Appeal decision

Appeal No. 2014-3961

Germany
Appellant BOEHRINGER INGELHEIM INTERNATIONAL GMBH

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The case of appeal against the examiner's decision of refusal of Japanese Patent Application No. 2011-531494, entitled "Treatment for diabetes in patients with insufficient glycemic control despite therapy with an oral or non-oral antidiabetic drug" [April 22, 2010 international publication, International Publication No. WO2010/043688, March 8, 2012 national publication, National Publication of International Patent Application No. 2012-505859] has resulted in the following appeal

decision:

Conclusion

The appeal of the case was groundless.

Reason

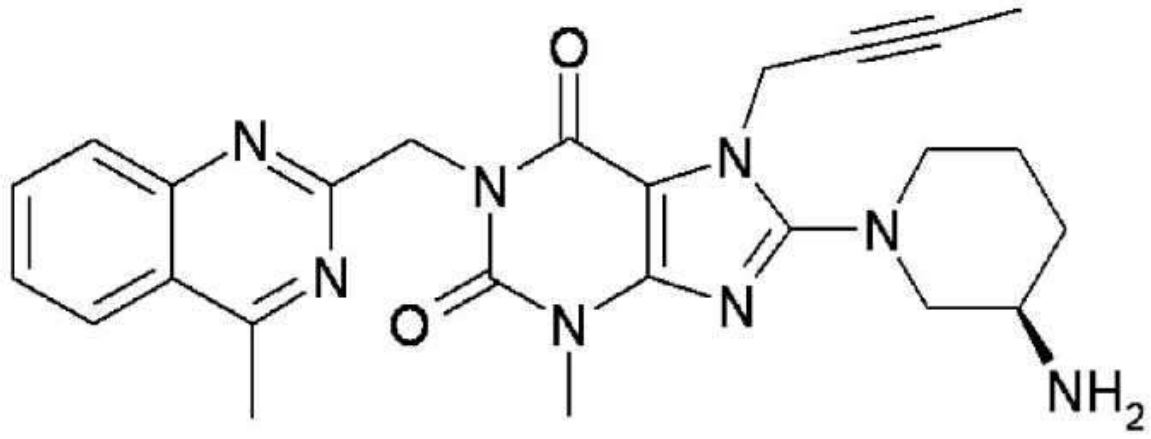
1. History of the procedures

The application was filed on October 15, 2009 (Priority Claim under the Paris Convention: October 16, 2008 (EP), Priority Claim: October 16, 2008 (US), Priority Claim: August 5, 2009 (EP)) as an international filing date, a notice of reasons for refusal was issued on February 7, 2013. Against this, the written opinion and the written amendment were submitted on August 14, 2013; however, a decision for refusal was issued on October 17, 2013. Against this, an appeal against the examiner's decision of refusal was filed on February 28, 2014, and reasons in the appeal were amended by the written amendment submitted on April 16, 2014.

2. The Invention

Among inventions according to the scope of claims of the application, it is found that inventions according to Claims 1 to 36 are specified by matters described in Claims 1 to 36 according to the scope of claims amended by the written amendment submitted on August 14, 2013, and the invention according to Claim 1 above (hereinafter referred to as the "Invention") is as follows.

"Use of a DPP-4 inhibitor represented by following formula or its pharmaceutically acceptable salt, for manufacturing pharmaceutical compositions used for a method of treating and/or preventing metabolic diseases in these patients with insufficient glycemic control despite therapy with one or more usual oral or non-oral antidiabetic drug selected from metformin, sulphonylureas, thiazolidinediones, glinides, alpha-glucosidase blockers, GLP-1 or GLP-1 analogues, and insulin or insulin analogues:



"

3. Cited Document

(1) Described matters in Cited Documents

In the Publication which was cited in reasons for refusal of the examiner's decision, has been distributed before the priority date of the application and is Cited Document 2 of the notice of reasons for refusal issued on February 7, 2013, Drugs of the Future, 2008, Volume 33, Issue 6, p. 473-477 (hereinafter also referred to as "Cited Document A"), the following technical matters are described.

a1 (Title)

BI-1356

8-[3(R)-Aminopiperidin-1-yl]-7-(2-butynyl)-3-methyl-1-(4-methylquinazolin-2-ylmethyl) xanthine

a2 (Abstract)

"BI-1356 is a dipeptidyl-peptidase IV (DPP IV, or CD26) inhibitor developed at Boehringer Ingelheim for the treatment of type 2 diabetes."

a3 (page 475, left-hand column, lines 18 to 20)

"BI-1356 is currently undergoing phase III clinical development for the treatment of type 2 diabetes."

a4 (page 475, right-hand column, lines 17 to 16 from bottom)

"Renal excretion of BI-1356 was low and was not the major pathway of elimination."

