

**UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY**

**AXSOME MALTA LTD. and AXSOME
THERAPEUTICS, INC.,**

Plaintiffs,

v.

**ALKEM LABORATORIES LTD.,
AUROBINDO PHARMA USA, INC.,
ALKEM USA INC., ALKEM LABS
LIMITED UNIT-V, ALKEM LABS LTD.,
HIKMA PHARMACEUTICALS USA INC.,
SANDOZ INC., and UNICHEM
LABORATORIES LTD.,**

Defendants.

Civil Action No. 23-20354 (MCA)(JBC)

DEFENDANTS' JOINT INVALIDITY CONTENTIONS

6. Kim (DEF_SOLRIAMFETOL_0000001-006)

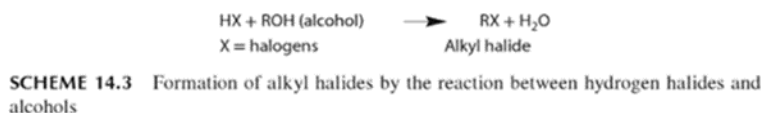
Kim, S., *Pharmaceutical Industry Practices on Genotoxic Impurities*, Chapter 14 “Salt Formation of Pharmaceutical Compounds and Associated Genotoxic Risks” 385–426 (Kim Lee ed., CRC Press 1st ed. 2014)(“Kim”) is a book chapter published on August 25, 2014 and, therefore, qualifies as prior art to the ’151, ’609, ’597, and ’354 patents under 35 U.S.C. § 102(a)(1), with no exceptions available under 35 U.S.C. § 102(b)(1).

Kim discloses that:

Alkyl halides are also well-known genotoxins that can be potentially generated during salt formation when hydrogen halides (e.g., HCl and HBr) used as counterions react with an alcohol used as solvent, as shown in Scheme 14.3. The genotoxins methyl chloride, ethyl chloride, and isopropyl chloride were reported to have been observed during the preparation of hydrochloride salts from methanol, ethanol, or isopropyl alcohol, respectively.

Kim, 417.

Kim further discloses:



Id. (see Scheme 14.3).

Kim further discloses that:

All of the aforementioned strong acids are the most frequently used counterions for API salt formation for basic drugs, and the salts from these strong acids account for a large majority of the API salts approved and marketed during recent decades, as discussed earlier. Alcohols (ethanol, isopropanol, *n*-propanol, and methanol) are also some of the most commonly used solvents, especially for API salt crystallization, due to their many favorable properties mentioned in Section 14.8. Therefore, avoiding these acids and alcohols altogether in salt forms or salt processes would be difficult, if not impossible.

Id. at 421.

Kim further discloses that:

On the other hand, the risk of genotoxin generation associated with the use of strong acids and alcohols in salt formation can be managed after weighing the available options and balancing the benefit of using these salts and alcohols against the potential risk. The risk can be minimized by developing and implementing the processes with robust process control in conjunction with rigorous analytical monitoring. Appropriate process control measures for salt formation can be put in place after systematic investigations to define the reliable ranges of process conditions that avert undesirable reactions producing the genotoxins. In addition, implementation of suitable control points in the manufacturing process along with prudently set in-process specifications based on

the permitted daily exposure or threshold of toxicological concern would ensure robust control of the genotoxic impurities.

Studies have shown that the formation of alkyl sulfonate esters in alcohols, for example, requires the presence of a strong acid in excess and is entirely inhibited by a slight excess of a base. The studies also showed that the undesired reactions producing alkyl sulfonates and alkyl halides are hindered by the presence of water in the solution and weaker acids such as phosphoric acid do not catalyze the reactions. Therefore, avoiding strongly acidic conditions and prolonged exposure of acids to an alcohol at a high temperature and incorporating water into the process when possible would reduce the chances of formation of these genotoxins. In salt crystallization processes using strong acids in general, precise control of the stoichiometric ratio of the acid to the base (according to the accurately quantified amount of the base in solution) would avoid strongly acidic conditions. This can be achieved by stringent in-process pH control during the salt formation process, controlled addition of the acid, and adequate mixing in the reactor during the acid addition.

Id.

Kim also discloses that:

Aspects of a properly designed crystallization include appropriate rates of temperature ramping, antisolvent addition, and/or counterion addition along with a well-planned seeding point at the right concentration/composition.

