Patent Right	Date	February 13, 2025	Court	Intellectual Property High Court, Fourth Division
	Case number	2023 (Gyo-Ke) 10093 (Case 1), 2023 (Gyo-Ke) 10094 (Case 2)		

- A case in which the court held that, in order for a cited invention to be found to be a medicinal use invention, a person ordinarily skilled in the art would have to be able to understand and recognize its feasibility of being put to the target usage, and determined that the JPO erred in finding in its trial decision (the JPO Decision) that the invention (Exhibit Ko 3 Invention) stated in the cited document (Exhibit Ko A3) has a medicinal usage and in finding this to be a common feature between Exhibit Ko 3 Invention and the present invention (the Invention).
- A case in which the court dismissed the claim, holding that a person ordinarily skilled in the art is not found to have been able to easily make the Invention based on Exhibit Ko 3 Invention, because a person ordinarily skilled in the art is not regarded to have been motivated to adopt Differences 1 and 2, which were correctly found by the JPO, as constituent features of the Invention, and also because the Invention has a prominent effect that could not have been expected by a person ordinarily skilled in the art, but determining that the abovementioned error in the finding in the JPO Decision does not affect the conclusion.

Case type: Rescission of Trial Decision to Maintain
Result: Dismissed
References: Article 29, paragraph (2) of the Patent Act
Related rights, etc.: Patent No. 4376630
Trial decision: Invalidation Trial No. 2020-800076

Summary of the Judgment

1. The present case is a lawsuit seeking rescission of the JPO Decision in which the JPO held that a request for trial for invalidation for the Defendant's patent (Patent No. 4376630) for an invention titled "Agent for treating movement disorders" was groundless, and the issue (the ground for rescission) in this case was an error in the JPO's determination on an inventive step of the Invention based on Exhibit Ko 3 Invention.
2. The court held as summarized below, and dismissed the Plaintiffs' claim, determining that although the JPO Decision contains an error in the finding of common features and differences between the Invention and Exhibit Ko 3 Invention, a person ordinarily

skilled in the art is not found to have been able to easily make the Invention based on Exhibit Ko 3 Invention, and the abovementioned error in the finding in the JPO Decision does not affect the conclusion.

(1) The Invention is an invention of a medicine that is administered to specific patients and is applied to specific symptoms (diseases) in those patients (a medicinal invention), and when finding common features and differences between the Invention and a cited invention, whether or not the cited invention is found to be a use invention should be closely examined, and if no common features can be extracted as a use invention, this should be clarified as a difference.

In the field of medicine, it is often difficult to predict the function and effect from the structure (the chemical substance specified by a chemical formula, etc.), and an invention in this field is completed as a use invention after verifying the feasibility through processes such as conducting various trials and experiments. Therefore, in order for a cited invention to be recognized as a use invention, the invention needs to be one for which a person ordinarily skilled in the art would have been able to understand and recognize its feasibility of being put to the target usage, such as that the invention is disclosed with backing by data sufficient for trusting that the substance (agent) is useful for the target usage. Unless such interpretation is adopted, there will be a risk that the novelty and an inventive step of a feasible medicinal use invention that has been completed through the abovementioned processes would be easily denied based on a cited invention that is hardly found to be feasible.

(2) While Exhibit Ko A3 shows trial results regarding the fact that theophylline has an action of causing decrease in the duration of OFF time in advanced Parkinson's disease patients who receive L-DOPA therapy, the trial was conducted as an "open trial" which is less accurate, the number of patients who completed the trial is small, and the document is only a report consisting of one page in English in the format of clinical/scientific notes, and the accuracy of the trial cannot be verified. Thus, it is difficult to evaluate Exhibit Ko A3 to be reliable clinical trial results on its own.

Although there were cases in which the influence of the adenosine A_{2A} receptor inhibiting action on Parkinson's disease symptoms was confirmed by administering more potent and selective adenosine A_{2A} receptor antagonists than theophylline, such as KW-6002, to various animal models, those animal models had not exhibited the wearing off phenomenon / ON-OFF fluctuations. Thus, as of the Priority Date, details had not been clarified about the presence of the mechanism of action of theophylline against the wearing off phenomenon / ON-OFF fluctuations, that is, the fact that adenosine A_{2A} inhibiting action, which is one of the multiple actions of theophylline,

has an effect of extending the duration of action of L-DOPA (reducing OFF time) in advanced Parkinson's disease patients who receive L-DOPA therapy.

Then, the agent of Exhibit Ko 3 Invention is not found to be one which a person ordinarily skilled in the art would have been able to understand and recognize as being usable (feasible) for "causing decrease in the duration of OFF time in advanced Parkinson's disease patients." Thus, the JPO erred in finding in the JPO Decision that Exhibit Ko 3 Invention has a medicinal usage, and in finding this to be a common feature between Exhibit Ko 3 Invention and the Invention.

(3) Regarding the ease of conceiving of Difference 1 that was correctly found (the fact that the Invention is an "agent" which is a use invention "administered to patients for reducing OFF time of the wearing off phenomenon and/or ON-OFF fluctuations in L-DOPA therapy," whereas Exhibit Ko 3 Invention is not found to be such use invention)

The results of the trial of Exhibit Ko A3 and the statement in its "Discussion" section that calls for additional studies can sufficiently motivate a person ordinarily skilled in the art to conduct further experiments and research about the presence or absence of the effects of theophylline by adopting a more rigorous trial, such as a "randomized, placebo-controlled, double-blind trial," in order to clarify whether or not theophylline is a therapeutically effective compound. However, the trial results shown in Exhibit Ko A3 are not sufficient for determining the efficacy of theophylline against the wearing off phenomenon and/or ON-OFF fluctuations in advanced Parkinson's disease patients, and while theophylline is a non-selective adenosine A_{2A} receptor antagonist, as of the Priority Date, details had not been clarified about the presence of the mechanism of action wherein the adenosine A_{2A} inhibiting action of adenosine A_{2A} receptor antagonists has an effect of reducing OFF time in advanced Parkinson's disease patients who receive L-DOPA therapy. Therefore, without having to see the results of further experiments and research, Exhibit Ko A3 cannot be regarded to motivate a person ordinarily skilled in the art to the extent of making the usage of the agent of Exhibit Ko 3 Invention the usage of the agent of the Invention.

(4) Regarding the ease of conceiving of Difference 2 that was correctly found (the fact that the adenosine A_{2A} receptor antagonist is KW-6002 in the Invention, whereas the adenosine A_{2A} receptor antagonist is theophylline in Exhibit Ko 3 Invention)

The results of the trial of Exhibit Ko A3 and the statement in its "Discussion" section to the effect that investigations should be conducted with more potent and more selective compounds once those become available for clinical testing sufficiently motivate a person ordinarily skilled in the art to adopt KW-6002 in place of theophylline to the extent of using it in the trial of Exhibit Ko A3 or further experiments and research

in order to clarify whether or not the abovementioned action is exhibited by the adenosine A_{2A} inhibiting action from among the multiple actions of theophylline. On the other hand, it cannot be said that the statements in Exhibit Ko A3 would go so far as to motivate a person ordinarily skilled in the art to adopt KW-6002 in making the usage of the agent of Exhibit Ko 3 Invention the usage of the agent of the Invention, beyond experiments and research.

(5) Regarding prominent function and effect

It can be identified from Example 1 of the description of the Invention (the Description) which adopted a "randomized, placebo-controlled, double-blind trial" that an agent comprising KW-6002 can be used "for reducing OFF time of the wearing off phenomenon and/or ON-OFF fluctuations in L-DOPA therapy."

On the other hand, Exhibit Ko A3 does not contain sufficient statements for a person ordinarily skilled in the art to recognize that theophylline can be used for reducing OFF time in advanced Parkinson's disease patients, and even if theophylline produced an effect, it was unknown whether it was caused by the adenosine A_{2A} receptor inhibiting action. Therefore, it should be said that the effect indicated in the Description is a prominent effect that could not have been expected by a person ordinarily skilled in the art.

Judgment rendered on February 13, 2025
2023 (Gyo-Ke) 10093 (Case 1), 2023 (Gyo-Ke) 10094 (Case 2)
Case of seeking rescission of the JPO decision
Date of conclusion of oral argument: December 2, 2024

Judgment

Plaintiff in Case 1 (an intervenor in the trial for patent invalidation):
Towa Pharmaceutical Co., Ltd.

Plaintiff in Case 2 (a petitioner in the trial for patent invalidation):
Kyowa Pharmaceutical Industry Co., Ltd.

Plaintiff in Case 2 (a petitioner in the trial for patent invalidation):
Nichi-Iko Pharmaceutical Co., Ltd.

Defendant (the respondent in the trial for patent invalidation):
Kyowa Kirin Co., Ltd.

Main text

1. The Plaintiffs' claim shall be dismissed.
2. The Plaintiffs shall bear the court costs.

Facts and reasons

[Abbreviations]

The abbreviations used in this judgment are as described in Attachment 1 "List of Abbreviations."

No. 1 Claim (common to both cases)

The trial decision rendered by the Japan Patent Office (JPO) on July 12, 2023 with regard to the case of Invalidation Trial No. 2020-800076 shall be rescinded.

No. 2 Background

1. Developments in procedures at the JPO, etc. (undisputed among the parties)

(1) Registration of establishment of the Patent

The Defendant filed a patent application (Patent Application No. 2003-563566) for an invention titled "Agent for treating movement disorders" of which the international filing date is January 28, 2003 (priority date: January 28, 2002 [the Priority Date]), and

obtained registration of establishment of a patent right relating to the patent in question (the Patent) on September 18, 2009 (number of claims: 1).