In the Publication which was cited in reasons for refusal of the examiner's decision, has been distributed before the priority date of the application, and is Cited Document 3 of the notice of reasons for refusal issued on February 7, 2013, Current Opinion in Drug Discovery & Development, 2008, Vol. 11, No. 4, p. 512-532 (hereinafter also referred to as "Cited Document B"), the following technical matters are described.

b1 (page 526, left-hand column, lines 14 to 21)
"Hepatic insufficiency did not alter the pharmacokinetics of sitagliptin, but, because sitagliptin is largely cleared via renal secretion, renal insufficiency in patients increased sitagliptin plasma levels [118]. Therefore, for patients with moderate (creatinine clearance < 50 ml/min) or severe (creatine clearance < 30 ml/min) renal insufficiency, the dose of sitagliptin should be reduced from 100 to 50 mg and 25 mg, respectively."

b2 (page 526, left-hand column, lines 40 to 45)
"GLP-1-based therapy (both GLP-1 receptor agonists and DPP-IV inhibitors) is a major breakthrough for treating diabetes. Given that monotherapy fails to achieve proper glycemic control for most patients as the disease progresses, DPP-IV inhibitors at minimum are a welcome new class of alternative oral antihyperglycemic agents."

b3 (page 528, following second line in cell on Table 4)

Table 4. Selected clinical trial results of sitagliptin (*continued*).

Study Type	Patients	Design/dose	Results	Reference
Efficacy of initial combination therapy with metformin	1091 patients with type 2 diabetes, with mean HbA1c = 8.8%.	Randomized, double-blind, placebo-controlled study: Sitagliptin (S) 0 or 100 mg, metformin (M) 1000 or 2000 g for 24 weeks.	Placebo-subtracted ΔHbA1c = -2.07% (S100/M2000); -1.57% (S100/M1000); -1.30% (M2000); -0.99% (M1000); -0.83 (S100).	[128]
Efficacy of combination therapy with metformin	28 patients with type 2 diabetes, with inadequate glycemic control on metformin monotherapy. Mean age = 55.9 years, BMI = 31.8 kg/m², HbA1c = 7.7%, FPG = 151.8 mg/dl.	Randomized, double-blind, placebo-controlled two period, single-dose crossover study. All patients received metformin throughout the trial. Cohort 1: placebo for 4 weeks, then 50 mg twice daily of sitagliptin for 4 weeks. Cohort 2: 50 mg twice daily of sitagliptin for 4 weeks, then placebo for 4 weeks.	Carryover of sitagliptin was observed. After the first period (4 weeks), differences between the two groups were: Δ(24-h WMG) = -32.8 mg/dl, ΔMDG = -28.0 mg/dl, ΔFPG = -20.3 mg/dl, ΔFS = -33.7 mmol/l. Parameters of β-cell functions improved. No weight gain or increase in adverse effects or hypoglycemia events.	[129]
Non-inferiority to glipizide (a sulfonylurea)	1172 patients with type 2 diabetes, with inadequate glycemic control using metformin. Mean (sitagliptin/glipizide) age = 56.8/56.6 years, HbA1c = 7.7/7.6%, FPG = 9.2/9.1 mmol/l, BMI = 31.2/31.3 kg/m².	Either 100 mg/day of sitagliptin or 5 mg/day of glipizide was added on to metformin (≥ 1.5 g/day) for 52 weeks.	ΔΔHbA1c = 0.0 (both -0.7%), ΔΔFPG = -0.14 mmol/l (-0.56 versus -0.42, sitagliptin versus glipizide), ΔΔBW = -2.6 kg (-1.5 versus +1.1 kg), ΔΔHOMA-β = -10.4% (+3.6 versus +14.0%). Hypoglycemic episode dramatically reduced by 27% (5 versus 32%).	[115]

(Note by the body: Table 4 shows clinical trial results of sitagliptin. In the middle column of Table 4 (continued) described in page 528, it is described that carrying out combination therapy with sitagliptin for patients with inadequate glycemic control on metformin monotherapy, improvement of the function of β cells was observed; however, no weight gain, or increase in adverse effects or hypoglycemia events was observed.)

