overall treatment period (up to Week 52)	Placebo/anagliptin group	Continued anagliptin group	
		37.5 (12/32)	33.9 (21/62)	

Mean ± SD
a) Missing data were imputed with LOCF.
b) Number of subjects who achieved HbA1c <6.5% at the last assessment/number of evaluated subjects
c) Week 0 (continued anagliptin group) or Week 12 (placebo/anagliptin group)

Safety analysis was performed. During Treatment Period I, the incidence of adverse events was 31.3% (10 of 32 subjects) in the placebo group and 40.3% (25 of 62 subjects) in the anagliptin group, and the incidence of adverse drug reactions was 0.0% (0 of 32 subjects) in the placebo group and 4.8% (3 of 62 subjects) in the anagliptin group. Table 19 shows adverse events and/or adverse drug reactions reported in ≥3% of subjects in the anagliptin group during Treatment Period I.

Table 19. Adverse events and/or adverse drug reactions reported in ≥3% of subjects in the anagliptin group during Treatment Period I
(Study DP1002 [combination with α-GI], safety analysis set)

Adverse event term	Adverse event		Adverse drug reaction	
	Placebo (n = 32)	Anagliptin (n = 62)	Placebo (n = 32)	Anagliptin (n = 62)
Periodontitis	0.0 (0)	3.2 (2)	0.0 (0)	0.0 (0)
Nasopharyngitis	12.5 (4)	12.9 (8)	0.0 (0)	0.0 (0)
Haematocrit decreased	0.0 (0)	3.2 (2)	0.0 (0)	3.2 (2)
Haemoglobin decreased	0.0 (0)	3.2 (2)	0.0 (0)	3.2 (2)
Occult blood positive	3.1 (1)	4.8 (3)	0.0 (0)	0.0 (0)
Intervertebral disc disorder	0.0 (0)	3.2 (2)	0.0 (0)	0.0 (0)

Incidence % (number of subjects with events), MedDRA/J ver. 12.1

In the overall treatment period (the duration of treatment with anagliptin, i.e., Week 12 to Week 52 for the placebo/anagliptin group and Week 0 to Week 52 for the continued anagliptin group), the incidence of adverse events was 68.8% (22 of 32 subjects) in the placebo/anagliptin group and 80.6% (50 of 62 subjects) in the continued anagliptin group, and the incidence of adverse drug reactions was 12.5% (4 of 32 subjects) in the placebo/anagliptin group and 29.0% (18 of 62 subjects) in the continued anagliptin group. Table 20 shows adverse events and/or adverse drug reactions reported in ≥3% of subjects during the overall treatment period.

Table 20. Adverse events and/or adverse drug reactions reported in ≥3% of subjects during the overall treatment period
(Study DP1002 [combination with α-GI], safety analysis set[a])

Adverse event term	Adverse event (n = 94)	Adverse drug reaction (n = 94)
Diarrhoea	3.2 (3)	0.0 (0)
Periodontitis	3.2 (3)	0.0 (0)
Gastroenteritis	4.3 (4)	0.0 (0)
Nasopharyngitis	29.8 (28)	2.1 (2)
Blood creatine phosphokinase increased	5.3 (5)	0.0 (0)
Haematocrit decreased	3.2 (3)	3.2 (3)
Blood urine present	3.2 (3)	1.1 (1)
Haemoglobin decreased	4.3 (4)	4.3 (4)
Occult blood positive	10.6 (10)	1.1 (1)
Back pain	3.2 (3)	0.0 (0)
Headache	3.2 (3)	1.1 (1)
Upper respiratory tract inflammation	8.5 (8)	1.1 (1)
Eczema	3.2 (3)	1.1 (1)
Hypertension	3.2 (3)	1.1 (1)

Incidence % (number of subjects with events), MedDRA/J ver. 12.1

a) Data from the overall treatment period (the duration of treatment with anagliptin, i.e., Week 12 to Week 52 for the placebo/anagliptin group and Week 0 to Week 52 for the continued anagliptin group). Data for both treatment groups include subjects who had their dose increased to 200 mg.

No deaths were reported. During Treatment Period I, serious adverse events were reported in 1 subject in the placebo group (large intestine carcinoma) and 2 subjects in the anagliptin group (2 events; colon cancer in 1 and presyncope in 1), but a causal relationship to the study drug was ruled out for these events. In the overall treatment period (based on the analysis of pooled data from Treatment Periods I and II), serious adverse events were noted in 3 subjects in the placebo/anagliptin group (3 events; injury in 1, uterine cancer in 1, and rectal cancer in 1) and 5 subjects in the continued anagliptin group (5 events; gastric cancer in 1, radius fracture in 1, myocardial infarction in 1, colon cancer in 1, and presyncope in 1), but a causal relationship to the study drug was ruled out for all events. No adverse events leading to study drug discontinuation were not noted during Treatment Period I. During the overall treatment period, adverse events leading to study drug discontinuation were noted in 3 subjects in the placebo/anagliptin group (uterine cancer, rectal cancer in 1, and large intestine carcinoma in 1) and 2 subjects in the continued anagliptin group (gastric cancer in 1 and myocardial infarction in 1); a causal relationship to the study drug was ruled out for all events. No events of hypoglycaemia were noted during Treatment Period I. The incidence of hypoglycaemia in the overall treatment period was 1.6% (1 of 62 subjects) in the continued anagliptin group; the event was considered an adverse drug reaction, but the severity was mild. Analysis of laboratory parameters, vital signs, body weight, and changes in resting 12-lead ECG revealed no clinically meaningful changes.

(b) Pioglitazone combination therapy

All of the 102 treated subjects (31 in the placebo group, 71 in the anagliptin group) were included in the safety analysis set and the FAS. The efficacy analysis was performed on the FAS. Of the 102 subjects, 99 (31 in the placebo group, 68 in the anagliptin group) completed Treatment Period I. Of the 99 subjects, 93 (29 in the placebo/anagliptin group, 64 in the continued anagliptin group) completed Treatment Period II. A total of 9 subjects discontinued the study, including 3 subjects in the anagliptin group (1 due to adverse event, 1 due to elevation of alanine aminotransferase, and 1 due to worsening of glycemic control) in Treatment Period I and 2 subjects in the placebo/anagliptin group (1 due to adverse event and 1 due to lack of efficacy) and 4 subjects in the continued anagliptin group (2 subjects due to adverse event and 2 due to worsening of glycemic control) in Treatment Period II. A total of 67 subjects (20 in the placebo/anagliptin group, 47 in the continued anagliptin group) had their anagliptin dose increased to 200 mg twice daily during Treatment Period II.

The primary efficacy endpoint was the change in HbA1c from baseline (Week 0) to the last assessment of Treatment Period I (Week 12 or discontinuation) in the FAS. The results are shown in Table 21, demonstrating the superiority of anagliptin over placebo.

Table 21. Change in HbA1c from baseline to the last assessment of Treatment Period I (Study DP1002 [combination with pioglitazone], FAS)

Treatment group	Baseline	At the last assessment	Change at the last assessment	Difference from placebo [95% CI]
Placebo (n = 31)	7.62 ± 0.84	7.93 ± 1.20	0.31 ± 0.66	−0.82 [−1.10, −0.53]
Anagliptin (n = 71)	7.60 ± 1.12	7.09 ± 1.25	−0.51 ± 0.67	

Unit, %; mean ± SD; missing data were imputed with LOCF.

The secondary endpoint was the time-course changes in HbA1c from baseline (Week 0 for the placebo and continued anagliptin groups, Week 12 [start of treatment with anagliptin] for the placebo/anagliptin group) to Week 52. The results are shown in Figure 5. The change (mean ± SD) [95% CI] in HbA1c from baseline or the start of treatment with anagliptin to the last assessment (Week 52 or discontinuation) was −1.17% ± 1.01% [−1.54, −0.80] in the placebo/anagliptin group and −0.73% ± 0.77% [−0.91, −0.54] in the continued anagliptin group, showing a decrease in HbA1c from baseline or the start of treatment with anagliptin in both groups.

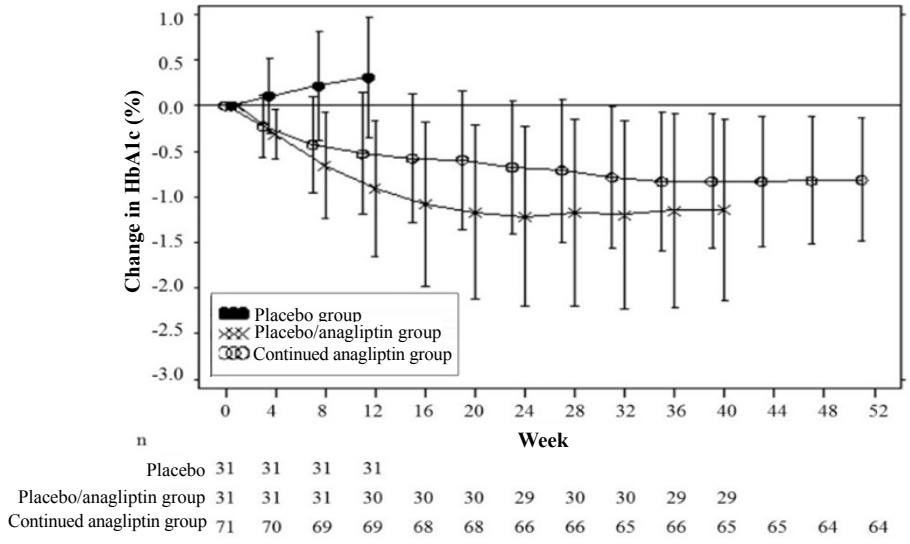

Figure 5. Time-course changes in HbA1c from baseline to Week 52 (Study DP1002 [combination with pioglitazone], FAS) (mean ± SD)

Table 22 shows the analysis results of other secondary endpoints.

Table 22. Analysis results of other secondary endpoints
(Study DP1002 [combination with pioglitazone], FAS)

Endpoint	Treatment group	Baseline or before the start of treatment with anagliptin[c)]	Change at the last assessment	95% CI of the change at the last assessment
Fasting blood glucose[a)] (mg/dL)	Placebo/anagliptin group	161.5 ± 32.1 (n = 31)	−21.0 ± 21.9 (n = 31)	[−29.0, −13.0]
	Continued anagliptin group	163.0 ± 43.3 (n = 71)	−19.3 ± 29.0 (n = 71)	[−26.2, −12.5]
2-hour postprandial blood glucose (mg/dL)	Placebo/anagliptin group	243.6 ± 67.1 (n = 31)	−48.7 ± 49.0 (n = 31)	[−66.7, −30.8]
	Continued anagliptin group	236.5 ± 72.1 (n = 71)	−39.5 ± 50.9 (n = 69)	[−51.7, −27.3]
Postprandial blood glucose AUC (mg·h/dL)	Placebo/anagliptin group	451.7 ± 92.8 (n = 31)	−81.2 ± 60.4 (n = 31)	[−103.3, −59.1]
	Continued anagliptin group	439.7 ± 110.2 (n = 71)	−66.3 ± 75.2 (n = 69)	[−84.3, −48.2]

Proportion of subjects with HbA1c <6.5%[b)]	Treatment Period I (up to Week 12)	Placebo group	Anagliptin group
		6.5 (2/31)	31.0 (22/71)
	Overall treatment period (up to Week 52)	Placebo/anagliptin group	Continued anagliptin group
		45.2 (14/31)	49.3 (35/71)

Mean ± SD
a) Missing data were imputed with LOCF.
b) Number of subjects who achieved HbA1c <6.5% at the last assessment/number of evaluated subjects
c) Week 0 (continued anagliptin group) or Week 12 (placebo/anagliptin group)

Safety analysis was performed. In Treatment Period I (Week 0 to Week 12), the incidence of adverse events was 51.6% (16 of 31 subjects) in the placebo group and 46.5% (33 of 71 subjects) in the anagliptin group, and the incidence of adverse drug reactions was 6.5% (2 of 31 subjects) in the placebo group and 8.5% (6 of 71 subjects) in the anagliptin group. Table 23 shows adverse events and/or adverse drug reactions reported in ≥3% of subjects in either group during Treatment Period I.

Table 23. Adverse events and/or adverse drug reactions reported in ≥3% of subjects in either group during Treatment Period I
(Study DP1002 [combination with pioglitazone], safety analysis set)

Adverse event term	Adverse event		Adverse drug reaction	
	Placebo (n = 31)	Anagliptin (n = 71)	Placebo (n = 31)	Anagliptin (n = 71)
Colonic polyp	3.2 (1)	2.8 (2)	0.0 (0)	0.0 (0)
Gastric ulcer	3.2 (1)	0.0 (0)	0.0 (0)	0.0 (0)
Bronchiolitis	3.2 (1)	0.0 (0)	0.0 (0)	0.0 (0)
Gastroenteritis	3.2 (1)	0.0 (0)	3.2 (1)	0.0 (0)
Nasopharyngitis	12.9 (4)	14.1 (10)	3.2 (1)	1.4 (1)
Patella fracture	3.2 (1)	0.0 (0)	0.0 (0)	0.0 (0)
Blood creatine phosphokinase increased	3.2 (1)	1.4 (1)	0.0 (0)	0.0 (0)
Occult blood positive	9.7 (3)	4.2 (3)	0.0 (0)	0.0 (0)
Diabetes mellitus	3.2 (1)	0.0 (0)	0.0 (0)	0.0 (0)
Arthralgia	3.2 (1)	0.0 (0)	0.0 (0)	0.0 (0)
Haemarthrosis	3.2 (1)	0.0 (0)	0.0 (0)	0.0 (0)
Hypoaesthesia	3.2 (1)	1.4 (1)	0.0 (0)	0.0 (0)
Alcoholism	3.2 (1)	0.0 (0)	0.0 (0)	0.0 (0)
Upper respiratory tract inflammation	3.2 (1)	4.2 (3)	0.0 (0)	0.0 (0)
Oropharyngeal pain	3.2 (1)	0.0 (0)	0.0 (0)	0.0 (0)

Incidence % (number of subjects with events), MedDRA/J ver. 12.1

In the overall treatment period (the duration of treatment with anagliptin, i.e., Week 12 to Week 52 for the placebo/anagliptin group and Week 0 to Week 52 for the continued anagliptin group), the incidence of adverse events was 74.2% (23 of 31 subjects) in the placebo/anagliptin group and 83.1% (59 of 71 subjects) in the continued anagliptin group, and the incidence of adverse drug reactions was 29.0% (9 of 31 subjects) in the placebo/anagliptin group and 19.7% (14 of 71 subjects) in the continued anagliptin group. Table 24 shows adverse events and/or adverse drug reactions reported in ≥3% of subjects during the overall treatment period.