(2) Request for the trial for patent invalidation in the present case and the JPO Decision

A. On August 31, 2020, the Plaintiffs in Case 2 filed a request for a trial for invalidation of the Patent with the JPO, and the JPO conducted proceedings on that request as the case of Invalidation Trial No. 2020-800076. Meanwhile, regarding the Patent, the case of a request for a trial for patent invalidation mentioned in (3) below was also pending before the JPO, but the JPO conducted the procedures for these cases separately without consolidating them.

B. On January 13, 2022, the Plaintiff in Case 1 filed an application for intervention on the petitioners' side, and received a ruling to permit the intervention on March 30, 2022.

C. On March 3, 2022, the Defendant filed a request for correction to change the claim of the Patent.

D. On July 12, 2023, the JPO rendered a decision to approve the request for correction referred to in C. above and hold that the request for a trial is groundless (the "JPO Decision"). A certified copy of the JPO Decision was served upon the Plaintiffs on July 21, 2023.

E. On August, 18, 2023, the Plaintiffs respectively filed the present actions seeking rescission of the JPO Decision.

(3) A request for trial for invalidation in another case and its outcome

A. On March 31, 2020, the Plaintiff in Case 1 filed a request for a trial for invalidation of the Patent with the JPO, and the Plaintiffs in Case 2 intervened on the petitioner's side.

The JPO conducted proceedings on that request as the case of Invalidation Trial No. 2020-800034, and on October 27, 2021, rendered a trial decision to approve correction of the claim requested by the Defendant and hold that the request for a trial is groundless.

B. The Plaintiff in Case 1 and the Plaintiffs in Case 2 filed a lawsuit seeking rescission of the abovementioned trial decision, but the Intellectual Property High Court handed down a judgment to dismiss the claim on January 12, 2023, and this judgment became final and binding on September 22, 2023 due to dismissal of a final appeal and a decision of non-acceptance of a final appeal.

2. Contents of the invention relating to the Patent

(1) Statement of the claim

The claim (Claim 1) of the Patent is as shown below.

Meanwhile, as the correction of the claim requested by the Defendant in the case of a request for a trial for patent invalidation mentioned in 1. (3) above was approved and

the trial decision premised on it has become final and binding, the Patent is deemed to have been registered based on the corrected claim pursuant to Article 128 of the Patent Act. Its contents are the same as those of the correction made in the procedure of trial for patent invalidation in the present case.

[Claim 1]

An agent comprising (E)-8-(3,4-dimethoxystyryl)-l,3-diethyl-7-methylxanthine, characterized in that:

said agent targets human Parkinson's disease patients that have reached the stage of exhibiting the wearing off phenomenon and/or ON-OFF fluctuations in L-DOPA therapy,

said agent is administered to said patients for reducing OFF time of the wearing off phenomenon and/or ON-OFF fluctuations in said L-DOPA therapy, and

said agent is co-administered with L-DOPA to said targets in said L-DOPA therapy.

(2) The statements and drawings in the Description (extract) are shown in Attachment 2. According to these, the Description is found to disclose the following.

A. The present invention is directed to methods of treating patients suffering from movement disorders comprising administering at least one adenosine A_{2A} receptor antagonist ([0001]).

B. There is no known cure for Parkinson's disease. Most early Parkinson's disease patients respond well to symptomatic treatment with dopamine replacement therapy, but disability increases with progression of the disease ([0005]).

Although L-DOPA provides robust and rapid therapeutic benefits in Parkinson's disease, eventually, severe adverse reactions to dopamine emerge, including motor complications such as the wearing off phenomenon (a decrease in the duration of L-DOPA action), ON-OFF fluctuations (a sudden, unacceptable loss of the "ON" state of therapeutic benefit of a medication, i.e. the period during which the patient is relatively free from the symptoms of Parkinson's disease, and onset of the "OFF" state, i.e. the parkinsonian state), and dyskinesia (abnormal involuntary movements) ([0007], [0009]).

C. Behavioral studies show that adenosine A_{2A} receptor antagonists improve motor dysfunction of several parkinsonian animal models (e.g., MPTP-treated [treatment by MPTP, which is a type of neurotoxin] monkeys), but also reveal features of A_{2A} receptor antagonists distinctive from dopaminergic agents. The findings in studies of antiparkinsonian effects of the selective adenosine A_{2A} receptor antagonist KW-6002 in MPTP-treated marmosets and cynomolgus monkeys suggest that adenosine A_{2A} antagonists might provide antiparkinsonian benefit as monotherapy in patients with early Parkinson's disease and might be able to improve antiparkinsonian response

without increasing dyskinesia in L-DOPA-treated patients with motor complications ([0032], [0033]).

D. The invention provides methods of reducing or suppressing the adverse effectiveness of L-DOPA therapy comprising administration or co-administration of one or more adenosine A_{2A} receptor antagonists to Parkinson's disease patients. Such treatment can be therapeutic such as to treat patients suffering from L-DOPA- or other dopaminergic-agent-induced motor complications to reduce OFF time and/or to suppress dyskinesias ([0039]).

A preferred adenosine A_{2A} receptor antagonist useful in accordance with the methods of the present invention comprises (E)-8-(3,4-dimethoxystyryl)-l,3-diethyl-7-methylxanthine (KW-6002) ([0121]).

The present invention is directed to reducing the adverse effectiveness of L-DOPA by increasing the proportion of the patients' awake time in an "ON" state ([0124]).

3. Summary of the grounds for the JPO Decision

The summary of the grounds for the JPO Decision is as follows.

(1) The JPO approves the correction made in the procedure of trial for patent invalidation in the present case as it is made for the purpose of restricting the claim and it satisfies other statutory requirements.

(2) Exhibit Ko 3 is found to contain statements of Exhibit Ko 3 Invention described below.

[Exhibit Ko 3 Invention]

An agent comprising adenosine receptor antagonist theophylline (a 1-week loading phase: daily increase, 100 mg bid; a 6-week steady-state phase: 600 mg/d; and a 1-week washout phase: daily decrease, 100 mg bid),

which is administered to L-DOPA-treated (764 ± 170 mg/d) patients with advanced Parkinson's disease (APD) exhibiting wearing-off, which is an L-DOPA-induced motor side effect, and

which has an effect of causing ~30% increase in the duration of ON time and, as a result, decrease in the duration of OFF time.

(3) The common features and the difference between the Invention and Exhibit Ko 3 Invention are as follows.

[Common features]

An agent comprising an adenosine A2A receptor antagonist,

wherein said agent targets human Parkinson's disease patients that have reached the stage of exhibiting the wearing off phenomenon and/or ON-OFF fluctuations in L-DOPA therapy,

wherein said agent is administered to said patients for reducing OFF time of the wearing off phenomenon and/or ON-OFF fluctuations in said L-DOPA therapy, and

wherein said agent is co-administered with L-DOPA to said targets in said L-DOPA therapy.

[Difference]

The adenosine A2A receptor antagonist is "(E)-8-(3,4-dimethoxystyryl)-l,3-diethyl-7-methylxanthine" in the corrected invention of the present case, whereas it is "theophylline" in Exhibit Ko 3 Invention.

(4) Determination on the difference

A. The authors of Exhibit Ko 3 recognize the possibility that applying a compound that has more potent and selective adenosine-receptor-blocking action than theophylline to L-DOPA-treated APD patients will reduce OFF time of the wearing off phenomenon, and a person ordinarily skilled in the art would have been able to understand that KW-6002 is a selective adenosine A2A antagonist, and that it is an agent that demonstrates more potent antiparkinsonian activity than theophylline in animal models. Moreover, a clinical trial that would serve as a premise for actually using KW-6002 as a therapeutic drug for Parkinson's disease in humans was underway as of the priority date of the Patent. Thus, it can be said that a person ordinarily skilled in the art would have been able to recognize adopting, in place of the theophylline of Exhibit Ko 3 Invention, KW-6002 which is a selective adenosine A2A antagonist that has more potent and selective adenosine-receptor-blocking action and which is expected to exhibit more potent antiparkinsonian activity than theophylline at a clinical level.

However, the influence of the placebo effect is significant in Parkinson's disease (PD), and Exhibit Otsu 17 (Exhibit Ko A80 in this lawsuit) indicates that theophylline failed to potentiate consistently the anti-PD action of levodopa in a double-blind, crossover, placebo-controlled trial conducted in response to the clinical trial results shown in Exhibit Ko 3. The trial in Exhibit Ko 3 itself is unclear in its details, and inconsistent results were obtained in an open-label trial using theophylline. It was known that theophylline is a non-selective adenosine receptor antagonist which also acts against adenosine receptors other than adenosine A2A receptors, and which has affinity for receptors other than adenosine receptors as well.

Moreover, Exhibit Ko 3 has not confirmed whether the effect of theophylline to reduce OFF time is based on an adenosine A2A receptor antagonist action, and it was common general technical knowledge as of the priority date of the Patent that important causes of occurrence of the wearing off phenomenon, etc. that occur through a long-term L-DOPA therapy had not been sufficiently elucidated. Thus, it cannot be said to

have been demonstrated as of the priority date of the Patent that the blockade of adenosine A2A receptors by an adenosine A2A receptor antagonist improves the wearing off phenomenon, etc.

Considering the above, it cannot be said that a person ordinarily skilled in the art would have reasonably presumed from the statements in Exhibit Ko 3 that adopting KW-6002, which is an adenosine A2A antagonist, in place of theophylline in Exhibit Ko 3 Invention actually reduces OFF time of the wearing off phenomenon, etc. in APD patients, that is, that KW-6002 can be used for "reducing OFF time of the wearing off phenomenon in L-DOPA therapy" as stated in the corrected invention of the present case.

