Appeal decision

Appeal No. 2019-13639

Appellant	Novipharma SA
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The case of appeal against the examiner's decision of refusal of Japanese Patent Application No. 2017-528477, entitled "Medicament for Slowing Parkinson's Disease" (International Publication on June 2, 2016, WO2016/083863; publication in Japan on January 11, 2018, Japanese Unexamined Patent Application Publication No. 2018-500300) has resulted in the following appeal decision.

Conclusion

The appeal of the case was groundless.

Reason

No. 1 History of the procedures

The present application is a patent application whose international filing date is November 28, 2014, and the history of the main procedures is as follows:

August 24, 2018:	Notification of reasons for refusal
March 4, 2019:	Written opinion and written amendment
June 3, 2019:	Decision of refusal
October 11, 2019:	Written appeal and written supplemental amendment

No. 2 Regarding the invention

Inventions according to Claims 1 to 19 of the present application are as disclosed in Claims 1 to 19 in the Scope of Claims as amended by the written amendment submitted on March 4, 2019 (hereinafter, referred to as "the Invention"), and Claim 1 is as follows:

"[Claim 1]

A medicament for use in slowing the progression of Parkinson's Disease in a patient not previously treated with opicapone, which medicament comprises:
(i) levodopa;
(ii) an AADC inhibitor; and
(iii) opicapone, wherein the dose of opicapone is 25 mg to 100 mg."

No. 3 Reasons for refusal

Since the reasons for refusal stated in the examiner's decision are such that, as the Invention is an invention disclosed in Cited Document 1, it falls under the provision of Article 29(1)(iii) of the Patent Act and could be easily invented by those skilled in the art based on the invention disclosed in Cited Document 1, it is not patentable under provisions of Article 29(2) of the Patent Act.

Cited Document 1: Japanese Unexamined Patent Application Publication No. 2014-505096 (Date of publication: February 27, 2014)

No. 4 Common technical knowledge as of the filing of the present application and description in Cited Document
1 Common technical knowledge on treatment of Parkinson's Disease
(1) Document A (Mebio, 2013, Vol. 30, No. 11, pp. 31-39)

Document A has the following descriptions.

"In Parkinson's Disease (PD), the intrastriatal decrease in the amount of dopamine caused by degeneration/loss of dopaminergic neurons projected from the nigra to the striatum is the cause of development of motor symptoms. Accordingly, there is generally carried out a treatment to replenish dopamine through projection of L-dopa (LD) that goes through the blood-brain barrier as dopamine precursor" (page 31, right column, lines 2 to 8).

"Entacapone is a COMT inhibitor that acts mainly in the periphery, and concomitant use with the combination of L-dopa (LD) and dopa decarboxylase inhibitor increases bioavailability by extending the half-life of LD" (page 31, left column, first paragraph).

"

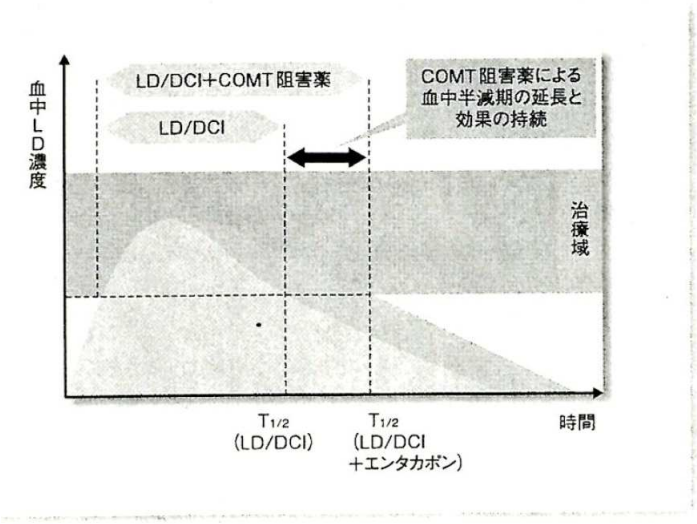


図3　LD/DCI合剤にCOMT阻害薬併用時
LD：L-ドパ
DCI：ドパ脱炭酸酵素阻害薬
COMT：カテコール-O-メチル基選択酵素

" (p. 33)

血中ＬＤ濃度　LD concentration in the blood
阻害薬　Inhibitor
ＣＯＭＴ阻害薬による血中半減期の延長と効果の持続　Extension of half-life in blood and persistence of the effect by COMT inhibitor
治療域　Therapeutic range
エンタカボン　Entacapone
時間　Time
図３　ＬＤ／ＤＣＩ合剤にＣＯＭＴ阻害薬併用時　Figure 3 When COMT inhibitor is used with combination of LD/DCI
Ｌ－ドバ　L-dopa
ドバ脱炭酸酵素阻害薬　Dopa decarboxylase inhibitor
カテコールー０－メチル基選択酵素　Catechol-O-methyl transferase

"MAOB inhibitor was expected as a disease modifying drug that has neuroprotective efficacy and inhibits development of disease, but such efficacy has not been acknowledged as the result of DATATOP study (...)7).

To patients with advanced stage of PD, it is effective even in cases in which LD has been taken for ten years or more and the efficacy has worn off 8), improvement can be observed ... in particular tremor at rest" (p. 36, right column, lines 16 to 25).

