PATENT COURT
THE FOURTH DEPARTMENT
DECISION

Case No. 2013Heo5759 Scope Confirmation (Patent)

Plaintiff (withdrawn): Bristol-Myers Squibb Company
Counsels for the Plaintiff:
Jongseok KIM, Attorney-at-law
Meesung SHIM, Patent attorney
Younghwan YANG, Patent attorney
Sangnam LEE, Patent attorney

Successor to Plaintiff Bristol-Myers Squibb Holdings Ireland
Counsels for the Successor:
Jongseok KIM, Attorney-at-law
Meesung SHIM, Patent attorney
Younghwan YANG, Patent attorney
Sangnam LEE, Patent attorney

Defendant: Jeil Pharmaceutical Co., Ltd.
Counsels for the Defendant:
Soyoung AHN, Patent attorney
Haesal HA, Patent attorney
Substitute for the Counsels:
Dongse KANG, Attorney-at-law

Closure of Hearing: April 2, 2014

Date of Decision: April 11, 2014

Order

1. The claim of the Successor to Plaintiff is dismissed.
2. The trial costs, including those incurred by succession, shall be borne by the Successor of the Plaintiff.

Tenor of Claim

The decision of the Intellectual Property Tribunal ("IPT") issued on April 30, 2013 in Case No. 2012Dang2418 shall be cancelled.

Reasoning

1. Background facts

A. The applied-for patented invention at issue ("Subject Patent")

1) Title of the invention: Low Dose Entecavir[1] (alternatively known as BMS-200475, it will be referred to as "BMS-200475" or "entecavir") Formulation and Use

2) Filing date/Priority claiming date/Registration date/Patent Number: August 26, 2002/February 29, 2000/September 3, 2007/Patent No. 757155

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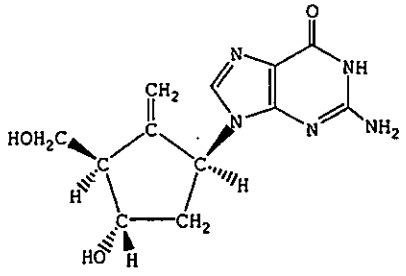
1) Entecavir has the chemical name "[1S-(1α, 3α, 4ß)]-2-amino-1, 9-dihydro-9-[4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]-6H-furine-6-one" and the following structure:



3) Patentee: Successor to Plaintiff [the right of the Subject Patent was transferred from the Plaintiff (withdrawn) on October 21, 2013]

4) Claims of the Subject Patent

[Claim 1] A pharmaceutical composition effective for once a day administration to treat hepatitis B virus infection comprising from 0.5 to 1.0 mg of entecavir adhered to the surface of a carrier substrate

[Claims 7-10, 12, 14-17, 19, 21, 23] omitted

[Claims 2-6, 11, 13, 18, 20, and 22] omitted

B. Compared Product

The description and the drawing of the Compared Product specified by the Defendant who filed the present action are annexed here as Attachment 1.

C. Prior Arts

1) Prior Art 1 (Exhibit No. K5)[2)]

Prior Art 1 is a publication directed to entecavir in Drugs of the Future, Vol. 24, Issue 11, pages 1173-1177 published in 1999, and its disclosures are summarized in Item 1 of Annex 2.

2) Prior Art 2 (Exhibit No. E6)[3)]

Prior Art 2 is an article entitled "Antiviral Chemotherapy for the Treatment of Hepatitis B Virus Infections" in Gastroenterology, vol. 118(2), pages S83~S103, which was published approximately in February 2000 and archived at a library on February 17, 2000. Its disclosures are summarized in Item 2 of Annex 2.

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2) Exhibit K4 was submitted as evidence in the Patent Court proceedings and this case. However, since it includes the same contents, Exhibit K5 has been designed as Prior Art 1 in this case.

3) It was a new Prior Art submitted during the Patent Court proceedings.

D. Procedural History of the IPT Decision

1) The Defendant filed a scope confirmation action (Case No. 2012 Dang 2418) against the Plaintiff with the IPT on September 13, 2012, on a ground that the Compared Product, which is produced by simple mixing of entecavir and an excipient, does not fall in the scope of Claim 1 because the Compared Product was expressly disclaimed by the Plaintiff from the scope of Claim 1; the Compared Product belongs to the public domain where a person having ordinary skill in the art ("PHOSITA") could have readily practiced the Compared Product in view of Prior Art 1 and the well-known technology.

2) On April 30, 2013, the IPT rendered a decision to hear the Defendant's claim on a ground that the Compared Product belongs to the public domain because it could have readily been conceived by Prior Art 1 and the well-known technology.

[Evidence: Undisputed facts, K1-K5, E6, and overall pleadings]

2. Summary of the IPT decision and the arguments by each party

A. Summary of the IPT decision and the arguments by the Successor of the Plaintiff

1) Since Claim 1 does not include any preparation limitation, the element ("adhered to the surface of a carrier substrate") should not be limited to being prepared by a particular preparation process. Thus, if entecavir of the Compared Product is adhered to the surface of a carrier substrate, it can be concluded that the Compared Product falls in the protection scope of Claim 1, regardless of the adhering method or preparation process.

2) Novelty of Claim 1 must consider the dosing amount and dosing cycle over Prior Art 1 and Prior Art 2. Prior Art 1 does not disclose

the effect and dose of entecavir for inhibiting hepatitis B virus in humans. Further, the element of "the oral dose of 0.5-2.5 mg per day" disclosed in Prior Art 2 is for woodchucks and is not viewed as an effective dose for humans.

3) Since the dosing amount and dosing cycle should be considered in determining whether the Compared Product belongs to the public domain, the Compared Product could not have readily been derived by PHOSITA from Prior Art 1 and Prior Art 2 for the reasons below:

a) As of the priority date of the Subject Patent, it was recognized in the art that a 1 to 50 mg/kg (60 to 3000 mg for 60 kg of body weight) dose of entecavir had to be administered several times daily for effectively treating hepatitis B infection; thus, the effect of the 1 mg dose of entecavir cannot be anticipated.

b) Prior Art 1 discloses preclinical trials where entecavir was administered to woodchucks carrying hepatitis B virus at doses of 0.02, 0.1, and 0.5 mg/kg and phase I trials where entecavir was administered to healthy volunteers in various doses (1, 2.5, 5, 10, 20, and 40 mg). However, human doses cannot be converted from the doses administered to woodchucks alone, and the 1 mg dose initially used in phase I trial is a starting dose for confirming safety, which is not considered to exhibit the pharmacological effects of entecavir. The human doses can be easily predicted based only on the serum drug concentration data in the woodchuck model in the preclinical trial and those in human patients in phase I trial, but Prior Art 1 does not provide such information. In addition, since the preclinical test showed that entecavir is very safe at a concentration that is 8000 times higher than its effective concentration, it provides a motivation to use a higher dose to assure that the treatment effect is exhibited. Thus, it is difficult to predict the effect of the 1 mg dose of entecavir from Prior Art 1.

c) Even if the woodchuck doses used in the woodchuck tests in Prior Art 1 can be converted to human doses, since the 0.02 mg/kg dose were shown to have superior effects in treating hepatitis B infection than the 0.1 mg/kg and 0.4 mg/kg in the woodchuck tests, PHOSITA would have likely selected 0.1 mg/kg and 0.5 mg/kg. Even if the woodchuck doses of 0.1 mg/kg and 0.5 mg/kg are converted to human doses as the method asserted by the Defendant, they correspond to 2 mg and 10 mg, respectively. Thus, it is still difficult to foresee the effect of the 1 mg dose of entecavir.

d) Prior Art 2 discloses an entecavir dose range of "0.5-2.5 mg p.o. daily for phase II." However, Prior Art 2 only presents the in vitro data and woodchuck test results and does not provide any disclosure related to phase II clinical trials. Thus, it can be understood that this dose range is for woodchuck tests which was calculated from the effective dose in Prior Art 2 (i.e., "0.1 and 0.5 mg") in consideration of about 5 kg of the woodchuck body weight. Thus, it is difficult to predict the effect of the 1 mg dose of entecavir from Prior Art 2.