Table 24. Adverse events and adverse drug reactions reported in ≥3% of subjects during the overall treatment period
(safety analysis set,[a)] combination with pioglitazone)

Adverse event term	Adverse event (n = 102)	Adverse drug reaction (n = 102)
Colonic polyp	5.9 (6)	0.0 (0)
Constipation	3.9 (4)	2.0 (2)
Dental caries	4.9 (5)	0.0 (0)
Gastritis	3.9 (4)	1.0 (1)
Seasonal allergy	3.9 (4)	0.0 (0)
Nasopharyngitis	20.6 (21)	1.0 (1)
Pharyngitis	4.9 (5)	0.0 (0)
Contusion	5.9 (6)	0.0 (0)
Blood creatine phosphokinase increased	3.9 (4)	1.0 (1)
Occult blood positive	11.8 (12)	0.0 (0)
Upper respiratory tract inflammation	9.8 (10)	0.0 (0)

Incidence % (number of subjects with events), MedDRA/J ver. 12.1

a) Data from the overall treatment period (the duration of treatment with anagliptin, i.e., Week 12 to Week 52 for the placebo/anagliptin group and Week 0 to Week 52 for the continued anagliptin group). Data for both treatment groups include subjects who had their dose increased to 200 mg.

No deaths were reported. During Treatment Period I, serious adverse events were reported in 1 subject in the placebo group (2 events, patella fracture and haemarthrosis in 1) and 2 subjects in the anagliptin group (2 events, myocardial ischaemia in 1 and meniscus injury in 1), but a causal relationship to the study drug was ruled out for all events. In the overall treatment period (based on the analysis of pooled data from Treatment Periods I and II), serious adverse events were reported in 1 subject in the placebo/anagliptin group (bladder cancer) and 5 subjects in the continued anagliptin group (5 events; gastric cancer in 1, cerebral infarction in 1, colonic polyp in 1, myocardial ischaemia in 1, and meniscus injury in 1), but a causal relationship to the study drug was ruled out for all events. During Treatment Period I, no adverse events leading to study drug discontinuation were reported in the placebo group, but 1 event was reported in 1 subject in the anagliptin group (oedema). During the overall treatment period, adverse events leading to study drug discontinuation were observed in 1 subject in the placebo/anagliptin group (bladder cancer) and 4 subjects in the continued anagliptin group (4 events; diabetes mellitus inadequate control in 1, gastric cancer in 1, cerebral infarction in 1, and oedema in 1), but a causal relationship to the study drug was ruled out for all events. During Treatment Period I, no events of hypoglycaemia were reported in the placebo group, but hypoglycaemia occurred in 2.8% (2 of 71) of subjects in the anagliptin group; both cases of hypoglycaemia were considered adverse drug reactions. The events were mild in severity. For the overall treatment period, hypoglycaemia was reported in 4.2% (3 of 71) of subjects in the continued anagliptin group; all the events were considered adverse drug reactions, but severity was mild. Analysis of laboratory parameters, vital signs, body weight, and changes in resting 12-lead ECG revealed no clinically meaningful changes.

2.(iii).A.(7) Phase III long-term study (combination therapy with sulfonylurea or biguanide) (5.3.5.1-6, Study SK-0403-02 [[redacted] to [redacted]])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted to evaluate the efficacy and safety of anagliptin in Japanese patients with type 2 diabetes mellitus with inadequate glycemic control on sulfonylurea (SU) or biguanide (BG)[9] (target sample size, 120 subjects for combination with SU [40 in the placebo group, 80 in the anagliptin group]; 90 subjects for combination with BG [30 in the placebo group, 60 in the anagliptin group]).

This study consisted of a run-in period (2-6 weeks), Treatment Period I (12 weeks), and Treatment Period II (40 weeks).

During Treatment Period I, placebo or anagliptin 100 mg was administered orally twice daily before morning and evening meals for 12 weeks. During Treatment Period II, anagliptin 100 mg was administered orally twice daily before morning and evening meals for 40 weeks. Beginning at Week 28 of treatment, the dose escalation was allowed based on HbA1c levels measured every 4 weeks from Week 24 to Week 36. The dose was increased to 200 mg twice daily in subjects who had HbA1c ≥6.5%.

[9] Key inclusion criteria: Patients with type 2 diabetes mellitus aged ≥20 and <75 years on diet or diet/exercise therapy with HbA1c of ≥6.5% and <10.0% in the run-in period (2-6 weeks prior to baseline) who were receiving SU or BG from at least 8 weeks before the start of the run-in period (2-6 weeks prior to baseline). Type and dosing regimen of the α-GI or pioglitazone had to remain unchanged for at least 8 weeks before the start of the run-in period.

The dosing regimen of concomitant SU or BG had to remain unchanged for 8 weeks before the start of the run-in period and throughout the study period. Data are presented below separately for the combination therapy with SU and the combination therapy with BG.

(a) SU combination therapy

All of the 136 treated subjects (46 in the placebo group, 90 in the anagliptin group) were included in the safety analysis set. Of these, 135 subjects (45 in the placebo group, 90 in the anagliptin group) were included in the FAS, which was used for the efficacy analysis, and the remaining 1 subject in the placebo group was excluded from analysis (discontinuation due to adverse event/subject's request). Of the 135 subjects, 134 (45 in the placebo group, 89 in the anagliptin group) completed Treatment Period I. Of the 134 subjects, 125 (41 in the placebo/anagliptin group, 84 in the continued anagliptin group) completed Treatment Period II. A total of 11 subjects discontinued the study, including 1 subject in the placebo group (due to an adverse event/subject's request) and 1 subject in the anagliptin group (due to medical judgment of the investigator or sub-investigator) in Treatment Period I and 4 subjects in the placebo/anagliptin group (3 due to adverse event, 2 due to worsening of glycemic control [1 subject discontinued for multiple reasons]) and 5 subjects in the continued anagliptin group (all due to adverse event) who discontinued during Treatment Period II. A total of 109 subjects (39 in the placebo/anagliptin group, 70 in the continued anagliptin group) had a dose increase of anagliptin to 200 mg twice daily during Treatment Period II.

The change in HbA1c from baseline (Week 0) to the last assessment in Treatment Period I (Week 12 or discontinuation) in the FAS, the primary efficacy endpoint, was as shown in Table 25, demonstrating the superiority of anagliptin over placebo.

Table 25. Change in HbA1c from baseline to the last assessment of Treatment Period I (Study SK-0403-02 [combination with SU], FAS)

Treatment group	Baseline	At the last assessment	Change at the last assessment	Difference from placebo [95% CI]
Placebo (n = 45)	7.77 ± 0.87	8.01 ± 0.99	0.24 ± 0.58	−0.77 [−0.95, −0.58]
Anagliptin (n = 90)	7.72 ± 0.87	7.19 ± 1.03	−0.52 ± 0.47	

Unit, %; mean ± SD; missing data were imputed with LOCF.

The time-course changes in HbA1c from baseline (Week 0 for the placebo and continued anagliptin groups, Week 12 [start of treatment with anagliptin] for the placebo/anagliptin group) to Week 52, the secondary endpoint, was as shown in Figure 6. The change (mean ± SD) [95% CI] in HbA1c from baseline or the start of treatment with anagliptin to the last assessment (Week 52 or discontinuation) was −0.54% ± 0.91% [−0.81, −0.27] in the placebo/anagliptin group and −0.25% ± 0.75% [−0.41, −0.09] in the continued anagliptin group; HbA1c decreased after the start of anagliptin treatment in both groups.

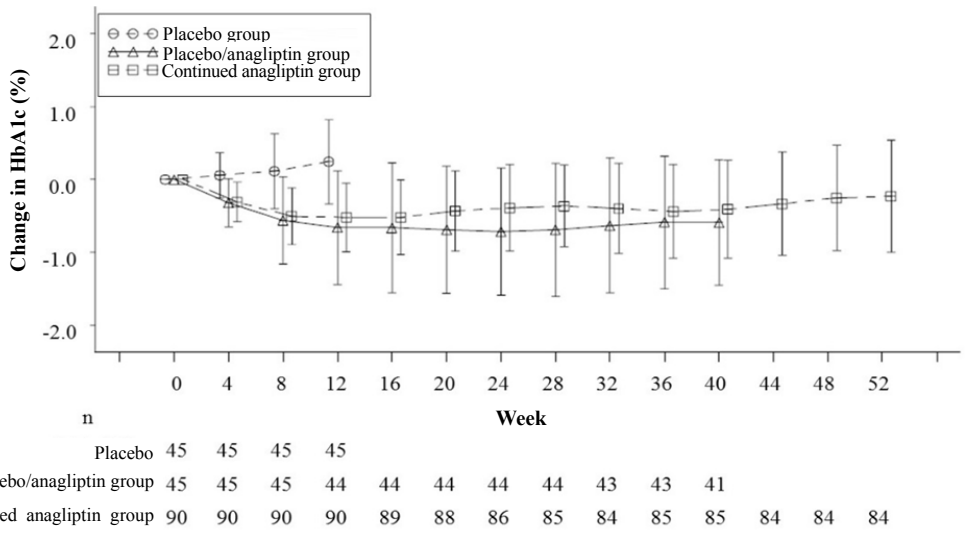

Figure 6. Time-course changes in HbA1c from baseline to Week 52 (Study SK-0403-02 [combination with SU], FAS) (mean ± SD)

Table 26 shows the analysis results of other secondary endpoints.

Table 26. Analysis results of other secondary endpoints (Study SK-0403-02 [combination with SU], FAS)

Endpoint	Treatment group	Baseline or before the start of treatment with anagliptin[c)]	Change at the last assessment	95% CI of the change at the last assessment
Fasting blood glucose[a)] (mg/dL)	Placebo/anagliptin group	162.9 ± 29.3 (n = 45)	−8.9 ± 27.8 (n = 45)	[−17.2, −0.5]
	Continued anagliptin group	159.2 ± 33.2 (n = 90)	−5.5 ± 26.7 (n = 90)	[−11.1, 0.0]
2-hour postprandial blood glucose (mg/dL)	Placebo/anagliptin group	258.4 ± 54.6 (n = 45)	−14.6 ± 49.1 (n = 44)	[−29.6, 0.3]
	Continued anagliptin group	251.2 ± 48.8 (n = 90)	−5.8 ± 40.4 (n = 90)	[−14.2, 2.7]
Postprandial blood glucose AUC (mg·h/dL)	Placebo/anagliptin group	461.7 ± 67.4 (n = 45)	−36.0 ± 66.4 (n = 44)	[−56.2, −15.8]
	Continued anagliptin group	453.5 ± 75.6 (n = 90)	−22.7 ± 62.9 (n = 90)	[−35.9, −9.5]

Proportion of subjects with HbA1c <6.5%[b)]	Treatment Period I (up to Week 12)	Placebo group	Anagliptin group
		2.2 (1/45)	22.2 (20/90)
	Overall treatment period (up to Week 52)	Placebo/anagliptin group	Continued anagliptin group
		8.9 (4/45)	20.0 (18/90)

Mean ± SD

a) Missing data were imputed with LOCF.

b) Number of subjects who achieved HbA1c <6.5% at the last assessment/number of assessed subjects

c) Week 0 (continued anagliptin group) or Week 12 (placebo/anagliptin group)

Safety analysis was performed. During Treatment Period I (Week 0 to Week 12), the incidence of adverse events was 58.7% (27 of 46 subjects) in the placebo group and 58.9% (53 of 90 subjects) in the anagliptin group, and the incidence of adverse drug reactions was 13.0% (6 of 46 subjects) in the placebo group and 13.3% (12 of 90 subjects) in the anagliptin group. Table 27 shows adverse events and/or adverse drug reactions reported in ≥3% of subjects in either group during Treatment Period I.

