

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HIKMA PHARMACEUTICALS USA INC.,
Petitioner

IPR2024-01418
U.S. Patent No. 11,560,354

**DECLARATION OF DR. SALVATORE LEPORE,
UNDER 37 C.F.R. § 1.68 IN SUPPORT OF
PETITION FOR *INTER PARTES* REVIEW**

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EXHIBIT LIST

No.	Exhibit Description
1001	U.S. Patent No. 11,560,354
1002	U.S. Patent No. 11,560,354 File History
1003	Declaration of Dr. Salvatore D. Lepore, Ph.D.
1004	CV of Dr. Salvatore Lepore, Ph.D.
1005	US Pub. No. 2009/0312416 (“ <u>Ahnaou</u> ”)
1006	US 2005/0080268 (“ <u>Choi268</u> ”)
1007	S. Kim, <i>Pharmaceutical Industry Practices on Genotoxic Impurities</i> , Chapter 14 “Salt Formation of Pharmaceutical Compounds and Associated Genotoxic Risks” 385–426 (Kim Lee ed., CRC Press 2015) (“ <u>Kim</u> ”)
1008	C.G. Fraga, <i>Profiling of Volatile Impurities in Tetramethylenedisulfote tramine (TETS) for Synthetic-Route Determination</i> 210 FORENSIC SCI. INT’L 164 (2011) (“ <u>Fraga</u> ”)
1009	Z. Sobol, <i>Genotoxicity Profiles of Common Alkyl Halides and Esters with Alkylating Activity</i> 633 MUTUAT RES. 80 (2007) (“ <u>Sobol</u> ”)
1010	Wayback Machine webpage – T. Kaleemullah et al., <i>Development and Validation of Gas Chromatography Method for Low Level Detection of Residual Methyl Chloride, Ethyl Chloride and Isopropyl Chloride in Ziprasidone Hydrochloride</i> 3(6) DER PHARM. CHEMICA 390 (2011) (https://web.archive.org/web/20160203013049/http://derpharmachemica.com/vol3-iss6/DPC-2011-3-6-390-399.pdf) (captured September 19, 2024)
1011	Declaration of Dr. Sylvia Hall-Ellis certifying the publication date of Ex. 1016
1012	Unichem Dismissal, Docket No. 103, June 14, 2024
1013	Stipulated Consolidation and Scheduling Order, Docket No. 110, September 24, 2024
1014	David Liu et al., <i>Recent Advances in Trace Analysis of Pharmaceutical Genotoxic Impurities</i> 51 J. PHARM. BIOMED. ANALYSIS 999 (2010) (“ <u>Liu</u> ”)

1015	Zadeo Cimarosti et al., <i>Application of Quality by Design Principles to Support Development of a Control Strategy for the Control of Genotoxic Impurities in the Manufacturing Process of a Drug Substance</i> 14 ORGANIC PROCESS RSCH. & DEV. 993 (2010) (“ <u>Cimarosti</u> ”)
1016	T. Kaleemullah et al., <i>Development and Validation of Gas Chromatography Method for Low Level Detection of Residual Methyl Chloride, Ethyl Chloride and Isopropyl Chloride in Ziprasidone Hydrochloride</i> 3(6) DER PHARM. CHEMICA 390 (2011) (“ <u>Kaleemullah</u> ”)
1017	Courtney M. Callis et al., <i>Risk Assessment of Genotoxic Impurities in Marketed Compounds Administered Over a Short-Term Duration: Applications to Oncology Products and Implications for Impurity Control Limits</i> 14(4) ORGANIC PROCESS RSCH. & DEV. 986 (2010) (“ <u>Callis</u> ”)
1018	<i>Guideline on the Limits of Genotoxic Impurities</i> , Committee for Medicinal Products for Human Use (CHMP), European Medicines Agency (Jun. 28, 2006) (“ <u>CHMP</u> ”)
1019	Q. Yang et al., <i>Controlling the Genotoxins Ethyl Chloride and Methyl Chloride Formed During the Preparation of Amine Hydrochloride Salts from Solutions of Ethanol and Methanol</i> 13 ORGANIC PROCESS RSCH. & DEV. 786 (2009) (“ <u>Yang</u> ”)

I, Dr. Salvatore D. Lepore, Ph.D., do hereby declare as follows:

I. INTRODUCTION

1. I am making this declaration at the request of Petitioner in the matter of the *Inter Partes* Review of U.S. Patent No. 11,560,354 (“the 354 Patent”) to Fionn Hurley.

2. I am being compensated for my work in this matter at my standard hourly rate. I am also being reimbursed for reasonable and customary expenses associated with my work and testimony in this proceeding. My compensation is not contingent on the outcome of this matter or the specifics of my testimony.

3. I have been asked to provide my opinions regarding whether the subject matter of claims 1-8 (“the Challenged Claims”) of the 354 Patent are anticipated or otherwise would have been obvious to a person having ordinary skill in the art (“POSITA”) at the time of the alleged invention, in light of the prior art. It is my opinion that the Challenged Claims would have been obvious to a POSITA.

4. In the preparation of this declaration, I have studied:

5. the 354 Patent, Ex.1001.

6. the prosecution history of the 354 Patent (“354 File History”), Ex.1002.

7. US Pub. No. 2009/0312416 to Ahnaou et al. (“Ahnaou”), Ex.1005.

8. US App. No. 10/680,979 to Choi et al., (“Choi268”), Ex.1006.

9. “Development and Validation of Gas Chromatography Method for Low Level Detection of Residual Methyl Chloride, Ethyl Chloride and Isopropyl Chloride in Ziprasidone Hydrochloride” (“Kaleemullah”), Ex.1016.

10. The additional references I refer to below and/or identified in the exhibit list.

11. In forming the opinions expressed below, I have considered: the documents listed above; the relevant legal standards, including the standard for obviousness; and my own knowledge and experience based upon my work in the field of network communications and security as described below.

12. Unless otherwise noted, all **emphasis** in any quoted material has been added. Claim terms are *italicized*.

II. QUALIFICATIONS AND PROFESSIONAL EXPERIENCE

13. My complete qualifications and professional experience are described in my *Curriculum Vitae*, a copy of which can be found in Ex.1004. The following is a brief summary of my relevant qualifications and professional experience.

14. I am a tenured full professor of Chemistry and Biochemistry at Florida Atlantic University (“FAU”) where I lead a team of researchers on projects related to the chemistry of drug discovery.

15. I obtained my Bachelor of Science degree in Chemical Engineering from the University of South Florida in 1992 and my Ph.D. in Organic Chemistry

from Purdue University in 1997. The focus of my dissertation research was the first total synthesis of a naturally occurring compound (“stipiamide”) and related analogs using several new chemical reactions. Stipiamide and its analogs reverse chemotherapy resistance in cancer cells.

16. My efforts while at Lilly (1997–2000) resulted in four peer-reviewed publications, three Patent applications, and one issued Patent (U.S. Patent 7,700,628) entitled “Aromatic ether derivatives useful as thrombin inhibitors.”

17. In August 2000, I joined the faculty at FAU as an Assistant Professor in the Department of Chemistry and Biochemistry. In 2006, I was awarded FAU University Researcher of the Year (one award university-wide) and promoted with tenure to Associate Professor. In 2011, I was promoted to Professor. In 2003, 2009, and 2019, I was named FAU Distinguished Science Teacher of the Year. In 2021, I was inducted into the FAU Chapter of the National Academy of Inventors (NAI).

18. My professorial responsibilities include the scientific oversight of a team of doctoral and postdoctoral students (usually 3–6) and other researchers. I teach undergraduate and doctoral level courses in the area of organic synthesis with an emphasis on medicinally relevant compounds.

19. I have been continuously funded by the National Institutes of Health (NIH) as a Principal Investigator for 21 years primarily to develop organic chemistry reactions and apply them to the synthesis of therapeutically valuable compounds.

One of these funded projects was to utilize the unique reactivity of allenes for the synthesis of bridged bicyclic compounds as potent neuroprotective agents against oxidative stress.

20. My most recent NIH funded efforts have been towards the development of antiseizure agents, which have resulted in three patents and one Patent application at FAU. One of my patents is currently being licensed by the biotech company Prolindox.

21. I served as a Scientific Advisory Board Member for CHS Pharma and as a subcontractor in their drug discovery effort for nearly 5 years. I have served as a consultant to several biotech and pharmaceutical companies.

22. Since 2017, I have been an Associate Editor for Letters in Organic Chemistry (“LOC”), an international, peer reviewed journal. While LOC publishes papers in several areas of organic chemistry, my editorial duties mainly involve the oversight of peer reviews and final publication decisions on works related to synthetic and medicinal chemistry. In addition to serving as a long-time and consistent reviewer of manuscripts for many of the pinnacle journals in my field (including the Journal of American Chemical Society and Organic Letters), I have also been a high frequency reviewer for the European Journal of Medicinal Chemistry earning a “top-tenth percentile reviewer” status.

23. I am the author of 34 peer-reviewed journal articles as an independent investigator for which I am the corresponding author in nearly all cases. In addition to numerous conference presentations, I have been invited to present my work throughout the United States and internationally. In 2015, I completed a sabbatical at the University of Rome (La Sapienza) as a Visiting Professor.

24. I have based my opinions in this case on over 25 years of experience in the organic and medicinal chemistry fields, on the specification and file histories of the 354 Patent, and on the materials listed in this report. I reserve the right to supplement my analysis and opinions based on any additional argument or information that comes to my attention.

25. I am being compensated for my time at the rate of \$550 per hour. My compensation is not contingent on the outcome of this IPR.

26. The opinions expressed in this declaration are based on my personal knowledge and experience in the field of chemistry. I have also reviewed the Patents-in-Suit and the materials cited in this declaration.

III. LEVEL OF ORDINARY SKILL IN THE ART

27. I understand there are multiple factors relevant to determining the level of ordinary skill in the pertinent art, including (1) the levels of education and experience of persons working in the field at the time of the invention; (2) the

sophistication of the technology; (3) the types of problems encountered in the field; and (4) the prior art solutions to those problems.

28. A Person of Ordinary Skill in the Art (“POSITA”) in September 2016 would have had a working knowledge of pharmacology and organic chemistry art that is pertinent to the 354 Patent. A POSITA would have had a Ph.D. in a field such as chemistry, biochemistry, medicinal chemistry, organic chemistry, analytical chemistry, pharmaceutical chemistry, pharmaceuticals, or the like. Alternatively, a POSITA would have had an M.S. or Bachelor’s Degree and several years of relevant experience in the research, development, and characterization of a pharmaceutical compound or an organic compound.

29. For purposes of this Declaration, in general, and unless otherwise noted, my statements and opinions, such as those regarding my own experience and what a POSITA would have understood or known generally (and specifically related to the references I consulted herein), reflect the knowledge that existed in the relevant field as of the priority date of the 354 Patent.