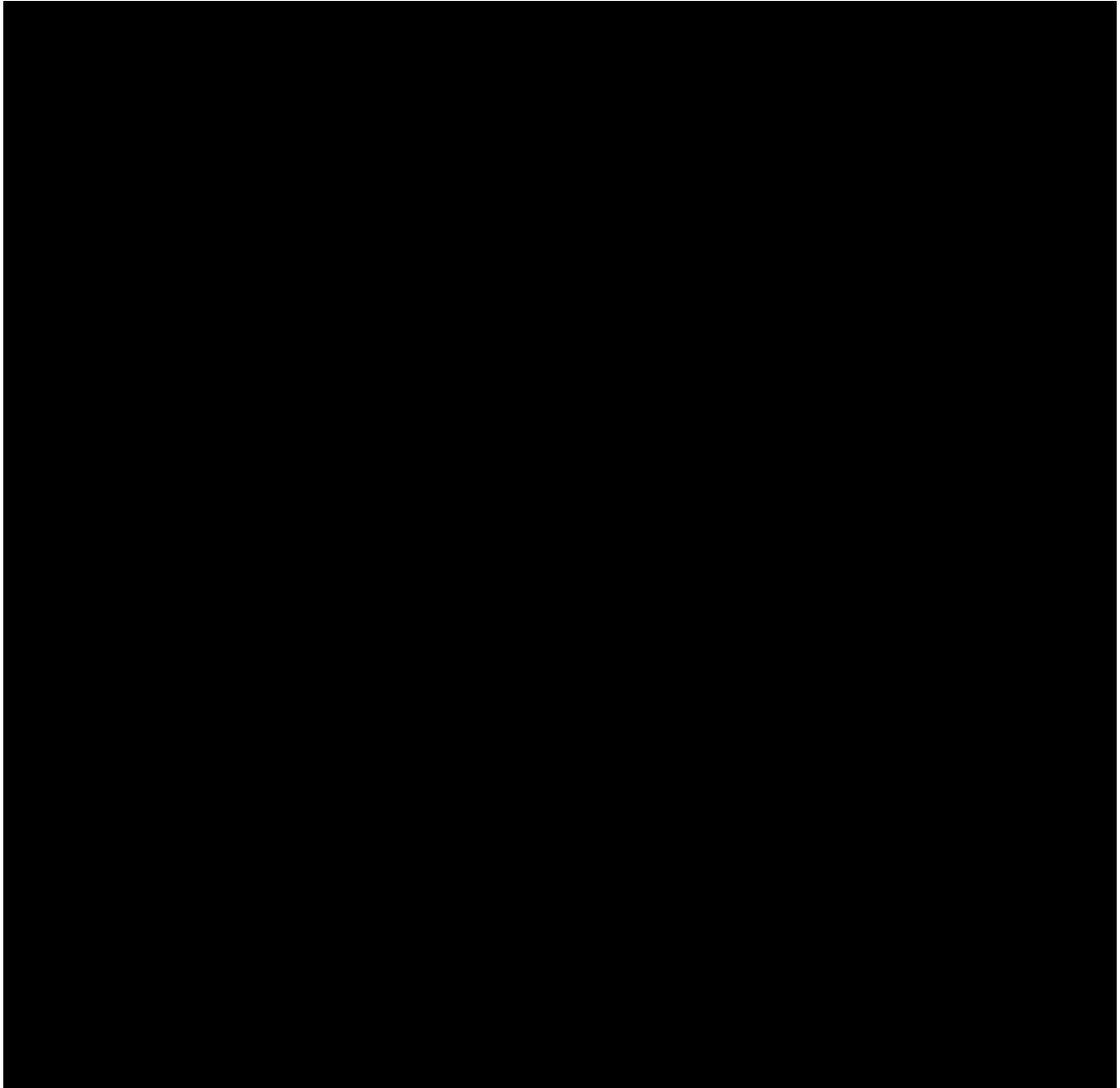
Poorly controlled processes pose risks even when genotoxic impurities are not formed in the actual process. Entrapped residual solvents, particularly alcohols, from uncontrolled precipitation can further react with strong acids in subsequent synthetic steps or during drying to create an undesired genotoxic compound. Even small amounts of residual alcohol in API can, in principle, interact with a strong acid used in the downstream formulation process to produce trace amounts of a genotoxin in the drug product. Therefore, prudent attention to any potential combination of residual alcohols in isolated compounds or APIs and use of strong acids in the subsequent steps is important to decrease the risk of formation of genotoxic impurities.

Id. at 422.

Kim further discloses that:

Sufficiently high aqueous solubility is a critical requirement in developing various pharmaceutical dosage forms, not only for **the most common solid oral dosage forms such as immediate release tablets and hard-gelatin capsules** but also for several other dosage forms including parenteral injections, oral syrups, nasal drops, eyedrops, and so on.

Id. at 387 (emphasis added).



15. The '268 Publication (DEF_SOLRIAMFETOL_0003346-355)

U.S. Patent Application Publication No. 2005/0080268 A1 (“the '268 publication”) was published on April 14, 2005, and, therefore, qualifies as prior art to the '151, '609, '597, and '354 patents under 35 U.S.C. § 102(a)(1), with no exceptions available under 35 U.S.C. § 102(b)(1).

The '268 publication discloses a method of preparing solriamfetol HCl using HCl and isopropanol, as Example 1:

Preparation of O-Carbamoyl-(D)-phenylalaninol

In a dry 2L three-neck round bottomed flask equipped with a mechanical stirrer, thermometer and 250 mL addition funnel, 838 mL of dichloromethane was charged followed by D-phenylalaninol (100 g, 0.66 mole) and sodium cyanate (85 g, 0.92 mole). The mixture was stirred in an ice-bath. The addition funnel was charged with methanesulfonic acid (222.3 g, 2.31 mol) which was slowly added to the reaction mixture so as to maintain the temperature below 5° C. The reaction mixture thickened after the completion of the addition. The ice-bath was removed and the reaction mixture was stirred until D-phenylalaninol was no longer detected by TLC analysis. To the reaction mixture, 80 grams of ice was added and the reaction mixture was cooled in an ice bath, and a 20% aqueous solution of sodium hydroxide was added at such a rate as to maintain the temperature below 5° C. until the pH of the aqueous phase was between 10 and 11 as measured by using pH paper. The mixture was transferred to a separatory funnel and the organic phase was separated. The aqueous phase was extracted with two 500 mL portions of dichloromethane, and the combined organic phase was washed with brine (350 mL) and dried over sodium sulfate (50 g) overnight. After removal of sodium sulfate by filtration, the organic phase was concentrated in vacuo to yield 115 g (89%) of the free base form of the desired product O-Carbamoyl-(D)-phenylalaninol as an oil.

O-Carbamoyl-(D)-phenylalaninol hydrochloride was prepared as follows. The crude reaction product O-Carbamoyl-(D)-phenylalaninol (115 g) was dissolved in 120 mL of isopropanol and was transferred to three-neck round bottom flask equipped with a mechanical stirrer. The mixture was chilled in an ice bath and the dropping funnel was charged with 100 mL of saturated HCl solution in isopropanol (6.5 M). The HCl solution was slowly added to the free base solution so as to maintain the temperature below 5° C. During the addition, precipitation of the desired product in HCl form was observed. After the complete addition the mixture was stirred for another hour and 660 mL of acetone was added. The mixture was stirred for another hour and the white precipitate was collected by filtration. The product was washed thoroughly with ice-chilled isopropanol-acetone (1/3, v/v), and dried in vacuo. The product O-Carbamoyl-(D)-phenylalaninol hydrochloride weighed 110 gram (71.5%) and was a white solid.

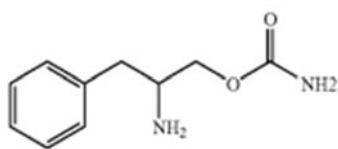
The '268 publication, Example 1 (¶¶ [0068]–[0069]).