4) Since Prior Art 1 does not present any serum concentration data in the woodchuck preclinical tests and human serum concentration data in the human phase I tests, which are required for determining doses suitable for phase II clinical trials, it is not likely that PHOSITA would have recognized the entecavir dose range of "0.5-2.5 mg" disclosed in Prior Art 2 as being suitable for clinical phase II trials. Accordingly, the 1 mg dose of entecavir could not have been conceived even from combining the teachings of Prior Art 1 and Prior Art 2.

5) Thus, the IPT decision reaching a different conclusion was not reasonable and must be revoked.

B. Arguments by the Defendant

1) In view of the specification of the Subject Patent, the constitutional element "adhered to the surface of a carrier substrate" refers to a form of entecavir coated on the surface of a carrier substrate with an adhesive substance. Since the specification of the Subject Patent describes that a composition comprising a low dose of entecavir cannot be prepared with good content uniformity by simply mixing the active substance and excipients, the Compared Product, which is produced by simply blending entecavir and excipients, is expressly disclaimed from the Subject Patent.

2) Since Claim 1 lacks novelty over the constitution of Prior Art 1 that discloses "the single oral administration of entecavir at a dose of 1 mg" or Prior Art 2 disclosing "the daily oral administration of entecavir at a dose of 0.5-2.5 mg" combined with the well-known conventional technology related to tablets, the scope of Claim 1 is not enforceable.

3) The Compared Product belongs to the public domain and PHOSITA could have readily been conceived from Prior Art 1 and Prior Art 2 by for the reasons below.

① The in vitro test disclosed in Prior Art 1 disclosed that entecavir exhibited its 50% efficacy on hepatitis B virus at a concentration of 0.00375 μmol/L (EC_{50} value), whereas it showed its 50% cytotoxicity at a concentration of 30 μmol/L (CC_{50} value), which was 8000 times higher than its EC_{50} value. This means that entecavir is more potent, and less toxic and more selective compared to other hepatitis B drugs. Thus, it can be expected that entecavir is effective at a much lower dose compared to other known hepatitis B drugs such as lamivudine, and the like. In addition, it can be found from the animal tests disclosed in Prior Art 1 that entecavir exhibited an effective hepatitis B

infection treatment when administered to woodchucks carrying hepatitis B virus at daily doses of 0.02, 0.1, and 0.5 mg/kg, and these doses are converted to 0.4, 2, and 10 mg, respectively, for a human weighing 60 kg. Thus, the effect of the 1 mg dose of entecavir can be predicted. In addition, the minimum dose of 0.02 mg/kg, which is shown to exhibit pharmacological activities (effectiveness) in the woodchuck animal tests in Prior Art 1, is converted to 0.4 mg for humans, and the 1 mg starting dose of phase I clinical trials reflects this dose. Accordingly, the effect of the 1 mg entecavir can be anticipated from Prior Art 1.

② Prior Art 2 discloses "0.5-2.5 mg p.o. daily for phase II," which refers to the human doses designed for phase II clinical trials. Table 2 in Prior Art 2 expressly describes "Phase II." As such, the dose of entecavir is expressed in "mg," instead of "mg/kg" used for the animal doses, the doses of the other hepatitis B drugs in Table 2 provided for human administration, and these doses are similar to the dose range of 0.4-2 mg, which is calculated from the woodchuck dose range of 0.02-0.1 mg/kg for humans. Thus, the effect of the daily administration of entecavir at a dose of 1 mg can be anticipated from Prior Art 2.

4) In preclinical tests, pharmacokinetics are required to be examined for animals. Conversely, pharmacokinetics are required in phase I tests and the phase II test doses are determined in consideration of the animal and human pharmacokinetic data. Prior Art 1 discloses that phase II trial for entecavir is ongoing after the preclinical and phase I trials had completed. Table 2 in Prior Art 2 describes "0.5-2.5 mg p.o. daily for phase II." From Prior Art 1 and Prior Art 2, PHOSITA would have recognized the "entecavir dose of 0.5-2.5 mg" in Table 2 as the phase II dosing in view of the conventional clinical trial procedures.

5) Accordingly, the Compared Product belongs to the public domain

and thus falls outside of the scope of Claim 1.

3. Whether the Compared Product belongs to the public domain

A. Comparison of the Technical Fields

According to K3, the Compared Product is "a tablet that can be administered once-daily to treat hepatitis B virus infection comprising 1.065 mg/tablet of entecavir monohydrate." (K3, page 21, 1st paragraph.)

Further, according to K5 and E6, Prior Art 1 discloses that "in the search for new antiviral agents ··· BMS-200475 was identified as being worthy of further evaluation. The compound was ··· although later studies proved its highly superior anti-HBV[4] activity" (K5, page 1175, left column, lower paragraph~right column, line 3). Prior Art 2 discloses that "[e]ntecavir (BMS-200475) is a carbocyclic deoxyguanosine analogue with potent antiherpes and antihepadnaviral activity. The EC50 for HBV in 2.2.15 cells is 0.00375μmol/L compared with 0.116μmol/L for lamivudine ··· In woodchucks infected with WHV,[5] treatment with entecavir produced 2-3 log10 reductions in viral load with undetectable serum HBV DNA in all treated woodchucks." (E6, "Entecavir" section on S94 and S95.)

In light of these facts, the Compared Product and Prior Art 1 and Prior Art 2 belong to the same technical field because they all relate to a hepatitis B virus infection treatment containing entecavir.

B. Comparison of the Objectives

According to K3, the specification of the Compared Product discloses that it "is a tablet that can be administered once-daily to treat hepatitis B virus infection comprising 1.065 mg/tablet of entecavir

4) Human hepatitis B virus

5) Woodchuck hepatitis virus

monohydrate [and] has an advantage of simple preparation of a tablet comprising entecavir with good content uniformity by uniformly mixing the components included in the tablet without forming agglomeration and directly tableting the mixture." (K3, pages 21-22, 1st paragraph and last paragraph of the Compared Product.) In light of these facts, it is clear that the objective of the Compared Product is to provide a tablet comprising 1 mg entecavir (it is undisputed that this is identical to 1.065 mg of entecavir monohydrate) that can be administered once-daily to treat hepatitis B, wherein the tablet has content uniformity and can be prepared in a simple manner.

Further, according to K5, Prior Art 1 discloses that "in the search for new antiviral agents ··· BMS-200475 was identified as being worthy of further evaluation ··· BMS-200475 was shown in early studies to be a potent inhibitor of hepatitis B virus replication in vitro in HepG2.2.15 cells (EC_{50} = 3.75 nM[6]), while inducing cytotoxicity only at concentrations which are 8000 times higher (CC_{50} = 30 μM[7])" (K5, page 1175, right column, lines 5-9), that "daily treatment of chronically infected animals with BMS-200475 (0.02-0.5mg/kg p.o.) for periods of 1-3 months led to effective suppression of WHV, as manifested by decreased levels of WHV DNA ···" (K5, page 1176, 3rd paragraph), and that "[i]n the first clinical trial conducted with the compound, BMS-200475 was administered to healthy volunteers as single oral doses of 1, 2.5, 5, 10, 20 or 40mg p.o. [and] was well tolerated with an incidence of treatment-related adverse events similar to that for placebo. BMS-200475 is currently in phase II trials in the U.S." (K5, page 1176, right column, the "Clinical Studies" section.) In light of these facts, it is clear that the objective of Prior Art 1 is to

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6) EC_{50} refers to the concentration of a drug effective to show a 50% effect (where the maximum effect is 100%). "EC_{50}=3.75nM" means that the concentration inhibiting 50% of the virus is 3.75nM.