B. The description in question states, as Example 1, that as a result of a clinical trial by way of a double-blind, placebo-controlled, randomized, parallel group, multicenter, exploratory study, subjects of the KW-6002 groups in which Parkinson's disease patients with L-DOPA-related motor complications, such as wearing off, were administered KW-6002, in combination with L-DOPA, in three stages progressing every four weeks (dose escalation of either (5/10/20 mg/day) or (10/20/40 mg/day)) experienced a significant decrease in OFF time compared to subjects of the placebo group (Figure 1). As it cannot be said that a person ordinarily skilled in the art would have reasonably presumed from the statements in Exhibit Ko 3 that adopting KW-6002 in place of theophylline in Exhibit Ko 3 Invention actually reduces OFF time of the wearing off phenomenon, etc. in APD patients, the abovementioned effect is an unexpected effect.

(5) Accordingly, it cannot be said that a person ordinarily skilled in the art would have been able to easily make the Invention based on Exhibit Ko 3 Invention.

4. Ground for rescission

An error in the JPO's determination on an inventive step of the Invention based on Exhibit Ko 3 Invention

No. 4 Summary of the court decision

1. Regarding the common general technical knowledge as of the Priority Date

As of the Priority Date, the following points are found to have been common general technical knowledge regarding Parkinson's disease.

(1) Parkinson's disease is caused by dopaminergic neuronal cell death, and it clinically exhibits the four major symptoms of rest tremor, cogwheel rigidity, bradykinesia, and postural instability, due to lack of dopamine content in the striatum. The basic treatment is symptomatic treatment which uses an L-DOPA preparation to supplement the lacking

dopamine (L-DOPA therapy) (Exhibits Ko A10 and A16 [Exhibit Ko A146; only Exhibit Ko A16 is cited below]).

(2) A stable anti-PD therapeutic benefit (drug efficacy) can be obtained in the early phase of an L-DOPA therapy. However, when L-DOPA is used over a long term, cases in which the duration of the drug efficacy shortens (a wearing off phenomenon) or even cases in which the efficacy suddenly disappears as if a switch has been turned off (ON-OFF fluctuations) become noticeable. In addition, there may be appearance of choreic involuntary movement at the peak L-DOPA concentration in the brain (peak dose dyskinesia) or biphasic appearance of dystonia (sustained, abnormal muscle contractions) or dyskinesia in the rising phase and the lowering phase of L-DOPA concentration in the brain. Meanwhile, the wearing off phenomenon / ON-OFF fluctuations and the dystonia or dyskinesia are not necessarily associated with each other, and are separate pathological conditions (Exhibits Ko A10, A14 through A16, and A43).

(3) The "wearing off phenomenon" is a phenomenon in which diurnal variations occur in Parkinson's disease symptoms due to the shortening of the drug efficacy period. The mechanism of its occurrence was considered to be such factors as changes in the L-DOPA absorption or metabolism due to long-term administration of L-DOPA and a decline in the dopamine-retaining capacity of dopamine neurons due to progression of the Parkinson's disease itself. Meanwhile, "ON-OFF fluctuations" is a phenomenon that shows rapid changes in symptoms as if an electric switch is turned on or off irrespective of the time of L-DOPA administration or the L-DOPA concentration in the blood. Its occurrence mechanism was presumed to be a decline in the dopamine receptor sensitivity due to long-term administration of L-DOPA (Exhibit Ko A10).

On the other hand, there are also indications that various presynaptic and postsynaptic events induced by continuous administration of L-DOPA are related to the wearing off phenomenon and ON-OFF fluctuations (Exhibits Ko A65 and A66), and it cannot be said that their causes have been sufficiently elucidated.

The dopamine agonists considered to be used in combination with L-DOPA were those that would suppress the wearing off phenomenon / ON-OFF fluctuations, dyskinesia, dsystonia, and mental symptoms associated with long-term administration of L-DOPA, and "COMT inhibitors" that inhibit catechol-O-methyl transferase (COMT), a metabolic enzyme of L-DOPA, were regarded to improve the wearing off phenomenon by extending the duration of action of L-DOPA (Exhibits Ko A43 and A52).

(4) Sometimes a placebo effect occurs, which is an effect where even if a placebo drug

without drug efficacy is administered to advanced Parkinson's disease patients who exhibit the wearing off phenomenon / ON-OFF fluctuations and receive L-DOPA therapy, a reduction in OFF time (an increase in ON time) is confirmed as compared to before the administration (Exhibits Ko A30 to A36, and A81). While there is a dispute among the parties regarding the presence/absence and the extent of the placebo effect in individual documents, the influence of the placebo effect, if any, is regarded to be about 3% (Exhibit Ko A31 Figure 2B, Week 12) to 13% (Exhibit Ko A81 Figure, Week 26) for example, and it is common general technical knowledge that a certain extent of placebo effect is found with regard to the wearing off phenomenon / ON-OFF fluctuations in advanced Parkinson's disease patients who receive L-DOPA therapy.

(5) Theophylline is a non-selective adenosine A_{2A} receptor antagonist which has affinity for not only adenosine A_{2A} receptors, but also for phosphodiesterase and guanosine receptors (Exhibits Ko A1 and A4).

In experiments on rodent (mouse or rat) models of Parkinson's disease, theophylline, when administered alone, showed antiparkinsonian effects including induction of normal rotational behavior, an increase in spontaneous motor activity, and a reduction in drug-induced catalepsy (muscle rigidity) (Exhibit Ko A4, Exhibit Ko A6 [Exhibit Ko A45], and Exhibit Ko A123). However, Parkinson's disease symptoms were induced in these animal models through the damaging of dopamine neurons by 6-hydroxydopamine (6-OHDA), and they had not exhibited the wearing off phenomenon / ON-OFF fluctuations.

In addition, clinical trials were being conducted as of the Priority Date for confirming whether or not theophylline has antiparkinsonian effects in advanced Parkinson's disease patients, and whether or not theophylline has an influence on the wearing off phenomenon / ON-OFF fluctuations (Exhibits Ko A3, A50, and A80).

(6) KW-6002 was recognized to be a selective adenosine A_{2A} receptor antagonist that demonstrates significantly superior adenosine A_{2A} receptor selectivity and affinity compared to agents with non-selective adenosine receptor antagonist action, such as theophylline and caffeine (Exhibit Ko A16).

Moreover, animal experiments were being conducted by using rodent (mouse or rat) and primate (common marmoset or cynomolgus monkey) models to confirm whether or not KW-6002 increases the antiparkinsonian effects of L-DOPA and whether or not it increases the duration of the antiparkinsonian effects of L-DOPA (Exhibits Ko A1, A2, A4, A7, and A64). Exhibit Ko A1 states in its abstract as follows: "The increase in total counts of apomorphine-induced turning by the adenosine A_{2A} receptor antagonists seems to be mainly attributable to prolongation of turning duration rather than

enhancement of intensity. These results suggest that these adenosine A_{2A} receptor antagonists may be useful to ameliorate shortening in the duration of dopaminergic drug response in patients with advanced Parkinson's disease." In addition, Exhibit Ko A2 states as follows: "In conclusion, adenosine A_{2A} receptor antagonists may be a useful treatment for Parkinson's disease not only as monotherapy but also in combination with L-DOPA and dopamine agonist drugs. In particular, in patients with 'wearing-off' and 'on-off' response fluctuation, compounds such as KW-6002 may be able to increase 'on time' without prolonging dyskinesia." Thus, a person ordinarily skilled in the art would have recognized that KW-6002 might be useful to ameliorate shortening in the duration of dopaminergic drug response in patients with advanced Parkinson's disease and that it may be able to increase ON time without prolonging dyskinesia. However, these animal models had not exhibited the wearing off phenomenon / ON-OFF fluctuations. Of the animal models, rodent models are as described in (5) above, and primate models are models in which dyskinesia had been induced by administration of MPTP (Exhibits Ko A2, A7, and A64), but dyskinesia is not associated with the wearing off phenomenon / ON-OFF fluctuations as described in (2) above. Accordingly, these animal experiments do not provide direct information about the influence of KW-6002 on the wearing off phenomenon / ON-OFF fluctuations beyond its influence on general antiparkinsonian effects of L-DOPA.

Furthermore, as mentioned in Exhibit Ko A16, as of the Priority Date, KW-6002 was under clinical development as an anti-Parkinson's disease drug in the United Kingdom and Japan, and although phase II trials targeting Parkinson's disease patients were underway in the United States, they did not go so far as to confirm whether OFF time would be reduced by administering a selective adenosine A_{2A} receptor antagonist, such as KW-6002, to advanced Parkinson's disease patients who exhibit the wearing off phenomenon / ON-OFF fluctuations and receive L-DOPA therapy. In addition, as the statement "Further clinical studies with more potent and selective antagonists of adenosine A_{2A} receptors are warranted" in Exhibit Ko A80 suggests, as of the Priority Date, there was no established knowledge backed by reliable clinical trials, etc. regarding the fact that the "adenosine A_{2A} receptor antagonist action," that is, the adenosine A_{2A} receptor inhibiting action, of KW-6002 "reduces OFF time in advanced Parkinson's disease patients who receive L-DOPA therapy," and this fact, including the actual effects and the mechanism of action, had not been sufficiently elucidated.

2. Regarding the ground for rescission (An error in the JPO's determination on an inventive step of the Invention based on Exhibit Ko 3 as the primary cited document)

(1) Statements in Exhibit Ko A3

Exhibit Ko A3 is "Clinical/Scientific Notes" consisting of one page in English, and it contains the following statements (the Japanese translation, particularly the translation of the direct citations in F. and G. below, follows that in the JPO Decision).

A. Theophylline increases "on" time in advanced parkinsonian patients (title)

B. L-dopa is the most effective symptomatic treatment for PD. Its chronic use, however, is frequently complicated by the development of disabling motor side effects.

These may result from alterations in the fine-tuned neurochemical balance in the output pathways of basal ganglia. Thus, experimental therapies combining L-dopa and agents that modulate the output pathways of basal ganglia should be encouraged. Based on past trial results by the authors of Exhibit Ko A3 (Document 4 [corresponding to Exhibit Ko A123]) showing that adenosine A_{2A} receptor blockade potentiates the anti-PD effects of dopamine agonists in a rat model of PD, an ideal therapeutic target is adenosine A_{2A} receptor.

