

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

INTAS PHARMACEUTICALS LTD.
Petitioners,

v.

ATOSSA THERAPEUTICS, INC.
Patent Owner.

PGR 2023-00043
Patent No. 11,572,334

**EXPERT DECLARATION OF STEPHEN GRAHAM DAVIES, D. PHIL. IN
SUPPORT OF PATENT OWNER'S PRELIMINARY RESPONSE**

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I, Stephen Graham Davies, D. Phil., declare and state as follows:

I. INTRODUCTION

1. Patent Owner, Atossa Therapeutics, Inc. (“Atossa”), has retained me to provide expert testimony in connection with Post-Grant Review (PGR) No. 2023-00043 (“Petition”), filed by Intas Pharmaceuticals Ltd. (“Petitioner”), challenging the patentability of all claims of U.S. Patent No. 11,572,334. My expert testimony responds to the invalidity arguments raised in the Petition and the accompanying expert testimony of Petitioner’s expert, Dr. Jason McConville.

2. The statements set forth in this declaration are based on my personal knowledge. I am being compensated at my usual rate for the time spent preparing this declaration, and my compensation is not contingent on the outcome of any matter or any of the opinions provided below. Beyond my fee for these expert services, I have no financial interest in this matter. I am not associated in any way with any of the parties at issue.

3. This declaration is based on the information currently available to me. To the extent that additional information becomes available, I reserve the right to continue my investigation and study, which may include a review of documents and information that may be produced, as well as testimony from depositions that have not yet been taken. I reserve the right to supplement my opinions to address any information obtained, or positions taken, based on any new information.

II. QUALIFICATIONS AND BACKGROUND

A. Education And Experience

4. I am an expert in the fields of organic chemistry and medicinal chemistry. My qualifications in these areas, as well as other areas of knowledge, are established below and by my *curriculum vitae*, attached as EX2013.

5. I am the Waynflete Professor of Chemistry Emeritus at the University of Oxford and Extraordinary Lecturer in Chemistry at New College, Oxford, England. I have been employed as a chemistry instructor at Oxford since 1980. I became a Professor of Chemistry at Oxford in 1996. From 2006 to 2011, I was Chairman of the Department of Chemistry. In this position, I had full responsibility for all teaching, research, financial and managerial matters in one of the largest chemistry departments in the world. I have also supervised more than 100 graduate students and 100 post-doctoral fellows in the areas of organic, organometallic, and medicinal chemistry.

6. In 1973, I earned a B.A. in Chemistry from the University of Oxford. In 1975, I earned a D. Phil. in Chemistry from the University of Oxford. In 1980, I received a D. Sc. in Chemistry from the University of Paris. I also completed two Postdoctoral fellowships between 1975 and 1980. I first held an ICI Postdoctoral Fellowship and later a NATO Fellowship, before joining the Centre National de la Recherche Scientifique (CNRS) at Gif-sur-Yvette as Attaché de Recherche as an

Attaché de Recherche (Research Assistant). I also have a Doctor Honoris Causa (honorary degree) from the University of Salamanca, Spain.

7. I have held several editorial appointments. I was the Founding Editor and Editor of the Organic Series of “Oxford Chemistry Primers” and “Oxford Chemistry Masters.” I was also the Founding Editor and Editor-in-chief of the journal, “Tetrahedron: Asymmetry” from 1990-2017. I am also the Editor of the “On Chemistry” Books, and for many years (1989-2017), I was an Executive Editorial Board Member of the “Tetrahedron” family of Journals.

8. Throughout my career, I have continuously conducted academic, peer-reviewed, grant-funded research in the areas of organic chemistry and medicinal chemistry. I have published over 600 peer-reviewed publications and have given scores of research lectures. I have also been a committee member of many professional bodies, a list of which can be found in my *curriculum vitae*.

9. Pertinent to the Petition at issue, I have been interested in research and have many publications on synthetic organic and medicinal chemistry, and in particular, the preparation of chemically and isomerically pure organic compounds, including the asymmetric and stereoselective synthesis of organic compounds for potential therapeutic use. I also have research experience and many publications on the identification, synthesis, and evaluation of small molecule inhibitors of

potential breast cancer biomarkers. A list of my more than 600 publications is included with my *curriculum vitae*.

10. I am also the founder of numerous companies including several focused on the preparation and development of compounds for potential pharmaceutical use. Along with several other colleagues, I founded Oxford Asymmetry, Ltd. in 1992, which became a division of Oxford Asymmetry International plc, with a mission to provide pharmaceutical companies with enantiomerically pure compounds of interest on any desired scale, from small amounts for biological evaluation and research, to commercial quantities. I am also the Founder of Summit Therapeutics plc and Summit Therapeutics Inc., which develop pharmaceutical compounds and have one such compound for treating Duchenne Muscular dystrophy which is currently being reformulated after a Phase II clinical trial. Similarly, a novel specific antibiotic against the *C. difficile* bacterium is being reevaluated after two phase III trials. I am also the Founder and Non-executive Director of Raphael Laboratories Limited, which is developing prophylactics against airborne respiratory viruses including COVID-19 and its variants, one of which successfully completed a Phase II clinical trial and is being prepared for a Phase III trial. Currently, I am the Founder and Non-executive Chairman of Sci-ink Ltd. I was also a Non-executive Director of Oxford University Innovation Ltd. In addition, I was the Founder and Non-executive

Director of OxStem Ltd., OxStem Neuro Ltd., Ox-Stem Cardio Ltd., OxStem Oncology Ltd., OxStem Ocular Ltd, Ox-Stem Beta Ltd, and OxStem Immuno Ltd. I am also the Founder and Non-executive director of OxReGen Ltd which uses AI and zebrafish for drug discovery.

11. Over the course of my career, I have received several awards, including the Hickinbottom Fellowship (1984); Pfizer Award for Chemistry (1985); 1984 Corday Morgan Medal, Royal Society of Chemistry (1986); Royal Society of Chemistry Award for Organometallic Chemistry (1987); Pfizer Award for Chemistry (1988); Royal Society of Chemistry Bader Award (1989); Tilden Lecture Award, Royal Society of Chemistry (1996); Royal Society of Chemistry Award in Stereochemistry (1997); Prize Lectureship of the Society of Synthetic Organic Chemistry, Japan (1998); Distinguished Technopreneur Award, Singapore (2008); Royal Society of Chemistry Perkin Prize for Organic Chemistry (2011); and Doctor Honoris Causa, University of Salamanca, Spain.

B. Information Considered In Forming My Opinions

12. In forming the opinions expressed in this declaration, I have considered the Petition (Paper 1), as well the attendant Petitioner's Exhibits, and Dr. McConville's expert declaration. Additionally, I have considered the exhibits listed by Patent Owner in the accompanying Patent Owner Preliminary Response.

I have also based my opinions on my professional and academic experiences in the relevant areas of organic and medicinal chemistry.

C. Scope Of The Work And Compensation

13. I am being compensated for my time spent on this matter at the rate of £450 per hour. No part of my compensation is contingent upon the outcome of this matter or any issue in it.

14. I may consider additional documents and information in forming any rebuttal opinions. Additionally, I reserve the right to prepare one or more visual aids or demonstratives to illustrate my opinions, including at trial. I also reserve the right to provide a technical tutorial to provide additional background information on my opinions.

15. The cases where I have testified at deposition and/or trial in the last four years are appended to my *curriculum vitae*. (EX2013.)

III. POST-GRANT PETITION

16. As previously stated, it is my understanding that Intas Pharmaceuticals Ltd. is challenging all claims of the '334 patent. (Pet. at 2.) I lay out my understanding of the grounds raised by Petitioner below.

17. In Ground 1, Petitioner asserts that Ahmad (EX1003) anticipates claims 1, 2, 4, 15, and 20-22 of the '334 patent.

18. In Ground 2, Petitioner alternatively asserts that the same claims 1, 2, 4, 15, and 20-22 of the '334 patent would be obvious over Ahmad alone.

19. In Ground 3, Petitioner asserts that claims 5-8, 16, and 17 of the '334 Patent would be obvious over Ahmad in view of Cole (EX1008).

20. In Ground 4, Petitioner asserts that claim 3 of the '334 patent would be obvious over Ahmad in view of Benameur (EX1010).

21. In Ground 5, Petitioner asserts that claims 9-13 of the '334 patent would be obvious over Ahmad in view of Stegemann (EX1011) and/or the Handbook of Pharmaceutical Excipients (HPE) (EX1012).

22. In Ground 6, Petitioner asserts that claims 14, 18, and 19 of the '334 patent would be obvious over Ahmad in view of Ahmad 2010 (EX1006) and Ahmad 2012 (EX1007).

IV. LEGAL STANDARDS

23. I have no formal legal training, but I have been informed by Atossa's counsel about the appropriate legal standards as set forth below for anticipation and obviousness and have applied these standards in rendering my opinions.

24. It is my understanding that anticipation occurs when a given prior art reference discloses each and every limitation of a claimed invention, either expressly or inherently. I have also been informed that an anticipatory reference must enable a person of ordinary skill in the art (POSA) to practice the invention.

25. I have been informed that the governing standard for anticipation involves assessing whether the teaching of a prior art reference “necessarily results,” as opposed to presenting a mere possibility of resulting, in the challenged claimed invention. I have also been informed that it is not enough that a prior art reference teaches a limitation that is “close enough” to the challenged limitation.

26. It is also my understanding that an anticipatory reference must enable a POSA how to make the invention “without undue experimentation.” I have been told that there are certain factors used to determine whether experimentation is undue, referred to as the “Wand factors,” and which include: the quantity of experimentation needed, the amount of guidance provided in the reference, the presence or absence of actual examples of the experimental procedure, the state of the knowledge already available concerning the subject matter at issue, and the predictability or unpredictability in the specific area of science or technology.

27. It is my understanding that an obviousness inquiry is a question of law but that it is undergirded by factual findings related to the scope of the prior art, whether a POSA would have a reason or motivation to combine or modify the prior art to arrive at the claimed invention, and so doing, having a reasonable expectation of success.

28. I have been informed and understand that to find a patent claim unpatentable for obviousness, the claimed invention, as a whole, when considered

against the prior art, as a whole, must have been obvious to a person having ordinary skill in the art at the time the invention was made. I understand that in evaluating obviousness, I must consider: 1) the level of skill in the art, 2) the scope and content of the prior art, 3) differences between the claimed invention and prior art, and 4) objective evidence of non-obviousness.

29. For the purposes of my opinions herein, I have assumed that the critical date for the '334 patent is no later than September 11, 2017.

30. I have also been informed and understand that the claimed invention and the prior art must each be looked at “as a whole” and that the party alleging obviousness has the burden of establishing that the art, as a whole, motivates the POSA to make the invention as claimed with a reasonable expectation of success in doing so. In this regard, I understand that a POSA would have considered teachings in the art that may suggest as well as “teach away” from the claimed invention. It is not sufficient to consider an isolated portion of one reference that is similar to disclosure and claims of the subject patent if that reference as a whole, another reference, or the prior art as a whole teaches or suggests something different than that isolated portion. I also understand that, in resolving whether an invention is obvious based on the teachings of multiple references, one must consider whether the combination yields no more than predictable results or achieves an unexpected result.