IV. RELEVANT LEGAL STANDARDS

30. I am not an attorney. In preparing and expressing my opinions and considering the subject matter of the 354 Patent, I am relying on certain basic legal principles that counsel has explained to me.

31. I understand that prior art to the 354 Patent includes patents and printed publications in the relevant art that predate the priority date of the 354 Patent. For purposes of this Declaration, I am applying September 6, 2016, as the priority date of the 354 Patent, but I take no position on that issue. I have been informed by counsel that SK Biopharmaceutics Co., Ltd., and Axsome Malta Ltd., are Patent Owners.

32. I have also been informed by counsel that a claimed invention is invalid if it is “anticipated” by the prior art. I understand that, for a Patent claim to be “anticipated” by the prior art, each and every requirement of the claim must be found, expressly or inherently, in a single prior art reference as recited in the claim. I understand that claim limitations that are not expressly described in a prior art reference may still be there if they are “inherent” to the thing or process being described in the prior art.

33. I understand that if a reference incorporates other documents by reference, the incorporating reference and the incorporated reference(s) should be treated as a single prior art reference for purposes of analyzing anticipation.

34. I understand that it is acceptable to consider evidence other than the information in a particular prior art document to determine if a feature is necessarily present in or inherently described by that reference.

35. I have been informed by counsel that a claimed invention is unpatentable under 35 U.S.C. § 103 if the differences between the claimed invention and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a POSITA. I have also been informed by counsel that the obviousness analysis considers factual inquiries, including the level of ordinary skill in the art, the scope and content of the prior art, and the differences between the prior art and the claimed subject matter.

36. I have been further informed by counsel that there are several recognized rationales for combining references or modifying a reference to show obviousness. These rationales include: (a) combining prior art elements according to known methods to yield predictable results; (b) simple substitution of one known element for another to obtain predictable results; (c) use of a known technique to improve a similar device (method, or product) in the same way; (d) applying a known technique to a known device (method, or product) ready for improvement to yield predictable results; (e) choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; and (f) some teaching, suggestion, or motivation in the prior art that would have led a POSITA to modify the prior art or to combine prior art teachings to arrive at the claimed invention.

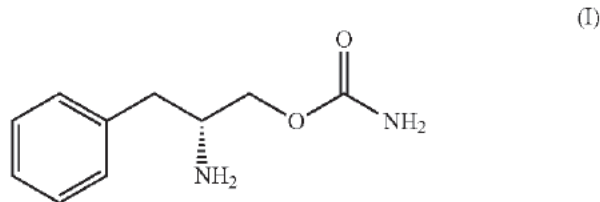
V. OVERVIEW OF THE 354 PATENT

37. The 354 Patent states that it is “a continuation of U.S. Patent application Ser. No. 16/331,069, filed Mar. 6, 2019, now U.S. Pat. No. 10,829,443,” and is entitled “Compositions Comprising (R)-2-amino-3-phenylpropyl carbamate and Uses Thereof.” 354 Patent, 1:7–9. The 354 Patent states it claims the priority benefit of U.S. Provisional Patent Application No. 62/383,822 filed Sep. 6, 2016.” 354 Patent, 1:12–15. I have been asked to assume that **September 6, 2016**, is the effective filing date, but I take no position on that issue.

38. I have reviewed the file history of the 354 Patent, including that of U.S. Patent No. 10,829,443, to which the 354 Patent claims priority.

39. U.S. Patent No. 11,560,354 (“the 354 Patent”) is generally directed to (R)-2-amino-3-phenylpropyl carbamate (APC) (see formula 1 below) in its hydrochloride salt form: “(R)-2-amino-3-phenylpropyl carbamate (APC) hydrochloride¹⁰, a method of preparing APC hydrochloride, and methods of using the same to treat disorders.” Ex. 1001, Abstract.

¹⁰ “(R)-2-amino-3-phenylpropyl carbamate (APC) hydrochloride,” “O-Carbamoyl-(D)-phenylalaninol hydrochloride,” “solriamfetol hydrochloride,” and “solriamfetol HCl” all refer to the same compound. As such, these terms are used interchangeably herein.



Ex. 1001, 4:40-50.

40. Methods of using the APC to treat disorders “include, without limitation, narcolepsy, cataplexy, excessive daytime sleepiness, drug addiction, sexual dysfunction, fatigue, fibromyalgia, attention deficit/hyperactivity disorder, restless legs syndrome, depression, bipolar disorder, or obesity.” Ex. 1001, 4:1–5. Further, “one aspect of the invention relates to an improved method of preparing APC hydrochloride in which contamination with 2-chloropropane is minimized. With this improved method, the level of 2-chloropropane in the final product may be less than about 10 ppm.” Ex 1001, 6:40–44. “[T]he method comprising crystallizing APC in the presence of aqueous HCl, thereby producing crystals of APC hydrochloride. The crystallization may be carried out with the free base of APC in a suitable solvent, e.g., isopropanol.” Ex. 1001, 6:48–52.

41. Initially, while the 354 Patent describes that 2-CP may be generated during the solriamfetol HCl manufacturing process, it contains no guidance on how to achieve a level “*less than about 5 ppm*” and “*less than about 1 ppm*” as required in claims 1 and 2. At best, the 354 Patent states that the level of 2-CP is

“preferentially at a level of no more than 5 ppm.” Ex. 1001 at 11:7–9. In describing its process that results in the generation of 2-CP, the 354 Patent states:

During the development of manufacturing processes for APC, it was found that unacceptable levels of the impurity 2-chloropropane (i.e., isopropyl chloride) could appear during the crystallization of APC hydrochloride. It is desirable to minimize 2-chloropropane as it is a potential genotoxic impurity. Thus, one aspect of the invention relates to an improved method of preparing APC hydrochloride in which contamination with 2-chloropropane is minimized.

Ex. 1001, 6:35–42.

42. Additionally, while the 354 Patent mentions achieving zero and non-zero 2-CP levels in multiple passages, there is no description of a technique to determine such levels, *e.g.*, the 354 Patent does not specify any limits of detection (LOD). In one instance, the 354 Patent describes a method in which “[n]o 2-CP was detected.” Ex. 1001, 12:15-16. Using this statement, for example, if the LOD had been 20ppm, then “[n]o 2-CP was detected” would mean 2-CP levels anywhere between 0 and 19ppm. The 354 Patent further discloses that in two additional batches made with the same process, “2-CP levels in the product were less than 1 ppm.” Ex. 1001, 12:17–19. “Less than” 1 ppm includes zero, and again there appears to be no positive indication that there was any 2-CP at all in the two batches described in the 354 Patent. Ex. 1001, 12:17–19.

43. In addition, the 354 Patent does not teach or suggest a method for measuring 2-CP with any particularity that would allow a POSITA to determine the lower end of the claimed range. For example, the 354 Patent does not specify any analytical parameters such as limit of detection (LOD) and limit of quantification (LOQ). A POSITA would have understood that different techniques for quantifying impurities have different limits of detection. The limited description in the 354 Patent does not describe a composition that comprises a non-zero amount of 2-CP less than about 5 ppm, *e.g.*, 0.1 to 5 ppm of 2-CP as well as ranges of 2-CP that are present but below the limit of detection.

VI. CLAIM CONSTRUCTION

44. It is my understanding that in order to properly evaluate the 354 Patent, the terms of the claims must first be interpreted. It is my understanding that for the purposes of this *inter partes* review, the claims are to be construed under the so-called *Phillips* standard, under which claim terms are given their ordinary and customary meaning as would have been understood by a POSITA in light of the specification and prosecution history, unless the inventor has set forth a special meaning for a term. I have also been informed that claim terms only need to be construed to the extent necessary to resolve the unpatentability inquiry.

VII. IDENTIFICATION OF HOW THE CLAIMS ARE UNPATENTABLE

45. The discussion in this Declaration provides a detailed analysis of how the asserted prior art teaches each limitation of the Challenged Claims.

46. As part of my analysis, I have considered, and discuss in detail, the scope and content of the prior art and any differences between the alleged invention and the prior art.

47. It is my opinion that the alleged invention recited in the Challenged Claims would have been obvious in view of the teachings of the asserted prior art and the knowledge of a POSITA.

VIII. THE PRINCIPAL PRIOR ART

A. Summary of Choi268

48. U.S. Patent Publication No. 2005/0080268 to Choi et al. (Ex. 1006) was filed on October 3, 2003, and published on April 14, 2005.

49. As a preliminary matter, Choi268 was cited in an Information Disclosure Statement, which was considered by the Examiner. *See* Ex. 1001, Cover; *see also* Ex. 1002, 43, 683.

50. Choi268 is generally directed to a method of preparing solriamfetol HCl using HCl and isopropanol, illustrated in Example 1. *See* Ex. 1006, [0068]–[0069]. Specifically, Choi268 discloses the preparation of Preparation of O-Carbamoyl-(D)-phenylalaninol free base (i.e., solriamfetol), and also the hydrochloride salt form (i.e., solriamfetol hydrochloride):

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.

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 (1/2, v/v), and dried in vacuo. The product Carbamoyl-(D)-phenylalaninol hydrochloride weighed 110 gram (71.5%) and was a white solid.

Ex. 1006, [0068]–[0069]; *see also* Ex. 1006, Example 6 (disclosing the synthesis process of O-Carbamoyl-(D)-phenylalaninol on large-scale industrial preparation).

B. Summary of Kaleemullah

51. Kaleemullah is a journal article published as: *Development and Validation of Gas Chromatography Method for Low Level Detection of Residual Methyl Chloride, Ethyl Chloride and Isopropyl Chloride in Ziprasidone Hydrochloride* (Ex.1016).

52. Kaleemullah discloses a sensitive analytical technique to detect residual methyl chloride, ethyl chloride and isopropyl chloride present in a drug substance, ziprasidone hydrochloride. Ex. 1016, Abstract. The analytical technique developed in Kaleemullah is a headspace gas chromatographic (GC) method with a flame ionization detector. Ex. 1016, 391.

53. Kaleemullah teaches a method to detect isopropyl chloride (2-CP) that may be produced when a drug containing an amine base moiety "is treated with hydrochloric acid leading to a precipitate" as a hydrochloride salt. Ex. 1016, 391.

54. Kaleemullah discloses that its method is capable of detecting 2-CP at levels as low as 0.93 ppm. Ex. 1016, 395 and Table 2. Kaleemullah explains

“methyl chloride, ethyl chloride and isopropyl chloride are reported as carcinogen and methyl chloride as teratogen. Therefore, it is necessary that, these residual impurities should be controlled to limits permitted by threshold of toxicological concern (TTC).” Ex. 1016, 391. For example, Kaleemullah states that its estimated TTC value was “1.5µg/person/day intake of a genotoxic impurity.” Ex. 1016, 391. Kaleemullah explains that 1.5µg/person/day intake of a genotoxic impurity as “an acceptable risk for most pharmaceuticals as per EMEA guideline on the limit of genotoxic impurities [CPMP/SWP/5199/02, EMEA/CHMP/QWP/251344/2006] as well as risk assessment literature.” Ex. 1016, 391.