These data prompted the authors to test the effect of the adenosine antagonist theophylline in PD patients.

C. All patients were diagnosed with clinically definite idiopathic PD and were divided into either early PD (EPD; Hoehn & Yahr stage ≤2 and not yet on L-dopa) or advanced PD (APD; Hoehn & Yahr stage >2 and on L-dopa) with L-dopa-induced motor side effects.

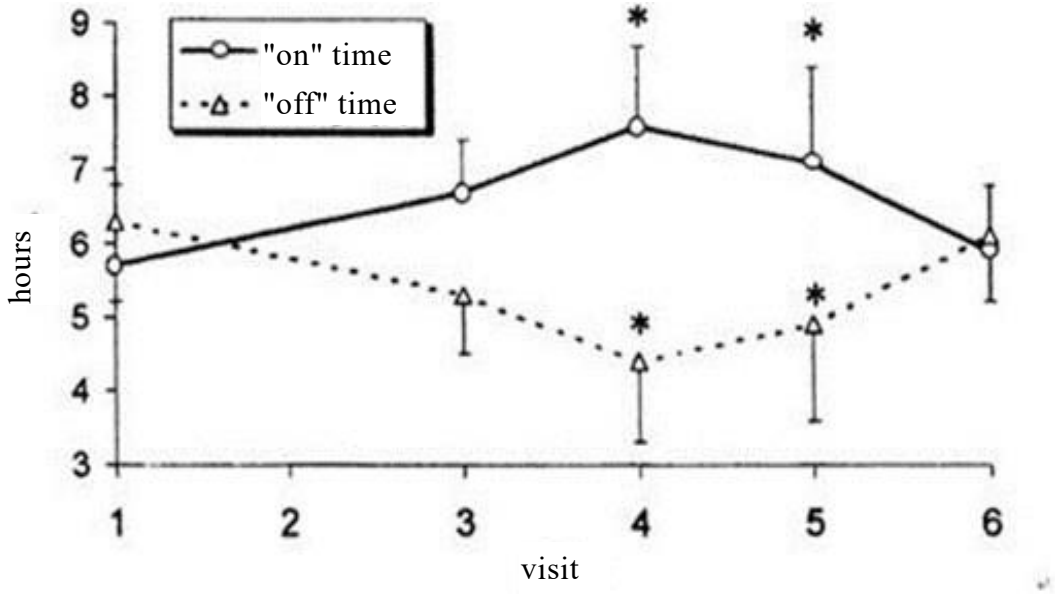
After the baseline visit (visit 1), patients underwent a 1-week loading phase (daily increase, 100 mg bid), a 6-week steady-state phase (600 mg/d), and a 1-week washout phase (daily decrease, 100 mg bid). The last visit was 1 week after theophylline was completely stopped.

D. Of 11 L-dopa-naïve EPD patients, 10 completed the study.

Of 12 APD patients, 9 completed the study (two of the three dropouts were lost to follow-up, and one withdrew from the trial).

In all the patients, theophylline was associated with a subjective improvement of parkinsonism. Theophylline also produced a nonsignificant trend toward improvement of the overall Unified Parkinson's Disease Rating Scale (UPDRS; ~10%) and of the UPDRS motor scores (items 19 to 31: ~15%).

In the APD patients, theophylline was associated with ~30% increase in the duration of time "on" and decrease in the duration of time "off" (figure).



E. The study results show that theophylline has minimal anti-PD effects. However, the symptomatic benefit was neither statistically significant nor clinically robust. In addition, theophylline did not potentiate L-dopa effects in the trial of Exhibit Ko A3. This is in contrast with the trial of Exhibit Ko A123, which clarified that theophylline has a synergistic effect on dopamine D-receptor agonists.

F. "The most striking finding of this trial is that theophylline significantly prolonged the duration of the 'on' phase in APD patients (and consequently shortened the duration of the 'off' phase). This effect is not trivial and is not associated with any detectable worsening in dyskinesia. This is a remarkable property because currently available anti-PD therapies that, by increasing their dosage, may extend the duration of the 'on' phase usually also increase dyskinesia severity."

G. "We believe that the modest beneficial effect reported here supports rather than undermines the value of adenosine antagonists in the treatment of PD and calls for additional studies to determine which compound at which dosage should be used to achieve optimal anti-PD action. We are also convinced that our study is strong proof of the principle that the blockade of adenosine receptors is an important avenue of treatment for PD and should be investigated with more potent and more selective compounds than theophylline once those become available for clinical testing."

(2) Finding of Exhibit Ko 3 Invention

According to the disclosure above, Exhibit Ko A3 states that theophylline caused ~30% increase in the duration of ON time and, as a result, decrease in the duration of OFF time in advanced Parkinson's disease patients, based on a clinical trial.

The trial of Exhibit Ko A3 was conducted as an open trial, as mentioned in Exhibit Ko A80 (an undisputed fact), and was not conducted as a randomized, placebo-controlled, double-blind trial like the one conducted in Exhibit Ko A80, which is known to be a more rigorous trial. Therefore, although it is understood from the abovementioned common general technical knowledge that the effect of reducing OFF time (the effect of increasing ON time) shown as the trial result of Exhibit Ko A3 may also include a placebo effect, it cannot be said that the result is entirely the placebo effect, and the very fact that the trial showed that theophylline "has an effect" of causing decrease in the duration of OFF time in advanced Parkinson's disease patients will not be denied.

Then, it follows that Exhibit Ko A3 is found to state Exhibit Ko 3 Invention as has been found in the JPO Decision.

(3) Common features and difference between the Invention and Exhibit Ko 3 Invention

A. "Theophylline" of Exhibit Ko 3 Invention and "KW-6002" of the Invention are common insofar as they are "adenosine A2A receptor antagonists."

In addition, "L-DOPA-treated (764 ± 170 mg/d) patients with advanced Parkinson's disease (APD) exhibiting wearing-off, which is an L-DOPA-induced motor side effect," of Exhibit Ko 3 Invention correspond to "human Parkinson's disease patients that have reached the stage of exhibiting the wearing off phenomenon and/or ON-OFF fluctuations in L-DOPA therapy" of the Invention.

The above points are as found in the JPO Decision, and are undisputed among the parties.

B. On the other hand, while the Invention is an invention of a "product," that is, an agent comprising KW-6002, it is an invention of a medicine that is administered to specific patients and is applied to specific symptoms (diseases) in those patients (a medicinal invention), which differs from an invention of a chemical substance itself, such as a compound, or an invention of a composition for an unspecified purpose of use (usage).

When finding common features and difference between the Invention as a use invention as mentioned above and a cited invention, whether or not the cited invention is found to be a use invention should be closely examined, and if no common features can be extracted as a use invention, this should be clarified as a difference.

Particularly in the field of medicine, it is often difficult to expect the function and effect from the structure (the chemical substance specified by a chemical formula, etc.), unlike in technical fields of machines, etc., and an invention in the field of medicine is normally completed as a use invention only after verifying the feasibility through time-

and cost-consuming processes, such as conducting animal experiments and clinical trials for clarifying the efficacy against the target disease or conducting an experiment that helps to understand that a specific mechanism of action of the chemical substance is closely associated with the efficacy against the target disease. Considering the consistency with this, in order for a cited invention to be recognized as a use invention, it is not sufficient for the substance (agent) relating to the cited invention to merely have a possibility of being put to the target usage, be expected to demonstrate efficacy, or have produced promising results although they are data only for reference obtained in a preliminary trial. It should be said that the cited invention needs to be one for which a person ordinarily skilled in the art would have been able to understand and recognize its feasibility of being put to the target usage, such as that the invention is disclosed with backing by data sufficient for trusting that the substance (agent) is useful for the target usage. Unless such interpretation is adopted, there will be a risk that the novelty and an inventive step of a feasible medicinal use invention that has been completed through the abovementioned processes would be easily denied based on a cited invention that is hardly found to be feasible, and such outcome must be considered unreasonable.

The Defendant's argument to the effect that, in order to regard that a medicinal use invention is stated in a publication, it needs to be stated in such a manner that a person ordinarily skilled in the art would be able to understand that the invention is feasible to be put to the relevant medicinal usage, is acceptable as having the meaning discussed above.

C. From such viewpoint, the question of whether the agent of Exhibit Ko 3 Invention is stated in Exhibit Ko A3 as an invention for which a person ordinarily skilled in the art would have been able to understand and recognize its feasibility of being put to the usage of "causing decrease in the duration of OFF time in advanced Parkinson's disease patients" is examined below.

(A) First, in Exhibit Ko A3, the trial was conducted as an "open trial," which is less accurate compared to the "randomized, placebo-controlled, double-blind trial" adopted in Example 1 of the Description. Further, the number of patients who completed the trial is small with nine persons, and the document is only a report consisting of one page in the format of clinical/scientific notes. Therefore, Exhibit Ko A3 lacks detailed statements on the trial method, which would have been naturally stated if it were in the format of a scientific paper (a full paper), and the accuracy of the trial cannot be verified, as it cannot even be identified whether or not a measure was taken to prevent a bias (such as an assumption that the administered drug will work) in patients who

participated in the trial, etc., and the document lacks basic information about matters such as how ON time and OFF time were measured. It is difficult to evaluate Exhibit Ko A3 with the abovementioned contents and format (clinical/scientific notes consisting of one page, which only indicates the outline of the trial) to be reliable clinical trial results on its own. Essentially, based on these results, the authors of Exhibit Ko A3 and other researchers would have been expected to proceed to make reports in the format of a scientific paper (a full paper) about trials conducted as to whether or not theophylline has an effect of reducing OFF time in advanced Parkinson's disease patients, but they have not made such reports. In light of such point, the trial results of Exhibit Ko A3 must be considered insufficient as data that show the abovementioned medicinal usage.