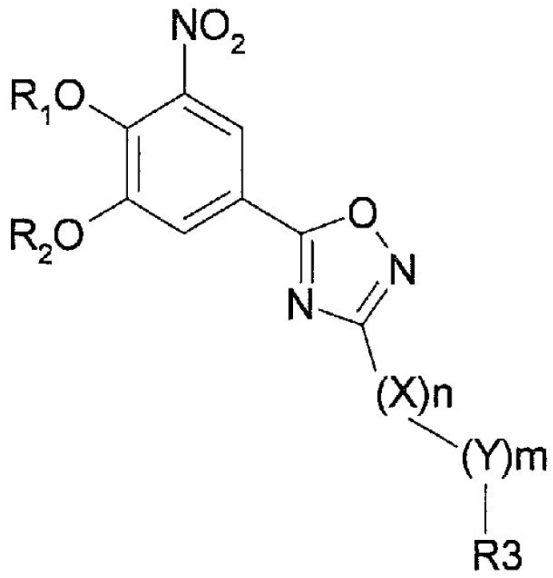
(2) Document B (BMC Neurology, 2013, 13:35.　Reference 3 attached by Appellant to its written opinion)

Document B has the following description.
"As drug therapy in Parkinson's Disease(PD) is currently symptomatic in nature, a key aim of PD research is the development of drugs which slow or even halt neurodegeneration and, therefore, clinical progression."(p. 1, left column, body text, lines 4 to 8).

(3) According to disclosures in above (1) and (2), Parkinson's Disease is a progressive nerve degenerating disease in which dopaminergic neurons are degenerated and missed, resulting in the intrastriatal decrease in the amount of dopamine, and, it is common practice to administer dopamine precursor (L-dopa (levodopa)) that passes the blood-brain barrier to replenish dopamine, and it can be deemed that, as of the filing date of the present application, it was common technical knowledge that (i) the efficacy of levodopa can be surmised from pharmacokinetics of the concentration of levodopa in the blood, and that (ii) drug therapy in Parkinson's Disease (PD) at present is practically speaking a symptomatic therapy in which symptoms are suppressed, and therapeutic agents that slow the progression of Parkinson's Disease by nerve degeneration (disease modifying drug) are sought.

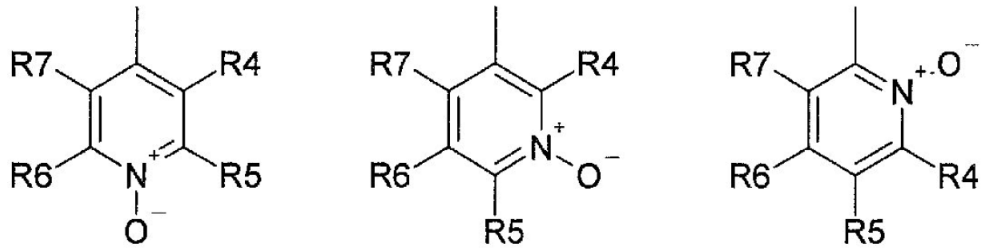
2 Description in Cited Document 1 and the Cited Invention
(1) Cited Document 1 has the following description. The underline was added by the body.

A "[Claim 1]
A compound of formula (I) to be used for preventing or treating a central or peripheral neuropathic disorder,
[Chemical Formula 1]



where R_1 and R_2 are the same or different and signify hydrogen atoms, groups hydrolysable under physiological conditions, or optionally substituted alkanoyls or aroyls; X signifies a methylene group; Y represents O, S, or NH; n represents 0, 1, 2 or 3; m represents is 0 or 1; and R_3 signifies a pyridine N-oxide group according to formula A, B, or C, which is connected as indicated by the unmarked bond:

[Chemical Formula 2]



A B C

where R_4, R_5, R_6, and R_7 are the same or different, and signify hydrogen, alkyl, thioalkyl, alkoxy, aryloxy, thioaryl, alkanoyl, aroyl, aryl, amino, alkylamino, dialkylamino, cycloalkylamino, heterocycloalkylamino, alkyklsulphonyl, arylsulphonyl, halogen, haloalkyl, trifluoromethyl, cyano, nitro, or heteroaryl; or two or more of R_4, R_5, R_6, and R_7 taken together signify aliphatic or heteroaliphatic rings or aromatic or heteroaromatic rings; the term, "alkyl" including its variant 'alk-' in terms such as 'alkoxy' and 'alkanoyl' means carbon residues, straight or branched, containing from one

to six carbon atoms; the term, "aryl" means a phenyl or naphthyl group; the term, 'heterocycloalkyl' represents a four to eight-membered cyclic ring optionally incorporating at least one atom of oxygen, sulphur, or nitrogen; the term, 'heteroaryl' represents a five or six-membered ring incorporating at least one atom of sulphur, oxygen, or nitrogen; the term, "halogen" represents fluorine, chlorine, bromine, or iodine; and if R_4, R_5, R_6, and R_7 represent alkyl or aryl they are optionally substituted by one or more hydroxy, alkoxy, or halogen groups; or a pharmaceutically acceptable salt, ester, carbamate, or phosphate thereof;

wherein compound of formula (I) is administered prior to sleep, before bedtime, or at bedtime.

...

[Claim 41]

A method of prophylaxis or treatment of a central and peripheral nervous system disorder, comprising administering to a patient suffering from said disorder, prior to sleep, before bedtime, or at bedtime, a therapeutically effective amount of a compound of formula (I) as defined in Claim 1.

...

[Claim 43]

The method according to Claim 41 or 42, wherein the compound of Formula (I) is 5-[3-(2,5-dichloro-4,6-dimethyl-1-oxy-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitrobenzene-1,2-diol or its pharmacologically acceptable salts, esters, carbamates, or phosphates.

...

[Claim 48]

The method according to any one of Claims 41 to 47, wherein the compound of Formula (I) is administered concomitantly with a catecholamine preparation.

[Claim 49]

The method according to Claim 48, wherein the catecholamine preparation is levodopa.