7) CC_{50} refers to the cytotoxic concentration of a drug sufficient to induce 50% cytotoxicity (where the maximum effect is 100%). "CC_{50}=30μM" means that the concentration inducing 50% cytotoxicity is 30 μM.

introduce entecavir as a novel therapeutic agent for hepatitis B virus, and to provide in vitro test information, woodchuck animal studies and phase I clinical trials.

According to E6, Prior Art 2 discloses that "[o]f the nucleoside analogues that have already undergone, or are about to enter, clinical trials, all representatives of the first category are pyrimidine derivatives (lamivudine, emtricitabine), whereas those in the second category are purine derivatives (ganciclovir, famciclovir/penciclovir, lobucavir, entecavir, and adefovir dipivoxil)" (E6, Table 2, S89, right column, 2nd paragraph), and "[e]ntecavir (BMS-200475) is a carbocyclic deoxyguanosine analogue with potent antiherpes and antihepadnaviral activity. The EC_{50} for HBV in 2.2.15 cells is 0.00375 μmol/L compared with 0.116 μmol/L for lamivudine." (E6, S94, right column, last paragraph.) Table 2 shows that, in phase II, entecavir was administered at a dose of 0.5~2.5mg (p.o. daily) and the EC_{50} value was 0.00375 μmol/L. In light of these facts, it is clear that the objective of Prior Art 2 is to introduce nucleoside analogues therapeutic against hepatitis B virus — in particular, entecavir, which has a strong inhibitory effect against hepatitis B virus replication at a lower concentration and dose.

In sum, Prior Arts 1 and 2 relate to entecavir which exhibits a superior effects at a lower concentration compared to other hepatitis B therapeutic agents, and their objectives partly overlap with those of the Compared Product (that is, to provide low dose entecavir). In addition, as seen in the "Comparison of Elements and Effects" section below, the objective of the Compared Product to provide a hepatitis B therapeutic agent that can be administered once-daily comprising 1 mg of entecavir, which PHOSITA could have readily derived from Prior Arts 1 and 2. Another objective of the Compared Product to provide a tablet that has content uniformity and simply preparation could easily have been derived from the widely known and conventionally used direct powder compression method. Since the resulting working effects do not appear to be remarkable, the objectives of the Compared

Product also are not unique compared to those of Prior Art 1 and 2.

C. Comparison of the Constitutions and Effects

1) The Compared Product

According to K3, the specification of the Compared Product discloses that it "is a tablet that can be administered once-daily to treat hepatitis B virus infection comprising 1.065 mg/tablet of entecavir monohydrate, wherein the tablet comprises entecavir as a main ingredient, a carrier, and an adhesive substance as a binder, and wherein the tablet is prepared by compression molding of a powder mixture comprising said substances and tableting the mixture. The entecavir tablet according to the invention is prepared by a direct powder compression method which comprises mixing a main ingredient, entecavir monohydrate, with a carrier and a binder, compression molding of the mixture, and tableting the mixture."

In light of these facts, it is clear that the Compared Product is "a tablet for use as a hepatitis B virus infection therapeutic agent that can be administered once-daily and comprises 1.065 mg/tablet of entecavir monohydrate ("Constitution 1"), wherein the tablet comprises entecavir as a main ingredient, a carrier, and an adhesive substance as a binder, and wherein the tablet is prepared by a direct powder compression method which comprises compression molding of a powder mixture comprising said substances and tableting the mixture." ("Constitution 2.").

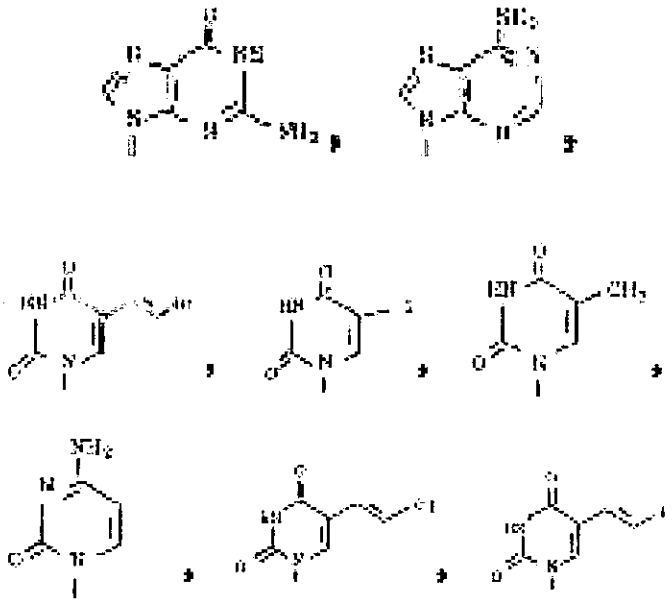
2) Constitution 1

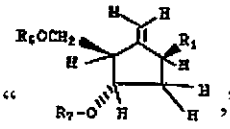
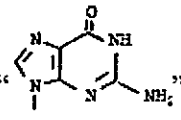
(A) Differences between Constitution 1 and the Prior Art Technology

"1) Again, Constitution 1 relates to "a hepatitis B virus infection therapeutic agent that can be administered once-daily and comprises 1.065 mg/tablet of entecavir monohydrate" (which corresponds to 1 mg of entecavir).

"2) However, according to K5 and K6, respectively, the specification of KR Patent No. 160,523 (a product patent in the same family as the Present Patent published before the priority date of the Present Patent) and Prior Art 1 disclose the following facts.

① The specification of KR Patent No. 160,523 (Title: HYDROXYMETHYL (METHYLENECYCLOPENTYL) PURINES AND PYRIMIDINES) discloses that "the compounds of formula 1 and the pharmaceutically acceptable salts thereof[8] are antiviral agents that can be used to treat viral infection in mammalian species such as domesticated animals (e.g., dogs, cats, horses and the like) and humans, and avian species (e.g., chickens and turkeys). The compounds of formula 1, wherein R1 is



8) Entecavir is a compound of formula 1 represented by "  ," wherein R1 is "  " and R6 and R7 are hydrogen atoms.

are effective against one or more of the following viruses: herpes simplex virus 1 and 2, varicella-zoster virus, cytomegalovirus, and human immunodeficiency virus (HIV). They are also believed to be active against a variety of other DNA and retroviruses. Exemplary DNA viruses in addition to those named above include ··· hepatitis B virus, and adenoviruses ··· The compounds of this invention may be administered parenterally (for example, by intravenous, intraperitoneal or intramuscular injection), orally or topically. The compounds may be administered orally or parenterally in an amount effective to treat the infection. The dosage will, of course, depend on the severity of the infection, but will likely be in the range of about 1.0 to 50 mg/kg of body weight. The desired dose may be administered several times daily at appropriate intervals." KR Patent No. 160,523, which claims compounds of formula 1 including entecavir and the pharmaceutically acceptable salts thereof, was granted on August 19, 1998 and its priority date is October 18, 1990.

② Prior Art 1 discloses that "BMS-200475 was shown in early studies to be a potent inhibitor of hepatitis B virus replication in vitro in HepG2.2.15 cells (EC_{50} = 3.75 nM), while inducing cytotoxicity only at concentrations which are 8000 times higher (CC_{50} = 30 μM) ··· BMS-200475 was shown to be more efficiently phosphorylated to its triphosphate form than lamivudine, penciclovir or lobucavir, and this phosphorylation of BMS-200475, especially at low concentrations, was indicated as being one reason for its high potency against HBV ··· The woodchuck is a commonly used animal model for hepatitis B infection. In one in vivo study, daily treatment of chronically infected animals with BMS-200475 (0.02-0.5mg/kg p.o.) for periods of 1-3 months led to effective suppression of WHV, as manifested by decreased levels of DNA and reduced endogenous hepadnaviral polymerase activity.