Also, the authors of Exhibit Ko A3 themselves have not gone so far as to say that "theophylline is therapeutically effective" or "a therapeutic drug can be provided if theophylline is used" with regard to the wearing off phenomenon / ON-OFF fluctuations in advanced Parkinson's disease patients.

(B) Moreover, although there were cases in which the influence of the adenosine A_{2A} receptor inhibiting action on Parkinson's disease symptoms was confirmed by administering more potent and selective adenosine A_{2A} receptor antagonists than theophylline, such as KW-6002, to various animal models of Parkinson's disease, those animal models had not exhibited the wearing off phenomenon / ON-OFF fluctuations. Thus, as of the Priority Date, details had not been clarified about the presence of the mechanism of action of theophylline against the wearing off phenomenon / ON-OFF fluctuations, that is, the fact that adenosine A_{2A} inhibiting action, which is one of the multiple actions of theophylline, has an effect of extending the duration of action of L-DOPA (reducing OFF time) in advanced Parkinson's disease patients who receive L-DOPA therapy.

(C) Then, it should be said that the agent of Exhibit Ko 3 Invention is not found to be one which a person ordinarily skilled in the art would have been able to understand and recognize as being usable (feasible) for "causing decrease in the duration of OFF time in advanced Parkinson's disease patients."

D. Based on the above premise, it must be said that, as argued by the Defendant, the JPO erred in finding in the JPO Decision that Exhibit Ko 3 Invention has a medicinal usage, holding that the agent of Exhibit Ko 3 Invention corresponds to an agent of the Invention that is described as "said agent is administered to said patients for reducing OFF time of the wearing off phenomenon and/or ON-OFF fluctuations in said L-DOPA therapy, and said agent is co-administered with L-DOPA to said targets in said L-DOPA

therapy" because Exhibit Ko 3 Invention "has an effect of causing ~30% increase in the duration of ON time and, as a result, decrease in the duration of OFF time" in "L-DOPA-treated" patients, and in finding this to be a common feature between Exhibit Ko 3 Invention and the Invention.

E. Thus, when the common features and differences between the Invention and Exhibit Ko 3 Invention are re-examined, they should correctly be found to be as follows.

[Common features]

An agent comprising an adenosine A_{2A} receptor antagonist,

wherein said agent targets human Parkinson's disease patients that have reached the stage of exhibiting the wearing off phenomenon and/or ON-OFF fluctuations in L-DOPA therapy, and

wherein said agent is co-administered with L-DOPA to said targets in said L-DOPA therapy.

[Difference 1]

The Invention is an "agent" which is a use invention "administered to patients for reducing OFF time of the wearing off phenomenon and/or ON-OFF fluctuations in said L-DOPA therapy," whereas Exhibit Ko 3 Invention is not found to be such use invention.

[Difference 2]

The adenosine A_{2A} receptor antagonist is "(E)-8-(3,4-dimethoxystyryl)-l,3-diethyl-7-methylxanthine (KW-6002)" in the Invention, whereas the adenosine A_{2A} receptor antagonist is "theophylline" in Exhibit Ko 3 Invention.

F. The Plaintiff in Case 1 and the Plaintiffs in Case 2 argue that there is no error in the JPO's finding of common features and differences between the Invention and Exhibit Ko 3 Invention. The reasons given by the Plaintiff in Case 1 is the title of the scientific paper of Exhibit Ko A3 and the fact that in the trial, theophylline was administered to patients exhibiting wearing off to measure a reduction in OFF time (an increase in ON time). The reason given by the Plaintiffs in Case 2 is that, while Exhibit Ko A3 states that theophylline was associated with ~30% increase in the duration of ON time and decrease in the duration of OFF time in advanced Parkinson's disease patients who were subject to theophylline administration, Exhibit Ko A28 and Exhibit Ko A80 state that the OFF time reducing effect of theophylline stated in Exhibit Ko A3 can be affirmed.

However, Exhibit Ko A3 is not considered to disclose the fact that theophylline is useful for the usage of "causing decrease in the duration of OFF time in advanced Parkinson's disease patients" with backing by data sufficient to be trusted by a person ordinarily skilled in the art, as mentioned above. In addition, in Exhibit Ko A28, no new experiment was conducted, and statements in Exhibit Ko A3 were merely confirmed in

the form that "The clinician noticed an increase in ON time after administration of theophylline, which is a non-selective A_{2A} antagonist, in treated PD patients with motor fluctuations (Document 55)" (Document 55 is Exhibit Ko A3). Further, Exhibit Ko A80 states that "In open-label trials, theophylline, a nonspecific adenosine A_{2A} antagonist, has been found to improve parkinsonian symptoms (21) and to increase ON time (22) in patients with advanced PD" (21 is Exhibit Ko A50 and 22 is Exhibit Ko A3), but also subsequently states that "Data from double-blind, placebo-controlled studies are still lacking,"; thus, it assumes that further verification is required, and does not state that Exhibit Ko A3 should be adopted.

From the statements in Exhibit Ko A3 mentioned in (1)G. above, the agent of Exhibit Ko 3 Invention can be regarded to prompt "additional studies to determine which compound at which dosage should be used to achieve optimal anti-PD action" or experiments using "more potent and more selective compounds than theophylline" for confirming "the principle that the blockade of adenosine receptors is an important avenue of treatment for PD," but it cannot be said that the agent itself is one which a person ordinarily skilled in the art would have been able to understand and recognize as being feasible for the usage wherein "said agent is administered to said patients for reducing OFF time of the wearing off phenomenon and/or ON-OFF fluctuations in said L-DOPA therapy, and said agent is co-administered with L-DOPA to said targets in said L-DOPA therapy."

(4) Regarding the ease of conceiving of the differences

The ease of conceiving of the differences found in (3) E. above is examined below.

A. Regarding Difference 1

It can be said that the results of the open trial on theophylline in Exhibit Ko A3 and the statement "We believe that the modest beneficial effect reported here ... calls for additional studies to determine which compound at which dosage should be used to achieve optimal anti-PD action" in the "Discussion" section of Exhibit Ko A3 can sufficiently motivate a person ordinarily skilled in the art to conduct further experiments and research about the presence or absence of the effects of theophylline by adopting a more rigorous trial, such as a "randomized, placebo-controlled, double-blind trial," in order to clarify whether or not theophylline can be used as an agent "for reducing OFF time of the wearing off phenomenon and/or ON-OFF fluctuations in L-DOPA therapy," that is, whether or not theophylline is a therapeutically effective compound.

However, the trial results shown in Exhibit Ko A3 are not sufficient for determining the efficacy of theophylline against the wearing off phenomenon and/or ON-OFF

fluctuations in advanced Parkinson's disease patients.

In addition, while theophylline is one of the adenosine A_{2A} receptor antagonists, it is non-selective, and as of the Priority Date, details had not been clarified about the presence of the mechanism of action wherein the adenosine A_{2A} inhibiting action of adenosine A_{2A} receptor antagonists, such as theophylline, has an effect of reducing OFF time in advanced Parkinson's disease patients who receive L-DOPA therapy, and no adenosine A_{2A} receptor antagonist was known to be therapeutically effective against the wearing off phenomenon and/or ON-OFF fluctuations in advanced Parkinson's disease patients.

Then, naturally, without having to see the results of further experiments and research on theophylline and other adenosine A_{2A} receptor antagonists, Exhibit Ko A3 cannot be regarded to motivate a person ordinarily skilled in the art to the extent of making the usage of the agent of Exhibit Ko 3 Invention the usage of the agent of the Invention.

B. Regarding Difference 2

It was common general technical knowledge as of the Priority Date that theophylline is a non-selective adenosine A_{2A} receptor antagonist and KW-6002 is a more potent and selective adenosine A2A receptor antagonist than theophylline.

In addition, Exhibit Ko A3 shows trial results regarding the fact that theophylline has an action of causing decrease in the duration of OFF time in advanced Parkinson's disease patients who receive L-DOPA therapy, and in its "Discussion" section, it states that the principle that the blockade of adenosine receptors is an important avenue of treatment for PD "should be investigated with more potent and more selective compounds than theophylline once those become available for clinical testing." In light of these, it can be said that Exhibit Ko A3 sufficiently motivates a person ordinarily skilled in the art to adopt KW-6002, which is a selective adenosine A_{2A} receptor antagonist, in place of theophylline, which is a non-selective adenosine A_{2A} receptor antagonist, (to preferentially make confirmation regarding KW-6002) in the agent of Exhibit Ko 3 Invention, to the extent of using it in the trial of Exhibit Ko A3 or further experiments and research in order to clarify whether or not the action of reducing the duration of OFF time, which was confirmed for theophylline in the trial of Exhibit Ko A3, is exhibited by the adenosine A_{2A} inhibiting action from among the multiple actions of theophylline. On the other hand, even by considering the common general technical knowledge, it cannot be said that the statements in Exhibit Ko A3 would go so far as to motivate a person ordinarily skilled in the art to adopt KW-6002 in place of theophylline in making the usage of the agent of Exhibit Ko 3 Invention the usage of the agent of the

Invention, beyond experiments and research.