C. Summary of Ahnaou

55. U.S. Publication No. 2009/0312416 to Ahnaou et al. (Ex.1005) was filed as International Application No. PCT/US06/22407, published as WO 2006133393, and subsequently published on December 17, 2009, as U.S. Pub. No. 2009/0312416.

56. Ahnaou is generally directed to a method of treating Excessive Daytime Sleepiness (EDS) where 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-aminobenzenepropyl) 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.”

Ex. 1005, [0028].

57. Ahnaou discloses that “an enantiomer of Formula Ib (R)-(betaamino-benzenepropyl) carbamate or (O-carbamoyl-(D)-phenylalaninol) predominates to the extent of about 98% or greater.” Ex. 1005, [0029].

58. Ahnaou further discloses that “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.” Ex. 1005, [0030]. Ahnaou teaches that “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.” Ex. 1005, [0067]. “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.” Ex. 1005, [0074].

59. Moreover, Ahnaou discloses that “[t]he 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.” Ex. 1005, [0055].

IX. GROUND 1: CHOI268, KALEEMULLAH, AND AHNAOU RENDER OBVIOUS CLAIMS 1-8

A. The Combination of Choi268, Kaleemullah, and Ahnaou

60. Choi268 does not expressly disclose the formation of “2-chloropropane” (“2-CP”) during the synthesis of solriamfetol hydrochloride (using both HCl and isopropanol as reagents during salt precipitation). However, a POSITA would have recognized that based on Choi268’s method of preparation, “2-chloropropane” (alternatively isopropyl chloride) would be formed, in view of Kaleemullah’s disclosure that treating ziprasidone base “in alcohol solvent (Methanol, Ethanol, or Isopropanol) . . . with hydrochloric acid” results in the formation of “[i]sopropyl chloride.” Thus, Kaleemullah’s express disclosure of the formation of “2-chloropropane” during salt precipitation with HCl and isopropanol would inform a POSITA that “2-chloropropane” would be formed in Choi268’s method of preparing solriamfetol hydrochloride.

61. Choi268 and Kaleemullah are analogous art to the 354 Patent because each is in the field of pharmaceutical chemistry. Indeed, similar to the 354 Patent,

Choi268 discloses methods of preparing solriamfetol hydrochloride, and more specifically, salt precipitation with HCl and isopropanol. Kaleemullah teaches that such use of precipitation treatment to synthesize a hydrochloric salt form of an active ingredient can result in the formation of 2-CP—the same impurity that the 354 Patent claims are directed to. In short, both Choi268 and Kaleemullah are applicable to drug substances, and are thus analogous art to the 354 Patent. Ex.1006, [0001]–[0002], [0069]; Ex. 1016, Abstract and 390–91. Moreover, both Choi268 and Kaleemullah teach use of HCl and isopropanol to form the hydrochloric salt of an active ingredient. Specifically, Choi268 discloses preparing O-Carbamoyl-(D)-phenylalaninol hydrochloride by dissolving O-Carbamoyl-(D)-phenylalaninol in isopropanol and charging the resulting mixture with “HCl solution in isopropanol.” Ex. 1006, [0069]. Kaleemullah teaches a method for detecting “residual” amounts of isopropyl chloride (2-CP) that may be produced when a drug containing an amine base moiety “is treated with hydrochloric acid leading to [a] precipitate” of the hydrochloride salt form. Ex. 1016, 391. For example, Kaleemullah describes that as a result of treating ziprasidone base “in alcohol solvent (Methanol, Ethanol, or Isopropanol) . . . with hydrochloric acid,” “[i]sopropyl chloride may form at the salt formation step.” Ex. 1016, 391. Moreover, similar to Kaleemullah’s ziprasidone, Choi268’s solriamfetol possesses a basic amine unit that can be converted to hydrochloride salt.

62. Moreover, the teachings of Choi268 and Kaleemullah are reasonably pertinent to the purported problem that was solved by the inventors of the 354 Patent. In particular, the 354 Patent states that the claimed invention “overcomes shortcomings in the art by providing . . . a method of preparing APC [solriamfetol] with minimal contaminants.” Ex. 1001, 1:42–44. As discussed above, Choi268 provides a “novel process” for synthesizing solriamfetol hydrochloride. Ex. 1006, [0001]. Kaleemullah discloses that the salt precipitation process used in Choi268 can result in the formation of genotoxic impurities (e.g., 2-CP), which should be minimized, at the very least, to a “threshold of toxicological concern.” Ex. 1006, 391. Accordingly, it would have been obvious to a POSITA that the process of synthesizing solriamfetol hydrochloride described in Choi268 as modified by Kaleemullah’s teachings of the formation and detection of “2-chloropropane” addresses the problem of preparing a drug substance that has minimal impurities.

63. Based on the teachings of Kaleemullah, Choi268’s method of preparing O-Carbamoyl-(D)-phenylalaninol hydrochloride for use in a pharmaceutical composition would be modified to additionally include Kaleemullah’s teachings of a method of detecting 2-CP in Choi268’s method of preparation of O-Carbamoyl-(D)-phenylalaninol hydrochloride. Ex. 1016, Table 2; *see also* Ex. 1016, 391–93 (describing details of Kaleemullah’s method of detecting 2-CP). In particular, Kaleemullah discloses that its analytical method (a headspace gas chromatography

technique), which is validated according to ICH guidelines, is capable of detecting 2-CP at levels as low as 0.93 ppm. Ex. 1016, Table 2 and 393. A POSITA would have been motivated to make the combination based the teachings of Kaleemullah since Kaleemullah is concerned with the levels of “2-chloropropane” that are formed during the salt precipitation process, and further emphasizes the importance controlling the levels of genotoxic impurities, including 2-CP. For example, Kaleemullah states that “methyl chloride, ethyl chloride and isopropyl chloride are reported as carcinogen and methyl chloride as teratogen. Therefore, it is necessary that, these residual impurities should be controlled to limits permitted by threshold of toxicological concern (TTC).” Ex. 1016, 393. Kaleemullah further discloses that, as of the priority date, the estimated TTC value was “1.5µg/person/day intake of a genotoxic impurity,” e.g., 2-CP. Ex. 1016, 391. Kaleemullah explains that a 1.5µg/person/day intake of a genotoxic impurity is “an acceptable risk for most pharmaceuticals as per EMEA guideline on the limit of genotoxic impurities [CPMP/SWP/5199/02, EMEA/CHMP/QWP/251344/2006] as well as risk assessment literature.” Ex. 1016, 391. A POSITA would have understood that 1.5µg/day translates to 1.5ppm per day, assuming¹¹ a daily dose of 1.0g of the API. Additionally, Callis, which reflects the knowledge of a POSITA, describes that the

¹¹ It was within the knowledge of a POSITA to assume a daily dose of 1.0g of API for conservatively determining genotoxic impurity (GTI) limits. See Ex. 1017, Table 2, footnote d.

“daily chronic limit” of “isopropyl chloride” (“*2-chloropropane*”) is “1.5ppm.” Ex. 1017, Table 2.

64. A POSITA would have recognized that Choi268’s method of preparing a drug substance (e.g., O-Carbamoyl-(D)-phenylalaninol hydrochloride) would be modified to include a method of detecting 2-CP, and a POSITA would have been motivated to do so, based on other teachings in the prior art that reflect a POSITA’s knowledge regarding the presence of genotoxic impurities (e.g., 2-CP) in drug substances, and the common concern to limit the daily intake of such impurities or otherwise reduce the level of such impurities in the composition of a drug substance. For example, Liu explains that “[g]enotoxic impurities (GTIs) in pharmaceuticals at trace levels are of increasing concerns to both pharmaceutical industries and regulatory agencies due to their potentials for human carcinogenesis. Determination of these impurities at ppm levels requires highly sensitive analytical methodologies ... in pharmaceutical R&D.” Ex. 1014, Abstract. As another example, Cimarosti recognizes the need for “developing and validating methods to measure trace levels of genotoxic impurities.” Ex. 1015, 993. As yet another example, Kim, reflecting the knowledge of a POSITA, highlights its concern for reducing 2-CP levels to “trace amounts.” 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.” Ex. 1007, 422. Consistent with these teachings, a POSITA would have understood the increased concern to limit genotoxic impurities in drug substances. In addition, a POSITA would have understood the need to reduce genotoxin levels in drug substances to limits even lower than toxicology-based requirements (e.g., lower than 1.5µg/person/day) in view of the EMEA guidelines cited in Kaleemullah and which disclose the—“as low as reasonably practicable” (ALARP principle)—for genotoxic impurities (such as 2-CP). Ex. 1018, 5. Thus, the EMEA guidelines, reflect the POSITA’s understanding that the levels of genotoxic impurities (such as 2-CP) in a drug substance should be limited as much as possible and provide the motivation to combine Choi268 and Kaleemullah such that the method of preparing solrimafetol hydrochloride, as described in Choi268 to additionally include Kaleemullah’s teachings of method of detecting 2-CP in the solrimafetol hydrochloride drug substance prepared using Choi268’s method. Furthermore, Callis, reflecting the knowledge of a POSITA, emphasizes the importance of the ALARP principle. “Consideration of the ALARP principle (as low as reasonably practicable) for impurities may achieve tighter control than toxicology-based limits require.” Ex. 1017, 986. “GTI control typically must be demonstrated at very low (ppm) levels in the API or synthetic intermediates.” Ex. 1017, 986. As such, Callis teaches that, “[w]hen considering potential risk to the patient, genotoxic impurities must often be controlled to much lower levels than required by the ICH Q3A(R2)

guideline for non-GTIs.” Ex. 1017, 990. These prior art references reflect the POSITA’s understanding of the concern to reduce genotoxin levels in drug substances to limits even lower than toxicology-based requirements. Accordingly, a POSITA would be motivated to combine Choi268 and Kaleemullah for at least these reasons.