3) In light of these facts, it is clear that the effect of entecavir as a hepatitis B therapeutic agent was known before the priority date of the Present Patent and that Constitution 1 is limited to a method of administering entecavir with a dose of 1 mg and the once-daily administration cycle. In response to KIPO's Notice of Preliminary Rejection issued in the examination of the application of the Present Patent, the Plaintiff submitted a response arguing that "[t]he present invention relates to a pharmaceutical composition for treating HBV infection comprising a low dose of entecavir, and the use of entecavir in the treatment of HBV infection was already known. The present invention comprises the use of a low dose of entecavir as a technical constituent of the invention." (K36, page 9.) In view of the foregoing, it is clear that the Present Patent features a limitation on the dose of entecavir.

(B) Whether technology directed only to limiting the administration method of a known pharmaceutical composition invention belongs to the public domain -

It is a common technical problem in the art to try to determine a dose and administration cycle for a known substance in the medicinal invention field within a range for maintaining its pharmacological effect without toxicity or side effects. The procedure for finding such a dose and administration cycle is well known to PHOSITA. Thus, for a pharmaceutical composition which is known to be effective for the treatment of a particular disease or a particular patient, PHOSITA can optimize a method of administration including a dose, administration cycle, etc. within an effective *and* tolerant range — solving the problem of increasing the pharmacological effects while decreasing side effects — using ordinary creativity. Where the administration method of a known pharmaceutical composition invention showing no unexpectedly remarkable effects to PHOSITA (and thus could be predicted by such a person), the technology belongs to the public domain.

(C) Conclusion

1) First, we review whether it was known to PHOSITA before the priority date of the Present Patent that 1 to 50 mg/kg entecavir was required to be administered several times daily.

According to K2, the specification of the Present Patent describes that "[e]ntecavir and its use in treating hepatitis B are disclosed by Zahler et al. in U. S. Patent 5,206,244. This patent discloses that an effective antiviral dose for oral or parenteral administration will likely be in the range of about 1.0 to 50 mg/kg of body weight and that the desired dose may be administered several times daily at appropriate intervals." (K2, paragraph <3>.) Further, according to K6, the specification of KR Patent No. 160,523 (the Korean counterpart of U.S. Patent No. 5,206,244), which is a product patent of the same family as the Present Patent, discloses that "[t]he compounds may be administered orally or parenterally in an amount effective to treat the infection. The dosage will, of course, depend on the severity of the infection, but will likely be in the range of about 1.0 to 50 mg/kg of body weight. The desired dose may be administered several times daily at appropriate intervals. (K6, page 4, lines 14-16.)

In light of these facts, it is clear that the typical entecavir dose-related description in the Present Patent directly relies on the specification of KR Patent No. 160,523 to determine whether the dosage will likely fall within the range of about 1.0 to 50 mg/kg of body weight (60 to 3000 mg for 60 kg of body weight).

However, the following facts from the disclosure of K6 make it clear that the specifications of the Present Patent and KR Patent No. 160,523 merely estimate the stated dose and administration cycle of entecavir: (i) the specification of KR Patent No. 160,523 merely discloses the dosages for all compounds effective to treat the infection and does not specify particular compounds or

dosages of particular diseases, (ii) the specification of KR Patent No. 160,523 discloses that the compounds have an antiviral effect against hepatitis B virus as well as herpes simplex virus (HSV-1 and HSV-2), varicella-zoster virus (VZV), cytomegalovirus (HCMV), and human immunodeficiency virus (HIV) (K6, page 4, 1st paragraph) but the working examples teach antivirus tests for each of HSV-1, HSV-2, VZV, HCMV and HIV (K6, page 40, Table 1) yet none for hepatitis B virus, (iii) the HSV-1, HSV-2, VZV, and HCMV antiviral assays also merely describe the ID_{50} values determined from a drug concentration for achieving a 50% plaque reduction compared to virus controls, and do not specifically teach a basis for the effective dosage of the antiviral agent in the range of about 1.0 to 50 mg/kg, and (iv) there is no data proving that, at the time of the priority date of KR Patent No. 160,523, entecavir clinical trials for treating hepatitis B were ever conducted.

Accordingly, before the priority date of the Present Patent, PHOSITA generally would not have thought that 1 to 50 mg/kg entecavir must be administered several times daily.

2) Next, we discuss whether it would have been possible to predict an once-daily administration cycle of 1 mg entecavir.

a) Clinical trial process

① According to the Prior Arts K29, K30, K41, E8, E15, and E16, and the expert testimonies by Lim Dong-Seok and Lee Bum-Jin, it is understood that a new drug development process includes a series of clinical trial processes as the following.

Ⓐ Pre-clinical tests are required to gather safety and efficacy information for a drug before carrying out human trials. In a drug safety test, the maximum safe dose at which no toxicities or side effects are observed (NOAEL: no observed adverse

effect level) is determined by administering the drug to test animals. To test the drug's efficacy, an in vitro test, a diseased animal model test (an in vivo test) and other similar tests are conducted. In the in vitro test, the drug response is identified and the effective concentration (EC_{50}) is determined in vitro using cell lines, etc. In the diseased animal model tests, the drug response of each dose is identified and pharmacokinetics data about the blood drug concentration, terminal half-life, rate of metabolism, rate of excretion, etc. is studied based on a diseased animal model.

Ⓑ Phase I clinical trials are required to confirm drug safety and gather pharmacokinetics information by administering the drug to healthy volunteers. In the drug safety test, abnormal reactions are checked by administering the drug at the maximum recommended starting dose (MRSD).[9]When calculating the MRSD, the maximum safe dose at which no adverse action was observed (NOAEL: no observed adverse effect level) in the animal tests is first determined, the NOAEL value is converted to a human equivalent dose (HED)[10] considering the body surface area, and the HED is divided by a safety factor (usually 10). The MRSD may be lowered based on the pharmacologically active dose (PAD, reflecting the HED) tested in the animal tests. At this stage, pharmacokinetics information about the blood drug concentration of each dose,

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9) The maximum recommended starting dose (MRSD) for phase I clinical trials is generally determined in accordance with the publication "Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers" (E8) published by the Center for Drug Evaluation and Research (CDER) of the U.S. FDA.

10) Human equivalent dose (HED) is calculated by multiplying the animal dose and a conversion factor considering the body surface area. The conversion factor is a ratio of human/animal km factors, where the km factor is a value calculated by dividing the body weight in kg by the surface area in m2.

terminal half-life, rate of metabolism, rate of excretion, etc. is obtained, and a dose, administration cycle and the like for phase II clinical trials are designed based on the pharmacokinetics information as well as the pharmacokinetics information obtained in the pre-clinical tests.

© Phase II clinical trials are required to identify clinical effects in patients with a particular disease, and to collect various information necessary to determine the dose, administration period, etc. At this stage, pharmacological efficacy is tested by designing two or three doses and then administering them to a small number of patients.

Ⓓ In phase III clinical trials, a dose chosen from phase II clinical trials is tested in a large number of patients to determine whether the dose is superior to existing therapeutic agents and also safe enough to apply for approval for commercialization once the efficacy is evaluated.

② In view of these facts, a new drug is developed by obtaining drug safety and efficacy data through a series of conventionally conducted clinical trial processes, and then determining the most suitable dose and administration cycle based on the data.

b) Review of prior art

① As shown in K5, K14, and E6, it is clear that Prior Arts 1 and 2 and the online journal at http://www.thebody.comcontentart 32934.html, which were all published before the priority date of the Subject Patent, include disclosures as described below.