[Claim 50]

The method according to Claim 48 or 49, wherein the compound of formula (I) is administered sequentially with the catecholamine preparation.

[Claim 51]

The method according to any one of Claims 48 to 50, wherein the compound of formula (I) is administered before or after the catecholamine preparation.

...

[Claim 55]

The method according to any one of Claims 48 to 54, wherein the catecholamine preparation is administered sequentially or concomitantly with an AADCi.

[Claim 56]

The method according to Claim 56, wherein the AADCi is cardidopa or benserazide.

[Claim 57]

The method according to any one of Claims 41 to 56, wherein the central and peripheral nervous system disorder is a mood disorder, gastrointestinal disturbance, edema formation state, hypertension, or a movement disorder.

[Claim 58]

The method according to Claim 57, wherein the movement disorder is Parkinson's disease.

[Claim 59]

A method for the prophylaxis or treatment of a central and peripheral nervous system disorder, particularly a movement disorder such as Parkinson's disease, comprising administering to a patient suffering from said disorder between intakes of food, a therapeutically effective amount of a compound of formula (I) as defined in Claim 1, particularly,5-[3-(2,5-dichloro-4,6-dimethyl-1-oxy-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitrobenzen-1,2-diol or its pharmaceutically acceptable salts, esters, carbamates, or phosphates, in combination with a catecholamine preparation, particularly levodopa, wherein the compound of formula (I) is administered once daily at least one hour after the last daily dose of the catecholamine preparation and prior to sleep, before bedtime, or at bedtime.

B "[Technical field]

[0001]

This invention relates to the use of substituted nitrocatechols of formula (I) in the treatment of central and peripheral nervous system disorders according to a specified administration (dosing) regimen (regime).

C "[Background Art]

[0002]

The rationale for the use of COMT inhibitors as adjuncts to levodopa/aromatic L-amino acid decarboxylase inhibitor (AADCi) therapy is based on their ability to reduce metabolic O-methylation of levodopa to 3-O-methl-levodopa (3-OMD). The

duration of levodopa-induced clinical improvement is brief as a result of the short in vivo half-life of levodopa, which contrasts with the long half-life of 3-OMD. Additionally, 3-OMD competes with levodopa for transport across the blood-brain barrier (BBB), which means that only a very limited amount of an orally administered dose of levodopa actually reaches the site of action; i.e., the brain. Commonly, within only a few years of starting levodopa therapy with the usual administration regime, levodopa-induced clinical improvement declines at the end of each dose cycle, giving rise to the so-called 'wearing-off' pattern of motor fluctuations. A close relationship between the 'wearing-off' phenomenon and accumulation of 3-OMD has been described (Tohgi, H., et al., Neurosci. Letters, 132:19-22, 1992). It has been speculated that this may result from impaired brain penetration of levodopa due to competition for the transport system across the BBB with 3-OMD (Reches, A. et al., Neurology, 32:887-888, 1982), or, more simply, that there is less levodopa available to reach the brain (Nutt, J.G., Fellman, J.H., Clin. Neuropharmacol., 7:35-49, 1984). In effect, COMT inhibition protects levodopa from O-methylation metabolic breakdown in the periphery, and particularly in the intestine, such that with repeated does of levodopa, the mean plasma levodopa concentration is raised. In addition to reduced competition for transport into the brain, a significantly greater percentage of the orally administered dose of levodopa is able to reach the site of action. Thus COMT inhibition serves to increase the bioavailability of levodopa, and the duration of antiparkinsonian action is prolonged with single administrations of levodopa (Nutt, J.G., Lancet, 351:1221-1222, 1998).

[0003]

The most potent COMT inhibitors reported thus far are 3,4-dihydroxy-4'-methyl-5-nitrobenzopheonon (Tolcapone, ...) and (E)-2-cyano-N,N-diethyl-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide (Entacapone, ...).

[0004]

... Shortly after its launch, tolcapone was withdrawn from the market after several cases of hepatotoxicity were reported, including three unfortunate deaths from fatal fulminant hepatitis.

[0005]

On the other hand, entacapone, although sharing the same nitrocatechol pharmacophore with tolcapone, is not associated with liver toxicity and is generally regarded as a safe drug. Unfortunately, however, entacapone is a significantly less potent COMT inhibitor than tolcapone and has a much shorter *in-vivo* half-life. This means that entacapone has a very limited duration of effect and as a consequence, the

drug must be administered in very high doses with every dose of levodopa taken by the patient. As such, the clinical efficacy of entacapone has been questioned - indeed a recent study (Parashos, S.A. et al., Clin. Neuropharmacol., 27(3): 119-123, 2004) revealed that the principal reason for discontinuation of entacapone treatment in Parkinson's disease patients is a perceived lack of efficacy.
[0006]

Furthermore, the relatively short *in-vivo* half-life of known COMT inhibitors requires continuous treatment regimens normally involving the administration of several doses a day, which many patients find to be burdensome. For example, tolcapone has to be administered three times a day. This factor can therefore interfere with patient compliance and quality of life."

D "[Problem to be solved by the invention]
[0007]

Accordingly, there is still a need for COMT inhibitors exhibiting balanced properties of bioactivity, bioavailability, and safety. In particular, there is a need for COMT inhibitors having a long in-vivo half-life and, thus, a prolonged action on COMT enabling fewer dosages to obtain the desired therapeutic effect."