C. Regarding the arguments of the Plaintiff in Case 1

(A) The Plaintiff in Case 1 argues as follows: the authors of Exhibit Ko A3 and Exhibit Ko A80 strongly encourage implementation of clinical trials using more potent and selective adenosine A_{2A} antagonists, based on the results of trials using theophylline in human patients; a reasonable attitude of a person ordinarily skilled in the art would be to consider that, if the effectiveness of theophylline is not clear, research should be conducted by using an agent that is expected to have a stronger effect; and because the only conventional treatment method available against Parkinson's disease was dopamine replacement therapy, which causes response fluctuations such as wearing off in most patients within several years, the adenosine A_{2A} antagonist route, which has a different mechanism, attracted extremely high attention among persons ordinarily skilled in the art, and it would have been a natural idea for a person ordinarily skilled in the art to try KW-6002, if it is expected to be effective. However, Exhibit Ko A3 ((1)G. above) merely encourages implementation of experiments and research, and it is unknown whether the action point of theophylline as an adenosine A_{2A} antagonist produced the effect. In addition, Exhibit Ko A80 merely states the need for further experiments and research by conducting a placebo-controlled trial, double-blind trial, and crossover trial against Parkinson's disease in humans by using theophylline, which is an adenosine A_{2A} antagonist, by stating "In conclusion, despite the abundant experimental data and the previous open-label trials suggesting the usefulness of theophylline in PD, according to our exploratory clinical protocol, theophylline failed to potentiate consistently the anti-PD action of levodopa. Whether the doses used during this study were excessive or insufficient to reveal clearly an anti-PD effect of theophylline remain to be determined. Further clinical studies with more potent and selective antagonists of adenosine A_{2A} receptors are warranted."

Then, it cannot be said that a person ordinarily skilled in the art would certainly try so far as to make a medicinal product that adopts KW-6002, beyond experiments and research.

(B) Moreover, the Plaintiff in Case 1 argues that, because OFF time of the wearing off will be reduced if KW-6002 is actually adopted and administered as stated in Exhibit Ko A3 and Exhibit Ko A80, the fact that matters such as the mechanism of action of theophylline, why the wearing off occurs, and why OFF time is reduced have not been elucidated or demonstrated does not provide a reason for denying the motivation to adopt KW-6002. However, given the situation where the details of the trial of Exhibit Ko A3 are unclear, theophylline is a non-selective adenosine A_{2A} antagonist, and

whether the action point of theophylline as an adenosine A_{2A} receptor antagonist produced the effect in Exhibit Ko A3 and Exhibit Ko A80 is also unclear, the very premise that a person ordinarily skilled in the art would have recognized that OFF time of the wearing off would be reduced if they actually adopt and administer KW-6002 does not exist, so the argument of the Plaintiff in Case 1 cannot be accepted.

(C) Other various arguments made by the Plaintiff in Case 1 cannot be accepted in that they are based on the following premises: that a person ordinarily skilled in the art would have been able to recognize making the usage of the agent of Exhibit Ko 3 Invention the usage of the agent of the Invention; and that the authors of Exhibit Ko A3 and Exhibit Ko A80 have gone so far as to encourage putting selective adenosine A_{2A} receptor antagonists to not only usage in experiments and research, but even usage as an agent.

D. Regarding the arguments of Plaintiffs in Case 2

(A) The Plaintiffs in Case 2 argue that there was a situation to expect that a certain effect would be produced if more potent and selective KW-6002 was adopted in place of theophylline of Exhibit Ko 3 Invention, based on the statements in Exhibit Ko A3 and common general technical knowledge, and a situation where some "effect is expected but the truth is unknown unless one tries" does not deny the motivation to replace theophylline of Exhibit Ko 3 Invention with KW-6002. However, this argument cannot be accepted in that it is based on a premise that a person ordinarily skilled in the art would have been able to recognize the medicinal usage of KW-6200 from Exhibit Ko 3 Invention.

(B) The Plaintiffs in Case 2 argue that, according to documents as of the Priority Date, the adenosine A_{2A} receptor antagonist action of theophylline was generally understood in association with antiparkinsonian activity.

However, Exhibit Ko A4 states that "Theophylline is not only a non-selective adenosine receptor antagonist, but it also has affinity for phosphodiesterase and guanosine receptors. Therefore, the action site of theophylline has yet to be determined," and Exhibit Ko A51 states that "ironically, it may be demonstrated that non-selective ones are more effective than selective ones." Thus, it must be said that the relationship of the adenosine A_{2A} receptor antagonist action of theophylline with antiparkinsonian activity, and further, with OFF time of the wearing off was unknown as of the Priority Date.

(C) The Plaintiffs in Case 2 also argue as follows: even if the mechanism of the wearing off phenomenon was not completely elucidated as of the Priority Date, since various anti-Parkinson's disease drugs were actually used in combination with L-DOPA for

easing the wearing off phenomenon, as long as Exhibit Ko A3 states that theophylline, which is an adenosine A_{2A} receptor antagonist, has an effect of reducing OFF time, and a person ordinarily skilled in the art understands that KW-6002 is an adenosine A_{2A} receptor antagonist, in the same manner as theophylline, the person ordinarily skilled in the art would be able to presume that using KW-6002 in place of theophylline would actually reduce OFF time in advanced Parkinson's disease patients, just as theophylline.

However, the agents that were used in combination with L-DOPA for reducing OFF time were, except for anticholinergic drugs (Exhibits Ko A10 and A170), those relating to dopamine and L-DOPA, such as the following: dopamine agonists that directly bind to dopamine receptors and exhibit dopamine-like pharmacological action (Exhibits Ko A10, A43, A168, etc.); amantadine hydrochloride that comprehensively enhances the activity of the dopaminergic system (Exhibit Ko A10); COMT inhibitors that extend the duration of action of L-DOPA (Exhibits Ko 43 and 52); monoamine oxidase inhibitors that inhibit the enzyme that breaks down dopamine (Exhibits Ko A10, A43, and A169); and zonisamide relating to long-term persistent activity of dopamine synthesis (Exhibit Ko A44). Therefore, it cannot be regarded that the existence of common general technical knowledge to the effect that non-dopamine system agents reduce OFF time was established as knowledge.

(5) Regarding prominent function and effect

A. The Description states, as Example 1, that subjects of the KW-6002 groups in which Parkinson's disease patients with L-DOPA-related motor complications were administered KW-6002, in combination with L-DOPA, in three stages progressing every four weeks with a dose escalation of either (5/10/20 mg/day) or (10/20/40 mg/day) experienced a significant decrease in OFF time compared to subjects of the placebo group (Figure 1) ([0147] onward). It can be identified from the results of this trial that KW-6002, which is a selective adenosine A_{2A} receptor antagonist, has an effect that is beneficial for providing a therapeutic drug, which is to reduce OFF time of the wearing off phenomenon and/or ON-OFF fluctuations in L-DOPA therapy in human patients, and that an agent comprising KW-6002 can be used "for reducing OFF time of the wearing off phenomenon and/or ON-OFF fluctuations in L-DOPA therapy."

B. On the other hand, as mentioned in (3)C. above, it can be understood from the trial results of Exhibit Ko A3 that theophylline, which is a non-selective adenosine A_{2A} receptor antagonist, showed an effect of causing decrease in the duration of OFF time in advanced Parkinson's disease patients who receive L-DOPA therapy, but it is not sufficient to understand that theophylline can be used for reducing OFF time in those patients.

In addition, as mentioned in 1.(5) above, theophylline, which is a non-selective adenosine A_{2A} receptor antagonist, used in the trial of Exhibit Ko A3 is a compound with multiple actions, which has affinity for not only adenosine A_{2A} receptor, but also for phosphodiesterase and guanosine receptor, and it cannot be identified from Exhibit Ko A3 which action point exhibited the effect.

Moreover, as mentioned in (3) above, there was the following common general technical knowledge as of the Priority Date regarding the "wearing off phenomenon" and "ON-OFF fluctuations": symptoms observed in an OFF state are the same as the symptoms of the Parkinson's disease; and while it was indicated that the causes of these symptoms include a decline in the dopamine-retaining capacity of dopamine neurons and a decline in the dopamine receptor sensitivity due to long-term administration of L-DOPA, this is not regarded to have been sufficiently elucidated, as it was recognized that other phenomena could also become important causes of the symptoms, and details had not been clarified about the presence of the mechanism of action that the adenosine A_{2A} inhibiting action has an effect of reducing OFF time in advanced Parkinson's disease patients who receive L-DOPA therapy. Accordingly, the understanding of a person ordinarily skilled in the art about the role played by the adenosine A_{2A} inhibiting action in relation to the wearing off phenomenon and/or ON-OFF fluctuations would have only led to creation of an "opportunity for development of a therapeutic agent" using an adenosine A_{2A} receptor antagonist, and had not reached the level of elucidating the presence of a compound that is effective in treatment for reducing OFF time, or in other words, that could be used as an agent for reducing OFF time in advanced Parkinson's disease patients who receive L-DOPA therapy by inhibiting adenosine A_{2A} receptors.

As stated above, Exhibit Ko A3 does not contain sufficient statements for a person ordinarily skilled in the art to recognize that theophylline can be used for reducing OFF time in advanced Parkinson's disease patients, and even if theophylline produced an effect, it was unknown whether it was caused by the adenosine A_{2A} receptor inhibiting action (this is because theophylline is a non-selective adenosine A_{2A} receptor antagonist, and because it had not been elucidated whether or not the adenosine A_{2A} inhibiting action has an effect of reducing OFF time in advanced Parkinson's disease patients who receive L-DOPA therapy). Therefore, it should be said that the effect indicated in the Description that KW-6002, which is a selective adenosine A_{2A} receptor antagonist, reduces OFF time of the wearing off phenomenon and/or ON-OFF fluctuations in L-DOPA therapy in advanced Parkinson's disease patients is a prominent effect that could not have been expected by a person ordinarily skilled in the art from the statements in

Exhibit Ko A3 and the common general technical knowledge as of the Priority Date.
C. The Plaintiff in Case 1 argues that the effect indicated in the Description is only within the scope that could have been expected by a person ordinarily skilled in the art, because Exhibit Ko A3 indicates that OFF time was reduced and ON time increased as a result of administering theophylline in combination with L-DOPA to patients exhibiting the wearing off phenomenon, and because both the authors of Exhibit Ko A3 and those of Exhibit Ko A80 strongly encourage clinical trials using a more potent and selective adenosine A_{2A} antagonist based on the results of trials using theophylline, and it can be expected that the reduction in OFF time and the increase in ON time will be demonstrated more clearly if a more potent and selective adenosine A_{2A} antagonist is used.