16. The '416 Publication (DEF_SOLRIAMFETOL_0003356–373)

U.S. Patent Application Publication No. 2009/0312416 A1 (“the '416 publication”) was published on December 17, 2009, and, therefore, qualifies as prior art to the '151, '609, '597, and '354 patents under 35 U.S.C. § 102(a)(1), with no exceptions available under 35 U.S.C. § 102(b)(1).

The '416 publication discloses that:

Embodiments of the invention include a method include the use of an enantiomer of Formula I substantially free of other enantiomers that is the enantiomer of Formula Ib (R)-(beta-amino-benzenepropyl) carbamate or (O-carbamoyl-(D)-phenylalaninol) or an enantiomeric mixture wherein the enantiomer of Formula Ib (R)-(beta-amino-benzenepropyl) carbamate or (O-carbamoyl-(D)-phenylalaninol) predominates.



Formula Ib

The '416 publication, ¶ [0028].

The '416 publication further discloses that:

Formula Ib (R)-(beta-amino-benzenepropyl) carbamate or (O-carbamoyl-(D)-phenylalaninol) wherein the enantiomer of Formula Ib (R)-(beta-amino-benzenepropyl) carbamate or (O-carbamoyl-(D)-phenylalaninol) predominates to the extent of about 90% or greater. More preferably, an enantiomer of Formula Ib (R)-(beta-amino-benzenepropyl) carbamate or (O-carbamoyl-(D)-phenylalaninol) predominates to the extent of about 98% or greater.

Id. at ¶ [0029].

The '416 publication further discloses that:

Embodiments of the invention include a methods wherein the cause of the EDS is chosen from the group consisting of; central nervous system (CNS) pathologic abnormalities, stroke, narcolepsy, idiopathic CNS hypersomnia; sleep deficiency, sleep apnea, obstructive sleep apnea, insufficient nocturnal sleep, chronic pain, acute pain, Parkinson's disease, urinary incontinence, multiple sclerosis fatigue, Attention Deficit Hyperactivity Disorder (ADHD), Alzheimer's disorder, Major Depression, Bipolar Disorder, cardiac ischemia; misalignments of the body's circadian pacemaker with the environment, jet lag, shift work); and sedating drugs.

Id. at ¶ [0030].

The '416 publication further discloses that:

The term “pharmaceutically acceptable salts or esters” shall mean non-toxic salts or esters of the compounds employed in this invention which are generally prepared by reacting the free acid with a suitable organic or inorganic base or the free base with a suitable organic or inorganic acid. Examples of such salts include, but are not limited to, acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynapthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate, pamaote, palmitate, panthothenate, phosphate/diphosphate, polygalacturonate, potassium, salicylate, sodium, stearate,

subacetate, succinate, tannate, tartrate, teoate, tosylate, triethiodide, valerate.

Id. at ¶ [0055].

The '416 publication further discloses that:

Methods are known in the art for determining therapeutically and prophylactically effective doses for the instant pharmaceutical composition. For example, for use as a treatment for EDS, the compounds of this invention can be employed at a daily dose in the range of about 0.1 mg to 1000 mg usually on a regimen of 1 to 3 times per day, for an average adult human. The effective amount, however, may be varied depending upon the particular compound used, the mode of administration, the strength of the preparation, the mode of administration, and the advancement of the disease condition. In addition, factors associated with the particular patient being treated, including patient age, weight, diet and time of administration, will result in the need to adjust dosages.

Id. at ¶ [0066].

The '416 publication further discloses that:

The compound may be administered to a subject by any conventional route of administration, including, but not limited to, intravenous, oral, subcutaneous, intramuscular, intradermal and parenteral. Depending on the route of administration, compounds of Formula (I) can be constituted into any form. For example, forms suitable for oral administration include solid forms, such as pills, gelcaps, tablets, caplets, capsules (each including immediate release, timed release and sustained release formulations), granules, and powders. Forms suitable for oral administration also include liquid forms, such as solutions, syrups, elixirs, emulsions, and suspensions. In addition, forms useful for parenteral administration include sterile solutions, emulsions and suspensions.

Id. at ¶ [0067].

The '416 publication further discloses that:

The pharmaceutical compositions herein will contain, per dosage unit, e.g., tablet, capsule, powder, injection, teaspoonful, suppository and the like, an amount of the active ingredient necessary to deliver an effective dose as described above. For example, the pharmaceutical compositions herein can contain, per

unit dosage unit, from about 10 to about 1000 mg of the active ingredient. Preferably, the range is from about 25 to about 200 mg of the active ingredient.

Id. at ¶ [0074].

The '416 publication further discloses that:

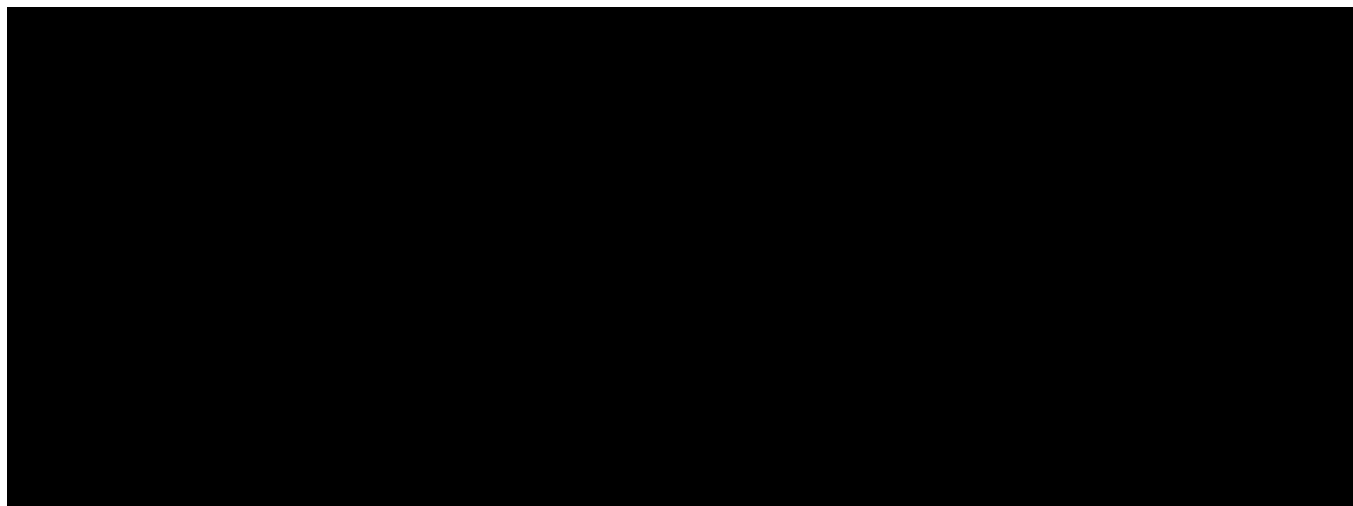
This study was undertaken to determine the effect of the (D) or (R) enantiomer of a phenylalkylamino carbamate of Formula I, specifically O-carbamoyl-(D)-phenylalaninol which can also be named (R)-(beta-amino-benzenepropyl) carbamate shown above as Formula Ib, referred to herein as “TEST COMPOUND” on the sleep-wake organization in rats after acute administration of test compound, in direct comparison to amphetamine and cocaine.