E "[Means for solving the problem]
[0008]

The applicant has previously discovered compounds which, despite having a relatively short half life, are very potent COMT inhibitors endowed with exceptionally long duration of action as compared to COMT inhibitors in the prior art (see WO2007/013830).
[0009]

These compounds, which are shown hereinbelow as compounds of general formula (I), also markedly enhance the bioavailability of levodopa and increase the delivery of levodopa to the brain. The compounds significantly augment the levels of dopamine in the brain over a long period of time.
[0010]

Even more surprisingly, the increased levels of levodopa are maintained steady over extended periods of time. These sustained effects upon both COMT actively and levodopa bioavailability after the administration of compounds of general formula (I) are markedly greater than those observed with tolcapone, the only COMT inhibitor thus far known to be endowed with a reasonably long duration of action. (Tolcapone has a

terminal half life of around 2 hours and must be administered around 3 times per day.) Furthermore, the compounds of general formula (I) produce a steady increase in levodopa delivery to the brain over extended periods of time, which contrasts with that observed with tolcapone, which is prone to induce marked oscillations in the brain delivery of levodopa. Thus compounds of general formula (I) are more likely to be endowed with therapeutic advantages due to sustained constant elevation of levodopa levels, whilst the use of tolcapone is likely to induce undesirable side-effects such as dyskinesia due to abrupt increases and decreases in levodopa levels.

F "[Description of Embodiments] ...

[0042]

Most preferably, in order to avoid the interaction between the compound of formula (I) and the catecholamine preparation, and also to administer the compound of formula (I) when the patient has a digestive system free of food, the compound of formula (I) is administered once daily prior to sleep, before bedtime, or at bedtime.

[0043]

As used herein, the term 'effective daily dose' is the effective daily amount of compound administered when administered according to the dosing periodicity.

[0044]

In the present invention, effective daily doses of compounds of general formula (I) are in the range of about 1 to about 1200 mg/day, preferably about 1 to about 900 mg/day, more preferably about 5 to about 400 mg/day, even more preferably about 25 to about 300 mg/day, for example specific daily doses of 1 mg, 3 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 50 mg, 100 mg, 200 mg, 400 mg, 800 mg, or 1200 mg.

[0045]

As used herein, the term "dosage" refers to the amount of compound administered in each dosing periodicity.

[0046]

It is preferred that individual dosage units of compounds of general formula (I) are in the range of about 1 to about 2400 mg, more preferably about 1 to about 1200 mg, even more preferably about 1 to about 800 mg, for example 1 mg, 3 mg, 5 mg, 10 mg 15 mg, 20 mg, 25 mg, 30 mg, 50 mg, 100 mg, 200 mg, 400 mg, 800 mg, or 1200 mg.

[0047]

As mentioned above, COMT inhibitors are often used as adjuncts to catecholamine compounds because they reduce their metabolic O-methylation. In particular, COMT inhibitors are often used as adjuncts to levodopa/aromatic L-amino

acid decarboxylase inhibitor (AADCi) therapy because they reduce metabolic O-methylation of levodopa to 3-O-methyl-levodopa (3-OMD).

[0048]

Therefore, preferably, the pathological states treated by the compounds are central and peripheral nervous system associated disorders of humans which benefit from administration of a COMT inhibitor.

[0049]

When the compound of formula (I) is administered in combination with a catecholamine preparation, it is possible that the catecholamine preparation is administered sequentially or concomitantly with an AADCi, in particular cardidopa or benserazide.

[0050]

The compounds of general formula (I), the catecholamine preparation, and the AADCi may be administered separately or in any combination. They may be administered concomitantly (for example, simultaneously) or sequentially, and with the same or differing dosing periodicity. For example, the compounds of general formula (I) can be concomitantly or sequentially administered with the catecholamine preparation.

...

[0052]

As used herein, the term treatment and variations such as 'treat' or 'treating' refer to any regime that can benefit a human or non-human animal. In addition, the compounds of formula (I) can be used for prophylaxis (preventive treatment). Treatment may include curative, alleviation, or reducing effects, such effects relating to one or more of the symptoms associated with the central and peripheral nervous system-associated disorders.

"[0089]

The compound of formula (I) is administered as a pharmaceutical composition.

[0090]

Preferably the pharmaceutical composition is in unit dosage form, e.g. a packaged preparation, the package containing discrete quantities of the preparation, for example, packaged tablets, capsules, and powders in vials or ampoules.

[0091]

In general, the compound of formula (I) is administered orally.

The compound of formula (I) typically is administered from once a day to about

once weekly.

For the avoidance of doubt, whenever the compound of formula (I) is administered with a periodicity lower than once a day (e.g. once a week), it is understood that it will be administered prior to sleep, before bedtime, or at bedtime, before or after the last daily dose of levodopa of the day(s) of the week where the compound of formula (I) should be administered, and not every day, as with levodopa."

G "[Examples]

[0094]

Example 1: Preparation of Compound A

(5-[3-(2,5-dichloro-4,6-dimethyl-1-oxy-pyridine-3-yl)- [1,2,4] oxadiazole-5-yl]-3-nitrobenzen-1,2 -diol

...

[0109]

Example 3b: Administration of levodopa and Compound A concomitantly and separated by 1 hour

The study was a single-center, open label, randomized, gender-balanced, cross over study with four consecutive single-administration treatment periods to assess the PK-PD interaction when standard release 25/100 mg carbidopa/levodopa is administered concomitantly with a 50 mg Compound A dose or 1 hour thereafter. Eighteen (18) subjects completed 2 treatment periods, 17 subjects completed 3 treatment periods, and 16 subjects completed all 4 treatment periods. A total of 18 male [10 (55.6%)] and female [8 (44.4%)] subjects were enrolled in this study.

...