65. Moreover, modifying Choi268’s method to additionally include a method of detecting 2-CP, as taught in Kaleemullah, would be a simple substitution well within the skill of a POSITA because it would only entail adding an extra analytical step to Choi268’s method. In particular, Kaleemullah’s method is an analytical technique that uses headspace gas chromatography to detect 2-CP levels in a drug substance (*see* Ex. 1016, Abstract), and Choi268 describes a method of synthesizing a drug substance (*see* Ex. 1006, Abstract). For example, in Choi268’s method, after the O-Carbamoyl-(D)-phenylalaninol hydrochloride product is “washed thoroughly with ice-chilled isopropanol-acetone and dried in vacuo” (Ex. 1006, [0069]), Kaleemullah’s “gas chromatographic methods ... for the quantitative determination of residual . . . Isopropyl chloride” (Ex. 1016, 391) can be implemented. A POSITA would recognize Table 1 of Kaleemullah teaches the gas chromatography conditions used in the proposed modification. Indeed, Choi268 contemplates “modifications in the practice of [its] invention.” Ex. 1006, [0077]. Choi268 states that the modifications “can be readily made by, those skilled in the

art without departing from the scope of the invention described above.” Ex. 1006, [0077]. “Those skilled in the art will recognize that the invention covers all alternatives, modifications and equivalents as may be included within the scope of the appended claims.” Ex. 1006, [0067]. Therefore, a POSITA would have understood that modifying Choi268’s method of preparing the drug substance to additionally Kaleemullah’s teachings of an analytical technique would not render Choi268’s method inoperative for its intended purpose. In fact, including Kaleemullah’s method of detecting 2-CP in Choi268’s method of preparing the drug substance would allow detection of impurities in the final drug substance, thereby leading to an improvement—a resulting drug substance with minimal impurities.

66. Although Kaleemullah discloses use of its analytical method in connection with an exemplary drug ziprasidone hydrochloride, its method has wider applicability to other drug substances, including *e.g.*, solrimafetol hydrochloride. Ex. 1016, 391–93. For example, Kaleemullah states that its method of detecting isopropyl chloride “has been applied to various drug substances,” and further discloses that it “was validated as per the ICH guideline . . . for specificity, limit of detection, limit of quantification, linearity, accuracy, precision and robustness.” Ex. 1016, 399, 393. Kaleemullah also elaborates upon details of evaluating the “accuracy” and “robustness” of its disclosed method. Ex. 1016, 396–97. As such, a POSITA would have understood that the method of detecting 2-CP as disclosed in

Kaleemullah is applicable to detecting 2-CP in other drug substances, e.g., solriamfetol hydrochloride. Indeed, Kaleemullah's results of various validation parameters confirmed that the method is "specific, robust, linear, precise and accurate" and as Kaleemullah discloses, is advantageously capable of detecting 2-CP at levels as low as 0.93 ppm. Ex. 1016, Table 2. Therefore, in modifying Choi268's method of preparing O-Carbamoyl-(D)-phenylalaninol hydrochloride based on the teachings in Kaleemullah of a method of detecting 2-CP in "*the composition*," a POSITA would have had a reasonable expectation of success in view of the afore-mentioned teachings of Kaleemullah.

67. A POSITA would have been further motivated to combine Choi268 and Kaleemullah (i.e., modify Choi268's method of preparing solriamfetol hydrochloride to include the teachings of Kaleemullah's related to the detection of 2-CP formed in the drug substance) because to do so would have been the arrangement of old elements (a process for preparing O-carbamoyl aminoalcohols using HCl and isopropanol and gas chromatography (GC) with a flame ionization detector) with each performing the same function it has been known to perform (chemical reactions and impurity detection) and yielding no more than what one would expect from such an arrangement (an improved method of preparing a drug substance based on detecting impurities in the drug substance), as Kaleemullah demonstrates. Indeed, Kaleemullah teaches several advantages of its method of

detecting 2-CP: “The developed gas chromatographic method has to evaluate reliable and economical result for the simultaneous determination of Methyl chloride, Ethyl chloride and Isopropyl chloride residue. . . . The results of various validation parameters confirmed that the method is specific, robust, linear, precise, and accurate. The method has been applied to various drug substances containing possible alkyl chloride moiety in the drug matrix. The experimental data shows that the method has potential application for the quantitative determination of alkyl chloride moiety present in the drug substances.” Ex. 1016, 399.

68. In addition, a POSITA would have had a reasonable expectation of success of arriving at a solriamfetol hydrochloride composition comprising “*less than about 5 ppm*” of 2-CP because it would have required only routine experimentation to optimize the salt formation process described in Choi268 to minimize the level of genotoxic impurities (e.g., 2-CP) present in the drug substance. Indeed, Choi268 teaches that “various other embodiments and modifications in the practice of the invention,” such as the synthesis described in Example 1, “will be apparent to, and can be readily made by, those skilled in the art.” Ex. 1006, [0077]. It would have been within the skill of a POSITA to adjust, for example, the reagents and reaction temperatures to arrive at a lower yield of 2-CP. *See, e.g.*, Ex. 1019, 789 (disclosing that “[f]or salt formation from methanolic solutions the critical parameters were using 37% aq HCl and maintaining the slurry at 10 °C during the

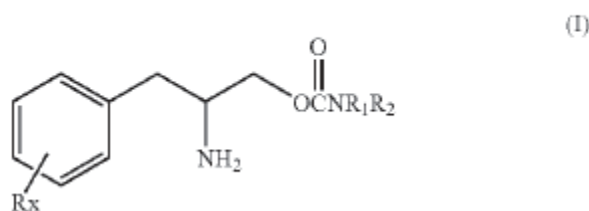
HCl addition,” which was able to reduce genotoxic impurities down to 1ppm); *see also* Ex. 1007, 41 (disclosing that “avoiding strongly acidic conditions and prolonged exposure of acids to an alcohol at a higher temperature and incorporating water into the [salt formation] process when possible would reduce the chances of formation of [] genotoxins”).

69. As demonstrated above, a POSITA would be motivated to combine Choi268 and Kaleemullah, with a reasonable expectation of success. Such a person would have been further motivated to combine Choi268 and Kaleemullah based on the teachings of Ahnaou, as explained below. While Choi268 and Kaleemullah do not expressly disclose how to prepare “[a] composition” using “(R)-2-amino-3-phenylpropyl carbamate hydrochloride,” it would have been obvious in view of Ahnaou. *See* Ex. 1005, [0068]. Ahnaou explains how to prepare “[a] composition.” Specifically, Ahnaou teaches that “[t]o prepare the pharmaceutical compositions of this invention, one or more compounds of formula (I) or salt thereof as the active ingredient,” such as solriamfetol hydrochloride, “is intimately admixed with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques.” Ex. 1005, [0068]. As discussed above, Choi268 provides that solriamfetol hydrochloride is a “pharmaceutically useful compound[]” that is “being developed for the treatment of central nervous system (CNS) disorders, particularly as antidepressants.” Ex. 1006, [0002]. Accordingly, a POSITA would have

understood that the product O-Carbamoyl-(D)-phenylalaninol hydrochloride of Choi268 can be “intimately admixed with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques,” as taught in Ahnaou, to prepare the “*composition*.” Ex. 1005, [0068]. Further, in view of Kaleemullah’s teachings of an analytical method for detecting “residual” amounts of 2-CP that would form in the process for synthesizing solriamfetol hydrochloride taught in Choi268, the Choi268/Ahnaou combination would be additionally modified to include Kaleemullah’s method of detecting 2-CP. As such, it would have been obvious to a POSITA that the resulting “pharmaceutical composition[]” prepared according to the combined teachings of Choi268/Ahnaou/Kaleemullah can be administered to patients for the treatment of neurological disorders such as narcolepsy, with a reasonable expectation of success, based on the methods disclosed in Ahnaou (*see* Ex. 1005, [0024], [0068]). Moreover, Choi268, Kaleemullah and Ahnaou commonly disclose pharmaceutical salt forms of active ingredients. Ex. 1006, [0068]–[0069]; Ex. 1016, 390–91; Ex. 1005, [0024].

70. Moreover, Ahnaou is analogous art to the 354 Patent because it similarly relates to the “fields of pharmacology, neurology and psychiatry,” and provides “methods for the use of certain carbamate compounds,” including solriamfetol hydrochloride, “for the treatment of sleep-wake disorders including excessive daytime sleepiness and pathological somnolence.” Ex. 1005, [0002]. For

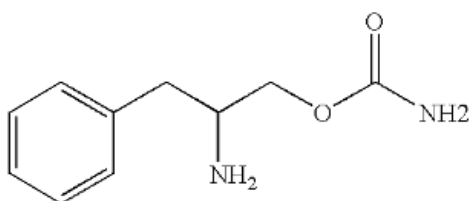
these same reasons, Ahnaou is also reasonably pertinent to the purported problem addressed by the 354 Patent, i.e., “the use of . . . the APC [solriamfetol] with increased purity for the treatment of disorders responsive to APC.” Ex. 1001, 1:51–54. Ahnaou discloses a “method of treating sleep disorders in a subject, including excessive daytime sleepiness (EDS) or pathological somnolence, comprising administering to a subject in need of such treatment, a therapeutically effective amount of a compound of the Formula (I) . . . or a pharmaceutically acceptable salt or ester thereof,” which includes solriamfetol hydrochloride. Ex. 1005, [0024]. Formula I in Ahnaou is reproduced below:



Ex. 1005, [0024]. Ahnaou further explains that “[e]mbodiments 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-aminobenzenepropyl) carbamate or (O-carbamoyl-(D)-phenylalaninol) or an enantiomeric mixture wherein the enantiomer of Formula Ib (R)-(beta-aminobenzenepropyl) carbamate or (O-carbamoyl-(D)-phenylalaninol) predominates.” Ex. 1005, [0028]. In other words, Ahnaou teaches O-carbamoyl-(D)-phenylalaninol

(i.e., Formula Ib, which is reproduced below) as a specific embodiment of a compound of Formula I that can be used in the methods and compositions disclosed therein. As noted above, O-carbomoyl-(D)-phenylalaninol is solriamfetol hydrochloride—the same compound disclosed in Choi268 and claimed in the composition of the 354 Patent.

Formula Ib



Ex. 1005, [0028].

71. A POSITA would have been motivated to combine the teachings of Choi268 and Kaleemullah to additionally include Ahnaou because of Ahnaou's teachings related to administering "*the composition*" to a subject. For example, Ahnaou discloses "*a dosage form*." "Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. . . . The tablets or pills can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pills can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former." Ex. 1005, [0070]. "[F]or 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.” Ex. 1005, [0066]. Accordingly, a POSITA would have been motivated to modify Choi268’s method of preparing solriamfetol hydrochloride to include the teachings of Kaleemullah’s related to the detection of 2-CP, and additionally modified to include the teachings of Ahnaou related to administering “*the composition*.” Moreover, a POSITA would have been motivated to combine the teachings of Choi268 and Kaleemullah to additionally include the teachings of the Ahnaou because of the beneficial effects of using (R)-(beta-amino-benzenepropyl) carbamate in effective reduction of sleepiness, as taught in Ahnaou. For example, Ahanou’s study indicates “significant enhancement of active wakefulness . . . observed during the first 3 hours following the administration of TEST COMPOUND.” Ex. 1005, [0137]; *see also* Ex. 1005, [0133]–[0138] (describing significant changes in the distribution of sleep-wake states upon administration of its TEST COMPOUND). Accordingly, in view of the therapeutic benefits of the compound demonstrated in Ahnaou’s tests in treating medical disorders (e.g., excessive daytime sleepiness), a POSITA would have had a reasonable expectation of success in modifying Choi268’s method of preparation of “(R)-2-amino-3-phenylpropyl carbamate hydrochloride,” as modified by Kaleemullah’s teachings of the formation and detection of “2-chloropropane,” to additionally include Ahnaou’s

teachings related to preparing and administering “*the composition*” comprising “(R)-2-amino-3-phenylpropyl carbamate hydrochloride” and “2-chloropropane.”