31. I have also been informed of the objective evidence of non-obviousness, which I have been informed can include: 1) a long-felt but unmet need for the claimed invention, 2) the failure of others in the prior art to fill this need, 3) unexpected or surprising results of the claimed invention, 4) skepticism as to the inventor's chances for success, 5) industry praise for the invention, and 6) commercial success of the claimed invention.

32. I have also been informed and understand that, in making an obviousness determination, it is improper to consider the prior art with a hindsight bias based on the teachings of the subject patent. Specifically, one must not use the subject patent as a template to suggest how the elements of the prior art could have been combined. It is thus my understanding that there must be a motivation to combine the chosen prior art references to satisfy the obviousness requirement. Furthermore, it is my understanding that any alleged basis for obviousness must be articulated with specific reasoning, beyond mere conclusory statements.

33. Finally, I have also been informed and understand that Petitioner must prove by a preponderance of the evidence that the challenged claims are unpatentable. I understand that the preponderance of the evidence standard is one characterized as "more likely than not." Because each claim is considered a separate invention, I understand that Petitioner's burden is applicable to each claim individually.

V. EXPERT OPINION SUMMARY

34. I have been asked to provide my expert opinion as to whether the claims of the '334 patent are patentable over Ahmad and certain other prior art references presented by Petitioner. It is my opinion that the claims of the '334 patent are valid and patentable and that Petitioner's grounds fail to establish that any claim in the '334 is invalid.

35. The Petitioner failed to establish how any of the cited references, in combination or standing alone, render any of the challenged claims anticipated or obvious. Moreover, Ahmad (EX1003), the keystone reference relied on by Petitioner for both anticipation and obviousness for all Grounds, is fatally flawed.

36. Ground 1: Ahmad does not anticipate the challenged claims of the '334 patent because it does not disclose or teach a POSA how to make an oral formulation comprising at least 90% (Z)-endoxifen free base. At best, Ahmad may teach synthesizing a highly impure endoxifen mixture, however, Ahmad does not provide any teachings for subsequent isomeric purification, or any oral formulation thereof, and therefore would not enable a POSA to obtain an isomerically pure (Z)-endoxifen composition suitable for the use in an oral formulation.

37. Ground 2: Ahmad alone does not render the challenged claims obvious. A POSA could not follow the teachings of Ahmad to make an oral formulation comprising at least 90% (Z)-endoxifen free base, nor does the

Petitioner provide any explanation for how a POSA would modify Ahmad to achieve the claimed invention.

38. Ground 3-5: Combining Ahmad with Petitioner's cited enteric capsule art and/or excipient art fails to render the challenged dependent claims obvious. None of the enteric capsule art nor the excipient art, alone or in combination, remedy the myriad flaws of Ahmad that would prevent a POSA from using its teachings to make an oral formulation comprising at least 90% (Z)-endoxifen free base in the first place. Further, it would require undue experimentation by a POSA to develop an oral formulation comprising isomerically pure endoxifen to have the desired properties such as enhanced stability and bioavailability.

39. Ground 6: Ahmad combined with two subsequent Ahmad publications (*i.e.*, Ahmad 2010 (EX1006) and Ahmad 2012 (EX1007)) does not render the dosing and pharmacokinetic claims of the '334 patent obvious. Specifically, the dosing and pharmacokinetic data in these three Ahmad publications fail to teach in any way dosing with an oral formulation comprising at least 90% (Z)-endoxifen free base or achieving any of the claimed pharmacokinetic parameters from such oral formulation. Instead, both Ahmad 2010 and Ahmad 2012 teach pharmacokinetic studies of an endoxifen citrate salt oral formulation, which are silent as to isomeric purity and have inferior pharmacokinetic properties as compared to the claimed invention of the '334 patent.

40. Finally, the objective indicia of non-obviousness, including significant unexpected results described in the '334 patent from isomerically purified (Z)-endoxifen oral formulations are sufficient to rebut any proper *prima facie* obviousness—even if established. The unexpected results include the bulk drug stability of the 90% (Z)-endoxifen compositions as well as superior and unexpected pharmacokinetic profiles resulting from oral formulations comprising 90% (Z)-endoxifen.

41. Accordingly, since Ahmad, alone or in combination with any other references cited by Petitioner, fails to teach or suggest oral formulations comprising greater than 90% (Z)-endoxifen, all grounds must fall.

VI. PERSON OF ORDINARY SKILL IN THE ART

42. I have been asked to opine concerning the qualifications and experience of the person of ordinary skill in the art (POSA). I am informed that the factors that may be considered in determining the level of ordinary skill in the art include: (1) the educational level of the inventor; (2) the type of problems encountered in the art; (3) prior art solutions to those problems; (4) the rapidity with which innovations are made; (5) the sophistication of the technology; and (6) the educational level of active workers in the field.

43. It is my opinion that an adequate skill for a person of ordinary in the art in the field of the '334 patent would be an individual holding a graduate degree

in organic chemistry, medicinal chemistry, pharmaceutical chemistry, or a related field, and four to six years of experience in the synthesis, purification, and design of pharmaceutical compounds and derivatives thereof as of the date of the claimed inventions. A POSA would have worked with a team of professionals with training in related disciplines, such as pharmacology, pharmacokinetics, formulation, drug discovery and/or drug development as of the date of the claimed inventions.

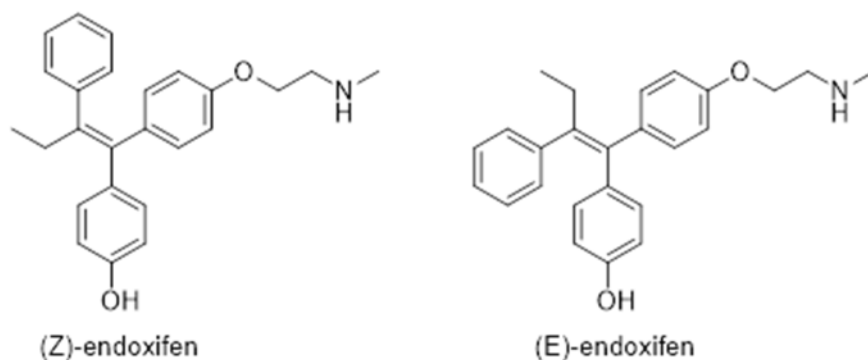
VII. TECHNICAL BACKGROUND

A. Endoxifen And Its Therapeutic Relevance

44. I understand that the compound 4-hydroxy-N-desmethyl-tamoxifen is commonly known as endoxifen. Endoxifen is a primary metabolite of tamoxifen that exists in two isomeric forms: (E)-endoxifen and (Z)-endoxifen. Estrogen receptor (ER)-positive breast cancer has long been treated with tamoxifen. (EX1001 at 1:63-66.) Tamoxifen acts as a selective ER modulator, binding to estrogen receptors and inhibiting growth and proliferation of cancer cells. While tamoxifen has long been used in the prevention and treatment of hormone-sensitive breast cancer and reproductive tract cancers, it is associated with a host of serious side effects, including increased risk of endometrial cancer and blood clots. (*Id.*) Tamoxifen is also associated with vasomotor symptoms such as hot flashes and

night sweats. (*Id.*) Most importantly, tamoxifen resistance is well documented, leading to treatment failure and cancer progression. (*Id.* at 2:3-6.)

45. Endoxifen has two stereoisomers, an (E) isomer and a (Z) isomer as shown below, which differ in the molecules' spatial orientation on either side of the double alkene bond.



Structures Of (Z)-Endoxifen And (E)-Endoxifen

46. Stereoisomers of a given compound, such as (Z) and (E) isomers, generally are chemically distinct and pharmacologically distinct. (EX2014 (FDA Guidance) at 2.) For example, the (Z) and (E) isomers of another tamoxifen metabolite, norendoxifen, have separate bioavailability and enzymatic inhibition activity. (EX2015 (Lv) at 24.)

47. Between the two endoxifen isomers, only the (Z)-endoxifen isomer has appreciable anti-estrogenic activity. (EX2002 (Elkins) at 2.) (Z)-endoxifen also exhibits much higher anti-estrogenic activity than the parent compound, tamoxifen. (EX1001 at 2:36-38; EX2002 (Elkins) at 2.) (Z)-endoxifen is currently

being evaluated in clinical trials for the prevention and treatment of ER-positive breast cancer. (EX1019 (Milroy) at 1.)

48. A POSA would appreciate that the stereoisomers of endoxifen may be separated by solid state techniques, such as fractional crystallization or chromatography, but that the yield of a given isomer is difficult or impossible to predict. Furthermore, a POSA would understand that there is considerable uncertainty involved in selecting the conditions best suited for purifying a given isomer as well as predicting the outcome of any such purification attempt. For example, purifying a composition containing a mixture of stereoisomers may result in only one of the isomers being purified and would require further characterization to determine which isomer was purified. Further, a POSA would not be able to predict the resulting isomeric ratio for a set of crystallization conditions or the particular conditions that would give rise to a highly purified isomeric composition. The purification parameters that can be independently varied include: solvent types, solvent ratios, rate of solvent addition, compound concentrations, temperature, agitation, and other conditions. (EX2018 (Jacques).) Realistically, there could be an almost unlimited number of feasible purification parameter combinations available to a POSA for optimizing compound purification and entire books have been devoted to this topic. (*See, e.g., Id.*). In my experience, having a goal of obtaining an isomerically pure compound is vastly

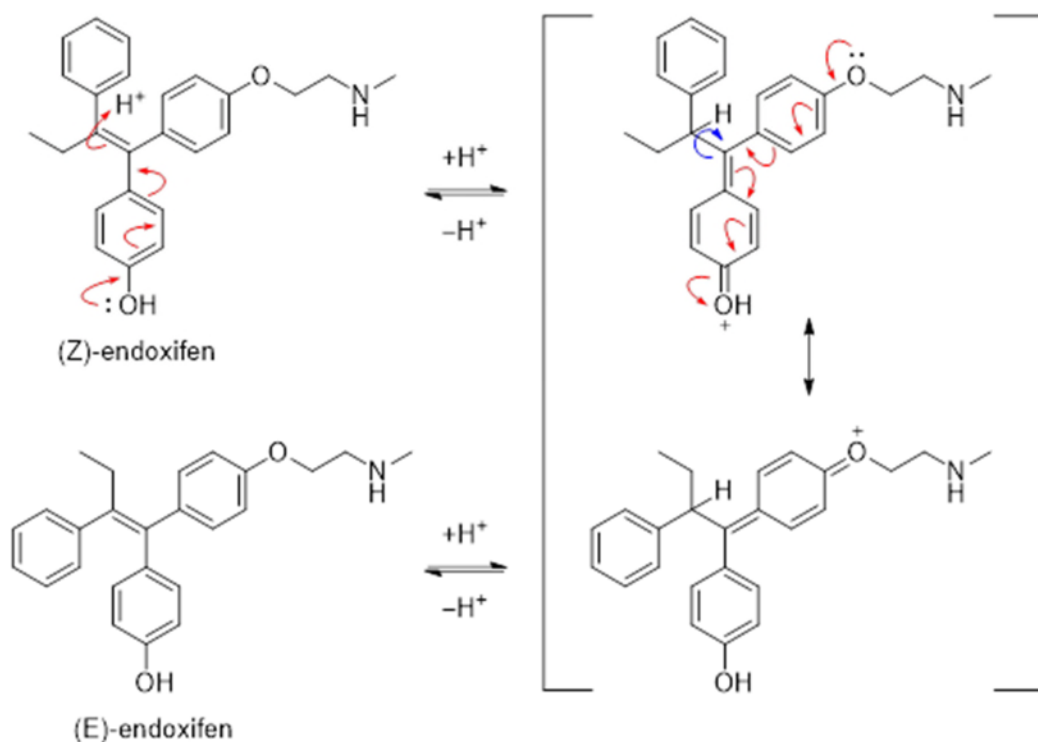
different from *actually* producing the isomerically pure compound, and a POSA would understand that this endeavor would involve undue experimentation.