Id. at ¶ [0120] (emphases added).

The '416 publication further discloses that:

A significant enhancement of active wakefulness was observed during the first 3 hours following the administration of TEST COMPOUND ($p < 0.01$). Concomitantly, a large reduction in the time spent in sleep e.g. light sleep ($p < 0.01$), deep sleep ($p < 0.01$) and REM sleep ($p < 0.01$), followed by a rebound effect particularly an increase in deep sleep after 3 hours following the administration of TEST COMPOUND. The latter effect lasted about 7 hours during the light period of the recording. It should be noted that the onset of activity of TEST COMPOUND was almost immediate namely around the first 30 minutes following administration.

Id. at ¶ [0137] (emphasis added).



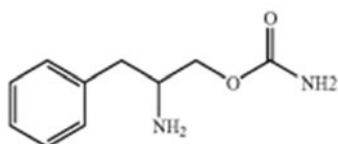
1. The Asserted Claims of the '354 patent would have been obvious over the '416 publication, the '268 publication, and Kim.

Claim 1. Independent claim 1 of the '354 patent recites:

1. A composition comprising (R)-2-amino-3-phenylpropyl carbamate hydrochloride and 2-chloropropane, wherein the composition comprises less than about 5 ppm 2-chloropropane.

The '416 publication discloses 2-amino-3-phenylpropyl carbamate:

Embodiments of the invention include a method include the use of an enantiomer of Formula I substantially free of other enantiomers that is the enantiomer of Formula Ib (R)-(beta-amino-benzenepropyl) carbamate or (O-carbamoyl-(D)-phenylalaninol) or an enantiomeric mixture wherein the enantiomer of Formula Ib (R)-(beta-amino-benzenepropyl) carbamate or (O-carbamoyl-(D)-phenylalaninol) predominates.



Formula Ib

The '416 publication, ¶ [0028].

The '416 publication further discloses embodiments in which an enantiomer, *e.g.*, (R)-2-amino-3-phenylpropyl carbamate predominates:

Formula Ib (R)-(beta-amino-benzenepropyl) carbamate or (O-carbamoyl-(D)-phenylalaninol) wherein the enantiomer of Formula

Ib (R)-(beta-amino-benzenepropyl) carbamate or (O-carbamoyl-(D)-phenylalaninol) predominates to the extent of about 90% or greater. More preferably, an enantiomer of Formula Ib (R)-(beta-amino-benzenepropyl) carbamate or (O-carbamoyl-(D)-phenylalaninol) predominates to the extent of about 98% or greater.

Id. at ¶ [0029].

The '416 publication further discloses pharmaceutically acceptable salts such as hydrochloride salts:

The term “pharmaceutically acceptable salts or esters” shall mean non-toxic salts or esters of the compounds employed in this invention which are generally prepared by reacting the free acid with a suitable organic or inorganic base or the free base with a suitable organic or inorganic acid. Examples of such salts include, but are not limited to, acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, **hydrochloride**, hydroxynapthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate, pamaote, palmitate, panthothenate, phosphate/diphosphate, polygalacturonate, potassium, salicylate, sodium, stearate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide, valerate.

Id. at ¶ [0055] (emphasis added).

The '416 publication discloses actual testing of the claimed compound:

This study was undertaken to determine the effect of the (D) or (R) enantiomer of a phenylalkylamino carbamate of Formula I, specifically O-carbamoyl-(D)-phenylalaninol which can also be named (R)-(beta-amino-benzenepropyl) carbamate shown above as Formula Ib, referred to herein as “TEST COMPOUND” on the sleep-wake organization in rats after acute administration of test compound, in direct comparison to amphetamine and cocaine.

The '416 publication, ¶ [120] (emphases added).

The '416 publication discloses significant enhancement of wakefulness when the claimed

compound was tested, motivating a POSA to prepare a composition comprising the claimed compound:

A significant enhancement of active wakefulness was observed during the first 3 hours following the administration of TEST COMPOUND ($p < 0.01$). Concomitantly, a large reduction in the time spent in sleep e.g. light sleep ($p < 0.01$), deep sleep ($p < 0.01$) and REM sleep ($p < 0.01$), followed by a rebound effect particularly an increase in deep sleep after 3 hours following the administration of TEST COMPOUND. The latter effect lasted about 7 hours during the light period of the recording. It should be noted that the onset of activity of TEST COMPOUND was almost immediate namely around the first 30 minutes following administration.

The '416 publication, ¶ [0137] (emphasis added).

The prior art discloses how to synthesize the claimed compound. As a non-limiting example, the '268 publication discloses, at Example 1, a method of synthesizing the claimed compound, including the use of HCl and isopropanol:

Preparation of O-Carbamoyl-(D)-phenylalaninol

In a dry 2L three-neck round bottomed flask equipped with a mechanical stirrer, thermometer and 250 mL addition funnel, 838 mL of dichloromethane was charged followed by D-phenylalaninol (100 g, 0.66 mole) and sodium cyanate (85 g, 0.92 mole). The mixture was stirred in an ice-bath. The addition funnel was charged with methanesulfonic acid (222.3 g, 2.31 mol) which was slowly added to the reaction mixture so as to maintain the temperature below 5° C. The reaction mixture thickened after the completion of the addition. The ice-bath was removed and the reaction mixture was stirred until D-phenylalaninol was no longer detected by TLC analysis. To the reaction mixture, 80 grams of ice was added and the reaction mixture was cooled in an ice bath, and a 20% aqueous solution of sodium hydroxide was added at such a rate as to maintain the temperature below 5° C. until the pH of the aqueous phase was between 10 and 11 as measured by using pH paper. The mixture was transferred to a separatory funnel and the organic phase was separated. The aqueous phase was extracted with two 500 mL portions of dichloromethane, and the combined organic phase was washed with brine (350 mL) and dried over sodium sulfate (50 g) overnight. After removal of sodium sulfate by filtration, **the organic phase was concentrated in vacuo to yield 115 g (89%) of the free**

base form of the desired product O-Carbamoyl-(D)-phenylalaninol as an oil.