72. Therefore, for the reasons explained above, a POSITA would have been motivated to modify Choi268’s method of preparing “(R)-2-amino-3-phenylpropyl carbamate hydrochloride” based on Ahnaou’s teachings of a method of preparing “[a] composition.” And, moreover, in view of Kaleemullah’s teachings of the formation and detection of “2-chloropropane,” the Choi268/Ahnaou combination would be additionally modified to include Kaleemullah’s method of detecting “2-chloropropane” resulting in “a composition” prepared according to the combined teachings of Choi268/Ahnaou/Kaleemullah.

B. Invalidity Analysis of Claims 1-8

1. Claim 1

a. [1.0] A composition comprising (R)-2-amino-3-phenylpropyl carbamate hydrochloride and

73. Choi268 and Ahnaou render obvious this element.

74. Choi268 and Ahanou disclose “[a] composition comprising (R)-2-amino-3-phenylpropyl carbamate hydrochloride.” For example, Choi268 discloses that “O-carbamoyl aminoalcohols comprise a new class of pharmaceutically useful compounds.” Ex. 1006, [0002]. In particular, Choi268 teaches that “**O-carbamoyl-(D)-phenylalaninol hydrochloride** and O-carbamoyl-(L)-3-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline hydrochloride **are being developed for treatment of**

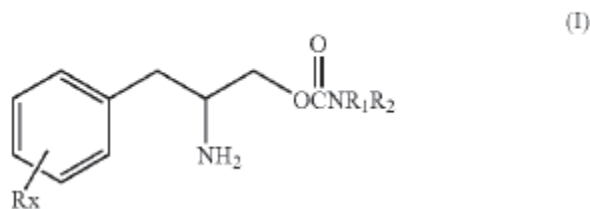
central nervous system (CNS) disorders, particularly as antidepressants.” Ex. 1006, [0002]. A POSITA would have understood from these disclosures that O-carbamoyl-(D)-phenylalaninol hydrochloride, *i.e.*, “(R)-2-amino-3-phenylpropyl carbamate hydrochloride,” can be formulated into “[a] composition” for pharmaceutical use, including for the treatment of Central Nervous System (CNS) disorders.

75. Choi268 does not expressly disclose how to prepare “[a] composition” using “(R)-2-amino-3-phenylpropyl carbamate hydrochloride.” However, Ahnaou expressly discloses how to prepare “[a] composition comprising” compounds of “formula (I) or salt thereof” as follows:

To prepare the pharmaceutical compositions of this invention, one or more compounds of formula (I) or salt thereof as the active ingredient is intimately admixed with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. Carriers are necessary and inert pharmaceutical excipients, including, but not limited to, binders, suspending agents, lubricants, flavorings, sweeteners, preservatives, dyes, and coatings. In preparing compositions in oral dosage form, any of the usual pharmaceutical carriers may be employed. For example, for liquid oral preparations, suitable carriers and additives include water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like; for solid oral preparations, suitable carriers and additives include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like.

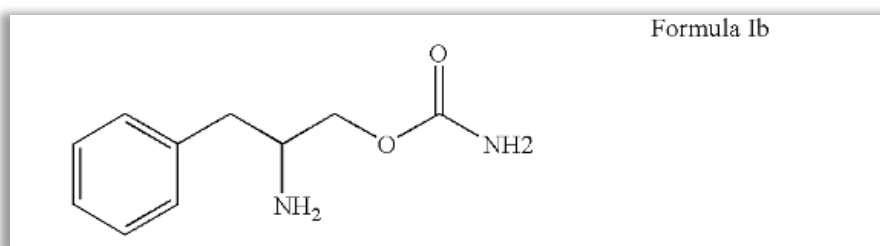
Ex. 1005, [0068].

76. Formula I in Ahnaou is reproduced below:



Ex. 1005, [0024]. Ahnaou further explains that “[e]mbodiments 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-aminobenzenepropyl) carbamate or (O-carbamoyl-(D)-phenylalaninol) or an enantiomeric mixture wherein the enantiomer of Formula Ib (R)-(beta-aminobenzenepropyl) carbamate or (O-carbamoyl-(D)-phenylalaninol) predominates.”

Ex. 1005, [0028]. In other words, Ahnaou teaches O-carbamoyl-(D)-phenylalaninol (i.e., Formula Ib, which is reproduced below) as a specific embodiment of a compound of Formula I that can be used in the methods and compositions disclosed therein. As noted above, O-carbamoyl-(D)-phenylalaninol is solriamfetol hydrochloride—the same compound disclosed in Choi268 and claimed in the composition of the 354 Patent.



Ex. 1005, [0028].

77. Therefore, a POSITA would have modified Choi268's method of preparing O-Carbamoyl-(D)-phenylalaninol hydrochloride to additionally include Ahnaou's teachings of a method of preparing "[a] *composition*" with a reasonable expectation of success. For example, such a person would have understood that the product O-Carbamoyl-(D)-phenylalaninol hydrochloride of Choi268 can be "intimately admixed with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques" to form the "*composition*." Ex. 1005, [0068]. *See* §IX.A.

78. Further, Choi268 discloses the synthesis of "(R)-2-amino-3-phenylpropyl carbamate hydrochloride." For example, Choi268 describes that O-Carbamoyl-(D)-phenylalaninol is first prepared, which is then used for the preparation of O-Carbamoyl-(D)-phenylalaninol hydrochloride ("(R)-2-amino-3-phenylpropyl carbamate hydrochloride"). More specifically, Choi268's synthesis procedure is as follows:

Preparation of O-Carbamoyl-(D)-phenylalaninol

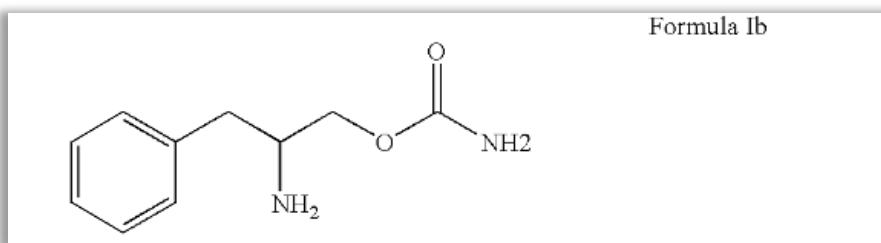
In a dry 2L three-neck round bottomed flask equipped with a mechanical stirrer, thermometer and 250 mL addition funnel, 838 mL of dichloromethane was charged followed by D-phenylalaninol (100 g, 0.66 mole) and sodium cyanate (85 g, 0.92 mole). The mixture was stirred in an ice-bath. The addition funnel 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.

Ex. 1006, [0068]–[0069] (emphasis added). Therefore, Choi268 discloses the synthesis of “(R)-2-amino-3-phenylpropyl carbamate hydrochloride.”

79. Choi268 further describes that its method of preparation is “a novel process” using a cyanate and an excess of acid in an organic medium. Ex. 1006, [0002]. Choi268 elaborates that “O-carbamoyl aminoalcohols comprise a new class of pharmaceutically useful compounds” and provides an example of using “O-carbamoyl-(D)-phenylalaninol hydrochloride and O-carbamoyl-(L)-3-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline hydrochloride” for treatment of central nervous system (CNS) disorders. Ex. 1006, [0002]. Choi268 highlights that its method of preparation is “**particularly advantageous for the preparation of O-carbamoyl-D-phenylalaninol,** O-carbamoyl-(L)-oxymethyl-1,2,3,4-tetrahydroisoquinoline, and carbamic acid 2-((4-fluorobenzoyl)piperidin-1-yl)-1-phenylethyl ester.” Ex. 1006, [0008].



80. Accordingly, Choi268 and Ahnaou render obvious “[a] composition comprising (R)-2-amino-3-phenylpropyl carbamate hydrochloride.”

b. [1.1] 2-chloropropane, wherein the composition comprises less than about 5 ppm 2-chloropropane.

81. Element [1.1] requires that “*the composition*” comprises “2-chloropropane” (alternatively termed herein as “2-CP” or “isopropyl chloride”), and specifically at a level “*less than about 5 ppm,*” *i.e.*, between 0 ppm and 5 ppm. Choi268, Kaleemullah and Ahnaou render this element obvious.

82. First, Kaleemullah discloses “2-chloropropane, . . . less than about 5 ppm 2-chloropropane.”

83. Kaleemullah discloses the formation of “2-chloropropane.” While Choi268 does not expressly disclose the formation of “2-chloropropane,” (“2-CP,” also commonly referred to in the art as isopropyl chloride), a POSITA would have understood 2-CP to form during the synthesis of solriamfetol hydrochloride as described in Example 1 of Choi268, in view of Kaleemullah.

84. For example, Kaleemullah discloses that during the synthesis of ziprasidone hydrochloride, “[i]sopropyl chloride may form at the salt formation step, as ziprasidone base in alcohol solvent (methanol, ethanol, or isopropanol) is treated with hydrochloric acid leading to precipitate of ziprasidone hydrochloride.” Ex. 1016, 391. Therefore, Kaleemullah discloses the formation of “2-chloropropane.”

85. Furthermore, similar to Kaleemullah’s ziprasidone, solriamfetol possesses a basic amine unit that can be converted to hydrochloride salt. Moreover,

the preparation of solriamfetol hydrochloride described in Choi268 likewise involves dissolving the free base form in isopropanol and treating the solution with hydrochloric acid to precipitate the HCl salt form. Ex. 1006, [0069]. A POSITA would have understood from the above-mentioned disclosures of Kaleemullah that HCl can react with isopropyl alcohol during the synthesis of solriamfetol hydrochloride described in Choi268, resulting in the formation of **isopropyl chloride** (“2-chloropropane”).

86. During prosecution, Patent Owners admitted the formation of 2-CP as a distinction to overcome the Examiner’s prior art rejection over US Patent No. 5,955,499 (“Choi499¹²”). In particular, Patent Owners distinguished from Choi499 arguing that that the prior art process of Choi499 could not have produced 2-CP, and that the claims of the 354 Patent “requires the presence of 2-CP.”

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 [Choi499].

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**

¹² Choi499 (which is referenced as “Choi” in the prosecution file history) is a different disclosure than Choi268 relied in the invalidity ground herein. *See, e.g.*, Ex. 1002, 675, 718.

as the crystallization solvent in the process of the present invention.