Table 27. Adverse events and/or adverse drug reactions reported in ≥3% of subjects in either group during Treatment Period I (Study SK-0403-02 [combination with SU], safety analysis set)

Adverse event term	Adverse event		Adverse drug reaction	
	Placebo (n = 46)	Anagliptin (n = 90)	Placebo (n = 46)	Anagliptin (n = 90)
Abdominal discomfort	4.3 (2)	0.0 (0)	4.3 (2)	0.0 (0)
Abdominal pain upper	2.2 (1)	4.4 (4)	0.0 (0)	1.1 (1)
Nasopharyngitis	8.7 (4)	10.0 (9)	0.0 (0)	0.0 (0)
Rhinitis	4.3 (2)	0.0 (0)	2.2 (1)	0.0 (0)
Blood pressure increased	4.3 (2)	0.0 (0)	2.2 (1)	0.0 (0)
White blood cell count increased	0.0 (0)	3.3 (3)	0.0 (0)	0.0 (0)
Occult blood positive	6.5 (3)	3.3 (3)	0.0 (0)	2.2 (2)
Hypoglycaemia	4.3 (2)	7.8 (7)	4.3 (2)	5.6 (5)
Upper respiratory tract inflammation	2.2 (1)	5.6 (5)	0.0 (0)	0.0 (0)
Eczema	0.0 (0)	5.6 (5)	0.0 (0)	0.0 (0)

Incidence % (number of subjects with events), MedDRA/J ver. 14.0

In the overall treatment period (the duration of treatment with anagliptin, i.e., Week 12 to Week 52 for the placebo/anagliptin group and Week 0 to Week 52 for the continued anagliptin group), the incidence of adverse events was 84.4% (38 of 45 subjects) in the placebo/anagliptin group and 92.2% (83 of 90 subjects) in the continued anagliptin group, and the incidence of adverse drug reactions was 31.1% (14 of 45 subjects) in the placebo/anagliptin group and 32.2% (29 of 90 subjects) in the continued anagliptin group. Table 28 shows adverse events and/or adverse drug reactions reported in ≥3% of subjects during the overall treatment period.

Table 28. Adverse events and/or adverse drug reactions reported in ≥3% of subjects during the overall treatment period
(Study SK-0403-02 [combination with SU], safety analysis set[a])

Adverse event term	Adverse event (n = 135)	Adverse drug reaction (n = 135)
Conjunctivitis	3.0 (4)	0.0 (0)
Abdominal pain upper	5.2 (7)	1.5 (2)
Constipation	8.1 (11)	5.2 (7)
Dental caries	3.7 (5)	0.0 (0)
Diarrhoea	3.0 (4)	1.5 (2)
Gastritis	3.7 (5)	0.0 (0)
Periodontitis	4.4 (6)	0.0 (0)
Seasonal allergy	6.7 (9)	0.0 (0)
Bronchitis	5.2 (7)	0.0 (0)
Nasopharyngitis	32.6 (44)	1.5 (2)
Pharyngitis	4.4 (6)	0.0 (0)
Tinea pedis	3.0 (4)	0.0 (0)
Contusion	3.0 (4)	0.0 (0)
Alanine aminotransferase increased	8.9 (12)	4.4 (6)
Aspartate aminotransferase increased	4.4 (6)	1.5 (2)
Blood creatine phosphokinase increased	5.9 (8)	0.0 (0)
Blood urea increased	3.0 (4)	0.0 (0)
Gamma-glutamyltransferase increased	4.4 (6)	2.2 (3)
White blood cell count increased	8.9 (12)	0.7 (1)
Occult blood positive	10.4 (14)	3.7 (5)
Hypoglycaemia	13.3 (18)	7.4 (10)
Arthralgia	3.7 (5)	0.0 (0)
Back pain	5.2 (7)	0.0 (0)
Periarthritis	3.0 (4)	0.0 (0)
Dizziness	3.0 (4)	0.7 (1)
Headache	3.7 (5)	0.0 (0)
Insomnia	3.0 (4)	0.0 (0)
Rhinitis allergic	3.7 (5)	0.0 (0)
Upper respiratory tract inflammation	11.1 (15)	0.7 (1)
Eczema	8.9 (12)	0.7 (1)
Hypertension	5.2 (7)	0.0 (0)

Incidence % (number of subjects with events), MedDRA/J ver. 14.0

a) Data from the overall treatment period (the duration of treatment with anagliptin, i.e., Week 12 to Week 52 for the placebo/anagliptin group and Week 0 to Week 52 for the continued anagliptin group). Data for both treatment groups include subjects increased their dose to 200 mg.

No deaths were reported. During Treatment Period I, serious adverse events were reported in 2 subjects in the anagliptin group (2 events; angina pectoris in 1 and colon adenoma in 1), but a causal relationship to the study drug was ruled out for both events. For the overall treatment period (based on the analysis of pooled data from Treatment Periods I and II), serious adverse events were reported in 4 subjects in the placebo/anagliptin group (4 events; radius fracture in 1, acute myocardial infarction in 1, atrioventricular block complete in 1, and heat illness in 1) and 5 subjects in the continued anagliptin group (5 events; angina pectoris in 1, colon adenoma in 1, colon cancer in 1, fall in 1, and gastric cancer in 1), but a causal relationship to the study drug was ruled out for all events. During Treatment Period I, an adverse event leading to study drug discontinuation was reported in 1 subject in the placebo group (abdominal discomfort), and the event was considered an adverse drug reaction. For the overall treatment period, adverse events leading to study drug discontinuation were reported in 3 subjects in the placebo/anagliptin group (4 events; radius fracture in 1, acute myocardial infarction in 1, and glycosylated haemoglobin increased and blood glucose increased in 1) and 5 subjects in the continued anagliptin group (6 events; angina pectoris in 1, colon cancer and occult blood positive in 1, fall in 1, eczema in 1, and gastric cancer in 1), but a causal relationship to the study drug was ruled out for all events. In Treatment Period I, the incidence of hypoglycaemia was 4.3% (2 of 46 subjects) in the placebo group and 7.8% (7 of 90 subjects) in the anagliptin group, and the cases of hypoglycaemia reported in 4.3% (2 of 46) of subjects in the placebo group and 5.6% (5 of 90) of subjects in the anagliptin group were considered adverse drug reactions; all these events were mild in severity. The incidence of hypoglycaemia for the overall treatment period was 11.1% (5 of 45 subjects) in the placebo/anagliptin group and 14.4% (13 of 90 subjects) in the continued anagliptin group, and the cases of hypoglycaemia reported in 4.4% (2 of 45) of subjects in the placebo/anagliptin group and 8.9% (8 of 90) of subjects in the continued anagliptin group were considered adverse drug reactions; all these events were mild in severity. No clinically meaningful changes were observed in laboratory parameters, vital signs, body weight, or 12-lead ECG.

(b) BG combination therapy

All of the 105 treated subjects (36 in the placebo group, 69 in the anagliptin group) were included in the safety analysis set and the FAS. The efficacy analysis was performed on the FAS. Of the 105 subjects, 102 (35 in the placebo group, 67 in the anagliptin group) completed Treatment Period I. Of the 102 subjects, 96 (33 in the placebo/anagliptin group, 63 in the continued anagliptin group) completed Treatment Period II. A total of 9 subjects discontinued the study, including 1 subject in the placebo group (due to adverse event/worsening of glycemic control) and 2 subjects in the anagliptin group (both due to adverse event) who discontinued in Treatment Period I and 2 subjects in the placebo/anagliptin group (both due to adverse event) and 4 subjects in the continued anagliptin group (2 due to subject's request, 1 due to adverse event, and 1 due to adverse event and aspartate aminotransferase or alanine aminotransferase ≥150 IU/L) who discontinued in Treatment Period II. A total of 72 subjects (26 in the placebo/anagliptin group, 46 in the continued anagliptin group) had their anagliptin dose increased to 200 mg twice daily during Treatment Period II.

The primary efficacy endpoint was the change in HbA1c from baseline (Week 0) to the last assessment of Treatment Period I (Week 12 or discontinuation) in the FAS. The results are shown in Table 29, demonstrating the superiority of anagliptin over placebo.

Table 29. Change in HbA1c from baseline to the last assessment of Treatment Period I (Study SK-0403-02 [combination with BG], FAS)

Treatment group	Baseline	At the last assessment	Change at the last assessment	Difference from placebo [95% CI]
Placebo (n = 36)	7.65 ± 1.00	8.09 ± 1.45	0.44 ± 0.89	−1.05 [−1.35, −0.74]
Anagliptin (n = 69)	7.75 ± 0.96	7.15 ± 1.01	−0.61 ± 0.66	

Unit, %; mean ± SD; missing data were imputed with LOCF.

The secondary endpoint was the time-course changes in HbA1c from baseline (Week 0 for the placebo and continued anagliptin groups, Week 12 [before the start of treatment with anagliptin] for the placebo/anagliptin group) to Week 52. Figure 7 shows the results. The change (mean ± SD) [95% CI] in HbA1c from baseline or the start of treatment with anagliptin to the last assessment (Week 52 or discontinuation) was −1.01% ± 1.04% [−1.36, −0.65] in the placebo/anagliptin group and −0.49% ± 1.14% [−0.76, −0.21] in the continued anagliptin group, showing a decrease in HbA1c from baseline or the start of treatment with anagliptin in both groups.

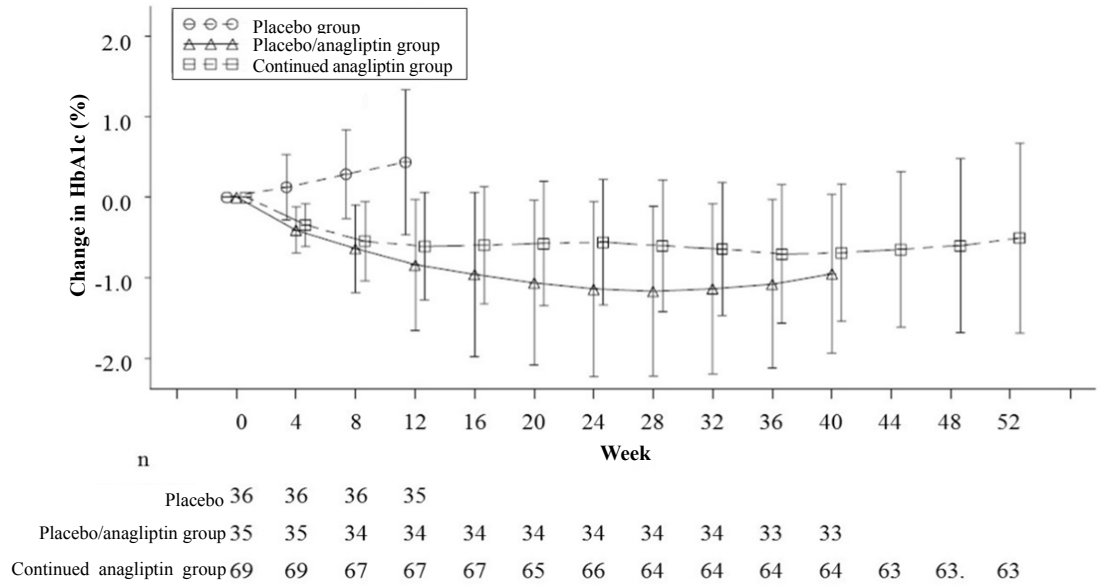

Figure 7. Time-course changes in HbA1c from baseline to Week 52 (Study SK-0403-02 [combination with BG], FAS) (mean ± SD)

Table 30 shows the analysis results of other secondary endpoints.

Table 30. Analysis results of other secondary endpoints
(Study SK-0403-02 [combination with BG], FAS)

Endpoint	Treatment group	Baseline or before the start of treatment with anagliptin [c)]	Change at the last assessment	95% CI of the change at the last assessment
Fasting blood glucose[a)] (mg/dL)	Placebo/anagliptin group	172.1 ± 44.9 (n = 35)	−23.9 ± 36.1 (n = 35)	[−36.3, −11.5]
	Continued anagliptin group	165.0 ± 38.5 (n = 69)	−10.6 ± 37.6 (n = 69)	[−19.6, −1.5]
2-hour postprandial blood glucose (mg/dL)	Placebo/anagliptin group	256.5 ± 67.6 (n = 35)	−29.9 ± 49.1 (n = 34)	[−47.0, −12.8]
	Continued anagliptin group	243.7 ± 63.2 (n = 68)	−22.3 ± 60.4 (n = 66)	[−37.1, −7.4]
Postprandial blood glucose AUC (mg·h/dL)	Placebo/anagliptin group	473.6 ± 109.9 (n = 35)	−61.9 ± 80.3 (n = 34)	[−89.9, −33.8]
	Continued anagliptin group	458.7 ± 96.9 (n = 68)	−43.7 ± 86.8 (n = 66)	[−65.0, −22.4]

Proportion of subjects with HbA1c <6.5%[b)]	Treatment Period I (up to Week 12)	Placebo group	Anagliptin group
		2.8 (1/36)	30.4 (21/69)
	Overall treatment period (up to Week 52)	Placebo/anagliptin group	Continued anagliptin group
		30.6 (11/36)	24.6 (17/69)

Mean ± SD
a) Missing data were imputed with LOCF.
b) Number of subjects who achieved HbA1c <6.5% at the last assessment/number of assessed subjects
c) Week 0 (continued anagliptin group) or Week 12 (placebo/anagliptin group)

Safety analysis was performed. During Treatment Period I (Week 0 to Week 12), the incidence of adverse events was 61.1% (22 of 36 subjects) in the placebo group and 60.9% (42 of 69 subjects) in the anagliptin group, and the incidence of adverse drug reactions was 11.1% (4 of 36 subjects) in the placebo group and 8.7% (6 of 69 subjects) in the anagliptin group. Table 31 shows adverse events and/or adverse drug reactions reported in ≥3% of subjects in either group during Treatment Period I.