O-Carbamoyl-(D)-phenylalaninol hydrochloride was prepared as follows. The crude reaction product O-Carbamoyl-(D)-phenylalaninol (115 g) was dissolved in 120 mL of isopropanol and was transferred to three-neck round bottom flask equipped with a mechanical stirrer. The mixture was chilled in an ice bath and the dropping funnel was charged with 100 mL of saturated HCl solution in isopropanol (6.5 M). The HCl solution was slowly added to the free base solution so as to maintain the temperature below 5° C. During the addition, precipitation of the desired product in HCl form was observed. After the complete addition the mixture was stirred for another hour and 660 mL of acetone was added. The mixture was stirred for another hour and the white precipitate was collected by filtration. The product was washed thoroughly with ice-chilled isopropanol-acetone (1/3, v/v), and dried in vacuo. The product O-Carbamoyl-(D)-phenylalaninol hydrochloride weighed 110 gram (71.5%) and was a white solid.

The '268 publication, Example 1 (¶¶ [0068]–[0069]) (emphases added).

A POSA would have been motivated by the disclosure of the '416 publication to prepare a composition comprising (R)-2-amino-3-phenylpropyl carbamate hydrochloride, and would have turned to the '268 publication at, *e.g.*, Example 1 (¶¶ [0068]–[0069]), to provide guidance for how to prepare (R)-2-amino-3-phenylpropyl carbamate hydrochloride for use in a composition disclosed in the '416 publication.

The synthesis and crystallization of the claimed compound with the use of HCl and isopropanol had a known risk of producing genotoxic 2-chloropropane ("2-CP"). In prosecution of the '222 application that matured into the '354 patent, the pending claims were rejected in part over the '499 patent. The applicant explained that

As 2-CP is the product of the reaction between isopropanol and HCl, the formation of 2-CP is not possible in the process of [the '499 patent].

In contrast, the composition of [the] present claim 20 requires the presence of 2-CP ('A composition comprising (R)-2-amino-3-phenylpropyl carbamate hydrochloride and 2-chloropropane'),

albeit in an amount less than about 5 ppm. **The formation of 2-CP in the composition of the present invention is due to the presence of isopropanol as the crystallization solvent in the process of the present invention.**

See May 12, 2022 Applicant Arguments/Remarks Made in an Amendment from the '354 patent prosecution history, 3–4 (emphases added).

The formation of 2-CP due to reaction of HCl and isopropanol was known in the prior art. For example, Kim discloses that:

Alkyl halides are also well-known genotoxins that can be potentially generated during salt formation when hydrogen halides (e.g., **HCl** and **HBr**) used as counterions **react with an alcohol used as solvent**, as shown in Scheme 14.3 The genotoxins methyl chloride, ethyl chloride, and **isopropyl chloride were reported to have been observed during the preparation of hydrochloride salts from** methanol, ethanol, or **isopropyl alcohol**, respectively.

Kim, 417 (emphases added).

Accordingly, a POSA would have known from at least the disclosure of Kim that HCl used in API salt formation can react with isopropyl alcohol used as a solvent, which can result in isopropyl chloride formation. Isopropyl chloride is another name for 2-chloropropane (2-CP). Further, as shown in the quote above, Kim identified 2-CP as a genotoxin, motivating a POSA to minimize the amount of 2-CP in a product prepared by a method involving the use of isopropanol as a crystallization solvent, and HCl, as disclosed in Example 1 (¶¶ [0068]–[0069]) of the '268 publication. Whereas reduction of 2-CP in such a product to zero ppm may be difficult, a POSA would have been motivated to at least reduce the amount of genotoxic 2-CP in a therapeutic product to an amount as low as possible, such as an amount under 5 ppm.

Kim provides guidance for minimizing the amount of 2-CP, which provides a reasonable expectation of success in doing so. Kim discloses:

On the other hand, the risk of genotoxin generation associated with the use of strong acids and alcohols in salt formation can be managed after weighing the available options and balancing the benefit of using these salts and alcohols against the potential risk. The risk can be minimized by developing and implementing the processes with robust process control in conjunction with rigorous analytical monitoring. Appropriate process control measures for salt formation can be put in place after systematic investigations to define the reliable ranges of process conditions that avert undesirable reactions producing the genotoxins. In addition, implementation of suitable control points in the manufacturing process along with prudently set in-process specifications based on the permitted daily exposure or threshold of toxicological concern would ensure robust control of the genotoxic impurities.

...

Therefore, avoiding strongly acidic conditions and prolonged exposure of acids to an alcohol at a high temperature and incorporating water into the process when possible would reduce the chances of formation of these genotoxins. In salt crystallization processes using strong acids in general, precise control of the stoichiometric ratio of the acid to the base (according to the accurately quantified amount of the base in solution) would avoid strongly acidic conditions. This can be achieved by stringent in-process pH control during the salt formation process, controlled addition of the acid, and adequate mixing in the reactor during the acid addition.

Id. at 421.

Kim provides further detail for controlling manufacturing processes to avoid genotoxin

(*e.g.*, 2-CP) impurity formation:

Aspects of a properly designed crystallization include appropriate rates of temperature ramping, antisolvent addition, and/or counterion addition along with a well-planned seeding point at the right concentration/composition.