Ⓐ Prior Art 1 (K5) includes the following disclosures:

[Introduction] Lamivudine, introduced in 1995 for HIV disease, was launched this year by BioChem Pharma and Glaxo Wellcome as the first oral antiviral treatment for chronic hepatitis B. Three nucleoside analogs, adefovir dipivoxil (Gilead), BMS-200475 (Bristol-Myers Squibb), and emtricitabine (Triangle) are

undergoing phase III, II, and I/II clinical development, respectively, while others are under preclinical evaluation ··· In the search for new antiviral agents, scientists at Bristol-Myers Squibb synthesized a series of 4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl purines and pyrimidines and identified SQ-34676 (BMS-200475) as being worthy of further evaluation. The compound was originally targeted as an antiherpes virus agent, although later studies proved its highly superior anti-HBV activity. [Pharmacological Actions] BMS-200475 was shown in early studies to be a potent inhibitor of hepatitis B virus replication in vitro in HepG2.2.15 cells (EC_{50}=3.75 nM), while inducing cytotoxicity only at concentrations which are 8000 times higher (CC_{50}=30μM) ··· In a separate study in human hepatoma cells, BMS-200475 was found to be specifically taken up and phosphorylated to its mono-, di-, and triphosphate esters. [···] BMS-200475 was shown to be more efficiently phosphorylated to its triphosphate form than lamivudine, penciclovir, lobucavir, and this phosphorylation of BMS-200475, especially at low concentrations, was indicated as being one reason for its high potency against HBV. [···] The woodchuck is a commonly used animal model for hepatitis B infection. In one in vivo study, daily treatment of chronically infected animals with BMS-200475 (0.02-0.5mg/kg p.o.) for periods of 1-3 months led to effective suppression of WHV, as manifested by decreased levels of WHV DAN and reduced endogenous hepadnaviral polymerase activity. [···] In another woodchuck study, BMS-200475 was administered once daily (0.02 or 0.1 mg/kg) to chronically infected WHV carriers for 84 days. WHV viremia was reduced by 10 to 1000-fold after just 1 week of treatment with the title compound at both doses. [···] In the first clinical trials conducted with the compound, BMS-200475 was administered to healthy volunteers as single oral doses of 1, 2.5, 5, 10, 20, or 40 mg p.o. according to a randomized, double-blind, placebo-controlled design. Pharmacokinetics

were evaluated using blood and urine samples collected for 14 days post-dosing. Safety was evaluated by physical examination. BMS-200475 was well tolerated, with an incidence of treatment-related adverse events similar to that for placebo (31% vs. 33% for placebo). Side effects of the study drug, all of which were mild and reversible, included drowsiness/fatigue, headache and lightheadedness/dizziness. Pharmacokinetic assessment revealed that the drug is well absorbed after oral dosing, with dose-dependent increases in peak plasma concentrations and AUC values. Plasma drug concentrations declined in a biexponential fashion, with a mean terminal $T_{1/2}$ of 55 h.

Ⓑ With regard to the nucleoside analogues which underwent clinical tests for treating hepatitis B infection, Prior Art includes Table 2 on the following facts (E6).

Table 2. Summary of Pharmacokinetic, In Vitro Antiviral Activity (EC_{50}), and Reduction of Serum HBV DNA and Proposed Mechanism of Action of Current Nucleoside Analogues in Clinical Trials

	OB (%)	Active form	$t_{1/2}$ of active metabolite (h)	Dose	EC_{50} (μmol/L) in vitro	SI	Reduction in serum HBV DNA	Proposed mechanism of action	Stage	Study (ref no.)
Lamivudine (−)-FTC	86	β-L-3TC-triphosphate	9.2	100 mg po daily	0.01	2870–8200	4–6 $\log_{10}$	Competitive inhibition with dCTP Chain termination	Approved	19, 48, 82, 83, 86, 87, 90, 120, 148, 149
Famciclovir (penciclovir)	77	Penciclovir-triphosphate	12–18	500 mg po 3 times daily	EC_{50}, 1.6 for intracellular replication; EC_{50}, 0.7 for viral release	280–630	80% from pre-treatment levels 1–2 $\log_{10}$	Competitive inhibition, dGTP Chain termination Inhibition of priming, first-, and second-strand synthesis	Phase III	19, 49, 115–117, 120, 121, 128, 129
Adefovir dipivoxil (bis-POM PMEA)		PMEA-diphosphate	16–18	5–30 mg po daily	0.05–0.7	214–858	4–6 $\log_{10}$	Competitive inhibition, dATP Inhibition of first-strand synthesis	Phase II–III	137, 144–146, 149, 150
Lobucavir (R-BHCG)	>50	R-BHCG-triphosphate	10	200 mg po 2–4 times daily	2.5	>80	2–4 $\log_{10}$	Competitive inhibition dGTP Chain termination Inhibition of first-strand synthesis	Discontinued	157–161, 165
Entecavir (BMS-200475)	90	BMS 200475 triphosphate	115	0.5–2.5 mg po daily	0.00375	8000	2–3 $\log_{10}$	Competitive inhibition dGTP Chain termination Inhibition of first-strand synthesis	Phase II	163–166
Emtricitabine (5-fluoro-lamivudine (FTC))	80–90	(−)-FTC-triphosphate	24		0.03	6000–200,000		Competitive inhibition with dCTP Chain termination Inhibition of first-strand synthesis	Phase I–II	167–169, 194

NOTE. EC_{50} values are based in vitro on studies in 2.2.15 cells or transient transfections of human hepatoma cells with infectious clones of HBV. The selectivity index (SI) is included where known. Only penciclovir has demonstrated significant activity against the viral CCC DNA form of DHBV in vivo [117]

OB oral bioavailability; po orally; ref, reference.

© The online journal at http://www.thebody.comcontentart 32934. html (K14) discloses that "a single daily dose of 5 mg should give plasma concentrations of the drug above the EC_{50} value against HBV for 24 hours."

② In light of these disclosures, the following facts are apparent.

Ⓐ Entecavir is effectively adsorbed and phosphorylated *in vitro* at a low concentration, and the concentration needed to inhibit 50% of hepatitis B virus (EC50) is 0.00375 μMol/L (=3.75nM), which is markedly low. Thus, entecavir would have been expected to exhibit its effect at a very low dose. On the other hand, since the concentration needed to induce 50% cytotoxicity (CC_{50}) is 30 μMol/L which is fully 8,000 times greater than the value of EC_{50}, entecavir would have been expected to be safe at a high dose. In clinical phase I for entecavir, a single oral dose of 1, 2.5, 5, 10, 20, or 40 mg p.o. was given to healthy volunteers and it was confirmed that entecavir does not cause toxicities or abnormal responses such as adverse side effects, etc.

Ⓑ The i*n vitro* concentrations of entecavir, lamivudine (approved and currently available in the market) and adefovir-dipivoxil (phase II to phase III) needed to inhibit 50% of hepatitis B virus (EC_{50}) was 0.00375 μMol/L, 0.01 μMol/L, and 0.05-0.7 μMol/L, respectively. Thus, the drug concentration of entecavir is remarkably lower than those of other hepatitis B infection drugs. The human oral daily doses for lamivudine and adefovir-dipivoxil are 100 mg and 5-30 mg, respectively. Thus, it would have been expected that entecavir would be effective at a lower dose than other hepatitis B infection drugs. In addition, since 5 mg entecavir was known to exhibit a serum drug concentration that is greater than the EC_{50} for

hepatitis B infection (HBV), PHOSITA would have expected that entecavir would be effective at a dose lower than 5 mg.