Table 31. Adverse events and/or adverse drug reactions reported in ≥3% of subjects in either group during Treatment Period I
(Study SK-0403-02 [combination with BG], safety analysis set)

Adverse event term	Adverse event		Adverse drug reaction	
	Placebo (n = 36)	Anagliptin (n = 69)	Placebo (n = 36)	Anagliptin (n = 69)
Nasopharyngitis	5.6 (2)	10.1 (7)	0.0 (0)	0.0 (0)
Alanine aminotransferase increased	0.0 (0)	4.3 (3)	0.0 (0)	0.0 (0)
Glycosylated haemoglobin increased	8.3 (3)	1.4 (1)	0.0 (0)	0.0 (0)
Occult blood positive	11.1 (4)	7.2 (5)	2.8 (1)	1.4 (1)
Pollakiuria	5.6 (2)	0.0 (0)	0.0 (0)	0.0 (0)
Rhinitis allergic	0.0 (0)	4.3 (3)	0.0 (0)	0.0 (0)
Upper respiratory tract inflammation	0.0 (0)	5.8 (4)	0.0 (0)	0.0 (0)

Incidence % (number of subjects with events), MedDRA/J ver. 14.0

Adverse events were summarized for the overall treatment period (the duration of treatment with anagliptin, i.e., Week 12 to Week 52 for the placebo/anagliptin group and Week 0 to Week 52 for the continued anagliptin group). The incidence of adverse events was 94.3% (33 of 35 subjects) in the placebo/anagliptin group and 91.3% (63 of 69 subjects) in the continued anagliptin group, and the incidence of adverse drug reactions was 28.6% (10 of 35 subjects) in the placebo/anagliptin group and 21.7% (15 of 69 subjects) in the continued anagliptin group. Table 32 shows adverse events and/or adverse drug reactions reported in ≥3% of subjects during the overall treatment period.

Table 32. Adverse events and/or adverse drug reactions reported in ≥3% of subjects during the overall treatment period
(Study SK-0403-02 [combination with BG], safety analysis set[a])

Adverse event term	Adverse event (n = 104)	Adverse drug reaction (n = 104)
Colonic polyp	5.8 (6)	0.0 (0)
Constipation	4.8 (5)	2.9 (3)
Dental caries	5.8 (6)	0.0 (0)
Diarrhoea	10.6 (11)	1.9 (2)
Reflux oesophagitis	3.8 (4)	0.0 (0)
Seasonal allergy	5.8 (6)	0.0 (0)
Nasopharyngitis	25.0 (26)	0.0 (0)
Alanine aminotransferase increased	13.5 (14)	3.8 (4)
Aspartate aminotransferase increased	11.5 (12)	2.9 (3)
Blood amylase increased	5.8 (6)	2.9 (3)
Blood creatine phosphokinase increased	6.7 (7)	1.0 (1)
Blood triglycerides increased	3.8 (4)	0.0 (0)
Gamma-glutamyltransferase increased	9.6 (10)	1.9 (2)
Blood urine present	10.6 (11)	1.9 (2)
White blood cell count increased	5.8 (6)	1.0 (1)
Occult blood positive	13.5 (14)	4.8 (5)
Back pain	5.8 (6)	0.0 (0)
Periarthritis	4.8 (5)	0.0 (0)
Rhinitis allergic	3.8 (4)	0.0 (0)
Upper respiratory tract inflammation	14.4 (15)	0.0 (0)
Hypertension	3.8 (4)	0.0 (0)

Incidence % (number of subjects with events), MedDRA/J ver. 14.0

a) Data from the overall treatment period (the duration of treatment with anagliptin, i.e., Week 12 to Week 52 for the placebo/anagliptin group and Week 0 to Week 52 for the continued anagliptin group). Data for both treatment groups include subjects who increased their dose to 200 mg.

Death occurred in 1 subject in the placebo/anagliptin group (pancreatic carcinoma), but a causal relationship to the study drug was ruled out for this event. No other serious adverse events were reported during Treatment Period I. In the overall treatment period (based on the analysis of pooled data from Treatment Periods I and II), serious adverse events were reported in 3 subjects in the placebo/anagliptin group (3 events; gastric cancer in 1, colonic polyp in 1, and inguinal hernia in 1) and 3 subjects in the continued anagliptin group (3 events; periarthritis in 1, intervertebral disc protrusion in 1, and chronic sinusitis in 1). A causal relationship to the study drug was ruled out for all events. During Treatment Period I, adverse events leading to study drug discontinuation were reported in 1 subject in the placebo group (glycosylated haemoglobin increased) and 2 subjects in the anagliptin group (2 events, blood urine present in 1 and rash generalised in 1). For the overall treatment period, adverse events leading to study drug discontinuation were reported in 2 subjects in the placebo/anagliptin group (2 events, rash in 1 and pancreatic carcinoma in 1) and 4 subjects in the continued anagliptin group (4 events; alanine aminotransferase increased in 1, oedema in 1, blood urine present in 1, and rash generalised in 1). A causal relationship to the study drug was ruled out for glycosylated haemoglobin increased (1 subject) and pancreatic carcinoma (1 subject) and the other events were considered adverse drug reactions. No events of hypoglycaemia were noted during Treatment Period I. In the overall treatment period, the incidence of hypoglycaemia was 2.9% (1 of 35 subjects) in the placebo/anagliptin group and 1.4% (1 of 69 subjects) in the continued anagliptin group. Hypoglycaemia reported in 2.9% (1 of 35) of subjects in the placebo/anagliptin group were considered an adverse drug reaction, but the severity was mild. No clinically meaningful changes were observed in laboratory parameters, vital signs, body weight, or 12-lead ECG.

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

2.(iii).B.(1) Clinical positioning of anagliptin

PMDA considers that anagliptin may become a therapeutic option for patients with type 2 diabetes mellitus regardless of the type of concomitant medication, on the grounds that anagliptin has been approved as monotherapy and in combination with α-GI, BG, SU, and TZD, and that its efficacy has been confirmed in the phase III study of anagliptin in combination with glinide (Study DP1007) and the phase III study of anagliptin in combination with insulin (Study DP1008) conducted for this application [see "2.(iii).B.(2) Efficacy"] and its safety is considered acceptable [see "2.(iii).B.(3) Safety"].

2.(iii).B.(2) Efficacy

The applicant's explanation:

In the phase III study of anagliptin in combination with glinide (Study DP1007), the HbA1c lowering effect was maintained for 52 weeks (Figure 1). In addition, in the phase III study of anagliptin in combination with insulin (Study DP1008), the superiority of anagliptin over placebo was demonstrated in terms of HbA1c reduction (Table 4), and the HbA1c lowering effect was maintained for 52 weeks (Figure 2). The efficacy of anagliptin plus glinide or insulin was not substantially different from that seen in clinical studies for the approved indications (Table 33).

Table 33. Change in HbA1c (Japanese long-term studies)[a)]

	DP1007	DP1008	SK-0403-01	DP1002		SK-0403-02	
	Anagliptin + glinide (n = 63)	Anagliptin + insulin (n = 61)	Anagliptin monotherapy (n = 150)	Anagliptin + α-GI (n = 62)	Anagliptin + TZD (n = 71)	Anagliptin + SU (n = 90)	Anagliptin + BG (n = 69)
Baseline HbA1c	8.14 ± 0.93	8.33 ± 0.90	8.21 ± 1.05	8.10 ± 0.97	8.01 ± 1.13	8.12 ± 0.87	8.16 ± 0.97
Change in HbA1c at the last assessment	−0.87 ± 0.71	−0.72 ± 0.64	−0.62 ± 0.84	−0.86 ± 0.82	−0.73 ± 0.78	−0.25 ± 0.76	−0.49 ± 1.15

Unit, %; mean ± SD; HbA1c, NGSP values

a) Data from subjects who completed 52 weeks of anagliptin treatment (including subjects increased their dose to 200 mg) (For Studies DP1008, DP1002, and SK-0403-02, changes in HbA1c at the last assessment in subjects in the continued anagliptin group who received anagliptin during the double-blind period)

In addition, subgroup analysis was performed to evaluate the impact of baseline characteristics on the efficacy of anagliptin in subjects who received combination therapy of anagliptin and insulin. The results showed that the change in HbA1c from baseline to the end of the double-blind period tended to be smaller in the following subgroups of subjects receiving anagliptin: subjects with baseline fasting serum C-peptide of ≥1.0 ng/mL, subjects using basal and bolus insulin, and subjects on anagliptin monotherapy. However, the change in HbA1c was not substantially different among subgroups of subjects receiving anagliptin, and HbA1c decreased in all the subgroups (Table 34).

Table 34. Changes in HbA1c from baseline to the end of the double-blind period by baseline characteristics (Study DP1008) (FAS)

Baseline characteristics		Treatment group	Number of subjects	HbA1c (%)	
				At baseline	Change
Baseline fasting serum C-peptide	<1.0 ng/mL	Placebo	34	8.08 ± 0.91	0.08 ± 0.62
		Anagliptin	36	8.19 ± 0.88	−0.81 ± 0.59
	≥1.0 ng/mL	Placebo	26	8.38 ± 1.10	0.16 ± 0.81
		Anagliptin	25	8.54 ± 0.92	−0.56 ± 0.67
Insulin treatment	Long-acting	Placebo	18	8.86 ± 1.26	0.49 ± 1.04
		Anagliptin	22	8.49 ± 1.11	−0.73 ± 0.84
	Pre-mixed	Placebo	22	8.07 ± 0.75	−0.06 ± 0.43
		Anagliptin	20	8.37 ± 0.64	−0.83 ± 0.57
	Basal + bolus[a)]	Placebo	15	7.81 ± 0.73	−0.01 ± 0.47
		Anagliptin	10	7.97 ± 0.75	−0.48 ± 0.28
	Others	Placebo	5	7.72 ± 0.51	−0.10 ± 0.22
		Anagliptin	9	8.28 ± 1.01	−0.66 ± 0.39
Daily dose of insulin	<20 units	Placebo	29	8.27 ± 1.08	0.32 ± 0.84
		Anagliptin	29	8.32 ± 0.99	−0.73 ± 0.60
	≥20 units	Placebo	31	8.16 ± 0.94	−0.08 ± 0.48
		Anagliptin	32	8.34 ± 0.84	−0.69 ± 0.67
Concomitant drug	None	Placebo	27	7.81 ± 0.77	0.08 ± 0.92
		Anagliptin	27	7.96 ± 0.71	−0.56 ± 0.38
	α-GI	Placebo	10	8.20 ± 0.75	0.20 ± 0.43
		Anagliptin	10	8.52 ± 0.75	−0.99 ± 0.41
	BG	Placebo	23	8.68 ± 1.15	0.11 ± 0.50
		Anagliptin	24	8.67 ± 1.02	−0.75 ± 0.86

Mean ± SD

a) A long-acting insulin was used as basal insulin, and a rapid-acting or ultra-rapid-acting insulin was used as bolus insulin.

In summary, the applicant considers that the efficacy of anagliptin in patients with type 2 diabetes mellitus has been confirmed.

PMDA's view:

The efficacy of anagliptin in combination with glinide and in combination with insulin has been demonstrated, on the grounds that the HbA1c lowering effect was maintained for 52 weeks (Figure 1)

in the phase III study of anagliptin in combination with glinide (Study DP1007), and that the superiority of anagliptin over placebo was demonstrated in terms of HbA1c reduction (Table 4) and the HbA1c lowering effect was maintained for 52 weeks (Figure 2) in the phase III study of anagliptin in combination with insulin (Study DP1008).

2.(iii).B.(3) Safety

The applicant's explanation:

Table 35 shows of a summary of adverse events reported in the phase III study of anagliptin in combination with glinide (Study DP1007), the phase III study of anagliptin in combination with insulin (Study DP1008), and the Japanese long-term studies conducted for the approved indications. There was no trend toward a substantial increase in the risk of overall adverse events, overall adverse drug reactions, serious adverse events, and adverse events leading to treatment discontinuation in subjects receiving the combination therapy with anagliptin and glinide, compared to that associated with the use of anagliptin for the approved indications in the incidence of overall adverse events. On the other hand, the incidence rate (number of events per patient-year) of overall adverse events and overall adverse drug reactions in subjects receiving combination therapy with anagliptin and insulin tended to be higher than that associated with the use of anagliptin in other therapies. However, no substantial difference was observed in the incidence rate (number of events per patient-year) of serious adverse events or adverse events leading to treatment discontinuation.

Table 35. Summary of adverse events (Japanese long-term studies)

	DP1007	DP1008[a)]	DP1001 DP1003 SK-0403-01	DP1002[a)]		SK-0403-02[a)]	
	Anagliptin + glinide (n = 63)	Anagliptin + insulin (n = 120)	Anagliptin monotherapy[b)] (n = 286)	Anagliptin + α-GI (n = 94)	Anagliptin + TZD (n = 102)	Anagliptin + SU (n = 135)	Anagliptin + BG (n = 104)
Overall adverse events	44 (69.8) [2.08]	99 (82.5) [5.78]	203 (71.0) [3.70]	72 (76.6) [2.40]	82 (80.4) [2.63]	121 (89.6) [4.19]	96 (92.3) [4.07]
Overall adverse drug reactions	17 (27.0) [0.55]	67 (55.8) [4.09]	55 (19.2) [0.52]	22 (23.4) [0.45]	23 (22.5) [0.36]	43 (31.9) [0.58]	25 (24.0) [0.51]
Serious adverse events	4 (6.3) [0.07]	9 (7.5) [0.11]	14 (4.9) [0.09]	8 (8.5) [0.10]	6 (5.9) [0.07]	9 (6.7) [0.07]	7 (6.7) [0.08]
Adverse events leading to treatment discontinuation	0 (0.0) [0.00]	8 (6.7) [0.09]	18 (6.3) [0.14]	5 (5.3) [0.05]	5 (4.9) [0.06]	8 (5.9) [0.07]	6 (5.8) [0.07]

Number of subjects with events (incidence %) [Incidence rate (events per patient-year)]

a) Data from Treatment Period II (Week 12 to Week 52) for the placebo/anagliptin group who received placebo during the double-blind period, and data for the overall treatment period (Week 0 to Week 52) for the continued anagliptin group who received anagliptin during the double-blind period. Data from both treatment groups include subjects who had their dose increased to 200 mg.

b) Data of subjects in the 100 mg group (including subjects who had their dose increased to 200 mg) based on the pooled data from Studies DP1001, DP1003, and SK-0403-01

PMDA asked the applicant to explain the impact of type and dose level of concomitant glinide on the safety in Study DP1007.