Poorly controlled processes pose risks even when genotoxic impurities are not formed in the actual process. Entrapped residual solvents, particularly alcohols, from uncontrolled precipitation can further react with strong acids in subsequent synthetic steps or during drying to create an undesired genotoxic compound. Even small amounts of residual alcohol in API can, in principle, interact

with a strong acid used in the downstream formulation process to produce trace amounts of a genotoxin in the drug product. Therefore, prudent attention to any potential combination of residual alcohols in isolated compounds or APIs and use of strong acids in the subsequent steps is important to decrease the risk of formation of genotoxic impurities.

Id. at 422.

As shown above, Kim explains that “[e]ven small amounts of residual alcohol in API can, in principle, interact with a strong acid used in the downstream formulation process to produce trace amounts of a genotoxin in the drug product.” *Id.* This supports a reasonable expectation that, in a process for forming (R)-2-amino-3-phenylpropyl carbamate hydrochloride using HCl for salt formation and isopropanol as a crystallization solvent, 2-CP can be formed in a non-zero, but “trace” amount. Accordingly, the combination of the ’416 publication, the ’268 publication, and Kim renders obvious a composition comprising (R)-2-amino-3-phenylpropyl carbamate hydrochloride and 2-chloropropane, wherein the composition comprises less than about 5 ppm 2-chloropropane.

Additional references support the obviousness of claim 1 of the ’354 patent. For example, each of Fraga, Sobol, and Norris and Taylor provide disclosure relevant to the formation of genotoxic 2-CP from the interaction of HCl and isopropanol.

Fraga discloses “2-chloropropane was only found in the route that used hydrochloric acid (TETS 2), and it might have been synthesized by the chlorination of 2- propanol (isopropyl alcohol) by hydrochloric acid.” Fraga, 168.

Sobol discloses “[d]rug synthesis and/or formulation can generate **genotoxic impurities**. For instance, **strong acid/alcohol interactions** during the process of drug salt formation **produce alkylating agents such as alkyl halides** and alkyl esters of alkyl sulfonic acids.” Sobol, Abstract (emphases added).

Norris and Taylor discloses “[t]he following alcohols are converted into chlorides when heated in an open vessel with concd. hydrochloric acid and zinc chloride: methyl, ethyl, *n*-propyl, **isopropyl**, *n*-butyl, *sec*-butyl, *iso*amyl, pentanol-2, cetyl, β -phenylethyl, γ -phenylpropyl, *m*-nitrobenzyl, *p*-nitrobenzyl.” Norris and Taylor, 757 (emphases added).

These disclosures from each of Fraga, Sobol, and Norris and Taylor independently provide motivation to modify a method of solriamfetol HCl manufacture using HCl and isopropanol, such as that of the '268 publication, *see* Example 1 (¶¶ [0068]–[0069]), to minimize generation of 2-CP and produce a drug product with minimal amounts of the genotoxin. A POSA would then use their ordinary skill, creativity, and knowledge, or the explicit disclosures of Kim, to optimize the method of manufacture to minimize 2-CP in the final solriamfetol HCl product, and would have had a reasonable expectation of success in doing so, given the techniques and measurement methods available to a POSA and those described in Kim. These are non-limiting, exemplary disclosures. Defendants reserve the right to rely on one or more of Fraga, Sobol, and Norris and Taylor to establish obviousness of the claims of the '354 patent, including portions of Fraga, Sobol, and Norris and Taylor not specifically cited herein.

By way of example, at least each of the following grounds supports obviousness of the claims of the '354 patent:

1. The '416 publication, the '268 publication, and Kim.
2. The '416 publication, the '268 publication, and the general knowledge in the art.
3. The '416 publication, the '268 publication, Fraga, and the general knowledge in the art.
4. The '416 publication, the '268 publication, Fraga, and Kim.

5. The '416 publication, the '268 publication, Sobol, and the general knowledge in the art.
6. The '416 publication, the '268 publication, Sobol, and Kim.
7. The '416 publication, the '268 publication, Norris and Taylor, and the general knowledge in the art.
8. The '416 publication, the '268 publication, Norris and Taylor, and Kim.

Moreover, any prior art reference described above that discloses the use of solriamfetol or a salt form thereof, such as solriamfetol HCl, can be exchanged with the '416 publication. Further, the ordinary skill, creativity, and knowledge of a POSA can replace much of the disclosure of the '416 publication, such as the disclosure of immediate oral dosage forms, such as immediate release tablets, which are well within the knowledge of a POSA. That is, **the '416 publication in any of the above eight enumerated grounds can be replaced with any prior art reference described above that discloses the use of solriamfetol or a salt form thereof, such as solriamfetol HCl, and optionally the general knowledge in the art.** As examples of replacing the '416 publication with a prior art reference described above, the '416 publication in the eight enumerated grounds above can be replaced with any one of:

- Ahnaou, which discloses, *e.g.*, methods of treating excessive daytime sleepiness with oral dosage forms such as immediate release capsules or tablets, which may contain binders and lubricants. Ahnaou, *e.g.*, 1:5–11, 19:7–29, and 32:14–26, and claims 4, 14, 17–19.
- Bogan, which discloses, *e.g.*, a clinical study of treating subjects with narcolepsy with JZP-110 (solriamfetol) and demonstrated efficacy for treating excessive sleepiness. Bogan, *e.g.*, Abstract.
- Ruoff, which discloses, *e.g.*, JZP-110 (solriamfetol HCl) as a wake-promoting drug, with statistically significant data for improvement of excessive sleepiness. Ruoff, *e.g.*, 1379–80.
- The '244 publication, which discloses, *e.g.*, oral administration of solid dosage forms of compounds encompassing solriamfetol and hydrochloride salts of disclosed compounds, including immediate release dosage forms, of solriamfetol which may

contain binders and lubricants. The '244 publication, *e.g.*, ¶¶ [0002], [0026], [0033], [0043]–[0044], [0057], and [0082].

- The '098 publication, which discloses, *e.g.*, methods of treating excessive daytime sleepiness with compounds encompassing solriamfetol, as well as immediate release tablets and capsules. The '098 publication, *e.g.*, claims 1, 4, and 21–22, and ¶¶ [0030], [0067].
- The '970 publication, which discloses, *e.g.*, methods of treating obesity (compare to the '354 patent, claim 6 reciting obesity), with compounds encompassing solriamfetol, and immediate release capsules and tablets. The '970 publication, *e.g.*, claim 1, and ¶¶ [0010] and [0059].
- Wozniak and Quinnell, which discloses, *e.g.*, JZP-110 (solriamfetol HCl) as reducing sleepiness according to the manufacturer. Wozniak and Quinnell, *e.g.*, 58.