Ex. 1002, Amendment Dated May 12, 2022 at 3–4 (emphases added). Kaleemullah’s teachings—involving, for example, the use of HCl and isopropanol that results in the formation of **isopropyl chloride** (“*2-chloropropane*”)—are thus consistent with Patent Owners’ statement during prosecution that “2-CP is the product of the reaction between isopropanol and HCl.” Ex. 1002, Amendment Dated May 12, 2022 at 3.

87. In addition, it was well-known in the prior art that 2-CP is produced during the salt formation process of an active ingredient, e.g., during the reaction between isopropanol and HCl. For example, 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.” Ex. 1008, 168. As another example, 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.” Ex. 1009, Abstract (emphases added).

Mapping #1

88. Kaleemullah discloses “*less than about 5 ppm 2-chloropropane*.” Kaleemullah discloses the formation of “*2-chloropropane*” (see Ex. 1016, 391) as

explained above, and also describes a method of detecting it at a level “*less than about 5 ppm*” (see Ex. 1016, 391–93).

89. In view of the teachings of Kaleemullah and the knowledge of a POSITA, a POSITA would have been motivated to limit the level of 2-CP that is present in a solriamfetol hydrochloride composition to a level “*less than about 5 ppm*,” with a reasonable expectation of success. For example, Kaleemullah states that “[i]sopropyl chloride [is] reported as carcinogen” and “[t]herefore it is necessary that[] these residual impurities should be controlled to limits permitted by threshold of toxicological concern (TTC).” Ex. 1016, 391. Moreover, Kaleemullah explains that a TTC value “estimated to be 1.5µg/person/day intake of a genotoxic impurity is considered to be associated with an acceptable risk for most pharmaceuticals as per EMEA guideline on the limit of genotoxic impurities [CPMP/SWP/5199/02, EMEA/CHMP/QWP/251344/2006] as well as risk assessment literature.” Ex. 1016, 391.

90. The EMEA guidelines cited in Kaleemullah (*i.e.*, CPMP/SWP/5199/02, EMEA/CHMP/QWP/251344/2006) (submitted herein as Ex. 1018) provide additional reasons explaining why genotoxic impurities in drug substances should be limited to a value of 1.5µg/day. In particular, the guidelines (published in 2006) specify that “for application of a TTC in the assessment of **acceptable limits of genotoxic impurities in drug substances [at] a value of 1.5 µg/day corresponding**

to a 10^{-5} lifetime risk of cancer can be justified as for pharmaceuticals a benefit exists.” Ex. 1018, 6. These guidelines also explain that “under certain conditions” TTC values higher than $1.5 \mu\text{g/day}$ may be acceptable,” such as “short-term exposure, for treatment of a life-threatening condition, when life expectancy is less than 5 years, or where the impurity is a known substance and human exposure will be much greater from other sources (e.g. food)” —none of which would apply to 2-CP or solriamfetol hydrochloride. Ex. 1018, 6. In particular, a POSITA would have known that solriamfetol hydrochloride is a therapeutic agent and not a curative, making it an active substance for long-term applications. Indeed, Ahnaou discloses that solriamfetol hydrochloride can be used for the treatment of “sleep disorders” such as narcolepsy, which “is a chronic disorder” and “requires long-term management of symptoms.” Ex. 1005, [0009], [0020], [0023], [0024]. Therefore, a POSITA would have understood from these disclosures that $1.5\mu\text{g/day}$ is the upper limit in terms of the level of genotoxic impurities present in a drug composition. In other words, a POSITA would have known, based on the teachings of Kaleemullah (including the cited references), that it would have been desirable to control the limit of genotoxic impurities (e.g., 2-CP) to less than $1.5\mu\text{g/day}$.

91. A POSITA would have further understood that a limit of $1.5\mu\text{g/person/day}$ translates to “*less than about 5 ppm.*” For example, the EMEA guidelines (cited in Kaleemullah) disclose a mathematical formula for translating

TTC (expressed in µg/day) to a concentration limit (expressed in ppm). Ex. 1018 describes that:

The concentration limits in ppm of genotoxic impurity in drug substance derived from the TTC can be calculated based on the expected daily dose to the patient using equation (1).

$$(1) \text{ Concentration limit (ppm)} = \frac{\text{TTC } [\mu\text{g/day}]}{\text{dose (g/day)}}$$

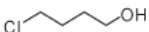
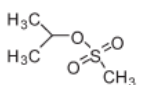
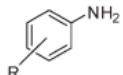
Ex. 1018, 6. Therefore, a POSITA reading Kaleemullah would have used this formula specified in the EMEA guidelines (cited in Kaleemullah) for translating a TTC value disclosed in Kaleemullah to a corresponding ppm value.

92. As I explain below, at the time of the claimed invention, it would have been within the knowledge of a POSITA to assume a daily dose of 1.0g of API for conservatively determining genotoxic impurity (GTI) limits. For example, Callis, which reflects the knowledge of a POSITA, discloses the use of “**a daily dose of 1000 mg API**” to arrive at a maximum daily intake of 1.5 ppm. Ex. 1017, Table 2, footnote d. Additionally, Callis discloses that it is desirable to assume a daily dose of 1000 mg API when calculating concentration limits because such an assumption would lead to a conservative GTI risk assessment: “[i]n all cases, an acceptable toxicology limit based on a two-year dosing duration, **an API dose of 1000 mg**, and the risk assessment methodology described below are substantially higher than limits determined using current risk assessment parameters.” Ex. 1017, 987. Thus, a POSITA would have known to assume a daily dose of 1000 mg API (or, equivalently

1.0g of API) in the above-mentioned formula, and further, such a person would have converted Kaleemullah's disclosure of "1.5µg/person/day" to "1.5 ppm." And, as explained above, Kaleemullah's description of the formation of "isopropyl chloride" ("2-chloropropane") as a carcinogen/genotoxic impurity that is limited to an estimated TTC value of "1.5µg/person/day intake" and a POSITA's knowledge of assuming a daily dose of 1.0g of API therefore discloses the formation of "2-chloropropane" and limiting its intake to "*less than about 5 ppm 2-chloropropane.*" Therefore, Kaleemullah discloses "2-chloropropane . . . *less than about 5 ppm 2-chloropropane.*"

93. Furthermore, at the time of the claimed invention, a POSITA would have understood the need to limit the level of "2-chloropropane" to "*less than about 5 ppm.*" For example, Callis reflecting the knowledge of a POSITA, provides toxicology limits for "2-chloropropane." Specifically, Table 2 in Callis shows that the "acceptable lifetime cumulative dose (daily chronic limit)" of "isopropyl chloride" ("2-chloropropane") is "1.5ppm." Ex. 1017, Table 2.

Table 2. Toxicology limits for genotoxic impurities (GTIs)

Compound	GTI Category ^a	Carcinogenicity Slope Factor (CSF) ^b	Acceptable Lifetime Cumulative Dose ^c (daily chronic limit) ^d	Acceptable 2-year weekly dose (short-term limit) ^d	Chosen limit for 2-year weekly dosing ^e
Acetamide 	Category 1 (Animal carcinogen) ^f	0.07/mg/kg/day ^g	255 mg (10 ppm)	2450 mcg ^h (2450 ppm)	1000 ppm ⁱ
Hydrazine 	Category 1 (Animal Carcinogen) ^f	3.0/mg/kg/day ^j	5960 mcg (0.2 ppm)	50 mcg ^k (50 ppm)	50 ppm
Isopropyl Chloride 	Category 2 (+ Ames)	NA ^l	TTC at 38 mg (1.5 ppm)	350 mcg ^m (350 ppm)	350 ppm
4-Chloro-1-butanol 	Category 2 (+ Ames)	NA ^l	TTC at 38 mg (1.5 ppm)	350 mcg ^m (350 ppm)	350 ppm
Isopropyl mesylate 	Category 2 (+ Ames) ⁿ	NA ^l	TTC at 38 mg (1.5 ppm)	350 mcg ^m (350 ppm)	350 ppm
Aniline Alert 	Category 3 (Structural Alert)	NA ^l	TTC at 38 mg (1.5 ppm)	350 mcg ^m (350 ppm)	350 ppm

Ex. 1017, Table 2 (annotated).

94. A POSITA would have had a reasonable expectation of success of arriving at a solriamfetol hydrochloride composition comprising “*less than about 5 ppm*” of 2-CP. It would have required only routine experimentation to optimize the salt formation process described in Choi268 to minimize the level of genotoxic impurities (e.g., 2-CP) present in the drug substance. Indeed, Choi268 teaches that

“various other embodiments and modifications in the practice of the invention,” such as the synthesis described in Example 1, “will be apparent to, and can be readily made by, those skilled in the art.” Ex. 1006, [0077]. It would have been within the skill of a POSITA to adjust, for example, the reagents and reaction temperatures to arrive at a lower yield of 2-CP. *See, e.g.*, Ex. 1019, 789 (disclosing that “[f]or salt formation from methanolic solutions the critical parameters were using 37% aq HCl and maintaining the slurry at 10 °C during the HCl addition,” which was able to reduce genotoxic impurities down to 1ppm); *see also* Ex. 1007, 41 (disclosing that “avoiding strongly acidic conditions and prolonged exposure of acids to an alcohol at a higher temperature and incorporating water into the [salt formation] process when possible would reduce the chances of formation of [] genotoxins”).

95. As explained above, a POSITA would have been motivated to modify Choi268’s method of preparing “(R)-2-amino-3-phenylpropyl carbamate hydrochloride” based on Ahnaou’s teachings of a method of preparing “[a] composition.” And, moreover, in view of Kaleemullah’s teachings of the formation and detection of “2-chloropropane,” the Choi268/Ahnaou combination would be additionally modified to include Kaleemullah’s method of detecting “2-chloropropane” resulting in “a composition” prepared according to the combined teachings of Choi268/Ahnaou/Kaleemullah. *See* §IX.A. And, in further view of Kaleemullah’s teachings limiting intake of genotoxic impurities to an estimated TTC

value of “1.5µg/person/day,” such a person would have found it obvious that “*the composition*” prepared according to the combined teachings of Choi268/Ahnaou/Kaleemullah “*comprises less than about 5 ppm 2-chloropropane.*” Therefore, the combination of Choi268, Kaleemullah, and Ahnaou render obvious “2-chloropropane, wherein the composition comprises less than about 5 ppm 2-chloropropane.”

Mapping #2¹³

96. Furthermore, for the additional reasons set forth below, Kaleemullah discloses “2-chloropropane . . . less than about 5 ppm 2-chloropropane.”