[0114]

The Point Estimates and 90% Confidence Interval of the mean pharmacokinetic parameters of levodopa following 50 mg Compound A concomitant administration (Test L1) and an administration separated 1 h (Test L2) with Sinemet® 100/25 are displayed in Table 2 (Sinemet® 100/25 alone was taken as Reference):

[0115]

[Table 2]

表２　シネメット（Ｓｉｎｅｍｅｔ（登録商標））１００／２５と化合物Ａ５０ｍｇの同時投与（試験Ｌ１）および１時間あけて投与（試験Ｌ２）後のレボドパの平均薬物動態パラメーターの推定値および９０％ＣＩ

比較	C_{max} PE (90%CI)	AUC_{0-t} PE (90%CI)	$AUC_{0-\infty}$ PE (90%CI)
試験 L1/対照 L	112.10 (96.94; 129.64)	104.23 (96.88; 112.14)	103.13 (94.02; 113.12)
試験 L2/対照 L	102.96 (89.36; 118.62)	114.56 (106.65; 123.05)	109.85 (100.22; 120.41)
試験 L2/試験 L1	91.84 (79.51; 106.09)	109.91 (102.17; 118.24)	108.51 (101.24; 116.31)

PE =推定値; CI = 信頼区間

表 2 シネメット（Sinemet (登録商標)）100/25 と化合物 A 50 mg の同時投与（試験L１）および１時間あけて投与（試験L２）後のレボドパの平均薬物動態パラメーターの推定値および９０％ＣＩ　Table 2 Point estimates and 90% CI of the mean pharmacokinetic parameters of levodopa following 50 mg Compound A concomitant administration (Test L1) and an administration separated 1 hour (Test L2) with Sinemet® 100/25

比較　Comparison
試験　Test
対照　Reference
推定値　Point estimate
信頼区間　Confidence interval

[0116]

A greater increase in the extent of exposure to levodopa (as assessed by AUC) occurred when Sinemet® 100/25 was administered 1 h after 50 mg Compound A.

...

[0124]

Conclusion

The results were highly consistent across the multiple analyses performed. ... This may have resulted in an early inhibition of COMT and consequent increase in levodopa systemic exposure.

[0125]

Example 3c: Effect of Compound A on patient's levodopa exposure after administration of L-dopa and Compound A concomitantly followed by further administration of L-dopa 24 h later

This study was a three-center, double-blind, randomized, placebo-controlled, cross-over study to investigate the tolerability and effect of a single administration of three dosages of Compound A (25, 50, and 100 mg) on the levodopa pharmacokinetics, motor response, and erythrocite soluble catechol-O-methyltransferase activity in 10 Parkinson's Disease patients concomitantly treated with levodopa/dopa-decarboxylase inhibitor.

[0126]

Subjects were eligible if they presented: a diagnosis of PD according to the UK PDS Brain Bank diagnostic criteria; predictable signs of end-of-dose deterioration despite "optimal" levodopa/AADCi therapy; being treated with a stable regimen of 3 to 8 doses of standard release levodopa/AADCi 100/25 mg per day within at least 1 week prior to randomization; modified Hoehn and Yahr stage of less than 5 in the off-state; and/or mean duration of OFF stage ≥ 1.5 h during waking hours. Concomitant anti-Parkinsonian medication (other than apomorphine, entacapone, or tolcapone) was allowed in stable doses for at least 4 weeks prior to randomization.

Manipulating the dose and frequency of levodopa administration is the common therapeutic approach to the onset of motor complications. This is usually described as optimization of levodopa therapy. "Optimal" levodopa/AADCi therapy is the levodopa/AADCi dosage and administration regime that produces the best motor response in a patient; i.e., absence or reduction to a minimum of end-of-dose deterioration (wearing-off) and/or motor complications.

[0127]

The study consisted of four consecutive treatment periods, corresponding to the 4 different treatment options (Compound A 25 mg, 50 mg, 100 mg, or placebo). In each of the four treatment periods, subjects were to be admitted to the study site 2 days prior to receiving the administration of Compound A/Placebo (Day 1) and were to remain hospitalized ("in-patient") until 48 h after receiving the administration of Compound A/Placebo. The washout period between administrations was to be at least 10 days. A follow-up visit was to occur approximately 2 weeks after the last treatment administration or early discontinuation. During each period, the Compound A /Placebo capsules were to be co-administered with the morning dose of levodopa/carbidopa 100/25 mg (1 tablet of Sinemet® 25/100) or levodopa/benserazide

100/25 mg (1 tablet of Madopar®/Restex® 125) on Day 3.

[0128]

A total of 10 subjects were enrolled in this study: 10 subjects completed 3 treatment periods and 9 subjects completed all 4 treatment periods. The mean (± SD) age, height, and weight were 58.40 ± 10.24 (range: 42 - 70) years, 1.69 ± 0.14 (1.52 - 1.95) m, and 71.5 ± 15.06 (50 - 100) kg, respectively.

[0129]

The results from this study can be found in Table 3 and Table 4.

[0130]

[Table 3]

表３．Day 2、Day 3およびDay 4におけるシネメット（Ｓｉｎｅｍｅｔ（登録商標））２５／１００またはマドパール（Ｍａｄｏｐａｒ（登録商標））／レステックス（Ｒｅｓｔｅｘ（登録商標））１２５単回経口投与後のレボドパの平均薬物動態（ＰＫ）パラメーター

	比較	治療	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-6} (ng.h/mL)	$t_{1/2}$ (h)
Day 2 化合物A 投与 24時間前	Group 1	-	2513	0.5	4325	1.70
	Group 2	-	2237	0.5	4294	1.63
	Group 3	-	2086	0.5	3830	1.88
	Group 4	-	1881	1.0	4141	1.78
Day 3 化合物A 同時投与	Group 1	偽薬	2103	0.5	3958	1.60
	Group 2	*化合物A* - 25 mg	2112	1.0	4545	1.97
	Group 3	*化合物A* - 50 mg	2366	0.5	4580	1.77
	Group 4	*化合物A* - 100 mg	2657	0.5	5440	2.05
Day 4 化合物A 投与 24時間後	Group 1	-	2128	0.5	3823	1.96
	Group 2	-	2369	0.5	4658	1.77
	Group 3	-	2583	0.5	5178	1.84
	Group 4	-	2479	1.0	5697	2.08