The applicant's response:

Table 36 shows the incidence of adverse events by type and dose level of glinide in Study DP1007. There was almost no tendency toward a higher incidence of adverse events, adverse drug reactions, or serious adverse events with a particular glinide. When analyzed by dose level, the incidence of adverse events and adverse drug reactions tended to be higher in subjects who received concomitant mitiglinide calcium hydrate at doses >30 mg/day, but no substantial difference was observed in the incidence of serious adverse events. Due to the limited number of subjects receiving concomitant repaglinide, the safety of this combination therapy could not be adequately evaluated.

Table 36. Incidence of adverse events by type and dose level of glinide (Study DP1007)

Name of drug	Dose level	Overall adverse events	Overall adverse drug reactions	Serious adverse events
Nateglinide	Total (n = 20)	13 (65.0)	5 (25.0)	0 (0.0)
	270 mg/day (n = 19)	13 (68.4)	5 (26.3)	0 (0.0)
	360 mg/day (n = 1)	0 (0.0)	0 (0.0)	0 (0.0)
Mitiglinide calcium hydrate	Total (n = 36)	27 (75.0)	9 (25.0)	3 (8.3)
	15 mg/day (n = 9)	4 (44.4)	2 (22.2)	1 (11.1)
	30 mg/day (n = 24)	20 (83.3)	5 (20.8)	2 (8.3)
	60 mg/day (n = 3)	3 (100.0)	2 (66.7)	0 (0.0)
Repaglinide	Total (n = 7)	4 (57.1)	3 (42.9)	1 (14.3)
	0.75 mg/day (n = 1)	0 (0.0)	0 (0.0)	0 (0.0)
	1.5 mg/day (n = 5)	4 (80.0)	3 (60.0)	1 (20.0)
	3 mg/day (n = 1)	0 (0.0)	0 (0.0)	0 (0.0)

Number of subjects with events (incidence %)

PMDA asked the applicant to explain the impact on the safety in Study DP1008 by type of insulin therapy, insulin dose level, and concomitant medication.

The applicant's response:
As shown in Table 37, the incidence of serious adverse events and adverse events leading to treatment discontinuation tended to be slightly higher in the subgroup of subjects using basal and bolus insulin, but no substantial difference was observed in the incidence of adverse events among other subgroups. Therefore, these factors are unlikely to have an impact on the safety of anagliptin in combination with insulin [see "2.(iii).B.(3).1) Hypoglycaemia" for the incidence of hypoglycaemia by type of insulin therapy, insulin dose level, and concomitant medication].

Table 37. Incidence of adverse events by type of insulin therapy, insulin dose level, and concomitant medication (all subjects[a)] in Study DP1008)

		Overall adverse events	Overall adverse drug reactions	Serious adverse events	Adverse events leading to treatment discontinuation
Insulin therapy	Long-acting (n = 40)	33 (82.5)	16 (40.0)	1 (2.5)	1 (2.5)
	Pre-mixed (n = 41)	32 (78.0)	25 (61.0)	3 (7.3)	3 (7.3)
	Basal + bolus[b)] (n = 25)	22 (88.0)	18 (72.0)	4 (16.0)	3 (12.0)
	Others (n = 14)	12 (85.7)	8 (57.1)	1 (7.1)	1 (7.1)
Daily dose of insulin	<20 units (n = 58)	47 (81.0)	26 (44.8)	3 (5.2)	4 (6.9)
	≥20 units (n = 62)	52 (83.9)	41 (66.1)	6 (9.7)	4 (6.5)
Concomitant medication	None (n = 54)	45 (83.3)	33 (61.1)	3 (5.6)	4 (7.4)
	α-GI (n = 20)	18 (90.0)	13 (65.0)	2 (10.0)	1 (5.0)
	BG (n = 46)	36 (78.3)	21 (45.7)	4 (8.7)	3 (6.5)

Number of subjects with events (incidence %)
a) Data from the overall treatment period (the duration of treatment with anagliptin, i.e., Week 12 to Week 52 for the placebo/anagliptin group and Week 0 to Week 52 for the continued anagliptin group). Data for both treatment groups include subjects who had their dose increased to 200 mg.
b) A long-acting insulin was used as basal insulin, and a rapid-acting or ultra-rapid-acting insulin was used as bolus insulin.

PMDA's view:
The data from Studies DP1007 and DP1008 demonstrated that the incidence of adverse events associated with the combination therapy with anagliptin and glinide or insulin was not substantially different from that associated with the use of anagliptin for the approved indications. Therefore, taking account also of the review of the individual events described below, the safety of anagliptin is acceptable, on the premise that appropriate precautions are taken. However, information should continue to be collected via post-marketing surveillance, because the number of subjects evaluated in the clinical studies is limited.

2.(iii).B.(3).1) Hypoglycaemia

PMDA asked the applicant to explain the risk of hypoglycaemia associated with the combination therapy with anagliptin and glinide or insulin, based on the results of the clinical studies including DP1007 and DP1008 as well as the post-marketing information.

The applicant's response:
An analysis was performed on data from Studies DP1007 and DP1008. The incidence and rate of hypoglycaemia reported as an adverse event reported in the studies were 9.5% (6 of 63 subjects) and 0.18 events per patient-year, respectively, in subjects who received anagliptin and glinide, and 44.2% (53 of 120 subjects) and 3.76 events per patient-year, respectively, in subjects who received combination

therapy with anagliptin and insulin. The incidence and rate of hypoglycaemia in the clinical studies conducted for the approved indications were 1.0% (3 of 286 subjects) and 0.02 events per patient-year, respectively, in subjects receiving anagliptin monotherapy; 1.1% (1 of 94 subjects) and 0.01 events per patient-year, respectively, in those receiving anagliptin plus α-GI; 2.9% (3 of 102 subjects) and 0.06 events per patient-year, respectively, in those receiving anagliptin plus TZD; 13.3% (18 of 135 subjects) and 0.18 events per patient-year, respectively, in those receiving anagliptin plus SU; and 1.9% (2 of 104 subjects) and 0.02 events per patient-year, respectively, in those receiving anagliptin plus BG. The incidence and rate of hypoglycaemia in subjects receiving anagliptin plus glinide, besides those receiving anagliptin plus SU, tended to be higher than those in subjects receiving other approved therapies. The incidence and rate of hypoglycaemia tended to be higher in subjects receiving anagliptin plus insulin than in subjects receiving other approved therapies, including anagliptin plus SU.

The risk of hypoglicaemia associated with combination therapy with anagliptin and insulin was evaluated. the incidence of hypoglycaemia as an adverse event during the double-blind period in Study DP1008 was 24.6% (15 of 61 subjects) in the placebo group and 25.8% (16 of 62 subjects) in the anagliptin group, and the incidence of hypoglycaemia related to study drug (adverse drug reaction) was 24.6% (15 of 61 subjects) in the placebo group and 24.2% (15 of 62 subjects) in the anagliptin group; no substantial difference was observed between groups, and all events were mild in severity. In addition, the incidence of hypoglycaemia was evaluated by type of insulin therapy, insulin dose level, and concomitant medication at baseline (Table 38). The analysis results for the anagliptin group in the double-blind period showed that the incidence of hypoglycaemia tended to be higher in subjects using basal and bolus insulin at baseline than in subjects receiving other types of insulin. A subgroup analysis by insulin dose level revealed that the incidence of hypoglycaemia tended to be higher in subjects receiving ≥20 units of insulin per day than in subjects receiving <20 units of insulin per day, but no substantial difference in the incidence was observed between subgroups for the overall population including subjects in the open-label period. A subgroup analysis by concomitant medication revealed a trend toward a higher incidence of hypoglycaemia in subjects receiving anagliptin plus α-GI, and showed that the adverse event occurred less frequently in subjects receiving anagliptin plus BG than in subjects receiving no concomitant medication.

Table 38. Summary of hypoglycaemia by type of insulin therapy, insulin dose level, and concomitant medication (all subjects[a)] in Study DP1008)

		Double-blind period		All subjects[a)]
		Placebo	Anagliptin	
Insulin treatment	Long-acting	1/18 (5.6)	3/22 (13.6)	12/40 (30.0)
	Pre-mixed	8/23 (34.8)	6/21 (28.6)	23/41 (56.1)
	Basal + bolus[b)]	4/15 (26.7)	4/10 (40.0)	12/25 (48.0)
	Others	2/5 (40.0)	3/9 (33.3)	6/14 (42.9)
Daily dose of insulin	<20 units	4/30 (13.3)	6/29 (20.7)	24/58 (41.4)
	≥20 units	11/31 (35.5)	10/33 (30.3)	29/62 (46.8)
Concomitant medication	None	10/27 (37.0)	7/27 (25.9)	25/54 (46.3)
	α-GI	3/11 (27.3)	5/11 (45.5)	12/20 (60.0)
	BG	2/23 (8.7)	4/24 (16.7)	16/46 (34.8)

Number of subjects with events/number of subjects analyzed (incidence [%])

a) Data from the overall treatment period (the duration of treatment with anagliptin, i.e., Week 12 to Week 52 for the placebo/anagliptin group and Week 0 to Week 52 for the continued anagliptin group). Data for both treatment groups include subjects who had their dose increased to 200 mg.

b) A long-acting insulin was used as basal insulin, and a rapid-acting or ultra-rapid-acting insulin was used as bolus insulin.

Data on "hypoglycaemia" (as an adverse event) were collected in the specified drug use-results survey intended for gathering post-marketing information on the long-term use of anagliptin.[10] Analysis of the collected data did not show a trend toward a particularly high incidence in subjects who received anagliptin or in combination with another therapy. No serious adverse events were observed.

Based on the above, the applicant considered that a precautionary statement regarding the risk of hypoglycaemia associated with the use of anagliptin in combination with glinide or insulin should be included in the package insert, etc., in addition to the current statement regarding the combination with SU.

[10] Patients receiving anagliptin monotherapy and combination therapy for the approved indication were identified from among [redacted] patients in the data locked as of [redacted], [redacted]. Data from the patients was evaluated as post-marketing information.

PMDA's view:
Appropriate precautions should be provided regarding the risk of hypoglycaemia associated with the combination therapy with anagliptin and glinide, because the incidence of hypoglycaemia in Study DP1007 tended to be higher than that in the clinical studies of the approved therapies other than combination with SU, although all the reported events were mild in severity. In Study DP1008, hypoglycaemic events occurred in subjects receiving anagliptin plus insulin in the double-blind period but all the events were mild in severity. Also, the incidence of hypoglycaemia did not tend to be substantially higher in the anagliptin group than in the placebo group. However, since the event tended to occur more frequently in this study than in the clinical studies of the approved therapies, due attention should be paid to the occurrence of hypoglycaemia when anagliptin is used in combination with insulin.

2.(iii).B.(3).2) Gastrointestinal disorders (including pancreatitis) and gastrointestinal haemorrhage

The applicant's explanation:
An analysis was performed on data from Studies DP1007 and DP1008 and the clinical studies for the approved indications. The incidence and rate of adverse events classified as gastrointestinal disorders (including pancreatitis) were 22.2% (14 of 63 subjects) and 0.34 events per patient-year, respectively, in subjects receiving anagliptin plus glinide; 19.2% (23 of 120 subjects) and 0.31 events per patient-year, respectively, in those receiving anagliptin plus insulin; 27.3% (78 of 286 subjects) and 0.67 events per patient-year, respectively, in those receiving anagliptin alone; 14.9% (14 of 94 subjects) and 0.18 events per patient-year, respectively, in those receiving anagliptin plus α-GI; 27.5% (28 of 102 subjects) and 0.46 events per patient-year, respectively, in those receiving anagliptin plus TZD; 37.8% (51 of 135 subjects) and 0.57 events per patient-year, respectively, in those receiving anagliptin plus SU; and 43.3% (45 of 104 subjects) and 0.70 events per patient-year, respectively, in those receiving anagliptin plus BG. The incidence and rate of gastrointestinal haemorrhage were 3.2% (2 of 63 subjects) and 0.03 events per patient-year, respectively, in subjects receiving anagliptin plus glinide; 0.0% (0 of 120 subjects) and 0.00 events per patient-year, respectively, in those receiving anagliptin plus insulin; 11.5% (33 of 286 subjects) and 0.20 events per patient-year, respectively, in those receiving anagliptin alone; 10.6% (10 of 94 subjects) and 0.12 events per patient-year, respectively, in those receiving anagliptin plus α-GI; 12.7% (13 of 102 subjects) and 0.14 events per patient-year, respectively, in those receiving anagliptin plus TZD; 10.4% (14 of 135 subjects) and 0.12 events per patient-year, respectively, in those receiving anagliptin plus SU; and 13.5% (14 of 104 subjects) and 0.15 events per patient-year, respectively, in those receiving anagliptin plus BG.

Data on the adverse events classified as gastrointestinal disorders (including pancreatitis) were collected in the specified drug use-results survey intended for gathering post-marketing information on the long-term use of anagliptin.[10] Analysis of the collected data did not show a trend toward a particularly high incidence in patients who received anagliptin alone or in combination with another therapy. Serious adverse events occurred in 3 subjects who received anagliptin alone, 1 subject who received anagliptin plus TZD, and 2 subjects who received anagliptin plus BG. No adverse events of gastrointestinal haemorrhage were reported.