However, the argument of the Plaintiff in Case 1 cannot be accepted, as it cannot be sufficiently understood from Exhibit Ko A3 that theophylline can be used for reducing OFF time in advanced Parkinson's disease patients, and both the authors of Exhibit Ko A3 and those of Exhibit Ko A80 merely encourage implementation of further clinical trials and, even if theophylline produced an effect in Exhibit Ko A3, it was unknown whether it was caused by the adenosine A_{2A} receptor inhibiting action.
D. The Plaintiffs in Case 2 state that a person ordinarily skilled in the art would have naturally expected that, if KW-6002 is applied in place of theophylline of Exhibit Ko 3 Invention, "it would at least have an effect that is equal to or greater than that of theophylline" due to the following: [i] Exhibit Ko A3 states that theophylline significantly reduced the duration of OFF time of the wearing off phenomenon by up to 30% compared to before the administration in Parkinson's disease patients who receive L-DOPA treatment; and [ii] there was common general technical knowledge that KW-6002 is an adenosine A_{2A} receptor antagonist, in the same manner as theophylline, and at the same time, unlike theophylline, it is a selective adenosine A_{2A} receptor antagonist that exhibits more potent antiparkinsonian activity, and it had been confirmed that the drug efficacy duration of KW-6002 is also far longer than that of theophylline, and that this length of the drug efficacy duration is also exhibited when used in combination with L-DOPA. On such basis, the Plaintiffs in Case 2 argue that the effect stated in the Description that subjects of the KW-6002 groups experienced a significant decrease in OFF time compared to subjects of the placebo group is only the level of effect which could have been expected by a person ordinarily skilled in the art based on Exhibit Ko A3 and common general technical knowledge.

However, Exhibit Ko A3 does not contain sufficient statements for a person ordinarily skilled in the art to recognize that theophylline can be used for reducing OFF

time in advanced Parkinson's disease patients, and even if theophylline produced an effect, it was unknown whether it was caused by the adenosine A_{2A} receptor inhibiting action, as mentioned above.

In addition, as of the Priority Date, the causes and mechanisms of the wearing off phenomenon and ON-OFF fluctuations were not identified, and it was understood that these were pathological conditions that result from complex phenomena in the brain undergoing various transformations due to advancement of Parkinson's disease symptoms. In actuality, symptoms could be suppressed by optimal L-DOPA in Parkinson's disease patients who had yet to exhibit the wearing off phenomenon, whereas after the appearance of the wearing off phenomenon, L-DOPA could not function sufficiently. Thus, it is not found to have been common general technical knowledge as of the Priority Date that treatment by the same pharmaceutical intervention approach can be adopted before and after the appearance of the wearing off phenomenon.

Moreover, it is not necessarily clear whether the drug efficacy duration of KW-6002 against Parkinson's disease was associated with the reduction in OFF time.

Then, even if it was known that an anti-Parkinson's disease drug used as an adjunctive agent of L-DOPA is more effective for reducing OFF time if its duration of action is longer, and that the drug efficacy duration of KW-6002 is longer than that of theophylline, as argued by the Plaintiffs in Case 2, it should be said that a person ordinarily skilled in the art would not have been able to expect whether or not KW-6002, which is a selective adenosine A_{2A} receptor antagonist, has an effect of causing decrease in the duration of OFF time in advanced Parkinson's disease patients, unless they actually confirmed it.

Accordingly, the argument of the Plaintiffs in Case 2 cannot be accepted.

(6) Summary

As discussed above, a person ordinarily skilled in the art is not found to have been able to easily make the Invention based on Exhibit Ko 3 Invention. Meanwhile, this means that the error in the finding in the JPO Decision indicated in (3)D. above does not affect the conclusion.

3. Conclusion

According to the above, the grounds for rescission of the JPO Decision argued by the Plaintiffs are groundless, and no reasons are found to rescind the JPO Decision. Thus, the Plaintiffs' claim is dismissed and the judgment is rendered as indicated in the main text.

Intellectual Property High Court, Fourth Division
Presiding judge: MIYASAKA Masatoshi
Judge: MOTOYOSHI Hiroyuki
Judge: IWAI Naoyuki

Attachment 1: List of Abbreviations

(Abbreviation)	(Meaning)
• The Patent	: The Patent of Patent No. 4376630 held by the Defendant
• The Priority Date	: The priority date of the Patent (January 28, 2002; priority country: the United States)
• The JPO Decision	: The trial decision rendered by the JPO on July 12, 2023 with regard to the case of Invalidation Trial No. 2020-800076 relating to the Patent (petitioners in the trial for invalidation: the Plaintiffs in Case 2; an intervenor in the procedure: the Plaintiff in Case 1) (the subject of this lawsuit)
• The Invention	: The invention relating to the Patent
• The Description	: The description relating to the Patent
• Exhibit Ko 3 Invention	: The contents found in the JPO Decision to be the invention stated in Exhibit Ko A3 (NEUROLOGY, 1999, Vol. 52, p. 1916; indicated in the JPO Decision as Exhibit Ko 3) (No. 2, 3 (2) in the text)
• KW-6002	: (E)-8-(3,4-dimethoxystyryl)-l,3-diethyl-7-methylxanthine
• Dopamine	: A neurotransmitter that exists in the central nervous system. While it is sometimes indicated as "ドパミン" (*dopamin*) or the like in Japanese, the expression "ドーパミン" (*dōpamin*) (translator's note: "dopamine" in this English translation) is used here, except in a direct citation from another document.
• L-DOPA	: A precursor of dopamine that is converted into dopamine by L-DOPA decarboxylase. While it is sometimes indicated as "Ｌ－ドパ" (*L-dopa*), "レポドパ" (*repodopa*) or the like in Japanese, the expression "Ｌ－ドーパ" (*L-dōpa*) (translator's note: " L-DOPA" in this English translation) is used here, except in a direct citation from another document.
• Adenosine A_{2A} receptor	: One of the four main subtypes on which adenosine acts. While it is sometimes indicated as "adenosine A2A receptor," the expression "adenosine A_{2A} receptor" is used here, except in a direct citation from another document or a trial decision.

Attachment 2: Statements and Drawings in the Description (Extract)

[Technical Field]

[0001]

The present invention is directed to methods of treating patients suffering from movement disorders comprising administering at least one adenosine A_{2A} receptor antagonist.

[Background Art]

[0005]

Usually the first symptom of Parkinson's disease is tremor (trembling or shaking) of a limb, especially when the body is at rest. The tremor often begins on one side of the body, frequently in one hand. Other common symptoms include other movement disorders such as slow movement (bradykinesia), an inability to move (akinesia), rigid limbs, a shuffling gait, and a stooped posture. Parkinson's disease patients often show reduced facial expression and speak in a soft voice. The disease can cause secondary symptoms of depression, anxiety, personality changes, cognitive impairment, dementia, sleep disturbances, speech impairments or sexual difficulties. There is no known cure for Parkinson's disease. Treatment is aimed at controlling the symptoms. Medications control symptoms primarily by controlling the imbalance between the neurotransmitters. Most early Parkinson's disease patients respond well to symptomatic treatment with dopamine replacement therapy, but disability increases with progression of the disease.

[0007]

Most Parkinson's disease symptoms arise from a deficiency of dopamine and most anti-Parkinson drugs restore dopamine or mimic dopamine's actions. However, the drugs do not permanently restore dopamine or exactly mimic dopamine's actions. While a loss of dopamine cells in the substantia nigra is the main feature of Parkinson's disease, non-dopamine nerve cells are also lost. Moreover, dopamine-responsive cells are present not only in the substantia nigra but in other brain regions. Thus, drugs that are effective in Parkinson's disease can, by stimulating these cells, cause side effects such as nausea, hallucinations, and confusion.

In 1967, L-DOPA was introduced and remains the most effective anti-Parkinson drug. Symptoms most likely to benefit from L-DOPA include bradykinesia, rigidity, resting tremor, difficulty walking, and micrographia. Symptoms least likely to benefit from L-DOPA include postural instability, action tremor, and difficulty swallowing. L-DOPA may worsen dementia. Although L-DOPA provides robust and rapid therapeutic benefits in Parkinson's disease, eventually, severe adverse reactions to dopamine emerge, including motor complications such as wearing off phenomenon / ON-OFF

fluctuations, and dyskinesia. Marsden et al. (1982). Once established, motor complications are not typically controllable with manipulation of L-DOPA or other dopaminergic drugs.

[0009]

... Thirty years after its discovery, L-DOPA is still the best treatment for Parkinson's disease. In the early stages of the disease, patients usually enjoy a good response to L-DOPA, but as the disease progresses, L-DOPA tends to become less helpful. This is not due to loss of L-DOPA efficacy, but rather to development of motor complications such as adverse fluctuations in motor response including end-of-dose deterioration or "wearing-off," and the "ON/OFF fluctuations," and dyskinesias. ON/OFF fluctuations are a sudden, unacceptable loss of therapeutic benefit of a medication ("ON" state, during which the patient is relatively free from the symptoms of Parkinson's disease) and onset of the parkinsonian state ("OFF" state). Wearing off phenomenon is a decrease in the duration of L-DOPA action, and characterized by the gradual reappearance of the "off" state, and shortening the "on" state. Dyskinesia can be broadly classified as chorea (hyperkinetic, purposeless dance-like movements) and dystonia (sustained, abnormal muscle contractions). In 1974, Duvoisin first focused on these abnormal involuntary movements, and found that over half of patients with Parkinson's disease developed dyskinesia within six months of treatment...

[0032]

... Behavioral studies show that adenosine A_{2A} receptor antagonists improve motor dysfunction of several parkinsonian animal models (e.g., MPTP-treated monkeys), but also reveal features of A_{2A} receptor antagonists distinctive from dopaminergic agents...