49. In general, a POSA would have appreciated that fractional crystallization could be used to separate (E)-endoxifen and (Z)-endoxifen based on differences in their solubilities. However, considering there could be an almost unlimited number of feasible fractional crystallization conditions available, a POSA would not have arrived at the particular conditions resulting in pure (E)-endoxifen or pure (Z)-endoxifen without significant and undue experimentation. Due to significant technical challenges and unpredictability involved in fractional crystallization, a POSA could not predict whether the (E)-endoxifen and/or (Z)-endoxifen was even crystalized, thus requiring additional characterization and experimentation.

50. As would be understood by a POSA, under certain circumstances, isomers are susceptible to isomeric interconversion, which further reduces isomeric purity. For example, (Z)-endoxifen has been shown to be unstable in aqueous solutions and to quickly isomerize to the less active isomer, (E)-endoxifen, in the presence of acidic conditions. (EX2002 (Elkins) at 8-9.)

51. As would be understood by a POSA, (Z)-endoxifen is prone to isomerize to (E)-endoxifen by acid-promoted isomerization as shown in the schematic below. Specifically, under acidic conditions, the alkene double bond of

(Z)-endoxifen is protonated (*i.e.*, addition of an H^+ to the double bond) yielding a protonated intermediate (right side in the schematic) with free rotation about the carbon bond (rotation is depicted with a blue arrow). As the protonated intermediate rapidly rotates about this carbon bond, it yields an equilibrated mixture of the protonated intermediate in both pre-(E) and pre-(Z) conformations. Subsequent deprotonation of the protonated intermediate produces a mixture of (E)-endoxifen and (Z)-endoxifen. Accordingly, under acidic conditions, either a pure (Z)-endoxifen or a pure (E)-endoxifen composition would be expected to isomerize to a composition of a mixture of (Z)-endoxifen and (E)-endoxifen, because protonation of either leads to the same intermediate. In addition, a POSA would understand that exposure to elevated temperatures would accelerate the isomeric conversion of (Z)-endoxifen or (E)-endoxifen to an equilibrated mixture of (Z)-endoxifen and (E)-endoxifen.



Acid-Promoted Isomerization Of (Z)-Endoxifen

52. In my opinion, the various similarities between endoxifen and the related compound, tamoxifen, would have motivated a POSA prior to the critical date to pursue salt forms similar to those used with tamoxifen rather than pursuing the free base of (Z)-endoxifen. Tamoxifen's low aqueous solubility has long been addressed in the art by converting it to a citrate salt (*i.e.*, the FDA approved form of tamoxifen), which increases its aqueous solubility and efficacy. (EX2016 (Buchanan) at 5.) Various references, such as Song (EX1005), teach the production of a citrate endoxifen salt using citric acid, presumably to achieve the same solubility benefits achieved with tamoxifen salts. In my opinion, a POSA would have investigated endoxifen salts to improve the stability, toxicity, or

manufacturability of a drug, (EX2017 (Gupta) at 2), such as preventing the nitrogen on tamoxifen or endoxifen from undergoing oxidative degradation, rather than pursuing the free base form of endoxifen as described in the '334 patent.

53. Determining whether a salt form would be suitable for a given scenario is unpredictable and requires significant experimentation. (EX2017 (Gupta) at 2.) For example, oral formulations comprising salts should be evaluated for compatibility with drug excipients and oral formulations (*e.g.*, controlled release oral formulations) because counterions can unpredictably influence drug stability, oral formulation stability, dissolution rates, and overall formulation to be used in clinical practice. (EX2017 (Gupta) at 9, 10.)

54. Although EX1006 and EX1007 describe endoxifen citrate salts, neither reports isomeric purity or stability of the endoxifen compositions used therein. Thus, neither appreciated the destabilizing effect of citrate counter anions on endoxifen stability. For example, as discussed previously, acidic conditions, such as the conditions needed for synthesis of a citrate salt using citric acid, would result in acid-promoted isomerization of a purified isomeric composition of (Z)-endoxifen leading to isomeric instability and degradation. To my knowledge, the inventors of the '334 patent were the first to appreciate the significant benefits of the highly pure free base (Z)-endoxifen versus the salt forms for use in oral formulations.

B. Prior Art Analysis

55. I have summarized my understanding of the relevant background art related to the synthesis and use of endoxifen in the field prior to the critical date of the '334 patent. Although there had been previous work done on the synthesis and purification of endoxifen, the inventors of the '334 patent were the first to produce and characterize highly pure and stable (Z)-endoxifen compositions for use in oral formulations and to demonstrate the superior bioavailability of oral formulations comprising purified (Z)-endoxifen. Notably, (Z)-endoxifen purity and bulk drug stability as taught in the '334 patent were new as compared to previous endoxifen teachings. The oral formulations claimed in the '334 patent performed significantly and unexpectedly better than any prior endoxifen oral formulation teachings, for example, as evidenced by significantly better stability and bioavailability.

1. Ahmad (EX1003)

56. It is my understanding that U.S. Patent No. 9,333,190 ("Ahmad") is at the center of Petitioner's PGR, being relied upon for Grounds 1 and 2 against the independent claims of the '334 patent and further relied upon against the remaining dependent claims in Grounds 3-6. Ahmad was issued on May 10, 2016, from a PCT application filed on November 21, 2007, claiming priority to provisional application No. 60/860,420, filed November 21, 2006. Ahmad's specification

broadly describes a synthetic pathway for endoxifen and the use of endoxifen in lipid complexes. To the extent Ahmad discloses isomeric purity of endoxifen, it does so as part of a generic list, (*see, e.g.*, EX1003 at 12:14-17, 16:46-52), and wholly lacks enabling disclosures on how to obtain pure (Z)-endoxifen compositions, as discussed in detail below.

57. Ahmad describes a four-step synthetic pathway for endoxifen synthesis using synthetic methods that differ in several respects from those presented in the '334 patent. (EX1003 at Examples 1-4.) The last step in Ahmad's endoxifen synthesis is an amination of the intermediate by monomethyl amine, after which the crude endoxifen product was then extracted and purified. Ethyl acetate was added to the crude solid product and heated until complete dissolution of the solid. The solution was then cooled to room temperature and the solvent, hexane, was added and stirred for 12 hours. The solid was then filtered and washed with a cold ethyl acetate-hexane mixture. (*Id.* at Col. 25, ll. 50-67.) Notably, the synthetic pathway described by Ahmad would be expected to result in endoxifen having a different isomeric composition than that of the '334 patent. Specifically, Ahmad's synthesis would most likely produce an isomeric mixture of endoxifen based on a similar synthetic pathway presented in Ali (EX2011) yielding an isomerically impure mixture of (Z)-endoxifen and (E)-endoxifen (*i.e.*, an E:Z

mixture of 5.8:4.2, quantified by HPLC) from an ethyl acetate/hexane crystallization. (EX2011 (Ali) at 22.)

58. Fractional crystallization is a purification method used by the '334 patent to separate compounds based on their differing solvent solubilities. During fractional crystallization, non-target compounds are dissolved into an appropriate solvent, while the target compound is crystallized out and collected as a solid. According to the '334 patent, (Z)-endoxifen is more soluble in ethyl acetate than (E)-endoxifen. (EX1001 at 68;64-65.) Thus, a POSA would expect that adding ethyl acetate during Ahmad's crystallization steps, as described above, would result in dissolving (Z)-endoxifen to a greater extent than (E)-endoxifen, and would thus enrich Ahmad's collected solid in (E)-endoxifen relative to (Z)-endoxifen. Thus, the use of ethyl acetate in Ahmad's crystallization steps necessarily teaches away from producing the purified (Z)-endoxifen compositions described in the '334 patent because it would predominantly result in an isomerically enriched (E)-endoxifen solid. Although a POSA would immediately understand that Ahmad's methods result primarily in an isomerically enriched (E)-endoxifen solid, at no point does Ahmad quantify the isomeric ratio of endoxifen during the synthetic reaction. Ahmad also does not suggest or provide any details as to the isomeric ratio that would be expected from any of its disclosed purification conditions.

59. Ahmad further teaches away from the '334 patent because it lacks an initial step for (Z)-endoxifen purification: first crystallizing out (E)-endoxifen to obtain an enriched solution of (Z)-endoxifen (*e.g.*, a mother liquor or filtrate). Accordingly, it is my opinion that Ahmad's disclosed purification methods for the crude endoxifen product (*i.e.*, prior to further purification) would not result in a pure (Z)-endoxifen composition but would rather likely be expected to result in a roughly 1:1 isomeric ratio of (E)-endoxifen:(Z)-endoxifen. My opinion is further supported by Ali (EX2011), which describes a crystallization from a crude endoxifen product in an ethyl acetate/hexane mixture resulting in a 5.8:4.2 (E:Z) ratio, as quantified by HPLC. (EX2011 (Ali) at 22.)

60. By contrast, to the teachings of Ahmad, the '334 patent uses ethyl acetate during a crystallization step in order to crystallize out and remove (E)-endoxifen and obtain a (Z)-endoxifen-enriched filtrate. The '334 patent teaches subjecting this (Z)-endoxifen-enriched filtrate to further purification steps, thereby producing highly pure (Z)-endoxifen.

61. Accordingly, Ahmad teaches away from the '334 patent claims by: (i) describing only methods of purifying endoxifen with ethyl acetate, which favors (E)-endoxifen solid collection, and (ii) failing to describe any method for producing and further purifying a (Z)-endoxifen-enriched filtrate.