Further, the '354 patent is not entitled to its claimed priority date, because it is not supported by the '822 provisional application filed on September 6, 2016, for at least the same reasons that the '354 patent is invalid under 35 U.S.C. § 112(a)—for lack of written description, and separately, for lack of enablement, as described herein. For example, the '822 provisional application does not indicate to a POSA that the applicant had possession of a composition of solriamfetol HCl having a non-zero amount of 2-CP less than 5 ppm, nor does the '822 provisional application teach or suggest a method to measure the amount of 2-CP on the lower end of the range, such as amounts lower than the limit of detection of a given detection method. Moreover, given the lack of written description and enablement for the '354 patent claims based on the disclosure of its specification, no priority application sharing the same specification (such as the immediate parent or priority PCT) can support the claims of the '354 patent. Accordingly, the effective filing date of the '354 patent is its actual filing date of November 6, 2020, and any prior art reference disclosed above having a publication or effective filing date prior to November 6, 2020, may be used to support the obviousness of the '354 patent claims. As a non-limiting example, Allphin claims priority to the '818 provisional application filed on September 6, 2016, and is prior art to the '354 patent because the '354 patent is not entitled to its claimed priority date.

Allphin discloses, *e.g.*, administration of solriamfetol to human subjects for treatment of excessive daytime sleepiness, and can be used in place of the '416 publication in any of the grounds described above to establish obviousness of the claims of the '354 patent. Other non-limiting examples of references that can be used in place of the '416 publication in any ground described above, provided the '354 patent is not entitled to its claimed priority date include:

- Carter 2018, which discloses, *e.g.*, solriamfetol as having “robust wake-promoting effects.” Carter, *e.g.*, Abstract.
- Strollo, which discloses, *e.g.*, effective treatment of excessive sleepiness with solriamfetol in adults with obstructive sleep apnea. Strollo, *e.g.*, Abstract, 365, 372.

Accordingly, claim 1 of the '354 patent would have been obvious under 35 U.S.C. § 103 at least in view of the '416 publication, the '268 publication, and Kim.

Claim 2. Claim 2 depends from claim 1 and further recites, “wherein the composition comprises less than about 1 ppm 2-chloropropane.”

As described above for claim 1, Kim would have motivated a POSA to minimize the amount of genotoxic 2-CP that may be formed in a process involving HCl and isopropanol as a solvent, *e.g.*, Example 1 (¶¶ [0068]–[0069]) of the '268 publication. As described above for claim 1, Kim’s disclosure further provides a reasonable expectation of success that manufacturing processes can be controlled to provide “trace” amounts of 2-CP. A POSA would have understood “trace” amounts of 2-CP to include amounts under 1 ppm. Kim, 422.

Accordingly, claim 2 of the '354 patent would have been obvious under 35 U.S.C. § 103 in view of the '416 publication, the '268 publication, and Kim.

Claim 2 is also obvious in view of the art combinations described in the discussion of claim 1, above.

Claims 3, 4, and 5. Claim 3 depends from claim 1 and further recites, “wherein the composition is a dosage form.” Claim 4 depends from claim 3 and further recites, “wherein the

composition is an immediate release oral dosage form.” Claim 5 depends from claim 4 and further recites, “wherein the composition is a tablet or a capsule.”

The ’416 publication discloses tablets, *e.g.*, by which a disclosed compound can be administered:

The compound may be administered to a subject by any conventional route of administration, including, but not limited to, intravenous, oral, subcutaneous, intramuscular, intradermal and parenteral. Depending on the route of administration, compounds of Formula (I) can be constituted into any form. For example, forms suitable for oral administration include solid forms, such as pills, gelcaps, tablets, caplets, capsules (each including immediate release, timed release and sustained release formulations), granules, and powders. Forms suitable for oral administration also include liquid forms, such as solutions, syrups, elixirs, emulsions, and suspensions. In addition, forms useful for parenteral administration include sterile solutions, emulsions and suspensions.

The ’416 publication, ¶ [0067].

The ’416 publication also explicitly describes such immediate release tablet or capsule dosage forms:

The compound may be administered to a subject by any conventional route of administration, including, but not limited to, intravenous, oral, subcutaneous, intramuscular, intradermal and parenteral. ... For example, **forms suitable for oral administration include solid forms**, such as pills, gelcaps, **tablets**, caplets, **capsules (each including immediate release**, timed release and sustained release **formulations)**, granules, and powders.

Id. (emphases added).

Tablets and capsules, such as immediate release tablets and capsules, are well known in the art, and well within the background knowledge of a POSA. Accordingly, if the composition of claim 1 of the ’354 patent would have been obvious, providing that composition in a dosage form, *e.g.*, a tablet or capsule form, or an immediate release version thereof, is also obvious.

Moreover, Kim explicitly identifies these as “the most common solid oral dosage forms”:

Sufficiently high aqueous solubility is a critical requirement in developing various pharmaceutical dosage forms, not only for **the most common solid oral dosage forms such as immediate release tablets and hard-gelatin capsules** but also for several other dosage forms including parenteral injections, oral syrups, nasal drops, eyedrops, and so on.

Kim, 387 (emphasis added).

Accordingly, it would have been obvious to provide the composition of claim 1 of the '354 patent in a dosage form, *e.g.*, a capsule or tablet, such as an immediate release capsule or tablet. For these reasons, in addition to the reasons discussed above with respect to claim 1, claims 3–5 are obvious over at least the '416 publication, the '268 publication, and Kim.

Accordingly, claims 3–5 of the '354 patent would have been obvious under 35 U.S.C. § 103 in view of the '416 publication, the '268 publication, and Kim.

Claims 3–5 are also obvious in view of the art combinations described in the discussion of claim 1, above.