© In addition, since the mean terminal half-life of entecavir was found to be 55 hours by a serum drug concentration test conducted during phase I, it could have been predicted that the effect of entecavir would be maintained in vivo for a prolonged period of time. Thus, entecavir could be administered with an once-a-day schedule.

Ⓓ Furthermore, Table 2 of Prior Art 2 describes an entecavir dose range of "0.5-2.5 mg p.o. daily for phase II." Although the entecavir relevant documents cited in Table 2 of Prior Art 2 (reference numbers 163-165) do not disclose phase II results, the dose required for phase II trials would have been designed based on the pharmacokinetic data obtained from preclinical and phase I trials, which would have been conducted according to conventional clinical trial procedures as described above. Thus, it can be seen from Prior Art 1 that entecavir was administered in phase II trials, and its pharmacokinetics were evaluated in preclinical and phase I. Although there are no specific serum drug concentration data, such data is an essential prerequisite for conducting a phase II trial. Thus, PHOSITA would have recognized the dose of entecavir set forth in Table 2 as one suitable for phase II stage based on the pharmacokinetic data. In addition, it would have been expected from the results of the preclinical and phase I tests that entecavir would be effective in a dose lower than 5 mg. Thus, it is highly likely the dose in Table 2 would have been understood as a dose suitable for phase II trials. Moreover, that all the doses for the other hepatitis B infection drugs are for humans, and that the dose of entecavir is expressed with "mg" (and not "mg/kg" which is used to express a dose for an animal) would have been difficult for PHOSITA to recognize the disclosed dose as one for an

animal. Thus, PHOSITA would have recognized the doses set forth in Table 2 as ones designed for phase II trials. Once the phase II trial was designed, it would have been much easier to predict the pharmacological effect of entecavir. Thus, it would have been expected from Table 2 that entecavir would be effective in the range of 0.5-2.5 mg.

3) Next, we consider whether there are any factors teaching away from predicting the effect of the 1 mg dose of entecavir.

a) According to the document referenced in Prior Art 2 (reference number 164 and K10), the effect of entecavir at 0.1 and 0.5 mg/kg was superior to that of 0.02 mg/kg in woodchucks, and the 0.1 and 0.5 mg woodchuck doses correspond to 2 and 10 mg/kg doses when converted to human equivalent doses (HED). We therefore consider whether such animal test data teaches away from predicting the effect of 1 mg entecavir.

① In general, an animal has a different metabolism mechanism from a human being. Furthermore, woodchuck hepatitis virus (WHV) and human hepatitis B virus (HBV) are different viruses. Thus, it is difficult to derive a human dose based only on a dose for a woodchuck.

② In phase I, the maximum recommended starting dose (MRSD) may be determined based on the pharmacologically active dose (PAD) obtained in an animal experiment, and the stability of the drug is confirmed and pharmacokinetic data is obtained by increasing the dose from the starting dose (MRSD). In phase II, a dose designed for phase II which is predicted to be a treatment effective dose is determined based on the pharmacokinetic data obtained from human phase I trials and the preclinical data obtained from animal trials. Thus, in stepwise clinical trials, the PAD for animals may be

considered to contribute to extrapolation of phase II doses. However, considering that the phase II dose is determined using pharmacokinetic data obtained from human trials as well as animals, it is understood that calculating human doses solely based on animal doses is a difficult task.

③ The FDA estimates a starting dose (MRSD) for phase I in view of human equivalent doses (HED). However, before pharmacokinetic data is obtained during a phase I trial, if there is not sufficient information to calculate a precise dose, the MRSD is calculated using the HED, but the HED, which value is divided by a safety factor (10), lacks precision.

In light of the above, PHOSITA would not have readily predicted a human dose solely based on an animal dose. Accordingly, the results of the animal test do not teach away from predicting the effect of 1 mg entecavir.

b) In addition, since the starting dose for the phase I trial (MSRD) is calculated by converting the NOAEL to the HED and the HED is divided by a safety factor of 10 to arrive at the lowest dose that may not exhibit toxicities. Thus, we consider whether the starting dose of entecavir is 1 mg teaches away from predicting the effective human dose of 1 mg entecavir.

① Since the effective *in vitro* concentration of entecavir was markedly low (EC_{50}=0.00375 μMol/L) and entecavir would have been expected to be effective at a dose that is lower than 5 mg, there was insufficient reason to persuade PHOSITA that entecavir is not effective at 1 mg.

② Although the starting dose of a phase I trial is not a dose designed to ensure the effectiveness of a drug according to conventional clinical trial procedures, a dose designed for a phase II trial, which is expected to be an effective treatment dose, is estimated based on human pharmacokinetic data obtained

for each dose from phase I trials and animal pharmacokinetic data obtained from preclinical trials. Thus, the starting dose could have been effective.

③ The dose of entecavir predicted to be treatment effective in a phase II trial was in the range of 0.5-2.5 mg.

In light of the above, the fact that the starting dose of 1 mg entecavir would have been sufficient for predicting the effect of 1 mg entecavir.

c) Further, we consider whether a preclinical test showed that entecavir is very safe at a concentration that is 8000 times greater than its effective concentration (thus providing a motivation to use a higher dose to assure that a treatment effect is shown) would have taught away from predicting the effect of 1 mg entecavir.

Although the preclinical toxicity test result showed that entecavir is safe at a high concentration, it nevertheless would have been impossible to rule out a case where entecavir exhibited unexpected toxicity when actually administered to a human patient. In this case, since PHOSITA would have likely selected a lower dose still within the effective range, such a toxicity test result does not teach away from predicting the effect of 1 mg entecavir.

(D) Results of review

Based on the above we conclude that Constitution 1 of the Compared Product is directed to an once-a-day dosage of 1 mg entecavir (a known hepatitis B infection drug). However, optimizing a dosing regimen — a dose, a dosing interval, etc. to exhibit a desired treatment effect within a safe range — falls within the conventional creativity of PHOSITA for the following reasons.

① Before the priority date of the Present Patent, PHOSITA would not have generally recognized that entecavir had to be administered several times a day at a dose of 1 to 50 mg

per 1 kg (60 to 3000 mg on the basis of 60 kg of an adult).

② The 1 mg entecavir administration was known to be safe, and there are no prior art that taught away from predicting the efficacy of 1 mg entecavir.

③ By comparing the effective concentration values (EC_{50}) and human doses of entecavir with other hepatitis B infection drugs and from the fact that 5 mg entecavir will exhibit a serum drug concentration that is greater than EC_{50} for HBV, PHOSITA would have expected that entecavir would be effective at a dose of 5 mg or less.

④ From the disclosure relating to a mean terminal half-life of 55 hours, the once-a-day administration of entecavir would have been anticipated.

⑤ From the dose range of "0.5-2.5 mg p.o. daily" in Table 2 of Prior Art 2, which is a dose designed for phase II, the administration of entecavir at a dose of 0.5-2.5 mg once a day would have been self-evident.

Thus, PHOSITA would have readily derived from Prior Art 1 and Prior Art 2 the once-a-day administration of 1 mg entecavir, which appears to be within a safe range while maintaining the pharmacological effectiveness, as found through repetitive experiments. PHOSITA would have anticipated the efficacy of Constitution 1 based on the teachings of Prior Arts 1 and 2.

3) Comparison of Constitution 2

As stated above, Constitution 2 is directed to a tablet "wherein the tablet comprises entecavir, carriers, and a binder that is an adhesive material and is prepared by a direct compression method wherein a powdery mixture of said substances are compressed and molded into a tablet."