62. It is my expert opinion that Ahmad does not provide a synthetic method of producing (Z)-endoxifen at any significant level, nor does it provide purification methods to achieve highly purified (Z)-endoxifen. Thus, Ahmad does not enable or suggest the claimed “at least 90% (Z)-endoxifen” limitation of the ’334 patent. Further, based on the synthetic and purification methods described in Ahmad, a POSA would not have been motivated to use Ahmad’s methods because the use of ethyl acetate would result in a solid composition of significantly higher (E)-endoxifen concentration, and thus, would have severely diminished activity and bioavailability of (Z)-endoxifen.

63. Further, none of Ahmad, EX1006, or EX1007 provide synthetic methods for making endoxifen citrate compositions, as claimed in Ahmad and used in EX1006 and EX1007. Notably, Ahmad provides only methods of formulating an endoxifen solution in 2% glacial acetic acid solely for toxicity testing. As discussed in detail above, exposing (Z)-endoxifen to an acidic environment, such as 2% glacial acetic acid, promotes undesirable isomerization from (Z)-endoxifen to an equilibrated mixture of (E)-endoxifen and (Z)-endoxifen, therefore further teaching away from a formulation of highly pure (Z)-endoxifen.

64. In summary, it is my opinion that Ahmad, at best, only teaches a synthetic pathway to reach an isomeric mixture of endoxifen and lacks disclosure sufficient to enable a POSA to purify (Z)-endoxifen from the isomeric mixture. It

is my opinion that a POSA would not be able to synthesize compositions of highly pure (Z)-endoxifen using the teachings of Ahmad. It is further my opinion that a POSA would not have been motivated to use Ahmad's endoxifen formulations because they contain acid, which would give rise to acid-promoted isomerization of any isomerically pure mixture. Ahmad's synthetic methods also teach away from purified (Z)-endoxifen compositions because the crystallization step described uses ethyl acetate, which a POSA would expect to favor purification of (E)-endoxifen over (Z)-endoxifen.

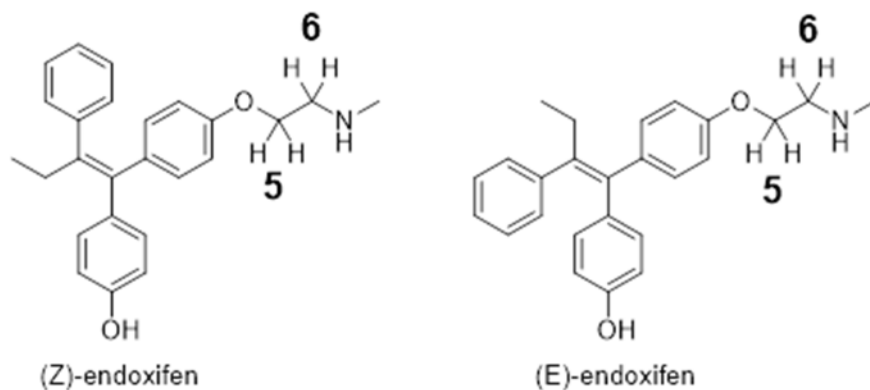
2. Elkins (EX2002)

65. According to Elkins, a (Z)-endoxifen hydrochloride salt ((Z)-endoxifen HCl) readily converts to (E)-endoxifen in aqueous conditions and temperatures above 25°C. (EX2002 (Elkins) at 8-9.) Elkins also provides an HPLC method for quantifying the isomeric concentrations of endoxifen HCl for evaluation of the kinetic parameters for isomerization. Elkins provides ¹H NMR spectra for (E)-endoxifen free base and compares the spectrum to a previous spectrum reported by Ali (EX2011) for (Z)-endoxifen. (EX2002 (Elkins) at 15.)

66. As would be appreciated by a POSA, ¹H NMR can be used to determine the identity and relative quantities of compounds in a mixture, including distinguishing between (E) and (Z) isomers. With ¹H NMR, the relevant protons from the compounds are assigned corresponding NMR shift values and the areas

under those respective peaks are used to calculate the concentration ratio between the two. The structures of (Z)-endoxifen and (E)-endoxifen are shown below with each of the relevant hydrogens explicitly shown for clarity and annotated for consistency with Elkins' hydrogen assignment convention, *i.e.*, **5** and **6**, which convention will be retained throughout this response. Importantly, and relevant to the discussion in this PGR, Elkins assigns the ^1H NMR of the methylene protons of **5** and **6** for (E)-endoxifen to be δ 4.03 ppm (*t*, $J=5.6$ Hz, 2H, $\text{CH}_2\text{-O}$) and δ 2.85 ppm (*t*, $J=5.6$ Hz, 2H, $\text{CH}_2\text{-N}$), respectively. Elkins also cites to Ali (EX2011) for the assignment of the methylene protons of **5** and **6** below for (Z)-endoxifen free base to be δ 3.86 ppm (*t*, $J=5.6$ Hz, 2H, $\text{CH}_2\text{-O}$) and δ 2.74 ppm (*t*, $J=5.6$ Hz, 2H, $\text{CH}_2\text{-N}$), respectively. (EX2002 (Elkins) at 11, 15.)

67. In summary, Elkins provides ^1H NMR characterization of the (E)-endoxifen free base, and further provides a direct comparison of the (E)-endoxifen free base to the (Z)-endoxifen free base as characterized in Ali (EX2011). Using the teachings of Elkins, it is possible to ascertain the presence and relative concentrations of (E)-endoxifen and (Z)-endoxifen as taught by others where ^1H NMR data is reported. Notably, Elkins also teaches that the (Z)-endoxifen HCl salt is unstable in aqueous formulations and in bulk drug stability testing as well as establishing that the major degradation product is (E)-endoxifen. (EX2002 (Elkins) at 8.)



Annotation of Methylene Protons of Endoxifen

3. Liu (EX1004)

68. It is my understanding that International Patent Application No. PCT/US2016/058413 published as WO2017/070651 (“Liu”). I further understand that Petitioner does not formally rely on Liu for any of the grounds but instead raises Liu as background art.

69. Liu provides a process for synthesizing endoxifen and purifying an isomeric mixture of endoxifen to obtain compositions of isomerically purified (Z)-endoxifen, albeit at impracticably low yields and absent any teaching regarding use in a pharmaceutical composition. Liu utilizes a completely distinct synthetic pathway from the '334 patent including using separate starting material reagents not used in the '334 patent, such as zinc bromide, 2-phenoxyethyl bromide, and phosphorous tribromide (EX1004 (Liu) at ¶ 62), which would likely result in an endoxifen composition with a different impurity profile and stability profile than the endoxifen obtained in the '334 patent. Liu obtains a 34% yield of 99%

isomerically pure (Z)-endoxifen through a series of crystallizations. (EX1004 (Liu) at ¶¶ 73-76.) Further, Liu does not provide any methods for evaluating the compositions generated therein for use in pharmaceutical formulations (*e.g.*, stability analysis or impurity analysis) and further does not teach formulations of any type, including oral formulations comprising purified (Z)-endoxifen.

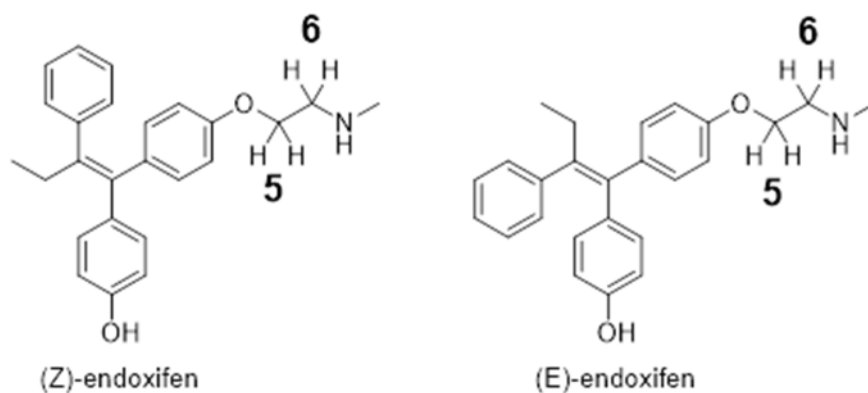
70. It is my opinion that Liu does not provide any disclosure or description that would enable a POSA to be motivated to use these compositions and methods of obtaining isomerically pure (Z)-endoxifen for use in an oral formulation as claimed in the '334 patent.

4. Ali (EX2011)

71. Ali et al., titled “Endoxifen is a new potent inhibitor of PKC: A potential therapeutic agent for bipolar disorder,” published in Bioorganic & Medicinal Chemistry Letters, reports an endoxifen synthetic method starting from commercially available materials including 4-bromophenol, α -phenyl butyric acid, and 2-chloroethoxybenzene. The synthetic steps producing crude endoxifen of Ali’s pathway resemble those of Ahmad. As noted above, the endoxifen synthetic pathway of Ali yields an isomerically impure mixture of (Z)-endoxifen and (E)-endoxifen (*i.e.*, an E:Z mixture of 5.8:4.2, quantified by HPLC). (EX2011 (Ali) at 22.)

72. Ali then builds on the synthetic pathway of Ahmad by adding an additional fractional crystallization purification step using benzene to obtain (Z)-endoxifen, which is then characterized by ^1H NMR, ^{13}C NMR, and high-resolution mass spectrometry. This fractional crystallization step in benzene is not described or enabled in Ahmad.

73. As discussed above, Ali assigns the methylene protons of (Z)-endoxifen free base shift values of δ 3.86 ppm (*t*, $J=5.56$ Hz, 2H, $\text{CH}_2\text{-O}$) and δ 2.74 ppm (*t*, $J=5.59$ Hz, 2H, $\text{CH}_2\text{-N}$) corresponding to the protons of **5** and **6**, respectively, as referenced below (hydrogens explicitly drawn for clarity and methylene protons of **5** and **6** labeled consistent with Elkins' numbering convention). Ali also notes that the methylene protons of (E)-endoxifen corresponding to the protons of **5** provided below have a shift value of δ 4.03 ppm.



Annotation of Methylene Protons of Endoxifen

74. Ali further describes using (Z)-endoxifen for *in vitro* Protein Kinase C (PKC) inhibition using enzymatic assays.

75. Notably, Ali discloses a final purification step using benzene to afford purified (Z)-endoxifen. However, such a composition would not be suitable for use in oral formulations due to benzene's highly carcinogenic nature. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) lists benzene as a Class 1 solvent that "should not be employed in the manufacture of drug substances, excipients, and drug products because of their unacceptable toxicity[.]" (EX2012 (ICH Guidelines) at 11.) The ICH guidelines set the concentration limit of benzene to be no more than 2 parts per million (ppm). (*Id.*) Ali also does not describe using these compositions for oral formulations. Because the use of benzene in Ali's process would render its resulting compositions wholly unsuitable for human use, a POSA would not have been motivated to use the teachings of Ali to produce oral formulations. Instead, Ali teaches away from such a therapeutic use for safety considerations.