In the Publication which was cited in reasons for refusal of the examiner's decision, has been distributed before the priority date of the application, and is Cited Document 9 of the notice of reasons for refusal issued on February 7, 2013, International Publication No. WO2005/117861 (hereinafter also referred to as "Cited Document C"), the following technical matters are described.

c1 (lines 19 to 22 on page 13)
"Preferably the invention relates to the use of metformin in combination with a DPP-IV inhibitor for the manufacture of a medicament to control the blood HbA1c or glucose level over an extended period of time in a patient (e.g. type II diabetic patient) not adequately controlled by metformin alone."

In the Publication which was cited in reasons for refusal of the examiner's decision, has been distributed before the priority date of the application, and is Cited Document 10 of the notice of reasons for refusal issued on February 7, 2013, Diabetes, Obesity and Metabolism, 2007, Vol. 9, Issue 5, p. 733-745 (hereinafter also referred to as "Cited Document D"), the following technical matters are described.

d1 (Title)
"Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, in patients with type 2 diabetes mellitus inadequately controlled on glimepiride alone or on glimepiride and metformin"

d2 (Conclusions in Abstract)
"Sitagliptin 100 mg once daily significantly improved glycemic control and β-cell function in patients with type 2 diabetes who had inadequate glycemic control with glimepiride or glimepiride plus metformin therapy. The addition of sitagliptin was generally well tolerated, with a modest increase in hypoglycemia and body weight, consistent with glimepiride therapy and the observed degree of glycemic improvement."

In the Publication which was cited in reasons for refusal of the examiner's decision, has been distributed before the priority date of the application, and is Cited Document 11 of the notice of reasons for refusal issued on February 7, 2013, Diabetes, Obesity and Metabolism, 2008, Vol. 10, Issue 11, p. 1047-1056 (hereinafter also referred to as "Cited Document E"), the following technical matters are described.

e1 (Conclusions in Abstract)
"In patients with T2DM inadequately controlled with prior SU monotherapy, addition of vildagliptin (50 or 100 mg daily) to glimepiride (4 mg once daily) improves glycemic control and is well tolerated. Addition of vildagliptin 50 mg daily to SU monotherapy may be a particularly attractive therapy in elderly patients."

(Note by the body: SU is an abbreviation of "sulfonylurea" and T2DM is an abbreviation of "type 2 diabetes mellitus," referring to Aim in Abstract.)

e2 (page 1047, left-hand column, line 2 to right-hand column, line 3)
"Vildagliptin is a potent and selective dipeptidyl peptidase (DPP)-4 inhibitor [1] that improves glycemic control in patients with type 2 diabetes mellitus (T2DM) by increasing both α-andβ-cell responsiveness to glucose [2,3]."

From the above a1 to a4, it is found that in Cited document A, "BI-1356 which is a DPP-4 inhibitor and of which renal excretion is not the major pathway of elimination, is a therapeutic agent of type 2 diabetes" is described, and it is found that the invention of "use of BI-1356 being a DPP-4 inhibitor, for manufacturing pharmaceutical compositions used for a method of treating type 2 diabetes" (hereinafter also referred to as "Cited Invention A") is described in Cited document A.

4. Comparison/judgment
(1) Comparison

We compare the Invention with Cited Invention A.

Cited Invention A of "BI-1356 being a DPP-4 inhibitor" corresponds to the Invention of "a DPP-4 inhibitor represented by following formula (Note by the body: the formula is omitted)" (hereinafter described as "linagliptin" being a generic name of the compound).

Since type 2 diabetes is a kind of metabolic disease, it is found that "a

therapeutic agent for type 2 diabetes" of Cited Invention A corresponds to the Invention of "treating metabolic diseases."

Therefore, comparing the Invention with Cited Invention A, the two inventions correspond in following points, and are different in following points.

<Corresponding feature>

Use of linagliptin, for manufacturing pharmaceutical compositions used for a method of treating metabolic diseases.