However, as discussed earlier, a monohydrate of entecavir is disclosed

in Prior Art 1 and Prior Art 2. According to the disclosures of K5 and E1, Prior Art 1 discloses that "the pharmacokinetic results suggest that entecavir is well absorbed after oral administration." (*See* K5, the right column of page 1176, lines 14-15 under the section heading "Clinical Studies.") The book titled "Pharmacy," published by Pharmaceutical Department of Korean Pharmacy School Conference on March 2, 1996, discloses that:

"[A] tablet is a formulation prepared by compressing pharmaceuticals into a fixed shape (e.g., lens form, disc form, etc.). Tablets and capsules are the most commonly used formulations and are expected to have systemic or topical (intra-oral, gastric, intestinal, vaginal) effects. Peroral tablets are the most representative tablet forms, and include uncoated tablets, sugar-coated tablets, enteric coating tablets, multilayered tablets, etc. The advantages of tablets are 1) they are easy to take; 2) they provide an accurately measured dose of the active ingredient; 3) it is possible to control the action modes of tablets with various techniques; 4) by using tablet coatings, tastes, odors, irritancy, etc. can be corrected; and 5) with appropriate packages, it is possible to prevent degeneration or contamination and maintain product quality for a prolonged period of time…" (see E1, lines 1-10 of page 280)

[and]

"In general, tablets are composed of several types of substances in addition to an active ingredient … Additive substances are classified according to [their] functions as excipients, binders, disintegrants, lubricants, etc.(see E1, page 281, lines 1-3 under the section heading "1-2. Additives of Tablets") … Most of the currently available tablets are compressed tablets prepared by compression molding, and the tableting methods can be classified as a direct powder compression method or a granule compression method depending on the compression method. A direct powder compression method is so-called because an excipient, a binder, a disintegrant, etc. are added to a crystalline or powdery active ingredient to form a uniform dry mixture, and the mixture is directly tableted." (See E1, "1-3 Tableting"

in page 286, and line 1 of page 287.)

In light of these facts, Prior Art 1 shows that entecavir is well-absorbed upon oral administration, and it is clear that the use of a tablet for oral administration. The direct compression method comprising an excipient, a binder, and a disintegrant to a crystalline or powdery drug to form a uniform dry mixture and directly compressing the mixture are conventional techniques in the field of drugs. Thus, PHOSITA would easily have derived Constitution 2 from Prior Art 1 and Prior Art 2 based on these conventional techniques, and the resulting effect would have been merely expected by PHOSITA from Prior Art 1 and Prior Art 2 in view of conventional techniques.

4) Ease of combination

We consider whether PHOSITA would have any technical difficulty in combining Prior Art 1 and Prior Art 2 with the conventional technology to derive the Compared Product. As discussed above, Prior Art 1 and Prior Art 2 belong to the same technical field in that they both relate to the treatment of hepatitis B infection virus with entecavir. In addition, they share the same technical goal of providing a hepatitis B infection treatment that exhibits a superior effect at a low dose. Taking into consideration of these circumstances plus K5 and E6, as well as the briefs submitted so far, the following facts are clear. Both Prior Art 1 and Prior Art 2 disclose entecavir clinical trials; the documents referenced therein do not teach away from combining Prior Art 1 and Prior Art 2 with the conventional technology relating to a direct powder compression method; and PHOSITA would not have had any difficulty in combining Prior Art 1 and Prior Art 2 with conventional technology. In view of these facts, there would have been no difficulty in combining Prior Art 1 and Prior Art 2 with conventional technology to derive the Compared Product.

D. Sub-conclusion

The Compared Product, Prior Art 1 and Prior Art 2 belong to the same technical field, and the objective of the Compared Product is not unique when compared to the objectives of Prior Art 1 and Prior Art 2. Further, PHOSITA would have readily derived the constitution of the Compared Product in view of Prior Art 1 and Prior Art 2 and conventional technology, and thus presents no constitutional difficulty. The relevant effect also would have been expected from Prior Art 1 and Prior Art 2 and conventional technology by PHOSITA thus, no remarkable effect has been shown.

Therefore, the Compared Product belongs to public domain technology that PHOSITA could have readily practiced in view of Prior Art 1 and Prior Art 2 together with conventional technology. As such, there is no need for comparison with Claim 1, because the Compared Product does not fall within the scope of protection of the claim.

4. Conclusion

As the IPT decision arriving at the above conclusion was lawful, the petition of the Successor of the Plaintiff is groundless and therefore is dismissed. The decision as described in the Order is hereby issued.

Presiding	Judge	Kyuhyun HAN
	Judge	Dawoo LEE
	Judge	Hyejin LEE

[Annex 1]

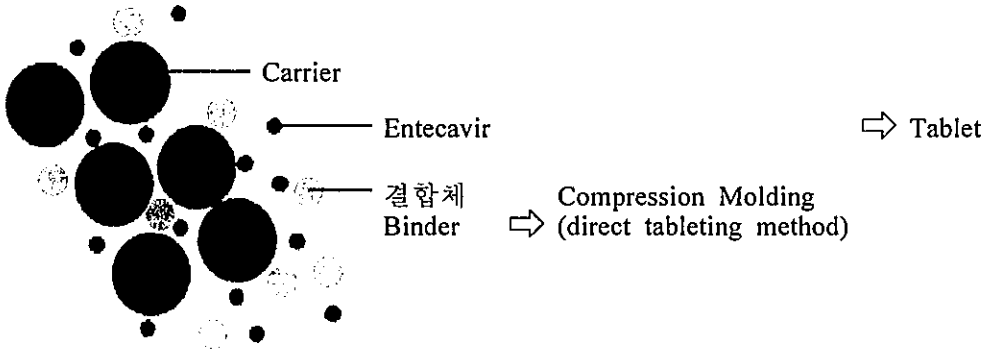
Compared Invention

The entecavir tablet of the Compared Invention is an once-a day dosage to treat hepatitis B virus infection comprising 1.065 mg per tablet of entecavir monohydrate. The tablet comprises the active ingredient (entecavir), a carrier and a binder (an adhesive substance). The tablet is prepared by a direct compression molding of a powder mixture comprising the listed substances.

The entecavir tablet of the Compared Invention is prepared by a direct powder compression method (*i.e.*, a direct tableting method), where the active ingredient, a carrier and a binder are blended to form a mixture, which is then compressed and molded into a tablet (see below Figure).

That is, the tablet is molded by uniformly mixing the active ingredient, a carrier, and a binder followed by compressing the mixture in powder form by a tableting machine. In the method, the active ingredient, a carrier, and a binder in solid powder form are condensed into a tablet by pressure.

[Figure]



The Compared Invention has the advantage of simply preparing an entecavir-comprising tablet having superior content uniformity by uniformly mixing the ingredients of the tablet and directly tableting them without the step of forming granules.

[Annex 2]

Disclosures of Prior Arts

1. Prior Art 1 (Exhibit No. K5)

Prior Art 1 relates to "BMS-200475 (Entecavir) and includes the following disclosures.

"In the search for new antiviral agents, scientists at Bristol-Myers Squibb synthesized a series of 4-hydroxy-3-(hydroxymethyl)-2-methylenecyclophyneyl purines and pyrimidines and identified SO-34676 (BMS-200475) as being worthy of further evaluation. The compound was originally targeted as an antiherpesvirus agent, although later studies proved its highly superior anti-HBV activity" (*see* page 1175, left column, line 5 from the bottom to right column, line 3).

"BMS-200475 was shown in early studies to be a potent inhibitor of hepatitis B virus replication in vitro in HepG2.2.15 cells (EC_{50}=3.75 nM), while inducing cytotoxicity only at concentrations fully 8000 times lower (CC_{50}0=30 μM)" (*see* page 1175, right column, lines 5-9).