76. In sum, Ali provides a synthetic pathway for producing an isomerically impure endoxifen mixture containing mostly (E)-endoxifen and using a process similar to Ahmad's synthetic pathway. Ali further purifies this isomerically impure mixture of endoxifen by fractional crystallization in benzene—a purification step absent in Ahmad—to produce purified (Z)-endoxifen that is then characterized. It is my opinion that the (Z)-endoxifen compositions

provided in Ali would not be suitable for oral formulations and strongly teach away from oral formulations comprising pure (Z)-endoxifen at least because a POSA would not be motivated to use a purification step in benzene to generate an isomerically pure (Z)-endoxifen composition, due to the extreme incompatibility and unsafe properties of benzene.

5. Song (EX1005)

77. It is my understanding that International Patent Application No. PCT/KR2010/009037 published as WO2012/050263 (“Song”) is also provided as background art in the Petition and is not formally relied upon for any of the Grounds.

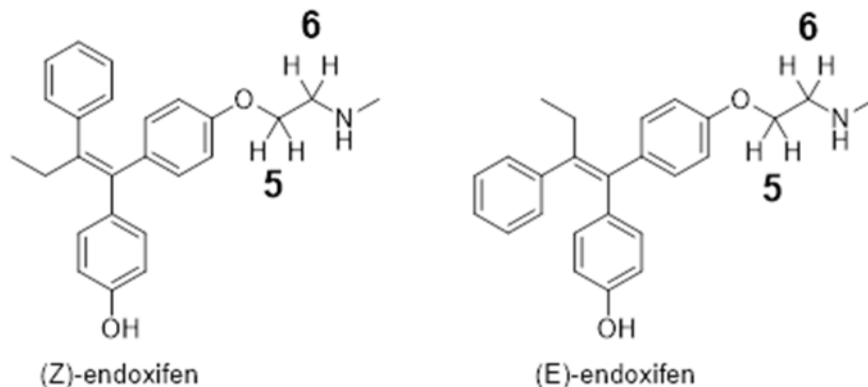
78. It is my opinion that Song teaches a synthetic method for endoxifen production and subsequent isomeric purification in an attempt to obtain an isomerically pure (Z)-endoxifen composition. However, as described in detail below, Song errs in concluding that a purified form of (Z)-endoxifen is produced by its methods. The root of this error appears to stem from an incorrect NMR shift assignment in the ¹H NMR spectra, which assignment is inconsistent with various other published sources. Based on the findings of Elkins and Ali, all of which contradict Song, it is my opinion that Song erroneously assigned (E)-endoxifen NMR shifts as (Z)-endoxifen NMR shifts, and *vice versa*. As such, it is my opinion that Song provides a method for synthesis of endoxifen and subsequent

crystallization that results in compositions of isomerically pure (E)-endoxifen, *not* (Z)-endoxifen.

79. Song provides a five-step synthetic pathway for endoxifen production resulting in an isomerically impure mixture of endoxifen which is then purified using fractional crystallization in an attempt to obtain purified (Z)-endoxifen, (EX1005 (Song) at ¶¶ 29-59 and Examples 1-9), the products of which are quantified and characterized by ^1H NMR. Specifically, Song describes the fifth step of the endoxifen synthetic route to be a reaction of (2-(4-(1-(4-hydroxy-phenyl)-2-phenyl-but-1-enyl)-phenyloxy)-ethyl)-methyl-carbamic acid ethyl ester in ethylene glycol with hydrazine monohydrate and potassium hydroxide. The crude product was extracted with diethyl ether and the organic layer was washed with water and saline before being dried on anhydrous magnesium sulfate, filtered, and dried by distillation. The solid was then recrystallized with ethanol/water (5/5) to obtain 95% of endoxifen. Song then characterizes the endoxifen product by ^1H NMR. (*See* EX1005 (Song) at ¶¶ 89-91 (Example 8).)

80. The endoxifen mixture comprises methylene protons corresponding to the protons of **5**, referenced below (hydrogens explicitly drawn for clarity and numbered consistent with Elkins' numbering convention), reported at two different values, δ 3.94 ppm (*t*, $J=4.0$ Hz, 0.7H) and δ 4.09 ppm (*t*, $J=4.0$ Hz, 1.3H), which

contrary to Song's conclusions, would be understood by a POSA to be (Z)-endoxifen and (E)-endoxifen, respectively. (*Id.* At ¶ 91.)



Annotation of Methylene Protons of Endoxifen

81. As previously discussed, Ali assigns the methylene protons corresponding to the protons of **5** in (Z)-endoxifen to be δ 3.86 ppm (*t*, $J=5.56$ Hz, 2H, CH₂-O) and Ali further assigns the protons of **5** in (E)-endoxifen to be at δ 4.03 ppm. (EX2011 (Ali) at 22-23.) Further, Elkins assigns the methylene protons corresponding to the protons of **5** in (E)-endoxifen to be δ 4.03 ppm. (EX2002 (Elkins) at 11, 15.)

82. Accordingly, from the NMR data provided in Ali and Elkins, it is my opinion that a POSA would assign the peaks in the ¹H NMR presented by Song at δ 3.94 ppm (*t*, $J=4.0$ Hz, 0.7H) to be the methylene protons of (Z)-endoxifen, and the peaks at δ 4.09 ppm (*t*, $J=4.0$ Hz, 1.3H) to be the methylene protons of (E)-endoxifen. Consequently, from the integration provided in the ¹H NMR, Song

produces an isomeric mixture of endoxifen at a ratio of 1.3:0.7 (65%:35%) of (E)-endoxifen:(Z)-endoxifen. (EX1005 (Song) at ¶91.)

83. Song then performs fractional crystallization in methanol, Example 9, to afford an isomerically pure endoxifen composition quantified and characterized by ¹H NMR. (*Id.* at ¶94.) Song describes the product of the fractional crystallization to be a 47% yield of (Z)-endoxifen. (*Id.* at ¶93). As discussed above, the crude endoxifen mixture starting material from Example 8 had an isomeric ratio of (65%:35%) of (E)-endoxifen:(Z)-endoxifen which would make a yield of 47% (Z)-endoxifen impossible since the starting endoxifen composition would have only had 35% (Z)-endoxifen prior to fractional crystallization. Song reports the methylene protons corresponding to the protons of **5** shown above to be at δ 4.09 ppm (*t*, *J*=4.0 Hz, 2H), and incorrectly assigns this to be (Z)-endoxifen and claims to have a ratio of 1/99 of (E)-endoxifen:(Z)-endoxifen. (*Id.* at ¶93). As established above, a POSA would understand that the peak at δ 4.09 ppm (*t*, *J*=4.0 Hz, 2H) should be assigned to the methylene protons, corresponding to the protons of **5**, shown above, to (E)-endoxifen. (EX2011 (Ali) at 22; EX2002 (Elkins) at 11, 15.) Thus, it is my opinion that Song, contrary to its assertions, produced a composition of 99% (E)-endoxifen.

84. Song then describes fractional crystallization in a variety of other solvents resulting in (Z)-endoxifen but no ¹H NMR data is provided for these

compositions. (EX1005 (Song) at ¶¶96, 98, 100, 102 (Examples 10-13).) Although I don't have direct evidence in the form of ¹H NMR data, it seems probable that the same (E)-endoxifen and (Z)-endoxifen mischaracterization was reproduced for these compositions. Song describes a fractional crystallization in ethyl acetate to yield an isomeric ratio of 95:5 of (E)-endoxifen:(Z)-endoxifen (*id.* at ¶96), fractional crystallization in ethanol to yield an isomeric ratio of 99:1 of (E)-endoxifen:(Z)-endoxifen (*id.* at ¶98), fractional crystallization in isopropanol to yield an isomeric ratio of 96:4 of (E)-endoxifen:(Z)-endoxifen (*id.* at ¶100), and a fractional crystallization in acetonitrile to yield an isomeric ratio of 63:37 of (E)-endoxifen:(Z)-endoxifen. (*Id.* at ¶102.) Song's choice of solvents is also consistent with purification of (E)-endoxifen. For example, the use of ethyl acetate for fractional crystallization in Song necessarily teaches away from the purified (Z)-endoxifen compositions described in the '334 patent. The '334 patent teaches that (Z)-endoxifen is more soluble in ethyl acetate than (E)-endoxifen (EX1001 at 68;64-65), and therefore a POSA would expect a crystallization in ethyl acetate to result in a solid with a higher concentration of (E)-endoxifen than (Z)-endoxifen. It is my opinion that none of the fractional crystallizations described in Song result in a highly pure (Z)-endoxifen composition, but rather in highly pure (E)-endoxifen compositions.

85. Accordingly, Song teaches purification of an (E)/(Z) isomeric mixture to obtain purified (E)-endoxifen, *effectively teaching away* from purified (Z)-endoxifen compositions and any methods used to achieve those.

86. Song also describes a synthetic method of synthesizing an endoxifen citrate salt by dissolving an endoxifen solid in a citric acid solution in Example 15. (EX1005 (Song) at ¶¶105-106.) Since Song incorrectly identified the isomerically purified composition as (Z)-endoxifen, Example 15 actually teaches a method for making an (E)-endoxifen citrate salt, effectively teaching away from the '334 patent. Further, as discussed previously, dissolving an isomerically pure composition of endoxifen in acidic conditions would result in acid-promoted isomerization of endoxifen and therefore would likely greatly diminish the isomeric purity of the endoxifen composition. Notably, Song neither quantifies the isomeric ratio of the resulting salt nor comments on the acid-promoted isomerization. (*Id.*)

87. In sum, Song describes a synthetic method for creating an isomeric mixture of endoxifen and subsequent fractional crystallizations that result in highly pure (E)-endoxifen compositions, as opposed to the desired (Z) isomer. Song also does not disclose any methods of formulation or suggest the use of these compositions for use in any oral formulations.

VIII. THE '334 PATENT

88. It is my understanding that only claims 1 and 15 of the '334 patent are independent claims. Independent claim 1 is directed to a formulation claim for Formula III of highly pure (at least 90%) (Z)-endoxifen. Independent claim 15 is similar to claim 1 but is a method of delivering (Z)-endoxifen through oral administration of the formulated (Z)-endoxifen.

89. I understand the '334 patent is a Continuation of application No. 16/641,985, filed as application No. PCT/US2018/050272 on Sep. 10, 2018, now Pat. No. 11,261,151 (the "Parent"). I further understand the '334 patent claims priority to provisional application No. 62/693,885, filed on Jul. 3, 2018, provisional application No. 62/624,787, filed on Jan. 31, 2018, provisional application No. 62/556,884, filed on Sep. 11, 2017, and earliest provisional application, No. 62/556,799, filed on Sep. 11, 2017. The '334 patent issued on Feb. 7, 2023, from application No. 17/580,428, filed on Jan. 20, 2022.

90. The '334 patent teaches a synthetic pathway to create stable, highly pure (Z)-endoxifen. The starting isomeric mixture of (E)/(Z)-endoxifen is first subjected to crystallization. Because the inventors determined that (E)-endoxifen is much less soluble than (Z)-endoxifen in a variety of solvents, this initial crystallization step results in an enriched (Z)-endoxifen component (*e.g.*, a mother liquor or filtrate). The enriched (Z)-endoxifen component is then subjected to

further crystallization to obtain pure (Z)-endoxifen solid as a free base composition. The (Z)-endoxifen free-base solid composition obtained is shown to have increased stability in ambient conditions, with reduced isomeric conversion to the (E)-isomer.