<The different feature>

In the Invention, patients to be administered are specified to "patients with insufficient glycemic control despite therapy with one or more usual oral or non-oral antidiabetic drug selected from metformin, sulphonylureas, thiazolidinediones, glinides, alpha-glucosidase blockers, GLP-1 or GLP-1 analogues, and insulin or insulin analogues"; on the other hand, such specification is not made in Cited Invention A.

(2) Judgment on different feature

As described in the above b2 and b3, as of the priority date of the application, it is found that conventional monotherapy for treating diabetes fails to achieve proper glycemic control for most patients as the disease progresses; on the other hand, the DPP-4 inhibitor has been expected as a new therapeutic agent for treating diabetes, and it is also found that sitagliptin being a kind of DPP-4 inhibitor has been known to have therapeutic effect for patients with inadequate glycemic control on metformin monotherapy. As described in the above c1, it can be confirmed that the above expectation for DPP-4 inhibitor existed. As described in the above d1 and d2, it is found that sitagliptin has been known to have therapeutic effect for patients with type 2 diabetes mellitus inadequately controlled on glimepiride alone or on glimepiride and metformin. Further, as described in the above e1 and e2, it is found that, in addition to sitagliptin, vildagliptin being a kind of DPP-4 inhibitor has been known to have therapeutic effect for patients with inadequate glycemic control on conventional monotherapy.

In this case, it is easy for a person ordinarily skilled in the art to arrive the matter that, similar to sitagliptin and vildagliptin, linagliptin being a kind of DPP-4 inhibitor is used for treatment for patients with type 2 diabetes mellitus who have inadequate

glycemic control on conventional therapeutic agents for treating diabetes such as metformin, glimepiride, and sulfonylurea. Further, even if the Invention has therapeutic effect for the patients, this effect could be predicted by a person skilled in the art from Cited Documents B to E.

(3) Regarding argument of demandant

The appellant alleges in the August 14, 2013 written opinion, relating to the effect of the Invention, that:

"Linagliptin of the Invention is a DPP-4 Inhibitor which does not need to decrease dosage even for patients having renal dysfunction of any degree and whose dosage is accepted as one dosage (5 mg/ day). The dosage adjustment of linagliptin is not required regardless of renal dysfunction and impaired liver function. Therefore, linagliptin has a more prominent effect of excellent balance between the efficacy and a clinically pharmacodynamic property such as distribution, metabolism, and excretion than that of other approved DPP-4 inhibitors, and use of linagliptin has effect (e.g., practical or convenient effect) for not requiring additional monitoring of the liver function and dosage adjustment with decline of liver function (see paragraphs 0036 to 0038, 0060 to 0063, and Examples in the description).

In this case, use of linagliptin for treating for specific patients (especially patients who have anxiety or risk for kidney (see Claim 28)) provided in the Invention is extremely advantageous, and linagliptin is especially suitable for specific patients provided in the Invention.",

and alleges in reasons of the appeal that:

"The above effect of the Invention could not be easily predicted by a person skilled in the art based on Cited Documents 1 and 2 in which use in patients having renal dysfunction and the dosage adjustment are not indicated at all, and Cited Documents 3, and 9 to 11 in which agents different from the Invention are indicated."

However, as described in the above b1, when administering sitagliptin being the DPP-4 inhibitor to patients with renal insufficiency, it had already been known that the dose should be reduced, since sitagliptin is removed via secretion from the kidney. It could be predicted by a person skilled in the art that linagliptin being the DPP-4 inhibitor in which renal excretion is not the main excretory passage does not need the reduction of dosage even if subjects to be administered are patients with renal insufficiency, and the effect alleged by the appellant is not a prominent effect that could not be predicted by a person skilled in the art.

As described in the above 4(2) and (3), the Invention could be appropriately made by a person ordinarily skilled in the art based on the inventions described in Cited Documents A to E which are Publications distributed before the priority date of the application, it is not found that the Invention has a prominent effect that exceeds the prediction of a person skilled in the art, and the Invention could be easily made by a person skilled in the art.

5. Conclusion

As described in the above reasons, the appellant should not be granted a patent for the invention according to Claim 1 of the application under the provisions of Article 29(2) of the Patent Act.

Therefore, the application should be rejected without examining other claims..

Therefore, the appeal decision shall be made as described in the conclusion.

July 7, 2015

Chief administrative judge: UCHIDA, Junko
Administrative judge: TATSUMI, Masao
Administrative judge: FUCHINO, Ruka