"BMS-200475 was shown to be more efficiently phosphorylated to its triphosphate form than lamivudine, penciclovir, or lobucavir, and this phosphorylation of BMS-200475, especially at low concentrations, was indicated as being one reason for its high potency against HBV." (*see* page 1176, left column, lines 4-9)

"The woodchuck is a commonly used animal model for hepatitis B infection. In one vi vivo study, daily treatment of chronically infected animals with BMS-200475 (0.02-0.5 mg/kg p.o.) for periods of 1-3 months led to effective suppression of WHV, as manifested by decreased levels of WHV DNA and reduced endogenous hepadnaviral polymerase activity. Viral DNA was nondetectable using a dot blog hybridization technique in animals treated for 3 months with BMS-200475; analysis using a more sensitive PCR assay showed that mean

WHV titers decreased significantly as a result of the treatment. Upon discontinuation of the drug, hepatitis viremia gradually returned to pretreatment levels." (*see* page 1176, left column, lines 21-33).

"In another woodchuck study, BMS 200475 was administered once daily (0.02 or 0.1 mg/kg) to chronically infected WHV carriers for 84 days. WHV viremia was reduced by 10- to 1000-fold after just 1 week of treatment with the title compound at both doses. All carriers treated at the higher dose and 4 of 6 treated at the lower dose had reductions of >1000-fold in WHV viremia by the third week of therapy; this level of suppression was maintained for 6-8 weeks after the drug was discontinued. Serum WHV DNA returned to pretreatment of detectable levels 8-12 weeks after discontinuing treatment" (*see* page 1176, left column, lines 34-44)

"A subsequent study evaluated the effects of maintenance therapy of chronically infected WHV carriers with BMS-200475. Nineteen woodchucks were treated once daily for 8 weeks with this agent (0.5 mg/kg p.o.); .and serum WHV DNA dropped below limits of detection after 1-5 weeks of treatment. Six woodchucks were then withdrawn from drug therapy, causing viral DNA to rebound to pretreatment levels within 1-8 weeks, while the remaining 13 continued treatment with BMS-200475 using a once-weekly dosing regimen (0.5 mg/kg p.0.). Viral DNA serum levels remained fully undetectable in 12 of 13 animals 16 weeks after discontinuation of daily drug dosing. These results indicate that once viral suppression is successfully achieved, maintenance therapy using a much less frequent dosing schedules is feasible" (*see* page 1176, left column, lines 45-49).

"The ability of BMS-20047S to inhibit DHBV infection in primary duck hepatocytes (EC50=0.13 nM) and in vivo ducklings has also been demonstrated. In vivo in injected ducks, BMS-200475 decreased viral DNA levels in the liver by 96, 83, and 45% at doses of 1.0. 0.1, and 0.01 mg/kg/day by oral gavage. Its activity was slightly superior to that of lobucavir and highly superior to that of lamivudine in vitro." (*see* page 1176, right column, lines 1-8).

"In the first clinical trial conducted with the compound, BMS-200475 was administered to healthy volunteers as single oral doses of 1, 2.5, 5, 10, 20, or 40 mg p.o. according to a randomized, double-blinded, placebo-controlled design. Pharmacokinetics were evaluated using blood and urine samples collected for 14 days postdosing. Safety was evaluated by physical examination and laboratory testing before escalation to each subsequent dosing level. BMS-200475 was well tolerated, with an incidence of treatment-treated adverse events similar to that for placebo (31% vs. 33% for placebo). Side effects of the study drug, all of which were mild and reversible, included drowsiness/fatigue, headache and lightheadedness/dizziness. Pharmacokinetic assessment revealed that the drug is well absorbed after oral dosing, with dose-dependent increases in peak plasma concentrations and AUC values. Plasma drug concentrations declined in a biexponential fashion, with a mean terminal t1/2 of 55 h. More than 50% of the administered dose was eliminated in the urine as unchanged drug. Renal tubular secretion appeared to play an important role, with renal clearance values ranging from 300-600 mL/min. BMS-200475 is currently in phase II trials in the U.S. Development of the compound is also being conducted outside the U.S." (*see* page 1176, "Clinical Studies")

2. Prior Art 2 (Exhibit No. E6)

Prior Art 2 relates to "Antiviral Chemotherapy for the Treatment of Hepatitis B Virus Infections" and includes the following disclosures.

"Entecavir [1S-(1α, 3α, 4β)]-2-amino-1,9-dihydro-9-[4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]-6H-furine-6-one (BMS-200475) a carbocyclic deoxyguanosine analogue with potent antiherpes and antihepadnaviral activity. The EC_{50} for HBV in 2.2.15 cells is 0.00375 μmol/L (Table 2) compared with 0.116 μmol/L for lamivudine. The CC_{50} in contrast, is 30 μmol/L, producing a selectivity index of > 8000. The Kd, for the HBV polymerase is 0.0012 μmol/L. In

woodchucks infected with WHV, treatment with entecavir produced 2-3 log10 reductions in viral load with undetectable serum HBV DNA in all treated woodchucks, although relapse occurred shortly after discontinuation of brief treatment. phase I-II clinical studies have been initiated with entecavir. Adverse effects of entecavir include headache, dizziness, and photophobia, consistent with neurological toxicity." (*see* page S94, right column, last paragraph – page S96, left column, line 8).

Table 2. Summary of Pharmacokinetic, In Vitro Antiviral Activity (EC_{50}), and Reduction of Serum HBV DNA and Proposed Mechanism of Action of Current Nucleoside Analogues in Clinical Trials

	OB (%)	Active form	$t_{1/2}$ of active metabolite (h)	Dose	EC_{50} (μmol/l) in vitro	SI	Reduction in serum HBV DNA	Proposed mechanism of action	Stage	Study (ref no.)
Lamivudine (β-L-3TC)	88	β-L-3TC-triphosphate	9.2	100 mg po daily	0.01	2870–8200	4–6 log_{10}	Competitive inhibition with dCTP Chain termination	Approved	18, 48 82, 83 86, 87 90 120 148 149
Famciclovir (penciclovir)	77	Penciclovir-triphosphate	12–18	500 mg po 3 times daily	EC_{50}, 1.6 for intracellular replication; EC_{50}, 0.7 for viral release	280–630	80% from pretreatment level 1–2 log_{10}	Competitive inhibition, dGTP Chain termination Inhibition of priming, first, and second-strand synthesis	Phase III	18, 43 115–117 120 121 128 129
Adefovir-dipivoxil (bis-POM PMEA)		PMEA-diphosphate	15–18	5–30 mg po daily	0.05–0.7	214–858	4–6 log_{10}	Competitive inhibition, dATP Inhibition of first-strand synthesis	Phase II–III	137 144–145 149 150
Loburcavir (R-BHCG)	>50	R-BHCG-triphosphate	10	200 mg po 2–4 times daily	2.5	>80	2–4 log_{10}	Competitive inhibition dGTP Chain termination Inhibition of first-strand synthesis	Discontinued	157–161 185
Entecavir (BMS-200475)	90	BMS 200475 triphosphate	115	0.5–2.5 mg po daily	0.00375	8000	2–3 log_{10}	Competitive inhibition dGTP Chain termination Inhibition of first-strand synthesis	Phase II	163–165
Emtricitabine [5 fluoro-thiacytidine (FTC)]	80–90	(–)FTC-triphosphate	2.4		0.03	6000–200,000		Competitive inhibition with dCTP Chain termination Inhibition of first-strand synthesis	Phase I–II	167–169 104

NOTE. EC_{50} values are based in vitro on studies in 2.2.15 cells or transient transfections of human hepatoma cells with infectious clones of HBV. The selectivity index (SI) is included where known. Only penciclovir has demonstrated significant activity against the viral CCC DNA form of DHBV in vivo [117]

OB oral bioavailability; po orally; ref, reference.