In summary, it is unlikely that gastrointestinal disorders (including pancreatitis) or gastrointestinal haemorrhage associated with the use of anagliptin in combination with glinide or insulin poses a particular problem compared with the use of anagliptin for the approved indications.

In light of the clinical study data etc., PMDA confirmed that the incidence of adverse events classified as gastrointestinal disorders (including pancreatitis) or gastrointestinal haemorrhage associated with the combination therapy with anagliptin and glinide or insulin was not substantially different from that associated with the use of anagliptin for the approved indications.

2.(iii).B.(3).3) Adverse events related to skin disorders and hypersensitivity

The applicant's explanation:
An analysis was performed on data from Studies DP1007 and DP1008 and the clinical studies for the approved indications. The incidence and rate of adverse events classified as skin and subcutaneous tissue disorders (including hypersensitivity reactions) were 7.9% (5 of 63 subjects) and 0.08 events per patient-year, respectively, in subjects receiving anagliptin plus glinide; 5.0% (6 of 120 subjects) and 0.06 events

per patient-year, respectively, in subjects receiving for anagliptin plus insulin; 17.5% (50 of 286 subjects) and 0.37 events per patient-year, respectively, in subjects receiving anagliptin alone; 10.6% (10 of 94 subjects) and 0.15 events per patient-year, respectively, in subjects receiving anagliptin plus α-GI; 11.8% (12 of 102 subjects) and 0.17 events per patient-year, respectively, in subjects receiving anagliptin plus TZD; 26.7% (36 of 135 subjects) and 0.44 events per patient-year, respectively, in subjects receiving anagliptin plus SU; and 20.2% (21 of 104 subjects) and 0.26 events per patient-year, respectively, in subjects receiving anagliptin plus BG.

Data on the adverse events classified as skin and subcutaneous tissue disorders (including hypersensitivity reactions) were collected in the specified drug use-results survey intended for gathering post-marketing information on the long-term use of anagliptin.[10] Analysis of the collected data did not show a trend toward a particularly high incidence in subjects who received anagliptin alone or in combination with another therapy, nor were any serious adverse events noted.

In summary, it is unlikely that the risk of adverse events related to skin and subcutaneous tissue disorders (including hypersensitivity reactions) associated with the use of anagliptin in combination with glinide or insulin poses a particular problem compared with the use of anagliptin for the approved indications.

In light of the clinical study data etc., PMDA confirmed that the incidence of adverse events related to skin disorder and hypersensitivity associated with the use of anagliptin in combination with glinide or insulin was not substantially different from that associated with the use of anagliptin for the approved indications.

2.(iii).B.(3).4) Cardiovascular risk

PMDA asked the applicant to explain the cardiovascular risk associated with combination therapy with anagliptin and glinide or insulin based on the clinical study results including those from Studies DP1007 and DP1008 and post-marketing information.

The applicant's response:

An analysis was performed on data from Studies DP1007 and DP1008 and the clinical studies for the approved indications. The incidence and rate of adverse events related to cardiovascular risk[11] and were 4.8% (3 of 63 subjects) and 0.07 events per patient-year, respectively, in subjects receiving for anagliptin plus glinide; 4.2% (5 of 120 subjects) and 0.05 events per patient-year, respectively, in those receiving anagliptin plus insulin; 7.7% (22 of 286 subjects) and 0.14 events per patient-year, respectively, in those receiving anagliptin alone; 6.4% (6 of 94 subjects) and 0.07 events per patient-year, respectively, in those receiving anagliptin plus α-GI; 5.9% (6 of 102 subjects) and 0.08 events per patient-year, respectively, in those receiving anagliptin plus TZD; 6.7% (9 of 135 subjects) and 0.07 events per patient-year, respectively, in those receiving anagliptin plus SU; and 6.7% (7 of 104 subjects) and 0.09 events per patient-year, respectively, in those receiving anagliptin plus BG. The changes in vital signs (systolic and diastolic blood pressure, and pulse rate), lipid parameters (total cholesterol, LDL cholesterol, and HDL cholesterol), and body weight from baseline (Week 0) to the last dose were not substantially different between anagliptin monotherapy and combination therapies (Table 39), and no changes of clinical relevance were observed.

[11] Identified by collecting adverse event terms classified under the SMQs "ischaemic cerebrovascular conditions," "haemorrhagic cerebrovascular conditions," "myocardial infarction," and "conditions associated with central nervous system haemorrhages and cerebrovascular accidents."

Table 39. Changes from baseline (Week 0) to the last dose

Endpoint	DP1007	DP1008[a)]	DP1001 DP1003 SK-0403-01	DP1002[a)]		SK-0403-02[a)]	
	Anagliptin + glinide	Anagliptin + insulin	Anagliptin monotherapy[b)]	Anagliptin + α-GI	Anagliptin + TZD	Anagliptin + SU	Anagliptin + BG
Systolic blood pressure (mmHg)	−0.6 ± 10.6 (63)	−1.5 ± 12.6 (119)	−2.4 ± 12.1 (285)	−1.4 ± 11.9 (94)	−0.8 ± 13.0 (102)	−1.2 ± 14.5 (135)	−1.0 ± 13.7 (104)
Diastolic blood pressure (mmHg)	0.0 ± 8.4 (63)	−0.3 ± 9.6 (119)	−1.1 ± 9.0 (285)	−1.6 ± 8.5 (94)	−0.1 ± 9.9 (102)	−0.9 ± 9.8 (135)	−2.6 ± 8.8 (104)
Pulse rate (beats/minute)	−2.0 ± 8.5 (63)	−1.3 ± 10.5 (119)	0.5 ± 8.6 (285)	1.4 ± 7.7 (94)	1.4 ± 9.2 (102)	1.8 ± 8.5 (135)	2.2 ± 9.1 (104)
Total cholesterol (mg/dL)	−4.8 ± 19.2 (63)	−4.2 ± 25.0 (119)	−7.6 ± 24.2 (285)	−11.4 ± 27.6 (94)	−8.8 ± 23.5 (102)	−11.3 ± 24.2 (135)	−11.1 ± 27.0 (104)
LDL cholesterol (mg/dL)	−3.0 ± 17.6 (63)	−3.4 ± 22.2 (119)	−5.0 ± 22.5 (285)	−10.6 ± 23.4 (94)	−4.8 ± 22.1 (102)	−6.6 ± 20.3 (135)	−7.3 ± 20.7 (104)
HDL cholesterol (mg/dL)	−0.1 ± 7.4 (63)	−2.0 ± 7.6 (119)	−1.4 ± 7.4 (285)	1.2 ± 7.6 (94)	−0.3 ± 9.7 (102)	−1.3 ± 6.8 (135)	−0.4 ± 7.6 (104)
Body weight (kg)	0.21 ± 1.99 (63)	0.97 ± 1.86 (119)	0.14 ± 1.72 (285)	0.26 ± 1.99 (94)	1.05 ± 2.56 (102)	0.80 ± 2.03 (135)	0.00 ± 2.52 (104)

Mean ± SD (number of subjects).

a) Data from Treatment Period II (Week 12 to Week 52) for the placebo/anagliptin group who received placebo during the double-blind period, and data for the overall treatment period (Week 0 to Week 52) for the continued anagliptin group who received anagliptin during the double-blind period. Data for both treatment groups include subjects who had their dose increased to 200 mg.

b) Pooled data for the 100 mg group (including subjects who had their dose increased to 200 mg) in Studies DP1001, DP1003, and SK-0403-01

Only 0 to 4 subjects (0.0%-3.4%) had abnormal ECG[12] in each treatment group in the Japanese long-term studies. The applicant therefore considered it unlikely that ECG findings become a clinical problem.

Data on the adverse events related to cardiovascular risk were collected in the specified drug use-results survey intended for gathering post-marketing information on the long-term use of anagliptin.[10] Analysis of the collected data did not show a trend toward a particularly high incidence in patients who received anagliptin alone or in combination with another therapy. Serious adverse events occurred in 2 subjects who received anagliptin alone, 2 subjects who received anagliptin plus α-GI, 1 subject who received anagliptin plus SU, and 2 subjects who received anagliptin plus BG.

In summary, it is unlikely that the risk of cardiovascular events associated with the use of anagliptin in combination with glinide or insulin poses a particular problem compared with the use of anagliptin for the approved indications.

In light of the clinical study data etc., PMDA confirmed that combination therapy with anagliptin and glinide or insulin did not induce an increase in the incidence of adverse events related to cardiovascular risk, that it had no apparent impact on vital signs, lipid parameters, or ECG findings, and that it did not clearly increase cardiovascular risk, compared with the use of anagliptin for the approved indications.

2.(iii).B.(3).5) Tumorigenesis

The applicant's explanation:

An analysis was performed on data from Studies DP1007 and DP1008 and the clinical studies for the approved indications. The incidence and rate of adverse events classified under the System Organ Class (SOC) "neoplasms benign, malignant and unspecified (incl cysts and polyps)" were 1.6% (1 of 63 subjects) and 0.02 events per patient-year, respectively, in subjects receiving anagliptin plus glinide; 2.5% (3 of 120 subjects) and 0.03 events per patient-year, respectively, in those receiving anagliptin plus insulin; 3.5% (10 of 286 subjects) and 0.06 events per patient-year, respectively, in those receiving anagliptin alone; 5.3% (5 of 94 subjects) and 0.07 events per patient-year, respectively, in those receiving anagliptin plus α-GI; 2.0% (2 of 102 subjects) and 0.02 events per patient-year, respectively, in those receiving anagliptin plus TZD; 2.2% (3 of 135 subjects) and 0.02 events per patient-year, respectively, in those receiving anagliptin plus SU; and 3.8% (4 of 104 subjects) and 0.04 events per patient-year, respectively, in those receiving anagliptin plus BG.

Data on the adverse events classified under the SOC "neoplasms benign, malignant and unspecified (incl cysts and polyps)" were collected in the specified drug use-results survey intended for gathering

[12] Subjects who had normal ECG at baseline and abnormal ECG at the last dose

post marketing information on the long-term use of anagliptin.[10] Analysis of the collected data show no trend toward a particularly high incidence of such events in subjects who received anagliptin alone or another therapy. Serious adverse events occurred in 1 subject who received anagliptin plus TZD and 1 subject who received anagliptin plus BG.

In summary, there was no trend suggestive of a substantially high risk of adverse events classified under the SOC "neoplasms benign, malignant and unspecified (incl cysts and polyps)" associated with the use of anagliptin in combination with glinide or insulin compared with the use of anagliptin for the approved indications.

Based on the clinical study data etc., PMDA confirmed that no findings were observed with the use of anagliptin in combination with glinide or insulin suggestive of increased risk of adverse events classified under the SOC "neoplasms benign, malignant and unspecified (incl cysts and polyps)", compared with the use for the approved indications.

2.(iii).B.(4) Indication

PMDA's view:

"On release of the Guideline for Clinical Evaluation of Oral Hypoglycemic Agents" (PFSB/ELD Notification No. 0709-1 dated July 9, 2010; hereinafter "OAD Guideline") states that when a study drug is confirmed to be useful in clinical studies conducted based on the OAD Guideline, including studies of two-drug therapy with the study drug and approved oral hypoglycaemic agents which are expected to be coadministered in clinical practice, the appropriate description of the indication is "type 2 diabetes mellitus." Since the long-term safety and efficacy of anagliptin in combination with glinide has been demonstrated in Study DP1007 which was conducted in accordance with the OAD guideline, PMDA concluded that there is no problem with the proposed change of indication to "type 2 diabetes mellitus," taking account also of the results of the approved monotherapy and combination therapies with an α-GI, BG, SU, and TZD. In general, if a drug is approved for the indication of "type 2 diabetes mellitus" in accordance with the OAD guideline, combination therapy with the drug and insulin will be warranted. Further, the safety and efficacy of anagliptin in combination with insulin have been confirmed in Study DP1008 conducted in Japan. In light of the above facts, there is no problem with the proposed change of indication to "type 2 diabetes mellitus."

2.(iii).B.(5) Dosage and administration

PMDA's view:

The approved dosage and administration should remain unchanged in this application because the long-term safety and efficacy of anagliptin in combination with glinide or insulin have been demonstrated in Studies DP1007 and DP1008 that were conducted with the approved dosage and administration.

2.(iii).B.(6) Special populations

2.(iii).B.(6).1) Patients with renal impairment

PMDA asked the applicant to explain the impact on the safety in patients with renal impairment based on the comparison of combination therapies evaluated in Studies DP1007 and DP1008 and the clinical studies conducted to support the approved indications.

The applicant's response:

The incidence of adverse events, adverse drug reactions, serious adverse events, and hypoglycaemia in Studies DP1007 and DP1008 was compared with that in the clinical studies submitted as the supportive data for the approved indications. Subgroup analysis was performed by level of renal function (normal, eGFR ≥90 mL/min/1.73 m^2; mild impairment, eGFR ≥60 and <90 mL/min/1.73 m^2; moderate impairment, eGFR <60 mL/min/1.73 m^2). Patients with severe renal impairment were excluded from these clinical studies. The results are shown in Table 40. The incidence of hypoglycaemia (as an adverse event) in subjects receiving anagliptin plus glinide, besides those receiving anagliptin plus SU, was higher than that in those receiving the other approved therapies, but there was no trend toward a particularly high incidence of overall adverse events, overall adverse drug reactions, serious adverse events, or hypoglycaemia, regardless of the level of renal function. The incidence of adverse drug reactions in subjects receiving anagliptin plus insulin was higher than that in those receiving the approved therapies. This was possibly because the incidence of hypoglycaemia was higher in subjects

receiving anagliptin plus insulin than in those receiving the approved therapies and because all events of hypoglycaemia were adverse drug reactions. However, there was no trend toward a particularly high incidence, regardless of the level of renal function. The incidence of serious adverse events in subjects receiving anagliptin plus insulin was higher in patients with moderate renal impairment, but a causal relationship to anagliptin was ruled out for all the events except for "hypoglycaemia" experienced by 1 subject. Based on the above, the degree of renal impairment is unlikely to have a substantial impact on the safety of anagliptin in combination with glinide or insulin.