97. As of the priority date, a POSITA would have known and understood the increased concern to limit genotoxic impurities (such as 2-CP) in drug substances to levels that are as low as possible. For example, Liu explains that “[g]enotoxic impurities (GTIs) in pharmaceuticals at trace levels are of increasing concerns to both pharmaceutical industries and regulatory agencies due to their potentials for human carcinogenesis. Determination of these impurities at ppm levels requires highly sensitive analytical methodologies . . . in pharmaceutical R&D.” Ex. 1014, Abstract. As another example, Cimarosti recognizes the need for “developing and validating methods to measure trace levels of genotoxic

¹³ The analysis for Mapping #2 satisfies the requirements of claim 2 which requires “*wherein the composition comprises less than about 1 ppm 2-chloropropane.*”

impurities.” Ex. 1015, 993. As yet another example, Kim, reflecting the knowledge of a POSITA, highlights its concern for reducing 2-CP levels to “trace amounts.” 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.” Ex. 1007, 422. Indeed, a POSITA would have understood the need to reduce genotoxin levels in drugs to limits even lower than toxicology-based requirements (e.g., lower than 1.5µg/person/day) in view of the EMEA guidelines cited in Kaleemullah. Specifically, these guidelines (published in 2006) specify that “pharmaceutical measurements should be guided by a policy of controlling levels to “as low as reasonably practicable” (ALARP principle), where avoiding is not possible.” Ex. 1018, 5. And, therefore, in view of the teachings of the ALARP principle, a POSITA would have understood to lower the level of genotoxic impurities such as “2-chloropropane” in drug substances to “*less than about 5 ppm.*”

5.2 Genotoxic Compounds Without Sufficient Evidence for a Threshold-Related Mechanism

The assessment of acceptability of genotoxic impurities for which no threshold mechanisms are identified should include both pharmaceutical and toxicological evaluations. In general, pharmaceutical measurements should be guided by a policy of controlling levels to “as low as reasonably practicable” (ALARP principle), where avoiding is not possible. Levels considered being consistent with the ALARP principle following pharmaceutical assessment should be assessed for acceptability from a toxicological point of view (see decision tree & following sections).

Ex. 1018, 5. Furthermore, Callis reflecting the knowledge of a POSITA, emphasizes the importance of the ALARP principle to achieve limits even lower than

toxicology-based requirements. Callis describes:¹⁴ “[c]onsideration of the **ALARP principle (as low as reasonably practicable) for impurities may achieve tighter control than toxicology-based limits require.**” Ex. 1017, 986. “**GTI control typically must be demonstrated at very low (ppm) levels in the API** or synthetic intermediates.” Ex. 1017, 986. As such, Callis teaches that, “[w]hen considering potential risk to the patient, genotoxic impurities must often be controlled to much lower levels than required by the ICH Q3A(R2) guideline for non-GTIs.” Ex. 1017, 990. Consequently, at least in view of the supported teachings of these references, a POSITA would have understood the increased concern to limit genotoxic impurities in drug substances.

98. Kaleemullah discloses “*2-chloropropane . . . less than about 5 ppm 2-chloropropane.*” As explained above, Kaleemullah discloses the formation of “*2-chloropropane*” (see Ex. 1016, 391) and Kaleemullah describes a method of detecting “isopropyl chloride” (“*2-chloropropane*”) (see Ex. 1016, 391–93). Further, Table 2 in Kaleemullah shows the lowest concentration of isopropyl chloride (“*2-chloropropane*”) that can be detected in a sample of a drug substance (i.e., the limit of detection).

¹⁴ Callis references the same EMEA guidelines cited in Kaleemullah, i.e., Ex. 1018.

Table 2. Evaluation of LOD and LOQ, Linearity data

Components	Methyl Chloride	Ethyl Chloride	Isopropyl Chloride
Concentration (μg/g)	8.8	8.8	9.1
S/N ratio	35.0	36.8	32.2
Limit of detection (μg/g)	0.83	0.79	0.93
Limit of quantification (μg/g)	2.51	2.39	2.83
Limit of detection precision (%RSD) ^a	12.9	13.4	10.9
Limit of quantification precision(%RSD) ^a	2.4	3.2	2.7
Slope	1105.1	1623.5	5112.7
STEY X	146.0	116.1	886.4
Correlation Co-efficient	0.9996	0.9999	0.9993
RSQ(r ²)	0.9992	0.9998	0.9986

^a Average of n=6 determinations

Ex. 1016, Table 2 (annotated). Specifically, Table 2 indicates that “[l]imit of detection (μg/g)” is “0.93” and that “[l]imit of detection precision (%RSD)” is “10.9” for isopropyl chloride. Put simply, Kaleemullah teaches that the limit of detection (LOD) for 2-CP in its analytical method is 0.93 μg/g ± 10.9%. Because, mathematically, the unit of μg/g is equivalent¹⁵ to parts per million (ppm), Kaleemullah demonstrates that its analytical method detects 2-CP at concentrations as low as 0.93 ppm ± 0.10 ppm. In other words, the limit for detecting “2-chloropropane” ranges from an upper limit of 1.03 ppm (= 0.93 + 0.10) to a lower limit of 0.83 ppm (= 0.93 - 0.10). Indeed, Kaleemullah confirms that its method of detecting isopropyl chloride “has been applied to various drug substances,” and

¹⁵ See Microgram/gram (ug/g) Unit Conversions, CONVERTN, https://convertn.com/concentration_percentage/microgram_gram.html (last visited Sept. 18, 2024).

further discloses that it “was validated as per the ICH guideline . . . for specificity, limit of detection, limit of quantification, linearity, accuracy, precision and robustness.” Ex. 1016, 399, 393. Kaleemullah discloses that its “experimental data shows that the method has potential application for the quantitative determination of alkyl chloride moiety present in the drug substances.” Ex. 1018, 399. Therefore, Kaleemullah discloses “*2-chloropropane . . . less than about 5 ppm 2-chloropropane*” for this additional reason.

99. As explained above, a POSITA would have modified Choi268’s method of preparing “*(R)-2-amino-3-phenylpropyl carbamate hydrochloride*” to additionally include Ahnaou’s method of preparing “[*a*] composition.” See §IX.A. Such a person would have understood “isopropyl chloride” (“*2-chloropropane*”) to form in the Choi268/Ahnaou combination in view of Kaleemullah’s teachings, and further in view of Kaleemullah’s Table 2 indicating that the limit of detection is 0.93µg/g (equivalently, 0.93ppm), such a person would have found it obvious that “*the composition*” prepared according to the combined teachings of Choi268/Ahnaou/Kaleemullah “*comprises less than about 5 ppm 2-chloropropane.*” Therefore, the combination of Choi268, Kaleemullah, and Ahnaou render obvious “*2-chloropropane, wherein the composition comprises less than about 5 ppm 2-chloropropane*” for this additional reason.

100. Accordingly, the combination of Choi268, Kaleemullah and Ahnaou render obvious claim 1.

2. Claim 2

- a. **[2.0] The composition of claim 1, wherein the composition comprises less than about 1 ppm 2-chloropropane.**

101. For the same reasons discussed above, the combination of Choi268, Kaleemullah, and Ahnaou renders obvious claim 2. *See* explanation with respect to Mapping #2 in element [1.1] above. As I discussed, Kaleemullah, citing the EMEA guidelines, discloses an estimated TTC value of “1.5µg/person/day” for the “intake of a genotoxic impurity” (*e.g.*, 2-CP), which translates to 1.5ppm (assuming¹⁶ a daily dose of 1.0g of the API). However, in my opinion, a POSITA would be motivated to control genotoxic impurities, such as 2-CP, to further reduce it to levels that are lower than 1.5 ppm, including “*less than about 1 ppm.*” For example, the same EMEA guidelines cited in Kaleemullah (published in 2006) specify that “pharmaceutical measurements should be guided by a policy of controlling levels to ‘as low as reasonably practicable’ (ALARP principle), where avoiding is not possible.” Ex. 1018, 5.

¹⁶ A POSITA would have understood to assume a daily dose of 1.0g of API for determining genotoxic impurity (GTI) limits. *See* Ex. 1017, Table 2, footnote d.

5.2 Genotoxic Compounds Without Sufficient Evidence for a Threshold-Related Mechanism

The assessment of acceptability of genotoxic impurities for which no threshold mechanisms are identified should include both pharmaceutical and toxicological evaluations. In general, pharmaceutical measurements should be guided by a policy of controlling levels to “as low as reasonably practicable” (ALARP principle), where avoiding is not possible. Levels considered being consistent with the ALARP principle following pharmaceutical assessment should be assessed for acceptability from a toxicological point of view (see decision tree & following sections).

Ex. 1018, 5. Therefore, in view of the teachings of the ALARP principle, a POSITA would have understood to further reduce the level of a genotoxic impurity such as “2-chloropropane” to “less than about 1 ppm 2-chloropropane.” Furthermore, Callis, reflecting the knowledge of a POSITA, emphasizes the importance of the ALARP principle to achieve limits even lower than toxicology-based requirements. Callis describes:¹⁷ “[c]onsideration of the ALARP principle (as low as reasonably practicable) for impurities may achieve tighter control than toxicology-based limits require.” Ex. 1017, 986. “GTI control typically must be demonstrated at very low (ppm) levels in the API or synthetic intermediates.” Ex. 1017, 986. As such, Callis teaches that, “[w]hen considering potential risk to the patient, genotoxic impurities must often be controlled to much lower levels than required by the ICH Q3A(R2) guideline for non-GTIs.” Ex. 1017, 990.

102. In addition, it is my opinion that a POSITA would have a reasonable expectation of success in arriving at a composition with “less than about 1 ppm 2-chloropropane” in view of Kaleemullah’s express disclosure of a “[l]imit of

¹⁷ Callis references the same EMEA guidelines cited in Kaleemullah, i.e., Ex. 1018.

detection ($\mu\text{g/g}$)” for isopropyl chloride that is “0.93” ppm. Ex. 1016, 393 and Table 2.

Table 2. Evaluation of LOD and LOQ, Linearity data

Components	Methyl Chloride	Ethyl Chloride	Isopropyl Chloride
Concentration ($\mu\text{g/g}$)	8.8	8.8	9.1
S/N ratio	35.0	36.8	32.2
Limit of detection ($\mu\text{g/g}$)	0.83	0.79	0.93
Limit of quantification ($\mu\text{g/g}$)	2.51	2.39	2.83
Limit of detection precision (%RSD) ^a	12.9	13.4	10.9
Limit of quantification precision(%RSD) ^a	2.4	3.2	2.7
Slope	1105.1	1623.5	5112.7
STEY X	146.0	116.1	886.4
Correlation Co-efficient	0.9996	0.9999	0.9993
RSQ(r^2)	0.9992	0.9998	0.9986

^a Average of n=6 determinations

Ex. 1016, Table 2 (annotated).