91. The '334 patent provides working examples describing synthesizing (Z)-endoxifen at high levels of purity. For instance, the '334 patent quantifies the purity of intermediate products during the synthetic and purification pathways, which becomes particularly relevant for any synthetic pathway scale up.

92. The '334 patent also teaches product storage stability at Example 11, and impurity-free compositions of (Z)-endoxifen at Example 12. To my knowledge, no other reference has reported comparable levels of (Z)-endoxifen purity and stability, nor has Petitioner presented any such teaching in the cited art. The '334 patent further provides data showing the improved pharmacokinetics of the claimed formulations comprising highly pure (Z)-endoxifen compositions and demonstrating improved bioavailability at Example 15.

93. Briefly, the '334 patent teaches methods for obtaining isomerically pure (Z)-endoxifen by first utilizing an enrichment step for obtaining an enriched (Z)-endoxifen solution (*e.g.*, a mother liquor or filtrate) followed by a subsequent crystallization step for obtaining highly pure (Z)-endoxifen. Unlike the references cited in the Petition or discussed above, the '334 patent teaches oral formulations

incorporating this highly pure (Z)-endoxifen. The '334 patent further provides a stability analysis showing that the (Z)-endoxifen compositions synthesized are stable at ambient temperature and in bulk drug formulations, which has significant value for use in oral formulations and pharmaceutical drug product development. None of the cited references describe the same superior (Z)-endoxifen stability taught in the '334 patent. The '334 patent then describes biological and clinical testing for the oral formulations comprising highly pure (Z)-endoxifen compositions, thereby demonstrating significant and surprising improvements in (Z)-endoxifen bioavailability, particularly when compared to the results achieved from other endoxifen oral formulations (*i.e.*, endoxifen citrate) prior to the critical date, for example, the results set forth in EX1006 and EX1007.

IX. CLAIM CONSTRUCTION

94. It is my understanding that the Petitioner asserts that all terms should be given their plain and ordinary meaning but then suggests that the term “enteric capsule” found in claims 1, 3-4, 8, and 14-15 be defined as “a capsule ‘with one or more enteric coating agents,’ or an intrinsically enteric capsule that does not need an additional coating to provide the enteric property.” (Pet. at 9-10) (citing EX1001 at 39:19-30, 40:31-36). While I agree that the plain and ordinary meaning of “enteric capsule” is appropriate, I note that Petitioner’s suggested definition, omits the following passage from the specification: “to control or delay

disintegration and absorption of the compositions comprising endoxifen or salts thereof in the gastrointestinal tract and thereby provide a sustained action over a longer period of time.” (EX1001 at 39:22-26.)

95. Nevertheless, Petitioner’s proposed construction of “enteric capsule” has no impact on my opinions that each of the six Grounds fails to render the challenged claims anticipated or obvious.

96. If any further constructions are proposed or adopted, I reserve the right to amend or supplement my expert opinions.

X. GROUND 1: AHMAD DOES NOT ANTICIPATE CLAIMS 1, 2, 4, 15, 20-22 OF THE ’334 PATENT

A. Ahmad Does Not Enable A Person Of Ordinary Skill In The Art To Obtain High Purity (Z)-Endoxifen

97. I am informed that to anticipate a claim, a single reference must disclose expressly or inherently all claim limitations. The reference must also enable the POSA to practice the claimed invention without undue experimentation.

98. Because it is my opinion that Ahmad does not enable a POSA to synthesize (Z)-endoxifen at high levels of purity, much less free base (Z)-endoxifen at levels of purity above 90%, as required by the ’334 invention, Ahmad cannot anticipate the claims of the ’334 patent. In short, it is my expert opinion that Ahmad is incapable of teaching a POSA how to purify (Z)-endoxifen at higher than 90% purity.

99. Ahmad does not teach, suggest, or describe any meaningful amounts, ranges, or workable examples to achieve the purported synthesis of highly pure (Z)-endoxifen. Indeed, there are no examples, data, or general guidelines contained in Ahmad that will generate at least 90% (Z)-endoxifen. Accordingly, it is my opinion that a POSA is left with conclusory statements that are not enabling. A POSA would need more information, such as the types of solvents, the ratio of solvents, temperature, and other crystallization parameters for such a teaching to be enabling. No such information is provided by Ahmad.

100. It is my understanding that Dr. McConville stated that Ahmad “teaches the use of the Z-isomer of endoxifen, that ‘[o]ne object of the present invention is to provide E-endoxifen or Z-endoxifen with at least 80% purity, such as at least 90% pure or at least 95% pure or at least 98% pure or at least 99% pure or at least 100% pure.’” (EX1020 (McConville Decl.) at ¶31 (citing EX1003).) Dr. McConville further states that “Ahmad teaches that this purification can be accomplished by using crystallization or chromatography[,]” and that “achieving such levels of purity was well known in the art as disclosed by several references.” (EX1020 (McConville Decl.) at ¶3.) I disagree with each assertion.

101. It is my expert opinion that Dr. McConville fails to be precise in what the prior art teaches, and does not teach, with respect to endoxifen purification by improperly conflating the making of a salt versus a free base. The '334 patent is

clear from the outset as to the distinction between salts and the free base, recognizing the commercial availability of certain (Z)-endoxifen salts: “Commercially, endoxifen is available as an E/Z isomer free base mixture, as well as $\geq 98\%$ (Z)-endoxifen HCl and (Z)-endoxifen citrate salts. Stability of Z-endoxifen HCl salt in aqueous and solid forms has been previously published (Elkins et al. J Pharm Biomed Anal. 2014 January; 88:174-179).” (EX1001 at 82:3-8 (citing EX2002 (Elkins)).)

102. Ahmad, on its face, does not teach a POSA how to obtain highly purified (Z)-endoxifen. There are no working examples, and no minimum guidelines as to how a POSA could synthesize highly pure (Z)-endoxifen. Column 11 of Ahmad purports to describe embodiments where (Z)-endoxifen may be separated. (See EX1003 at 11:17-42.) However, specific values or guidance for temperature, solvent combinations, solvent ratios, agitation conditions, or other parameters are nowhere to be found. Only general statements are provided. Tellingly, no working example is found in the specification or described elsewhere. Ahmad presents vague statements such as “When a mixture of two solvents is used in the present invention, examples of ratios of one solvent to another are *e.g.*, in a range such as 9:1 to 1:9. (*e.g.*, 8:2, 7:3, 6:4; 5:5; 4:6; 3:7; 2:8; 1:9, and the like.).” (EX1003 at 11:36-39.) But the very next sentence, the specification states: “[h]owever, mixtures for use in the present invention are not limited to these ratios,

or to mixtures comprising only two solvents.” (EX1003 at 11:40-42.) In other words, because there are no meaningful guardrails, or boundaries, a POSA would be reduced to exhaustive trial and error with an almost unlimited number of possible combinations of parameters, the hallmark of undue experimentation.

103. Ahmad’s file history does not offer any additional guidance in enabling a POSA to make highly pure (Z)-endoxifen. I hold the same conclusion even if one is to incorporate by reference all of the references mentioned during Ahmad’s prosecution history. Ahmad and its progeny of incorporated references lack disclosures that characterize (Z)-endoxifen or sufficient descriptions of steps taken demonstrating success (*i.e.*, working examples). The references incorporated by Ahmad during its prosecution history, and that I have considered in detail, are EX1006 and EX1007. Thus, even considering all the documents referenced during the prosecution history of the Ahmad patent, including affidavits by the inventors, Ahmad does not enable a person of ordinary skill in the art to synthesize highly pure (>90%) (Z)-endoxifen for oral formulation.

104. Tellingly, Ahmad does not characterize either (E)-endoxifen or (Z)-endoxifen, and as consequence the isomerization ratios remain unquantified and unknown. It is my understanding that Petitioner recognized as much: “Ahmad 2010 and 2012 do not disclose whether the endoxifen is (E), (Z) or a mix.” (Pet. at 55.) Without this critical data, a POSA would be attempting to get to pure (Z)-

endoxifen through mere guesswork. This is untenable and constitutes undue experimentation.

105. Ahmad also teaches an entirely different synthetic pathway than what is described in the '334 patent, and thus it likely starts with and produces different (E)/(Z) ratios, as discussed above. Ahmad does not enable a POSA to obtain an isomerically pure endoxifen composition, at least because Ahmad does not teach any methods for purification from the endoxifen composition obtained. As discussed above, a critical step to for (Z)-endoxifen purification would be a first crystallization from an endoxifen isomeric mixture to obtain an enriched (Z)-endoxifen solution with a subsequent crystallization to afford a pure (Z)-endoxifen solid. Instead, the synthetic pathway described in Ahmad ends with an ethyl acetate-heptane crystallization of the crude endoxifen product with no analysis or characterization to determine the isomeric ratio. As previously discussed, an ethyl acetate crystallization effectively teaches away from the '334 patent because the '334 patent teaches that (Z)-endoxifen is more soluble in ethyl acetate than (E)-endoxifen (EX1001 at 68;64-65), and therefore a POSA would expect a crystallization in ethyl acetate to result in a solid with a higher concentration of (E)-endoxifen than (Z)-endoxifen. As discussed in my consideration of Ali, which presents a similar synthetic pathway to Ahmad, an ethyl acetate-heptane

crystallization from the crude endoxifen product would likely result in an (E):(Z) ratio of 5.8:4.2. (EX2011 (Ali) at 22.)

106. At best, Ahmad's file history does no more than merely suggest that Ahmad synthesized and purified 80% (Z)-endoxifen citrate salt, although no method for purification or characterization of a (Z)-endoxifen composition of 80% purity is described at any point in Ahmad. Further, there is a complete lack of any description of the synthesis of a citrate salt in the original specification of Ahmad or any of the references relied on during its prosecution (*e.g.*, EX1006, EX1007).

107. Although the Petitioner and Dr. McConville attempt to paint a picture that this is "close enough" to free base (Z)-endoxifen, a salt form of (Z) is fundamentally distinct, at a minimum, due to the variation of stability between a salt of (Z)-endoxifen and a free base of (Z)-endoxifen, as evaluated in the '334 patent. (EX1001 at Example 11.) Further, a POSA would appreciate that various oral formulations, such as a salt oral formulation and a free base oral formulation, would have a significant influence on drug stability, oral formulation stability, dissolution rates, and overall formulations to be used in clinical practice. (EX2017 (Gupta) at 9, 10.) As already stated, the '334 patent specification recognized the commercial availability of (Z)-endoxifen citrate salts, (EX1001 at 82:3-5), but noted that "[t]here remains a need for (Z)-endoxifen free base preparations that are sufficiently stable for preparation of pharmaceutical compositions . . . suitable for

administering to subjects, for instance, at ambient temperatures as well as at higher temperature and humidity.” (*Id.* at 82:37-42.) As described in Elkins, a (Z)-endoxifen HCl salt showed “facile conversion of (Z)- to (E)-isomer at temperatures above 25°C,” (EX2002 (Elkins) at 9), as compared to the stability of the (Z)-endoxifen free base compositions described in the ’334 patent (*see* EX1001 at Example 11). Hence, to the extent the Petition and/or Dr. McConville imply as much, I disagree.