表３．Ｄａｙ ２、Ｄａｙ ３およびＤａｙ ４におけるシネメット （登録商標）２５／１００またはマドパール（Ｍａｄｏｐａｒ（登録商標））／レステックス（Ｒｅｓｔｅｘ（登録商標））１２５単回経口投与後のレボドパの平均薬物動態 (PK) パラメータ Table 3. Mean pharmacokinetic (PK) parameters of levodopa following single oral administration of Sinemet® 25/100 or

Madopar® / Restex® 125 on Day 2, Day 3, and Day 4

比較	Comparison
治療	Treatment
化合物	Compound
投与２４時間前	24 hours before administration
同時投与	Concomitant administration
偽薬	Placebo
投与２４時間後	24 hours after administration

[0131]

[Table 4]

表４．Day 3およびDay 4におけるシネメット（Ｓｉｎｅｍｅｔ（登録商標））２５／１００またはマドパール（Ｍａｄｏｐａｒ（登録商標））／レステックス（Ｒｅｓｔｅｘ（登録商標））１２５と、偽薬、化合物Ａ２５ｍｇ、５０ｍｇおよび１００ｍｇとの単回経口投与後のレボドパの平均ＰＫパラメーターの推定値（ＰＥ）および９０％ＣＩ
* 有意差あり

比較	C_{max} PE (90%CI)	AUC_{0-6} PE (90%CI)
Day 3 (化合物 A 同時投与)		
偽薬 - Day 3/ Day 2	93.49 (62.23; 140.45)	82.11 (55.90; 120.61)
化合物A 25 mg - Day 3/ Day 2	90.10 (60.66; 133.84)	100.68 (66.58; 152.24)
化合物A 50 mg - Day 3/ Day 2	117.00 (78.87; 173.56)	121.94 (88.57; 167.89)
化合物A 100 mg - Day 3/ Day 2	144.54 (104.41; 200.09)*	133.18 (90.22; 196.60)
Day 4 (化合物 A 投与 24 時間後)		
偽薬- Day 4/ Day 2	83.26 (55.84; 124.16)	93.45 (63.99; 136.48)
化合物A 25 mg - Day 4/ Day 2	109.18 (80.03; 148.94)	110.54 (77.14; 158.40)
化合物A 50 mg - Day 4/ Day 2	128.79 (87.21; 190.19)	138.79 (101.18; 190.38)*
化合物A 100 mg - Day 4/ Day 2	120.93 (79.59; 183.74)	132.36 (86.56; 202.39)

表 4. Day 3 および Day 4 におけるシネメット (Sinemet (登録商標) 25/100 またはマドパール（Madopar (登録商標)）/レステックス (Restex (登録商標)) 125)と偽薬、化合物 A 25 mg、50 mg および 100 mg との単回経口投薬後のレボドバの平均 PK パラメータの推定値（PE）および 90% CI　Table 4. Point estimates (PE) and 90% CI of mean PK parameters of levodopa following single oral administration of Sinemet® 25/100 or Madopar® / Restex® 125 and placebo, 25 mg, 50 mg, and 100 mg Compound A on Day 3 and Day 4

＊有意差あり　*significantly different

比較　Comparison

（化合物 A 同時投与）	(concomitant administration with Compound A)
偽薬	Placebo
化合物	Compound
(化合物 A 同時投与 24 時間後)	(24 hours after concomitant administration with Compound A)

...

[0136]

Example 3e: Clinical trial in patients with Parkinson's disease: dosage prior to sleep and 1 hour after food intake

In a double blind, placebo controlled study, patients with Parkinson's disease maintained on levodopa/AADCi are treated as follows. Patients take either the placebo or Compound A (25 mg or 50 mg) in the evening at least one hour after the last dose of the day of levodopa/AADCi therapy (the bedtime dose (administration)).

[0137]

Subjects are required to fast for 1 hour before and for at least 1 hour after intake of the treatment.

[0138]

Patients who take Compound A are expected to show improved effects relative to those taking the placebo."

(2) According to the description in above (1), Cited Document 1 states that a COMT inhibitor used as an adjunct to levodopa/AADCi (aromatic L-amino acid decarboxylase inhibitor) therapy protects levodopa against peripheral metabolic degradation, and increases bioavailability of levodopa, resulting in prolonged duration of anti-parkinsonian action of single administration of levodopa ([0002]), and that, while there is a need for COMT inhibitors having a long in-vivo half-life and, thus, a prolonged action on COMT enabling fewer dosages to obtain the desired therapeutic effect ([0007]), the compound of formula (I), particularly, Compound A (5-[3-(2,5-dichloro-4,6-dimethyl-1-oxy-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitrobenzene-1,2-diol), was found to be such a COMT inhibitor, and there is a possibility that the compound of formula (I) has better therapeutic advantages due to sustained and constant increase in the amount of levodopa ([Claim 43], [Claim 59], [0008] to [0010], and [0094]).

In addition, it is stated that the compound of formula (I) is normally administered from once a day to about once a week, prior to sleep, before bedtime, or at bedtime before or after the last administration of the day of levodopa (([0091]), the effective

daily dose is "even more preferably about 25 to about 300 mg/day, for example specific daily doses of 1 mg, 3 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 50 mg, 100 mg, 200 mg, 400 mg, 800 mg or 1200 mg" ([0044]), and that it is used as an adjunct to levodopa/AADCi therapy ([0047] to [0050]).