103. As described above in §IX.A, a POSITA would have modified Choi268’s method of preparing “(R)-2-amino-3-phenylpropyl carbamate hydrochloride” to additionally include Ahnaou’s method of preparing “[a] composition.” Such a person would have understood “isopropyl chloride” (“2-chloropropane”) to form in the Choi268/Ahnaou combination in view of Kaleemullah’s teachings. Moreover, in view of Kaleemullah’s Table 2 indicating that the limit of detection for 2-CP is 0.93 $\mu\text{g/g}$ (equivalently, 0.93ppm), it would have been obvious to a POSITA that “the composition” prepared according to the combined teachings of Choi268/Ahnaou/Kaleemullah “comprises less than about 1

ppm 2-chloropropane.” See also Ex. 1016, 391–93 (describing details of Kaleemullah’s method of detecting “2-chloropropane”). Therefore, the combination of Choi268, Kaleemullah, and Ahnaou render obvious claim 2.

3. Claim 3

a. [3.0] The composition of claim 1, wherein the composition is a dosage form.

104. It is my opinion that the combination of Choi268, Kaleemullah and Ahnaou renders obvious claim 3.

105. In addition, it is my opinion that Ahnaou discloses “a dosage form.” For example, Ahnaou teaches that “[p]referably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories, for oral parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation.” Ex. 1005, [0072]. In addition, “[t]he 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.” Ex. 1005, [0067]. “Because of their ease in administration, **tablets and capsules represent the most advantageous oral dosage unit form**, in which case solid pharmaceutical carriers are obviously employed. . . . The tablets or pills can be coated or otherwise compounded to **provide a dosage form** affording the advantage of prolonged action.

For example, the tablet or pills can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former.” Ex. 1005, [0070].

106. As explained above, a POSITA would have been motivated to modify Choi268’s method of preparing “(R)-2-amino-3-phenylpropyl carbamate hydrochloride” based on Ahnaou’s teachings of a method of preparing “[a] composition.” And, moreover, in view of Kaleemullah’s teachings of the formation and detection of “2-chloropropane,” the Choi268/Ahnaou combination would be additionally modified to include Kaleemullah’s method of detecting “2-chloropropane” resulting in “a composition” prepared according to the combined teachings of Choi268/Ahnaou/Kaleemullah. See §IX.A. Given Ahnaou’s disclosure of “a dosage form,” it is my opinion that a POSITA would have found it obvious that “the composition” prepared according to the combined teachings of Choi268/Kaleemullah/Ahnaou “is a dosage form.”

107. Accordingly, the combination of Choi268, Kaleemullah and Ahnaou render obvious claim 3.

4. Claim 4

a. [4.0] The composition of claim 3, wherein the composition is an immediate release oral dosage form.

108. For the same reasons discussed above, it is my opinion that the combination of Choi268, Kaleemullah and Ahnaou render obvious claim 4. See [3.0] above.

109. Furthermore, it is my opinion that Ahnaou discloses an “*immediate release oral dosage form*.” Ahnaou explains that “compounds of Formula (I) can be ... [in] forms suitable for oral administration [that] 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.” Ex. 1005, [0067] (emphasis added).

110. As explained above, a POSITA would have been motivated to modify Choi268’s method of preparing “*(R)-2-amino-3-phenylpropyl carbamate hydrochloride*” based on Ahnaou’s teachings of a method of preparing “[a] *composition*.” And, moreover, in view of Kaleemullah’s teachings of the formation and detection of “*2-chloropropane*,” the Choi268/Ahnaou combination would be additionally modified to include Kaleemullah’s method of detecting “2-

chloropropane” resulting in “*a composition*” prepared according to the combined teachings of Choi268/Ahnaou/Kaleemullah. See §IX.A. In addition, given Ahnaou’s disclosure of “*an immediate release oral dosage form*,” it is my opinion that a POSITA would have found it obvious that “*the composition*” prepared according to the combined teachings of Choi268/Kaleemullah/Ahnaou “*is an immediate release dosage form*.”

111. Accordingly, the combination of Choi268, Kaleemullah and Ahnaou render obvious claim 4.

5. Claim 5

a. [5.0] The composition of claim 4, wherein the composition is a tablet or a capsule.

112. It is my opinion that the combination of Choi268, Kaleemullah and Ahnaou render obvious claim 5.

113. In addition, it is my opinion that Ahnaou discloses “*a tablet or a capsule*.” See [3.0] and [4.0] above.

114. As explained above, a POSITA would have been motivated to modify Choi268’s method of preparing “*(R)-2-amino-3-phenylpropyl carbamate hydrochloride*” based on Ahnaou’s teachings of a method of preparing “[*a composition*.” And, moreover, in view of Kaleemullah’s teachings of the formation and detection of “*2-chloropropane*,” the Choi268/Ahnaou combination would be additionally modified to include Kaleemullah’s method of detecting “2-

chloropropane” resulting in “*a composition*” prepared according to the combined teachings of Choi268/Ahnaou/Kaleemullah. See §IX.A. Moreover, in further view of Ahnaou’s disclosure of “*a tablet or a capsule*,” it is my opinion that a POSITA would have found it obvious that “*the composition*” prepared according to the combined teachings of Choi268/Kaleemullah/Ahnaou “*is a tablet or a capsule*.”

115. Accordingly, the combination of Choi268, Kaleemullah and Ahnaou render obvious claim 5.

6. Claim 6

- a. [6.0] 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.

116. It is my opinion that the combination of Choi268, Kaleemullah and Ahnaou render obvious claim 6.

117. In addition, Ahnaou discloses the following:

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.

Ex. 1005, [0030] (emphasis added). Ahnaou discloses that “[t]he present invention is directed to **a method of treating sleep disorders in a subject, including excessive daytime sleepiness (EDS) or pathological somnolence comprising, administering to a subject in need of such treatment, a therapeutically effective amount of a compound of the Formula (I),**” including solriamfetol hydrochloride.

Ex. 1005, [0024] (emphasis added).

118. As explained above, a POSITA would have been motivated to modify Choi268’s method of preparing “*(R)-2-amino-3-phenylpropyl carbamate hydrochloride*” based on Ahnaou’s teachings of a method of preparing “[a] *composition*.” And, moreover, in view of Kaleemullah’s teachings of the formation and detection of “*2-chloropropane*,” the Choi268/Ahnaou combination would be additionally modified to include Kaleemullah’s method of detecting “*2-chloropropane*” resulting in “*a composition*” prepared according to the combined teachings of Choi268/Ahnaou/Kaleemullah. See §IX.A. In addition, in further view of Ahnaou’s afore-mentioned disclosures, it is my opinion that a POSITA would have found it obvious that “*the composition of claim 1*” prepared according to the combined teachings of Choi268/Kaleemullah/Ahnaou can be “*administer[ed] to [a] subject*” in “[a] *method of treating narcolepsy, . . . excessive daytime sleepiness . . .*

attention deficit/hyperactivity disorder, . . . depression, bipolar disorder . . . in [the] subject.”

119. Accordingly, the combination of Choi268, Kaleemullah and Ahnaou render obvious claim 6.

7. Claim 7

- a. [7.0] The method of claim 6, wherein the composition is administered once per day.**

120. It is my opinion that the combination of Choi268, Kaleemullah and Ahnaou render obvious claim 7.

121. In addition, Ahnaou 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.” Ex. 1005, [0066] (emphasis added). In addition, claim 14 of Ahnaou discloses administration of (R)-2-amino-3-phenylpropyl carbamate and pharmaceutically acceptable salts thereof (“(R)-2-amino-3-phenylpropyl carbamate hydrochloride”) for the treatment of, e.g., excessive daytime sleepiness.

122. As explained above, a POSITA would have been motivated to modify Choi268’s method of preparing “(R)-2-amino-3-phenylpropyl carbamate hydrochloride” based on Ahnaou’s teachings of a method of preparing “[a] composition.” And, moreover, in view of Kaleemullah’s teachings of the formation and detection of “2-chloropropane,” the Choi268/Ahnaou combination would be

additionally modified to include Kaleemullah's method of detecting "2-chloropropane" resulting in "*a composition*" prepared according to the combined teachings of Choi268/Ahnaou/Kaleemullah. See §IX.A. In addition, in further view of Ahnaou's afore-mentioned disclosures, it is my opinion that a POSITA would have found it obvious that "*the composition*" prepared according to the combined teachings of Choi268/Kaleemullah/Ahnaou "*is administered once per day*" for the treatment of sleep disorder such as EDS.

123. Accordingly, the combination of Choi268, Kaleemullah and Ahnaou render obvious claim 7.

8. Claim 8

a. [8.0] The method of claim 6, wherein the composition is administered more than once per day.

124. It is my opinion that the combination of Choi268, Kaleemullah and Ahnaou render obvious claim 8.

125. In addition, Ahnaou discloses "*administer[ing] more than once per day.*" See [7.0] above.

126. As explained above, a POSITA would have been motivated to modify Choi268's method of preparing "*(R)-2-amino-3-phenylpropyl carbamate hydrochloride*" based on Ahnaou's teachings of a method of preparing "[*a composition.*" And, moreover, in view of Kaleemullah's teachings of the formation and detection of "2-chloropropane," the Choi268/Ahnaou combination would be

additionally modified to include Kaleemullah's method of detecting "2-chloropropane" resulting in "*a composition*" prepared according to the combined teachings of Choi268/Ahnaou/Kaleemullah. See §IX.A. In addition, in further view of Ahnaou's afore-mentioned disclosures, it is my opinion that a POSITA would have found it obvious that "*the composition*" prepared according to the combined teachings of Choi268/Kaleemullah/Ahnaou "*is administered more than once per day*" for the treatment of a sleep disorder such as EDS.

127. Accordingly, the combination of Choi268, Kaleemullah and Ahnaou render obvious claim 8.

X. OBJECTIVE INDICIA OF NON-OBVIOUSNESS

128. I am not aware of any objective indicia of non-obviousness that would change my opinion that the challenged claims of the 354 Patent are obvious in view of the prior art discussed above in this declaration. It is my opinion that any potential objective indicia of non-obviousness would not overcome the clear disclosures in the prior art showing that the subject matter of these claims would have been obvious to a POSITA as of September 6, 2016. However, I reserve the right to supplement my opinions in the event that Patent Owners allege or offer any purported evidence of objective indicia of non-obviousness.

XI. CONCLUSION

129. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code.

Dated: September 24, 2024



Salvatore D. Lepore, Ph.D.

CLAIM LISTING

Claim 1
[1.0] A composition comprising (R)-2-amino-3-phenylpropyl carbamate hydrochloride and
[1.1] 2-chloropropane, wherein the composition comprises less than about 5 ppm 2-chloropropane
Claim 2
[2.0] The composition of claim 1, wherein the composition comprises less than about 1 ppm 2-chloropropane.
Claim 3
[3.0] The composition of claim 1, wherein the composition is a dosage form.
Claim 4
[4.0] The composition of claim 3, wherein the composition is an immediate release oral dosage form.
Claim 5
[5.0] The composition of claim 4, wherein the composition is a tablet or a capsule.
Claim 6
[6.0] 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.
Claim 7
[7.0] The method of claim 6, wherein the composition is administered once per day.
Claim 8
[8.0] The method of claim 6, wherein the composition is administered more than once per day.