108. It is also my understanding that anticipation requires more than the prior art being “close enough.” Because the salt and free base forms of endoxifen are distinct chemical entities with completely separate properties, they are certainly not “close enough,” and Ahmad does not anticipate the challenged claims.

B. Ahmad’s Synthetic Pathway Is Incapable Of Yielding Isomerically Pure (Z)-Endoxifen

109. It is my opinion that the synthetic pathway as described by Ahmad, at best, yields higher ratios of (E)-endoxifen, or a ratio of isomers that is close to 1:1. This is in large part because Ahmad fails to recognize that there is an enrichment step needed to be performed prior to crystallization as presented in the ’334 patent. One glaring problem with Ahmad is that nowhere in Ahmad is there a teaching of a purification method or any characterization of isomeric purity.

110. Moreover, Ahmad, taken as a whole—including the prosecution history—suggests the use of an endoxifen citrate salt oral formulation, the

synthesis of which would be deleterious to the stability of (Z)-endoxifen. As discussed, previously, acidic conditions, such as citric acid solutions described in the cited art, would result in acid-promoted isomerization of a pure isomeric composition of endoxifen. Absent specific methods that would overcome the problem of acid-promoted isomerization, it is my opinion that a POSA would not be able to arrive at an isomerically pure endoxifen salt and would more likely have a salt with an isomeric mixture of (Z)-endoxifen and (E)-endoxifen.

111. As previously mentioned, none of the references discussed during prosecution or adduced by Petitioner rectify Ahmad's inability to teach a POSA how to obtain isomerically pure (Z)-endoxifen.

C. Ahmad's Lack Of Enablement Cannot Be Remedied By Relying On Background References Liu And Song

112. As a threshold matter, it is my understanding that a reference not formally raised as the basis for a ground can still serve to provide the background knowledge of an ordinarily skilled artisan. Accordingly, it is my understanding that Petitioner discussed Liu and Song in this circumscribed role. (Pet. at 30.) I offer my analysis of both references below.

113. With respect to Liu (EX1004), Dr. McConville states that "Liu teaches an efficient method of generating highly pure (Z)-endoxifen through crystallization. Liu teaches that its method achieved '1698 g (34%) of (Z)-endoxifen, with an isomeric purity of 99% (HPLC analysis). In short, Liu teaches

a method of making highly pure (Z)-endoxifen.” (EX1020 (McConville Decl.) at ¶35 (internal citation omitted).) I have provided further description of Liu in the background art section of this declaration.

114. However, Dr. McConville’s oversimplification fails to recognize that, as discussed above, Liu’s synthetic pathway is distinct from what is taught in the ’334 patent and could result in a different stability profile and different impurity profiles, both of which are important to characterize for further use of a composition for an oral formulation. Therefore, based on the disclosure of Ahmad and the background art of Liu, a POSA would not have been motivated to use the compositions of endoxifen described therein to make an oral formulation comprising at least 90% (Z)-endoxifen as taught in the ’334 patent.

115. Accordingly, a POSA could not merely “pick Liu off the shelf” to synthesize pure (Z)-endoxifen suitable for use in an oral formulation in the hopes of bridging Ahmad’s enablement gap. Without more, Liu cannot serve as a “background reference.”

116. With respect to Song (EX1005), Dr. McConville states that Song discloses “a method of preparing endoxifen . . . and provid[ing] Z-form endoxifen of at least 99% purity in the mixture to have a therapeutic effect. . . . In short, Song also teaches a method of making highly pure (Z)-endoxifen.” (EX1020 (McConville Decl.) at ¶ 37 (internal citations and quotation marks omitted).)

117. As discussed in detail above, it is my opinion that Song has incorrectly assigned the ¹H NMR spectra to (Z)-endoxifen where it should instead be correctly assigned as (E)-endoxifen. Therefore, it is my opinion that Song actually teaches methods of making highly pure (E)-endoxifen.

118. It is my opinion that similarly to Ahmad, Song fails to recognize that an enrichment step is critical to purifying (Z)-endoxifen over (E)-endoxifen. As discussed in detail previously, this is so because a first crystallization of a crude endoxifen isomeric mixture would likely result in pure (E)-endoxifen compositions and further purification is needed to afford a pure (Z)-endoxifen composition.

119. Accordingly, Song is not only inadequate as a background reference, but Song is antithetical to aims of the '334 patent invention.

XI. GROUND 2: AHMAD DOES NOT RENDER CLAIMS 1, 2, 4, 15, 20-22 OF THE '334 PATENT OBVIOUS

A. Because Ahmad Is A Standalone Reference, Its Lack Of Enablement Forecloses Its Use In An Obviousness Reference

120. As a threshold matter, it is my understanding that a reference must enable the portions of the disclosure being relied upon in an obviousness analysis if that reference is a “standalone” reference. Ahmad is a standalone reference for purposes of Ground 2.

121. Because Ahmad does not enable a POSA to synthesize highly purified (Z)-endoxifen or oral formulations thereof, Ahmad cannot render independent

claims 1 and 15 of the '334 patent obvious. And I did not see any explanation in the Petition or in the expert declaration of Dr. McConville as to how a POSA would be able to modify Ahmad to end up with the claimed 90% (Z)-endoxifen or oral formulations thereof. All other claims fall because they necessarily depend on independent claims 1 or 15.

122. The same analysis outlined under Ground I is appropriate here. Specifically, Ahmad, along with all incorporated and/or considered references during prosecution—EX1006 and EX1007—would not render the challenged claims obvious. The lack of enablement, demonstrated by the lack of workable examples, ranges, examples, or data, forecloses the viability of Ahmad as a standalone obviousness reference.

B. Liu And Song, Though Not Formally Forming The Basis For Ground 2, Cannot Salvage Petitioner's Obviousness Challenge

123. It is my understanding that a POSA could theoretically leverage enabling disclosures of other references to bridge any existing gaps in a standalone reference. Because of this possibility, I offer my expert analysis as to the background references of Liu and Song.

124. As I have previously noted, Liu has a different synthetic pathway to that of the '334 invention as well as to the synthetic pathway of Ahmad. This distinction already raises serious questions as to any motivation to combine. That is, it is highly unlikely that a POSA implementing the Liu synthetic pathway would

go down the same or similar path outlined in the '334 patent. As to Song, I have already described how Song is antithetical to the '334 patent by teaching methods of purifying pure (E)-endoxifen compositions.

125. Critically, neither Song nor Liu teach any subsequent steps that are significantly free from impurities for the purposes of devising an oral formulation for human use. Thus, this central aim of the '334 invention is not met. Similarly, neither Liu nor Song discuss the stability profile of the end products. As such, Liu and Song also flout this second central aim of the '334 invention. These two objectives of the '334 patent invention are necessary considerations and prerequisites for pharmaceutical commercialization.

126. It is my opinion that Liu and Song could not be combined with Ahmad to yield the '334 invention, at least because of the deficiencies abovementioned. It is also my opinion that Liu and Song do not bridge the enablement gaps of Ahmad. Notably, none of the references of Ahmad, Liu, or Song, or any combination thereof, teach oral formulations of greater than 90% (Z)-endoxifen or the surprising and superior drug stability and bioavailability results described in the '334 patent when compared to other oral formulations of endoxifen (*i.e.*, endoxifen citrate from EX1006 or EX1007).

C. There Is No Evidence That A POSA Would Have A Reasonable Expectation Of Success In Making The Claimed 90% (Z)-Endoxifen

127. No evidence was adduced as to reasonable expectation of success at synthesizing stable (Z)-endoxifen at high levels of purity by Petitioner, and no such evidence exists upon consideration of the myriad considered references in combination with Ahmad.

128. It is my opinion, after careful consideration of the references in the prosecution history and Petitioner's exhibits, that a POSA would not have a reasonable expectation of success at attaining the '334 patent invention.

129. To the contrary, as previously discussed, Ahmad, in teaching the use of an endoxifen citrate salt oral formulation for administration to a subject (solely by reliance on EX1006 in the prosecution history), arguably teaches away from an isomerically stable (Z)-endoxifen composition. In other words, the use of an endoxifen citrate salt oral formulation further strengthens my opinion that Ahmad is not enabled and that a POSA, in possession of Ahmad, would not have a reasonable expectation of success. Also as previously discussed, salt oral formulations and free base oral formulations would be expected by a POSA to have significantly different properties including: drug stability, oral formulation stability, dissolution rates, and overall formulations to be used in clinical practice. (EX2017 (Gupta) at 9, 10.)

130. Compounding on the failure to furnish a POSA with the means to synthesize a (Z)-endoxifen suitable for a pharmaceutical formulation, EX1003 also fails to acknowledge the importance of an isomerically stable (Z)-endoxifen composition that would not equilibrate with (E)-endoxifen at ambient temperatures and humidity over time. Neither Ahmad, nor any of the references cited by Petitioner, including background references Liu and Song, provide data on the stability of synthesized (Z)-endoxifen. Thus, a POSA would not have a reasonable expectation of success at attaining a stable oral formulation via the use of Ahmad, standing alone, or in combination with any other reference adduced by Petitioner and Dr. McConville.

131. Tellingly, Dr. McConville does not articulate how Ahmad should be modified, in light of the background references, in order to achieve the '334 invention with a reasonable expectation of success.

XII. GROUND 3: AHMAD IN VIEW OF COLE DO NOT RENDER CLAIMS 5-8, 16, 17 OF THE '334 PATENT OBVIOUS

132. It is my expert opinion that there is no articulable motivation to combine Ahmad with Cole and expect a reasonable expectation of success from said combination to reach the claimed invention of the '334 patent.

133. Cole as a reference teaches methods of formulating enteric compositions suitable for oral formulation including HPMC capsules with an enteric coating. Cole is silent to the use of these formulation with endoxifen

compositions and instead investigates the enteric properties of these compositions with a different pharmaceutical, Paracetamol. Cole does not describe any methods or compositions relating to endoxifen and therefore would not provide any motivation or enabling disclosure to make the enteric formulations disclosed therein with a composition comprising at least 90% (Z)-endoxifen.

134. As discussed above, Ahmad also does not enable the synthesis of compositions comprising at least 90% (Z)-endoxifen suitable for the use in oral formulations.