Table 40. Incidence of adverse events by level of renal function

		DP1007	DP1008[a)]	DP1001 DP1003 SK-0403-01	DP1002[a)]		SK-0403-02[a)]	
	Degree of renal impairment	Anagliptin + glinide	Anagliptin + insulin	Anagliptin monotherapy[b)]	Anagliptin + α-GI	Anagliptin + TZD	Anagliptin + SU	Anagliptin + BG
Overall adverse events	Normal	15/21 (71.4) [2.38]	21/29 (72.4) [5.72]	65/88 (73.9) [3.52]	22/28 (78.6) [2.14]	30/39 (76.9) [2.51]	41/46 (89.1) [3.50]	45/48 (93.8) [3.92]
	Mild impairment	26/36 (72.2) [1.93]	51/61 (83.6) [6.36]	127/185 (68.6) [3.78]	44/60 (73.3) [2.58]	47/58 (81.0) [2.69]	73/82 (89.0) [4.41]	47/50 (94.0) [4.41]
	Moderate impairment	3/6 (50.0) [1.99]	27/30 (90.0) [4.73]	11/13 (84.6) [3.92]	6/6 (100.0) [1.99]	5/5 (100.0) [2.88]	7/7 (100.0) [6.05]	4/6 (66.7) [2.47]
Overall adverse drug reactions	Normal	6/21 (28.6) [0.59]	12/29 (41.4) [4.14]	18/88 (20.5) [0.52]	5/28 (17.9) [0.23]	6/39 (15.4) [0.29]	13/46 (28.3) [0.47]	13/48 (27.1) [0.59]
	Mild impairment	9/36 (25.0) [0.40]	37/61 (60.7) [4.60]	33/185 (17.8) [0.48]	15/60 (25.0) [0.57]	16/58 (27.6) [0.39]	28/82 (34.1) [0.64]	11/50 (22.0) [0.47]
	Moderate impairment	2/6 (33.3) [1.32]	18/30 (60.0) [3.07]	4/13 (30.8) [1.01]	2/6 (33.3) [0.36]	1/5 (20.0) [0.41]	2/7 (28.6) [0.64]	1/6 (16.7) [0.19]
Serious adverse events	Normal	1/21 (4.8) [0.05]	1/29 (3.4) [0.04]	3/88 (3.4) [0.05]	1/28 (3.6) [0.04]	3/39 (7.7) [0.09]	3/46 (6.5) [0.07]	3/48 (6.3) [0.07]
	Mild impairment	3/36 (8.3) [0.09]	3/61 (4.9) [0.06]	9/185 (4.9) [0.09]	7/60 (11.7) [0.14]	3/58 (5.2) [0.06]	5/82 (6.1) [0.07]	3/50 (6.0) [0.07]
	Moderate impairment	0/6 (0.0) [0.00]	5/30 (16.7) [0.26]	2/13 (15.4) [0.38]	0/6 (0.0) [0.00]	0/5 (0.0) [0.00]	1/7 (14.3) [0.16]	1/6 (16.7) [0.19]
Hypoglycaemia	Normal	2/21 (9.5) [0.20]	10/29 (34.5) [3.87]	2/88 (2.3) [0.05]	0/28 (0.0) [0.00]	1/39 (2.6) [0.06]	2/46 (4.3) [0.07]	0/48 (0.0) [0.00]
	Mild impairment	3/36 (8.3) [0.14]	30/61 (49.2) [4.29]	1/185 (0.5) [0.01]	1/60 (1.7) [0.02]	2/58 (3.4) [0.06]	13/82 (15.9) [0.19]	2/50 (4.0) [0.05]
	Moderate impairment	1/6 (16.7) [0.33]	13/30 (43.3) [2.65]	0/13 (0.0) [0.00]	0/6 (0.0) [0.00]	0/5 (0.0) [0.00]	3/7 (42.9) [0.80]	0/6 (0.0) [0.00]

Number of subjects with events (incidence %) [Incidence rate (events per patient-year)]

a) Data from Treatment Period II (Week 12 to Week 52) for the placebo/anagliptin group who received placebo during the double-blind period, and data for the overall treatment period (Week 0 to Week 52) for the continued anagliptin group who received anagliptin during the double-blind period. Data for both treatment groups include subjects who had their dose increased to 200 mg.

a) Pooled data for the 100 mg group (including subjects who had their dose increased to 200 mg) in Studies DP1001, DP1003, and SK-0403-01

PMDA asked the applicant to explain whether the incidence of adverse events tended to increase in patients with renal impairment after the dose of anagliptin was increased.

The applicant's response:

The incidence and rates of adverse events before and after dose increase in subjects who had their dose of anagliptin increased in Studies DP1007 and DP1008 are shown by renal function in Table 41. The incidence of adverse events increased after the dose of anagliptin was increased in patients with mild renal impairment receiving anagliptin plus glinide, but the incidence rate (number of events per patient-year) did not tend to increase following dose increase in any of the subgroups.

Table 41. Incidence of adverse events before and after dose increase

		Degree of renal impairment	Incidence of adverse events (number of subjects with events [incidence %])		Incidence rate of adverse events (number of events per patient-year)	
			Before dose increase	After dose increase	Before dose increase	After dose increase
DP1007	Anagliptin + glinide	Normal	11/18 (61.1)	7/18 (38.9)	2.36	1.89
		Mild impairment	11/25 (44.0)	14/25 (56.0)	2.21	1.80
		Moderate impairment	2/3 (66.7)	1/3 (33.3)	4.35	2.14
DP1008	Anagliptin + insulin	Normal	12/21 (57.1)	13/21 (61.9)	3.30	2.45
		Mild impairment	30/42 (71.4)	26/42 (61.9)	6.95	4.13
		Moderate impairment	15/19 (78.9)	12/19 (63.2)	6.53	2.85

PMDA's view:
There was no trend toward a particularly high risk of adverse events in subjects receiving anagliptin plus glinide, regardless of the level of renal function. Meanwhile, it should be noted that the incidence of hypoglycaemia associated with combination therapy with anagliptin and insulin was slightly higher in patients with renal impairment. Only a limited number of patients with renal impairment with eGFR <60 mL/min/1.73 m^2 were evaluated, and in particular, anagliptin has not been studied in patients with severe renal impairment. For this reason, information on the safety in patients with renal impairment should continue to be collected via post-marketing surveillance.

2.(iii).B.(6).2) Patients with hepatic impairment
PMDA asked the applicant to explain the impact on the safety in patients with hepatic impairment based on the comparison of combination therapies evaluated in Studies DP1007 and DP1008 and the clinical studies conducted to support the approved indications.

The applicant's response:
The incidence of adverse events, adverse drug reactions, serious adverse events, and hypoglycaemia in subjects with and without comorbidities classified under the SOC "hepatobiliary disorders" at screening in Studies DP1007 and DP1008 were compared with that in the clinical studies submitted as the supportive data for the approved indications. The results are shown in Table 42. The incidence of overall adverse events and overall adverse drug reactions associated with the combination therapy of anagliptin and glinide tended to be higher in the subgroup of patients with concurrent hepatobiliary disorders than in patients without concurrent hepatobiliary disorders. However, the difference in the incidence was not considered to have a substantial impact on the safety of the combination therapy with anagliptin and glinide because (1) the incidence of serious adverse events and hypoglycaemia was not significantly different between patients with and without concurrent hepatobiliary disorders, and (2) the incidence was not substantially different from that observed with the approved therapies. The incidence of adverse drug reactions in subjects receiving anagliptin plus insulin was higher than that in those receiving the approved therapies. This was possibly because the incidence of hypoglycaemia was higher in subjects receiving anagliptin plus insulin than those receiving the approved therapies, and because all events of hypoglycaemia were considered adverse drug reactions, but there was no trend toward a particularly high incidence in subjects with or without hepatobiliary disorders. The incidence of serious adverse events associated with combination therapy with anagliptin and insulin was higher in the subgroup of patients with concurrent hepatobiliary disorders than in the subgroup of patients without concurrent hepatobiliary disorders, but a causal relationship to anagliptin was ruled out for all events. Based on the above, the presence or absence of concurrent hepatobiliary disorders is unlikely to have a substantial impact on the safety of anagliptin in combination with glinide or insulin.

Table 42. Incidence of adverse events by presence or absence of concurrent hepatobiliary disorders

		DP1007	DP1008[a]	DP1001 DP1003 SK-0403-01	DP1002[a]		SK-0403-02[a]	
	Concurrent hepatobiliary disorders	Anagliptin + glinide	Anagliptin + insulin	Anagliptin monotherapy[b]	Anagliptin + α-GI	Anagliptin + TZD	Anagliptin + SU	Anagliptin + BG
Overall adverse events	No	21/34 (61.8) [1.71]	57/72 (79.2) [6.09]	104/147 (70.7) [3.61]	55/66 (83.3) [2.48]	48/60 (80.0) [2.66]	81/95 (85.3) [3.96]	53/58 (91.4) [3.81]
	Yes	23/29 (79.3) [2.53]	42/48 (87.5) [5.30]	99/139 (71.2) [3.78]	17/28 (60.7) [2.23]	34/42 (81.0) [2.59]	40/40 (100.0) [4.74]	43/46 (93.5) [4.40]
Overall adverse drug reactions	No	6/34 (17.6) [0.39]	39/72 (54.2) [4.55]	28/147 (19.0) [0.62]	15/66 (22.7) [0.41]	14/60 (23.3) [0.36]	26/95 (27.4) [0.49]	15/58 (25.9) [0.57]
	Yes	11/29 (37.9) [0.75]	28/48 (58.3) [3.40]	27/139 (19.4) [0.43]	7/28 (25.0) [0.54]	9/42 (21.4) [0.34]	17/40 (42.5) [0.80]	10/46 (21.7) [0.44]
Serious Adverse event	No	2/34 (5.9) [0.06]	3/72 (4.2) [0.05]	6/147 (4.1) [0.09]	8/66 (12.1) [0.14]	5/60 (8.3) [0.10]	7/95 (7.4) [0.08]	5/58 (8.6) [0.10]
	Yes	2/29 (6.9) [0.07]	6/48 (12.5) [0.20]	8/139 (5.8) [0.09]	0/28 (0.0) [0.00]	1/42 (2.4) [0.03]	2/40 (5.0) [0.06]	2/46 (4.3) [0.05]
Hypoglycaemia	No	3/34 (8.8) [0.21]	34/72 (47.2) [4.36]	2/147 (1.4) [0.02]	1/66 (1.5) [0.02]	1/60 (1.7) [0.04]	11/95 (11.6) [0.13]	1/58 (1.7) [0.02]
	Yes	3/29 (10.3) [0.14]	19/48 (39.6) [2.86]	1/139 (0.7) [0.02]	0/28 (0.0) [0.00]	2/42 (4.8) [0.08]	7/40 (17.5) [0.30]	1/46 (2.2) [0.02]

Number of subjects with events (incidence %) [Incidence rate (events per patient-year)]

a) Data from Treatment Period II (Week 12 to Week 52) for the placebo/anagliptin group who received placebo during the double-blind period, and data for the overall treatment period (Week 0 to Week 52) for the continued anagliptin group who received anagliptin during the double-blind period. Data for both treatment groups include subjects who had their dose increased to 200 mg.

b) Pooled data for the 100 mg group (including subjects who had their dose increased to 200 mg) in Studies DP1001, DP1003, and SK-0403-01

PMDA asked the applicant to explain whether the incidence of adverse events tended to increase in patients with hepatic impairment after the dose of anagliptin was increased.

The applicant's response:
The incidence and rates of adverse events before and after dose increase in the subjects who had their dose of anagliptin increased in Studies DP1007 and DP1008 are shown by presence or absence of concurrent hepatobiliary disorders in Table 43. There was no trend toward a rise in adverse events following dose increase in either of the subgroups.

Table 43. Incidence of adverse events before and after dose increase

		Concurrent hepatobiliary disorders	Incidence of adverse events (number of subjects with events [incidence %])		Incidence rate of adverse events (number of events per patient-year)	
			Before dose increase	After dose increase	Before dose increase	After dose increase
DP1007	Anagliptin + glinide	No	12/24 (50.0)	10/24 (41.7)	2.56	1.26
		Yes	12/22 (54.5)	12/22 (54.5)	2.23	2.52
DP1008	Anagliptin + insulin	No	24/43 (55.8)	27/43 (62.8)	4.45	3.02
		Yes	33/39 (84.6)	24/39 (61.5)	7.51	3.84

PMDA's view:
Subgroup analysis of subjects who received anagliptin in combination with glinide or insulin confirmed that there was no trend toward a substantially higher risk in subjects with hepatic impairment compared with subjects without hepatic impairment. Since only a limited number of patients with hepatic impairment was evaluated, information on the safety in patients with hepatic impairment should continue to be collected via post-marketing surveillance.

2.(iii).B.(6).3) Elderly patients

PMDA asked the applicant to explain the impact on the safety in elderly patients based on the comparison of combination therapies evaluated in Studies DP1007 and DP1008 and the clinical studies conducted to support the approved indications.