In addition, Example 3b discloses that, in tests to administer to male/female subjects 50 mg of Compound A and 25 mg of carbidopa/100 mg of levodopa concomitantly and separated by 1 hour, a greater increase in the extent of exposure to levodopa (as assessed by AUC) occurred when Compound A was administered 1 h after carbidopa/levodopa ([0109] to [0124]).

In Example 3c, Table 3 and Table 4 disclose the result of measurement of pharmacokinetics of levodopa (C_{max}, T_{max}, AUC, etc.) when three doses (25, 50, and 100 mg) of Compound A were given as single administration and, further, levodopa/carbidopa 100/25 mg or levodopa/benserazide 100/25 mg is administered concomitantly or after 24 hours to patients with Parkinson's Disease being treated with a stable regimen of 3 to 8 doses of standard release of levodopa/AADCi daily 100 mg/25 mg as levodopa/AADCi therapy ([0125] to [0131]).

Based on the results of such experiments, Example 3e discloses a clinical trial program in which patients with Parkinson's Disease maintained on levodopa/AADCi are treated as follows. Patients take Compound A (25 mg or 50 mg) in the evening at least one hour after the last dose of the day of levodopa/AADCi therapy (the bedtime dose (administration)), and states that "patients who take Compound A are expected to show improved effects relative to those taking the placebo" ([0136] to [0138]).

Although Example 3c of Cited Document 1 discloses the result of measurement of pharmacokinetics of levodopa (C_{max}, T_{max}, AUC, etc.) when a combination of Compound A and levodopa/AADCi (carbidopa or benserazide) was given to patients with Parkinson's Disease maintained on levodopa/AADCi, it has not been confirmed whether the symptoms were actually inhibited.

However, since it was common technical knowledge as of the time of filing the present application as described in above 1, (3), that (i) the effect of treatment with levodopa can be surmised from pharmacokinetics of the concentration of levodopa in the blood, and that (ii) drug therapy in Parkinson's Disease (PD) at present is practically speaking a symptomatic therapy, those skilled in the art can understand that the combination of the compound of Formula (I) and levodopa/AADCi therapy disclosed in Cited Document 1, in particular, the combination of drugs in Example 3c, can inhibit symptoms of Parkinson's Disease; namely, it is a medicament for treating Parkinson's

Disease.

Accordingly, it is acknowledged that Cited Document 1 discloses the following invention (hereinafter, referred to as the "Cited Invention").

"A medicament for treating patients with Parkinson's Disease maintained on levodopa/AADCi which medicament consists of a combination of:
(i) levodopa,
(ii) AADCi as carbidopa or benserazide, and
(iii) 5-[3-(2,5-dichloro-4,6-dimethyl-1-oxy-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitrobenzene-1,2-diol (Compound A): 25 mg, 50 mg or 100 mg."

No. 5 Comparison and Judgment
1 Comparison

The Invention and the Cited Invention are compared.

Since "AADCi" of the Cited Invention is an aromatic L-amino acid decarboxylase inhibitor ([0002] in Cited Document 1), it corresponds to "AADCi inhibitor" of the Invention.

On the other hand, according to the compound name of opicapone mentioned in [0005] in the specification of the present application, "5-[3-(2,5-dichloro-4,6-dimethyl-1-oxy-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitrobenzene-1,2-diol (Compound A)" of the Cited Invention corresponds to "opicapone" of the Invention.

In addition, "for treating Parkinson's Disease" of the Cited Invention and "for use in slowing the progression of Parkinson's Disease" of the Invention coincide with each other to the extent they are "for Parkinson's Disease."

Furthermore, "A medicament ...consisting of a combination of ..." of the Cited Invention corresponds to "A medicament ... which medicament comprises" of the Invention.

Then, the corresponding features and the tentative different features between the Invention and the Cited Invention are as follows:

<Corresponding Feature>
"A medicaments for patients with Parkinson's Disease comprising
(i) levodopa,
(ii) AADC inhibitor, and
(iii) opicapone."
<Different Feature 1>

While patients in the Invention are "not previously treated with opicapone," patients in the Cited Invention are "patients maintained on levodopa/AADCi therapy."

<Different Feature 2>

While the dose of opicapone is "from 25 mg to 100 mg" in the Invention, it is "25 mg, 50 mg, or 100 mg" in the Cited Invention.

<Different Feature 3>

While the medicament is "for use to slow the progression of Parkinson's Disease" in the Invention, it is "for treating Parkinson's Disease" in the Cited Invention.

2 Judgment

(1) Regarding Different Feature 1

As explained in above No. 4, 2, (2), judging from the fact that Cited Document 1 published before the filing date of the present application discloses that, while there were needs for COMT inhibitors with a long in-vivo half-life that result in a prolonged action on COMT enabling fewer dosages to obtain the desired therapeutic effect, opicapone (Compound A) was found to be a such COMT inhibitor, and that it does not mention experience of treatment with opicapone as a condition for subjects that are deemed eligible in Example 3c, it is reasonable to understand that "patients with Parkinson's Disease maintained on levodopa/AADCi" in the Cited Invention are "patients not previously treated with opicapone."

Therefore, Different Feature 1 is not a substantial difference.

(2) Regarding Different Feature 2

Since "from 25 mg to 100 mg" of the Invention means that the dose is within the range from 25 mg to 100 mg, it covers "25 mg, 50 mg, or 100 mg" of the Cited Invention, and the doses of both cases overlap and coincide with each other.

Therefore, Different Feature 2 is not a substantial difference.