[0033]

The antiparkinsonian effects of the selective adenosine A_{2A} receptor antagonist KW-6002 have been studied in MPTP-treated marmosets and cynomolgus monkeys. ... In MPTP-treated marmosets, oral administration of KW-6002 induced an increase in locomotor activity lasting up to 11 hours in a dose-related manner. ... Locomotor activity was increased to the level observed in normal animals, whereas L-DOPA induced locomotor hyperactivity. Furthermore, in L-DOPA-primed MPTP-treated marmosets, treatment with KW-6002 for 21 days induced little or no dyskinesias, whereas under the same conditions, treatment with L-DOPA induced marked dyskinesias. When KW-6002 (20 mg/kg) was administered once a day for 5 days with a threshold dose of L-DOPA to MPTP-treated marmosets primed to exhibit dyskinesias, antiparkinsonian activity was potentiated without an increase in dyskinesia. ... Taken together, these findings suggest that adenosine A_{2A} antagonists might provide

antiparkinsonian benefit as monotherapy in patients with early Parkinson's disease and might be able to improve antiparkinsonian response without increasing dyskinesia in L-DOPA-treated patients with motor complications.

[0034]

Although the mechanisms by which adenosine A_{2A} antagonists exert an antiparkinsonian effect remain to be fully elucidated, the following mechanism is now proposed.

In either Parkinson' s disease or MPTP treatment of primates, following destruction of the nigro-striatal dopaminergic pathway, the most relevant alteration is hyperactivity in the striatopallidal pathway, and such hyperactivity is attributed to an imbalance between the direct striatonigral pathway and the indirect striatopallidal pathway to give rise to parkinsonian state...

[0036]

The action mechanism via A_{2A} receptors could work independently of dopamine D2 receptors ..., which are co-localized with A_{2A} receptors in the striatopallidal medium spiny neurons...

[0038]

Therefore, non-dopaminergic drug therapies, which effect an adenosine A_{2A} receptor blockade, offer a means to treat Parkinson's disease. Moreover, adenosine A_{2A} receptor antagonists, which provide antiparkinsonian effects with little or no risk of typical dopaminergic drug adverse effects, i.e., increasing or developing motor complications, are desirable...

[Disclosure of the Invention]

[Means for Solving the Problem]

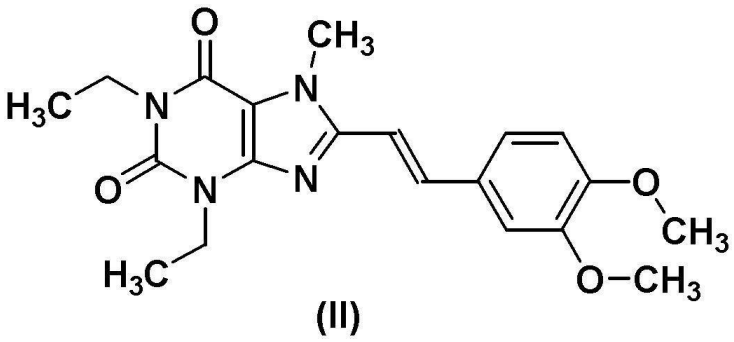
[0039]

The invention provides methods of reducing or suppressing the adverse effectiveness of L-DOPA therapy comprising administration or co-administration of one or more A_{2A} receptor antagonists to Parkinson's disease patients. Such treatment can be therapeutic such as to treat patients suffering from L-DOPA- or other dopaminergic-agent-induced motor complications to reduce OFF time and/or to suppress dyskinesias.

[0121]

... A preferred adenosine A_{2A} receptor antagonist useful in accordance with the methods of the present invention comprises (E)-8-(3,4-dimethoxystyryl)-l,3-diethyl-7-methylxanthine (the following formula (II)).

[0122]
[Formula 121]



(II)

Formula II is also identified in accordance with the present invention as KW-6002.
[0123]

By "reducing or suppressing the adverse effectiveness of L-DOPA" is understood in accordance with the present invention to mean that the compounds of the present invention reduce the patients' amount of awake time in an "OFF" state. An OFF state is understood in accordance with the invention to mean the period of time where the therapeutic benefit of a dose of a parkinsonian medication have worn off, such that the patient experiences symptoms of Parkinson's disease such as are classified by the Unified Parkinson's Disease Rating Scale (UPDRS) and the Hoehn and Yahr (HY) scale, for example.
[0124]

The present invention is also directed to reducing the adverse effectiveness of L-DOPA by increasing the proportion of the patients' awake time in an "ON" state. By ON state is meant, the period of time following a dose of a parkinsonian medication during which the patient is relatively free of the symptoms of Parkinson's Disease as classified by the UPDRS and the HY scale. Patients treatable by the methods of the present invention include patients at early, intermediate and advanced stages of Parkinson's disease with or without motor complications as determined by the Parkinson Dyskinesia Scales (PDS)...
[Example 1]
[0147]

The safety and efficacy of the adenosine A_{2A} receptor antagonist KW-6002 as a treatment for Parkinson's disease complicated by L-DOPA-related motor complications was examined in a 12-week, multicenter, exploratory study. PD subjects with motor complications were randomly and blindly assigned to 1 of 3 parallel treatment arms:

placebo (n=29); KW-6002 up to 20 mg/d (n=26); KW-6002 up to 40 mg/d (n=28). There were 2 primary efficacy measures: 1) change in "off" time as determined by the study investigator during 8-hour clinic visits and 2) change in "off" time as determined by subjects' home motor diaries.

[0148]

Sixty-five of the 83 enrolled subjects completed the study; withdrawal rates were equally distributed across treatment arms. KW-6002 treatment was significantly more effective than placebo treatment in reducing the proportion of awake time that patients spent in an "off" state. As assessed by home diaries, subjects assigned to KW-6002 experienced a reduction in the proportion of awake time spent in the OFF state of 7.1% compared to an increase of 2.2% in the placebo group (p=0.008). There was a 1.7 hour greater reduction in OFF time in the KW-6002 group than the placebo group (p= 0.004). Results for the investigators' on/off 8 hour evaluation approached statistical significance (p=0.054). Patients treated with KW-6002 spent 0.51 fewer hours in the "off" state than did patients in the placebo group (p=0.061).

The study also showed a reduction in early morning dystonia in patients treated with KW-6002 from baseline to Week 12 compared to the placebo group.

[0149]

Methods

This was a 12-week, double-blind, placebo-controlled, randomized, parallel group, multicenter, exploratory study of the safety and efficacy of KW-6002 as adjunctive therapy in L-DOPA-treated PD patients with motor complications. Eligible patients were those who met United Kingdom PD Society (UKPDS) brain bank diagnostic criteria (Daniel et al. (1993)), had been on L-DOPA/carbidopa for at least one year, were taking at least four doses of L-DOPA/carbidopa per day, and were experiencing motor complications including end-of-dose wearing off...

[0151]

Subjects who successfully completed screening and baseline evaluations were randomized to one of two dose regimens of KW-6002 or matching placebo in a 1:1:1 ratio. Patients randomized to KW-6002 received either 5 mg/day during weeks 1–4, 10 mg/day during weeks 5–8, and 20 mg/day during weeks 9–12 (5/10/20 group) or 10 mg/day during weeks 1–4, 20 mg/day during weeks 5–8, and 40 mg/day during weeks 5–9 (10/20/40 group) (Figure 1). Study medication was taken daily as a single dose with the subjects' normal breakfast...

[0152]

Results

Eighty-three subjects underwent randomization.

No notable difference of demographic and baseline characteristics were found among the study groups.

Subjects in all three treatment groups were 99% compliant with their study medication based on pill counts. During the study, there were no significant changes in mean daily L-DOPA doses in any treatment group or comparing the two abovementioned KW6002 groups combined and the placebo group.

[0153]

Subjects randomized to the two abovementioned KW-6002 groups experienced a significant decrease in OFF time compared to subjects randomized to placebo as assessed by home diaries (Figure 1). Subjects assigned to KW-6002 experienced a reduction in the proportion of awake time spent in the OFF state of 7.1% compared to an increase of 2.2% in the placebo group (p=0.008). Both the two abovementioned KW-6002 dose groups exhibited a significant decrease in percent OFF time compared to the placebo group. Similarly, the two abovementioned KW-6002 group combined, as well as each KW-6002 group, experienced a significant reduction in total hours OFF. Subjects assigned to KW-6002 experienced a reduction in OFF time of 1.2 hours compared to an increase of 0.5 hours in the placebo group (p=0.004) (Figure 1).

[0154]

Assessment of OFF time by investigators during 8-hour in-office evaluations identified a trend for greater reduction in OFF time in the two abovementioned KW-6002 groups combined compared to the placebo group. Subjects assigned to KW-6002 exhibited a 10.0% decrease in OFF time compared to a decrease of 3.3% in the placebo group (p=0.05). Similarly, subjects assigned to KW-6002 exhibited a decrease in OFF time of 0.8 hours compared to a decrease of 0.3 hours in the placebo group (p=0.06). Off time reduction at the higher dose KW-6002 group (10/20/40 group) was significant (P=0.02).

Early morning dystonia in patients treated with KW-6002 was reduced from baseline to Week 12 compared to the placebo group.

[0155]

...

In this study, under a variety of concomitant medication with dopamine agonists (e.g., Pramipexol, Pergolide, Ropinirol, Bromocriptine), COMT inhibitors (e.g., Entacapone, Tolcapone) and a MAO inhibitor selegiline, KW-6002 showed significant OFF time reduction, and safety and good tolerability.

Based on the findings of this study, the adenosine A_{2A} receptor antagonist KW-6002 can safely and effectively reduce off time in Parkinson's disease patients with L-DOPA motor complications.

[Figure 1]