135. Petitioner attempts to oversimplify the challenges encountered when preparing oral formulations (*e.g.*, enteric compositions), such as in the '334 patent. For example, Dr. McConville suggests that it “would have been very routine in the art to simply take endoxifen made by the processes discussed [therein] and enclose them in a capsule and use enteric coating to ensure that the drug was released in the intestine rather than the stomach,” (EX1020 (McConville Decl.) at ¶ 71.) I strongly disagree with Dr. McConville’s oversimplification of what a POSA would readily understand to be a highly technical and unpredictable endeavor. As just a few non-limiting examples of the challenges faced, a POSA must consider potential interactions between enteric coatings and pharmaceutical compositions as well as variations in release profiles for salts versus corresponding free acids or bases of a given oral formulation. (EX2017 (Gupta) at 10.)

136. It is my opinion that a POSA would not have been motivated to combine the teachings of Cole with the endoxifen compositions of Ahmad to reach the claimed invention of the '334 patent, at least because a POSA would not have been able to synthesize a composition comprising at least 90% (Z)-endoxifen for the use in an oral formulation from either reference. Further, a POSA would not know how to achieve the desired characteristics of a delayed release oral formulation (*e.g.*, enteric formulation) without undue experimentation. Tellingly, the Petition and Dr. McConville's declaration do not shed any light on the lack of motivation to combine, beyond conclusory statements.

137. Accordingly, Cole cannot cure Ahmad's deficiency and as such the combination cannot render the challenged dependent claims obvious.

XIII. GROUND 4: AHMAD IN VIEW OF BENAMEUR DO NOT RENDER CLAIM 3 OF THE '334 PATENT OBVIOUS

138. It is my expert opinion that there is no articulable motivation to combine Ahmad with Benameur and expect a reasonable expectation of success from said combination to reach the claimed invention of the '334 patent.

139. Benameur describes enteric formulations comprising capsule dosage forms integrated with enteric functionalities for uncoated oral formulations. Benameur describes that an uncoated enteric formulation is beneficial to avoid the high temperatures associated with enteric coating applications for increased stability of active pharmaceuticals that may be sensitive to thermal degradation.

Benameur, like Cole, does not describe oral formulations comprising endoxifen or provide a motivation to combine the enteric formulations with an endoxifen composition comprising at least 90% (Z)-endoxifen.

140. As discussed above, Ahmad also does not enable the synthesis of compositions comprising at least 90% (Z)-endoxifen suitable for the use in oral formulations.

141. Also as discussed above, oral formulations are known to have different controlled-release characteristics (*e.g.*, enteric properties) dependent on the oral formulation used (*e.g.*, a salt oral formulation or a free base oral formulation). (EX2017 (Gupta) at 10.)

142. It is my opinion that a POSA would not have been motivated to combine the teachings of Benameur with the endoxifen compositions of Ahmad to reach the claimed invention of the '334 patent, at least because a POSA would not be able to synthesize a composition comprising at least 90% (Z)-endoxifen for the use in an oral formulation from either reference. Further, a POSA would not know how to achieve the desired characteristics of a delayed release oral formulation (*e.g.*, enteric formulation) without undue experimentation. Tellingly, neither the Petition nor Dr. McConville's declaration shed any light on the lack of motivation to combine, beyond conclusory statements.

143. Accordingly, Benameur cannot cure Ahmad's deficiency and as such the combination cannot render the challenged dependent claim obvious.

XIV. GROUND 5: AHMAD IN VIEW OF STEGEMANN AND/OR THE HPE DO NOT RENDER CLAIMS 9-13 OF THE '334 PATENT OBVIOUS

144. It is my expert opinion that there is no articulable motivation to combine Ahmad with Stegemann and/or HPE and expect a reasonable expectation of success from said combination to reach the claimed invention of the '334 patent.

145. Stegemann describes hard gelatin capsules for use in oral formulations. The Handbook of Pharmaceutical Excipients (HPE) describes excipients for the use in pharmaceutical formulations. Neither reference describes oral formulations comprising endoxifen or provides a motivation to combine the gel capsules or pharmaceutical excipients with an endoxifen composition comprising at least 90% (Z)-endoxifen.

146. As discussed above, Ahmad also does not enable the synthesis of compositions comprising at least 90% (Z)-endoxifen suitable for the use in oral formulations.

147. Oral formulations are known to have variable compatibilities (*e.g.*, chemical stabilities and chemical interactions) with pharmaceutical excipients, and those interactions depend on the oral formulation used (*e.g.*, a salt oral formulation or a free base oral formulation). (EX2017 (Gupta) at 9.)

148. It is my opinion that a POSA would not have been motivated to combine the teachings of Stegemann or the HPE with the endoxifen compositions of Ahmad to reach the claimed invention of the '334 patent, at least because a POSA would not have been able to synthesize a composition comprising at least 90% (Z)-endoxifen for the use in an oral formulation from either reference. The Petition and Dr. McConville's declaration do not shed any light on the lack of motivation to combine, beyond conclusory statements.

149. Accordingly, because neither Stegemann and/or HPE can cure Ahmad's deficiencies, the alleged combination cannot render the challenged dependent claims obvious.

XV. GROUND 6: AHMAD IN VIEW OF AHMAD 2010 AND AHMAD 2012 DO NOT RENDER CLAIMS 14, 18, AND 19 OF THE '334 PATENT OBVIOUS

150. It is my expert opinion that Ahmad, in view of Ahmad 2010 and Ahmad 2012, do not render claims 14, 18 and 19, related to dosing and pharmacokinetics, obvious. A POSA would not have had a reasonable expectation of success for producing the oral formulations of the '334 patent comprising at least 90% pure (Z)-endoxifen free base in view of the prior teachings of superior solubility and efficacy for tamoxifen citrate oral formulations (EX2016 (Buchanan) at 5) as well as prior teachings of oral formulations of endoxifen citrate (EX1006 and EX1007). Despite the lack of expectation of success, the '334 patent

establishes that oral formulations comprising the free base of (Z)-endoxifen surprisingly exhibited superior bioavailability as compared to oral formulations of endoxifen citrate. (EX1001 at 95:59-62.)

151. The references relied upon do not inherently disclose the pharmacokinetic limitations recited in claims 18 and 19 of the '334 invention. As previously discussed, Ahmad at best synthesized an endoxifen isomeric mixture around a 1:1 ratio of (E)-endoxifen:(Z)-endoxifen. Further, both EX1006 and EX1007 describe administration of an endoxifen citrate salt oral formulation and are silent as to isomeric purity. Based solely on the file history of Ahmad, the endoxifen compositions used in EX1006 was “at least 80% Z-endoxifen and was in the form of a citrate salt of endoxifen.” (EX2010 (Ahmad File History) at 96.) No explanation is given by Petitioner or Dr. McConville as to why a POSA would expect the pharmacokinetic profile of 90% (Z)-endoxifen free base to be subsumed within the pharmacokinetic profile of 80% (Z)-endoxifen in citrate salt form. If anything, a POSA would presume that different compounds, even stereoisomers, present distinct pharmacokinetic profiles. For example, related oral formulations (*e.g.*, free base formulations and salt oral formulations) can vary not only in their solubility, but also in stability, bioavailability, formulation properties, and formulation considerations. (EX2017 (Gupta) at 13.)

152. The dosage range, as recited in claim 14 of the '334 patent, is determined after careful consideration of various factors, including safety and efficacy of the precise compound being dosed. Based on my experience, a POSA would not simply infer dosage of 90% (Z)-endoxifen free base oral formulation from dosage range for a less pure (Z)-endoxifen citrate salt oral formulation. Ahmad does not disclose an oral formulation of 90% pure (Z)-endoxifen and does not enable a POSA to devise such dosage without engaging in a significant amount of experimentation.

153. As to claims 18 and 19, which deal with Area Under the Curve (AUC) and maximum blood plasma concentration (C_{max}), it is my understanding that the '334 invention has distinct pharmacokinetic profiles when compared to the Ahmad references. As demonstrated in Table 22 of the '334 patent, which compared the bioavailability of the '334 invention against the data from the Ahmad references (and other references), the pharmacokinetic profile of the claimed invention is not identical to the pharmacokinetic profile of the formulations tested in EX1006 and EX1007. In fact, the bioavailability of the '334 invention is *superior*. (See EX1001 at 95:59-62 (showing the claimed formulation exhibited 154%, 204%, and 150% higher average drug concentration at steady state than the Ahmad formulations).) The notable improvement in bioavailability for the compositions of

the '334 patent suggest tangible differences between, and improvement over, the Ahmad compositions.

154. This superior bioavailability data evinces the unexpected results of the '334 invention, further strengthening the fact that the '334 invention is non-obvious over the prior art.

XVI. SECONDARY INDICIA OF NONOBVIOUSNESS

155. As I understand it, some examples of objective indicia of non-obviousness can reveal the non-obvious nature of an invention. It is my opinion that *at least* the following factors are present with respect to the '334 invention: unmet need and unexpected or surprising results of the claimed invention.

156. With respect to a long felt need, the '334 patent establishes that “there remains unmet medical need for new compositions and methods for the treatment and/or prevention of hormone-dependent breast and reproductive tract (gynecologic) disorders,” (*see* EX1001 at 2:50-54), which the enteric oral formulations comprising the stable purified (Z)-endoxifen compositions described therein achieve. Specifically, the enteric oral formulations comprising at least 90% (Z)-endoxifen achieve superior bioavailability as compared to EX1006 and EX1007, (EX1001 at 95:59-62), demonstrating their ability for use as new compositions for treatment and/or prevention of hormone-dependent breast and reproductive tract (gynecologic disorders).

157. With respect to unexpected results, the methods of synthesizing endoxifen and purifying (Z)-endoxifen resulted in isomerically purified (Z)-endoxifen compositions with unexpected stability as compared to the hydrochloride salt. Specifically, Example 11 of the '334 patent demonstrates surprising stability of the (Z)-endoxifen free base purified by methods described therein with stability of at least 90% (Z)-endoxifen for “at least 6 months under conditions of ambient and high temperature and humidity.” (EX1001 at 82:42-49.) The bulk drug stability of (Z)-endoxifen is shown to be stable for at least 9 months at 5°C and 25°C at 60% relative humidity (RH) which is predictive of long-term stability (at least 18 months) at ambient temperatures. (EX1001 85:18-27.) The results of superior bioavailability of the oral formulations of the '334 patent were also unexpected due to the prior teachings of the FDA-approved tamoxifen citrate oral formulations and endoxifen citrate oral formulations. (EX1006 and EX1007). Without the benefit of the teachings of the '334 patent, the citrate salt oral formulations would have been contemplated by a POSA to increase endoxifen's aqueous solubility and efficacy. (EX2016 (Buchanan) at 5.) However, as shown in the '334 patent, oral formulations comprising the free base of endoxifen surprisingly exhibited superior bioavailability as compared to oral formulations of endoxifen citrate. (See EX1001 at 95:59-62 (showing the claimed formulation

exhibited 154%, 204%, and 150% higher average drug concentration at steady state than the endoxifen citrate formulations of EX1006 and EX1007).)

XVII. CONCLUSION

158. For at least the reasons I discuss above, it is my opinion that the challenged claims of the '334 patent are not anticipated and non-obvious.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

November 29, 2023

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'SGD', written over a horizontal line.

Stephen Graham Davies, D. Phil.