(3) Regarding Different Feature 3

A As explained in above No. 4, 1 (3), as of the time of filing the present invention, it was common technical knowledge that drug therapy in Parkinson's Disease (PD) was basically a symptomatic therapy, and therapeutic agents that slow progression of Parkinson's Disease by nerve degeneration (disease modifying drug) were sought.

Based on the above common technical knowledge, "a medicament for use in slowing the progression of Parkinson's Disease" in the Invention is a medicament for treating Parkinson's Disease, but it is not a mere medicament that inhibits symptom of

Parkinson's Disease but a medicament that slows the progression of Parkinson's Disease itself.

B On the other hand, taking into consideration the fact that Cited Document 1 discloses that "treatment may include curative, alleviation, or reducing effects, such effects relating to one or more of the symptoms associated with central and peripheral nervous system-associated disorders" ([0052]), "'Optimal' levodopa/AADCi therapy is the levodopa/AADCi dosage and administration regime that produces the best motor response in a patient; i.e., absence or reduction to a minimum of end-of-dose deterioration (wearing-off) and/or motor complications" ([0126]), the "medicament for treating Parkinson's Disease" in the Cited Invention can cover effects to cure, alleviate, or lower symptoms of Parkinson's Disease, but, it is not especially recognized that it has an efficacy to lower the progression of Parkinson's Disease.

Therefore, it is understood that the Cited Invention relates to "a medicament for treating Parkinson's Disease" that delivers an efficacy to inhibit symptoms.

C Under such circumstances, it is examined below whether "a medicament for use in slowing the progression of Parkinson's Disease" in the Invention and "a medicament for treating Parkinson's Disease" in the Cited Invention can be deemed to be "different uses."

(A) Patient groups

For patients with Parkinson's Disease, both inhibition of symptoms and lowering of the progression of the disease are desired. There is no difference between the patient group that is the target of "a medicament for use in slowing the progression of Parkinson's Disease" and the patient group that is the target of "a medicament for treating Parkinson's Disease" that exhibits efficacy to suppress the symptoms.

In addition, the specification of the present application neither mentions nor suggests that the patient group that is the target of the medicament that slows the progression of Parkinson's Disease is different from the patient group that is the target of the medicament used for symptomatic treatment.

Accordingly, the patient group for which the "medicament for use in slowing the progression of Parkinson's Disease" of the Invention is applied and the patient group for which the "medicament for treating Parkinson's Disease" of the Cited Invention is applied cannot be discriminated.

(B) Concrete use conditions such as dosage and administration, etc.

It cannot be deemed that, as of the time of filing the present application, there was common technical knowledge that concrete use conditions such as dosage and administration, etc. for using "a medicament for use in slowing the progression of Parkinson's Disease" are different from those for "a medicament for treating Parkinson's Disease."

The specification of the present application states that opicapone is administered with a dose of 5 to 100 mg once a day, one hour before or after the last administration of levodopa, for example, prior to sleep ([0011], [0012]), and these overlap descriptions in Cited Document 1 ([0091]). In addition, the present specification states with respect to the duration of administration that "for example, it may be two weeks ... or 24 months" ([0010]), but it can be deemed that, since, in general, treatment of Parkinson's Disease lasts for a long period, the duration of administration in the Cited Invention is assumed to be a long duration from about two weeks to about 24 months.

Accordingly, "a medicament for use in slowing the progression of Parkinson's Disease" of the Invention and "a medicament for treating Parkinson's Disease" of the Cited Invention cannot be discriminated with their concrete use conditions such as their dosage and administration.

(C) As explained in above (A) and (B), as far as no discrimination can be made with respect to patient group or concrete using conditions such as dosage and administration, it cannot be deemed that "a medicament for use in slowing the progression of Parkinson's Disease" of the Invention and "a medicament for treating Parkinson's Disease" of the Cited Invention are different from each other, and Different Feature 3 is not a substantial difference.

(4) Summary

As explained above, Different Features 1 to 3 are not substantial differences, and we must say that the Invention is substantially same as the Cited Invention and is the invention disclosed in Cited Document 1.

3 Appellant's allegation

Appellant alleges that "the Invention relates to a medicine to be used for slowing of progression of Parkinson's Disease in patients not previously treated with opicapone. Since the test design was such that it does not allow observation of efficacy on the progression of diseases, such efficacy is not disclosed in Cited Document 1. Not only

is the form of the test inappropriate to measure the progression of the disease, but also the test period is short (3 doses of opicapone and follow-up check for 10 days at the maximum), and the effect on the symptoms is not recorded. It was impossible to observe reduction in symptoms and there was no delay starting group to be compared.

Accordingly, we believe that Cited Document 1 does not disclose the Invention, and the Invention has novelty over Cited Document 1" (Written Appeal, page 15, last line to page 16, line 9).

However, as explained in above 2 (3), since the Invention and the Cited Invention cannot be discriminated by targeted patient groups or concrete use conditions such as dosage and administration, even if the Invention found that the object of the Invention has the property "slowing the progression of Parkinson's Disease" that the Cited Invention intrinsically has and that those skilled in the art expected as a property that a medicament for treating Parkinson's Disease should have, the Invention cannot be deemed to be an invention that found that the object of the Invention is suited by the property "slowing the progression of Parkinson's Disease" to be used for a new application which differs from that of the Cited Invention.

Therefore, the allegation of the appellant discussed above cannot be accepted.

No. 6 Closing

As described above, since the invention according to Claim 1 of the present application falls under the provision of Article 29(1)(iii) of the Patent Act and is not patentable, the present application should be rejected even without examining inventions according to other claims.

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

December 20, 2019

Chief administrative judge: INOUE, Noriyuki
Administrative judge: FUJIWARA, Hiroko
Administrative judge: FUCHINO, Ruka