The applicant's response:
The incidence of adverse events, adverse drug reactions, serious adverse events, and hypoglycaemia in Studies DP1007 and DP1008 was compared with that in the clinical studies submitted as the supportive data for the approved indications, and subgroup analysis was performed by age at screening (<65 years

or ≥65 years). The results were as shown in Table 44. The incidence of overall adverse events, overall adverse drug reactions, and serious adverse events in subjects who received anagliptin plus glinide was not substantially different from that in subjects who received the approved therapies. The incidence of hypoglycaemia in subjects who received anagliptin plus glinide was higher than those who received the approved therapies. Comparison of subjects who received anagliptin plus glinide versus SU showed no significant difference in the incidence between the therapies for subjects aged <65 years, while hypoglycaemia occurred less frequently in subjects aged ≥65 years who received anagliptin plus glinide. There was no trend toward a substantially high incidence of adverse events, adverse drug reactions, serious adverse events, or hypoglycaemia in the subgroup of subjects aged ≥65 years. The incidence of adverse drug reactions in subjects who received anagliptin plus insulin was higher than that in those who received the approved therapies. This was possibly because the incidence of adverse events of hypoglycaemia was higher in subjects who received anagliptin plus insulin than in those who received the approved therapies and because all the events of hypoglycaemia were considered adverse drug reactions. The incidence of hypoglycaemia was higher in subjects aged ≥65 years who received anagliptin plus insulin in subjects than in the subjects aged <65 years. This was not inferred to be due to anagliptin, because (1) the incidence of hypoglycaemia in subjects aged <65 and ≥65 years in Treatment Period I of the phase III study of anagliptin in combination with insulin (Study DP1008) was 9.4% (3 of 32 subjects) and 41.4% (12 of 29 subjects), respectively, in the placebo group and 25.6% (10 of 39 subjects) and 26.1% (6 of 23 subjects), respectively, in the anagliptin group; and (2) an imbalance in age was observed also in the placebo group. Based on the above, advanced age is unlikely to have a substantial impact on the safety of anagliptin in combination with glinide or insulin in elderly patients.

Table 44. Incidence of adverse events by age category (<65 years or ≥65 years)

		DP1007	DP1008[a)]	DP1001 DP1003 SK-0403-01	DP1002[a)]		SK-0403-02[a)]	
	Age	Anagliptin + glinide	Anagliptin + insulin	Anagliptin monotherapy[b)]	Anagliptin + α-GI	Anagliptin + TZD	Anagliptin + SU	Anagliptin + BG
Overall adverse events	<65 years	23/34 (67.6) [1.99]	56/70 (80.0) [4.82]	145/207 (70.0) [3.29]	52/70 (74.3) [2.32]	59/75 (78.7) [2.59]	81/91 (89.0) [4.18]	80/85 (94.1) [4.22]
	≥65 years	21/29 (72.4) [2.19]	43/50 (86.0) [7.15]	58/79 (73.4) [4.87]	20/24 (83.3) [2.66]	23/27 (85.2) [2.76]	40/44 (90.9) [4.22]	16/19 (84.2) [3.38]
Overall adverse drug reactions	<65 years	10/34 (29.4) [0.51]	31/70 (44.3) [2.95]	34/207 (16.4) [0.40]	15/70 (21.4) [0.46]	19/75 (25.3) [0.36]	26/91 (28.6) [0.50]	23/85 (27.1) [0.58]
	≥65 years	7/29 (24.1) [0.60]	36/50 (72.0) [5.72]	21/79 (26.6) [0.87]	7/24 (29.2) [0.43]	4/27 (14.8) [0.34]	17/44 (38.6) [0.76]	2/19 (10.5) [0.19]
Serious adverse events	<65 years	2/34 (5.9) [0.06]	5/70 (7.1) [0.12]	4/207 (1.9) [0.03]	7/70 (10.0) [0.11]	3/75 (4.0) [0.04]	5/91 (5.5) [0.06]	6/85 (7.1) [0.08]
	≥65 years	2/29 (6.9) [0.07]	4/50 (8.0) [0.09]	10/79 (12.7) [0.25]	1/24 (4.2) [0.05]	3/27 (11.1) [0.13]	4/44 (9.1) [0.10]	1/19 (5.3) [0.06]
Hypoglycaemia	<65 years	5/34 (14.7) [0.27]	24/70 (34.3) [2.71]	1/207 (0.5) [0.02]	1/70 (1.4) [0.02]	3/75 (4.0) [0.07]	12/91 (13.2) [0.17]	2/85 (2.4) [0.03]
	≥65 years	1/29 (3.4) [0.07]	29/50 (58.0) [5.25]	2/79 (2.5) [0.05]	0/24 (0.0) [0.00]	0/27 (0.0) [0.00]	6/44 (13.6) [0.21]	0/19 (0.0) [0.00]

Number of subjects with events (incidence %) [incidence rate (events per patient-year)]

a) Data from Treatment Period II (Week 12 to Week 52) for the placebo/anagliptin group who received placebo during the double-blind period, and data for the overall treatment period (Week 0 to Week 52) for the continued anagliptin group who received anagliptin during the double-blind period. Data for both treatment groups include subjects who had their dose increased to 200 mg.

b) Pooled data for the 100 mg group (including subjects who had their dose increased to 200 mg) in Studies DP1001, DP1003, and SK-0403-01

PMDA asked the applicant to explain whether the incidence of adverse events tended to increase in elderly subjects after the dose of anagliptin was increased.

The applicant's response:

The incidence and rates of adverse events before and after a dose increase in subjects who had their dose of anagliptin increased in Studies DP1007 and DP1008 are shown by age subgroup in Table 45. There was no trend toward a rise in adverse events following dose increase in the elderly (aged ≥65 years) or non-elderly (aged <65 years) subgroup.

Table 45. Incidences of adverse events before and after dose increase

		Age	Incidence of adverse events (number of subjects with events [incidence %])		Incidence rate of adverse events (number of events per patient-year)	
			Before dose increase	After dose increase	Before dose increase	After dose increase
DP1007	Anagliptin + glinide	<65 years	12/26 (46.2)	11/26 (42.3)	2.27	1.82
		≥65 years	12/20 (60.0)	11/20 (55.0)	2.56	1.91
DP1008	Anagliptin + insulin	<65 years	30/52 (57.7)	33/52 (63.5)	3.67	3.27
		≥65 years	27/30 (90.0)	18/30 (60.0)	9.76	3.64

PMDA's view:
Subgroup analysis of subjects who received anagliptin plus glinide confirmed that there was no trend toward a substantially higher risk in subjects aged ≥65 years compared with subjects aged <65 years. Meanwhile, it should be noted that there was a trend toward a slightly higher incidence of hypoglycaemia in subjects aged ≥65 years who received anagliptin plus insulin. Information on the safety in elderly patients should continue to be collected via post-marketing surveillance.

2.(iii).B.(7) Post-marketing investigations
The applicant plans to conduct a specified drug use-results survey to evaluate the long-term safety and efficacy of anagliptin in combination with glinide or insulin, with a target sample size of 1000 and an observation period of 1 year.

PMDA's view:
In addition to gathering the safety information regarding hypoglycaemia, gastrointestinal disorders, pancreatitis, etc., the applicant should collect information on the impact on the safety by type and dose of concomitant oral hypoglycemic agent and insulin, as well as information on the safety in patients with renal or hepatic impairment and in elderly patients. The above issues will be finalized, taking account of comments from the Expert Discussion.

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

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

Document-based compliance inspection and data integrity assessment were conducted in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics for the data submitted in the new drug application. 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 Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics, for the data submitted in the new drug application (5.3.5.1-1, 5.3.5.2-1). PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

IV. Overall Evaluation

Based on the submitted data, the efficacy of anagliptin in the treatment of patients with type 2 diabetes mellitus has been demonstrated and its safety is acceptable in view of its observed benefits. The safety issues such as hypoglycaemia, gastrointestinal disorders, and pancreatitis, the impact on the safety by type and dose of concomitant oral hypoglycemic agent and insulin, and the safety in patients with renal or hepatic impairment and in elderly patients need to be further investigated via post-marketing surveillance.

This application may be approved if anagliptin is considered to have no problems based on comments from the Expert Discussion.

Review Report (2)

November 9, 2015

I. Product Submitted for Registration

[Brand name]	Suiny Tab. 100 mg
[Non-proprietary name]	Anagliptin
[Name of applicant]	Sanwa Kagaku Kenkyusho Co., Ltd.
[Date of application]	February 4, 2015

II. Content of the Review

The comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined in the following sections. The expert advisors for the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for registration, in accordance with the provisions of the "Rules for Convening Expert Discussions etc. by the Pharmaceuticals and Medical Devices Agency" (PMDA Administration Rule No. 8/2008 dated December 25, 2008).

(1) Efficacy and safety

PMDA concluded as follows:

The efficacy of anagliptin in combination with rapid-acting insulin secretagogue (glinide) or insulin has been demonstrated, on the grounds that the HbA1c lowering effect was maintained for 52 weeks in the phase III study of anagliptin in combination with glinide (Study DP1007), and that the superiority of anagliptin over placebo was demonstrated in terms of HbA1c reduction and the HbA1c lowering effect was maintained for 52 weeks in the phase III study of anagliptin in combination with insulin (Study DP1008). In addition, the safety of anagliptin is acceptable on the premise that appropriate precautions are provided, based on the data from Studies DP1007 and DP1008 where the incidence of adverse events associated with the combination of anagliptin with glinide or insulin was not significantly different from that observed with the use of anagliptin for the approved indications. However, considering the limited number of subjects evaluated in clinical studies, information on the safety of each combination therapy should continue to be collected via post-marketing surveillance.

The above conclusion by PMDA was supported by the expert advisors [for post-marketing surveillance, see "(3) Draft risk management plan"].

(2) Indication

PMDA's view:

"On release of the Guideline for Clinical Evaluation of Oral Hypoglycemic Agents" (PFSB/ELD Notification No. 0709-1 dated July 9, 2010, OAD Guideline) states that when a study drug is confirmed to be useful in clinical studies conducted based on the OAD Guideline, including studies of two-drug therapy with the study drug and approved oral hypoglycaemic agents which are expected to be coadministered in clinical practice, the appropriate description of the indication is "type 2 diabetes mellitus." Since (1) the long-term safety and efficacy of anagliptin in combination with glinide has been demonstrated in Study DP1007 which was conducted in accordance with the OAD guideline, and (2) the safety and efficacy of anagliptin in combination with insulin has been demonstrated in Study DP1008, PMDA concluded that there is no problem with the proposed change of indication to "type 2 diabetes mellitus," taking account also of the results of the approved monotherapy and combination therapies with an α-GI, BG, SU, and TZD. There is no problem with the lack of clinical studies of anagliptin in combination with human glucagon-like peptide-1 (GLP-1) receptor agonist, whose primary mechanism of action is similar to that of anagliptin, because at present it is unlikely that the combination of these agents will be recommended in clinical practice.

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

(3) Draft risk management plan

PMDA concluded that the following issues should be additionally evaluated in the post-marketing surveillance, taking account of the "2.(iii).B.(7) Post-marketing investigations" in Review Report (1) and comments from the expert advisors at the Expert Discussion:

- Impact on the safety by type and dose level of concomitant oral hypoglycemic agent and insulin
- Safety in elderly patients

PMDA asked the applicant to address the above issues. The applicant presented the summary of the draft risk management plan (Tables 46 and 47) and the outline of the specified drug use-results survey plan (draft) (Table 48). PMDA confirmed that the contents of these plans were adequate.

Table 46. Safety and efficacy specifications in the draft risk management plan

Safety specifications		
Important identified risks	Important potential risks	Important missing information
• Hypoglycaemia • Intestinal obstruction	• Acute pancreatitis • Infections • Malignant tumors • Serious skin disorders	• Safety of anagliptin in elderly patients • Safety of anagliptin in patients with renal impairment • Safety of anagliptin in patients with hepatic impairment • Impact on cardiovascular risk
Efficacy specifications		
• Long-term efficacy • Efficacy of anagliptin in combination with a rapid-acting insulin secretagogue, an insulin preparation, or an sodium glucose co-transporter 2 (SGLT2) inhibitor etc.		

Table 47. Summary of additional pharmacovigilance activities and risk minimization activities in the draft risk management plan

Additional pharmacovigilance activities	Additional risk minimization activities
• Specified drug use-results survey (combination therapy with rapid-acting insulin secretagogue, insulin, or SGLT2 inhibitor, etc.)	• Preparation and provision of materials for patients

Table 48. Outline of the specified drug use-results survey plan (draft)

Objective	Evaluate the safety and efficacy of anagliptin in combination with hypoglycemic agents including rapid-acting insulin secretagogues, insulin preparations, SGLT2 inhibitors, etc., which were not evaluated in the ongoing specified drug use-results survey[a)].
Survey method	Central registration system
Patients population	Patients with type 2 diabetes mellitus
Observation period	1 year
Target sample size	1000 patients
Main survey items	Patient characteristics, exposure to anagliptin, use of concomitant medication, concomitant therapy, efficacy assessment (e.g., HbA1c levels), safety assessment (e.g., hypoglycaemia)

a) Specified drug use-results survey of long-term treatment

III. Overall Evaluation

As a result of the above review, PMDA has concluded that anagliptin may be approved for the indication and the dosage and administration as shown below, with the following condition. The re-examination period should be equal to the remaining of the re-examination period (until September 27, 2020).

[Indication] Type 2 diabetes mellitus

[Dosage and administration] The usual adult dosage is 100 mg of anagliptin orally administered twice daily (morning and evening). If the clinical response is not adequate, the dose may be increased up to 200 mg only when the patient's clinical course is closely monitored.

(Not changed)

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