Claim 6. Claim 6 recites

A method of treating narcolepsy, cataplexy, **excessive daytime sleepiness**, drug addiction, sexual dysfunction, fatigue, fibromyalgia, attention deficit/hyperactivity disorder, restless legs syndrome, depression, bipolar disorder, or obesity **in a subject in need thereof**, or promoting smoking cessation in a subject in need thereof, **comprising administering to the subject the composition of claim 1.**

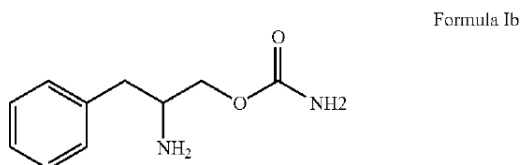
(Emphases added).

As described above, the composition of claim 1 would have been obvious at least in view of the '416 publication, the '268 publication, and Kim. Administering that obvious composition for the treatment of, *e.g.*, excessive daytime sleepiness³, would have been obvious in view of the

³ The '416 publication provides additional disclosure for alternative conditions or causes of sleepiness encompassed by claim 6, such as narcolepsy, cataplexy,

'416 publication, which discloses “This invention is directed to a method of treating Excessive daytime Sleepiness (EDS) in a subject” The '416 publication, Abstract.

The '416 publication discloses a compound designated Formula Ib:



The '416 publication, ¶ [0041].

Claim 4 of the '416 publication discloses, in part, “[a] method of treating Excessive Daytime Sleepiness (EDS) in a subject, comprising the step of administration, to a subject in need of such treatment, of a therapeutically effective amount of an enantiomer of Formula I substantially free of other enantiomers ... or a pharmaceutically acceptable salt or ester thereof” Claim 14 of the '416 publication discloses, in part, “[t]he method of claim 4 wherein the enantiomer of Formula I substantially free of other enantiomers is the (D) or the (R) enantiomer of Formula Ib” (R)-2-amino-3-phenylpropyl carbamate hydrochloride is a pharmaceutically acceptable salt of the (R) enantiomer of Formula Ib. Taken together, a POSA would have understood claim 14 of the '416 publication to disclose a method of treating, *e.g.*, excessive daytime sleepiness with a composition comprising (R)-2-amino-3-phenylpropyl carbamate hydrochloride. Therefore, a POSA would have been motivated by the disclosure of the '416 publication to administer a composition comprising (R)-2-amino-3-phenylpropyl carbamate hydrochloride (as in claim 1 of the '354 patent) to treat, *e.g.*, excessive daytime sleepiness

fatigue, attention deficit hyperactivity disorder, major depression, and bipolar disorder. *See* the '416 publication, ¶ [0030]. Defendants reserve the right to supplement these contentions in the event that Plaintiff contests the disclosure of excessive daytime sleepiness in the '416 publication.

according to claim 6 of the '354 patent.

A POSA would have had a reasonable expectation of treating, *e.g.*, excessive daytime sleepiness with (R)-2-amino-3-phenylpropyl carbamate hydrochloride because the '416 publication teaches effective reduction in sleepiness with Formula Ib.

This study was undertaken to determine the effect of the (D) or (R) enantiomer of a phenylalkylamino carbamate of Formula I, specifically O-carbamoyl-(D)-phenylalaninol which can also be named (R)-(beta-amino-benzenepropyl) carbamate shown above as Formula Ib, referred to herein as “TEST COMPOUND” on the sleep-wake organization in rats after acute administration of test compound, in direct comparison to amphetamine and cocaine.

The '416 publication, ¶ [0120] (emphases added).

The '416 publication discloses favorable results of this study:

A significant enhancement of active wakefulness was observed during the first 3 hours following the administration of TEST COMPOUND ($p < 0.01$). Concomitantly, a large reduction in the time spent in sleep *e.g.* light sleep ($p < 0.01$), deep sleep ($p < 0.01$) and REM sleep ($p < 0.01$), followed by a rebound effect particularly an increase in deep sleep after 3 hours following the administration of TEST COMPOUND. The latter effect lasted about 7 hours during the light period of the recording. It should be noted that the onset of activity of TEST COMPOUND was almost immediate namely around the first 30 minutes following administration.

The '416 publication, ¶ [0137] (emphasis added).

Accordingly, a POSA would have had a reasonable expectation of success in treating excessive daytime sleepiness in a subject with the composition of claim 1 of the '354 patent, according to the requirements of claim 6.

Accordingly, in view of the '416 publication, the '268 publication, and Kim, it would have been obvious to administer the composition of claim for the treatment of, *e.g.*, excessive daytime sleepiness. For these reasons, in addition to the reasons discussed above with respect to claim 1, claim 6 would have been obvious over the '416 publication, the '268 publication, and

Kim.

Accordingly, claim 6 of the '354 patent would have been obvious under 35 U.S.C. § 103 at least in view of the '416 publication, the '268 publication, and Kim.

Claim 6 is also obvious in view of the art combinations described in the discussion of claim 1, above.

Claim 7. Claim 7 depends from claim 6, which depends from claim 1, and further recites, “wherein the composition is administered once per day.”

The '416 publication discloses “for use as a treatment for EDS, the compounds of this invention can be employed at a daily dose in the range of about 0.1 mg to 1000 mg **usually on a regimen of 1 to 3 times per day**, for an average adult human.” The '416 publication, ¶ [0066] (emphasis added). Accordingly, a POSA would have been motivated from the disclosure of the '416 publication to administer (R)-2-amino-3-phenylpropyl carbamate hydrochloride once per day. As described above, claim 14 of the '416 publication discloses administration of (R)-2-amino-3-phenylpropyl carbamate and pharmaceutically acceptable salts thereof (*e.g.*, (R)-2-amino-3-phenylpropyl carbamate hydrochloride) for the treatment of, *e.g.*, excessive daytime sleepiness. Given the successful promotion of wakefulness disclosed in the '416 publication (described above), a POSA would have had a reasonable expectation of success in treating, *e.g.*, excessive daytime sleepiness with with administration of (R)-2-amino-3-phenylpropyl carbamate hydrochloride once per day.

For these reasons, in addition to the reasons discussed above with respect to claims 1 and 6, claim 7 would have been obvious under 35 U.S.C. § 103 at least in view of the '416 publication, the '268 publication, and Kim.

Accordingly, claim 7 of the '354 patent would have been obvious under 35 U.S.C. § 103

in view of the '416 publication, the '268 publication, and Kim.

Claim 7 is also obvious in view of the art combinations described in the discussion of claim 1, above.

