

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

INTAS PHARMACEUTICALS LTD.
Petitioner,

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 RESPONSE**

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 (“the ’334 Patent”). My expert testimony responds to the laboratory work performed by Petitioner’s expert, Dr. Ron Bihovsky (“Dr. Bihovsky”), and the invalidity opinions associated therewith (EX1030).

2. In forming the opinions expressed in this supplemental declaration, I have considered Petitioner’s Reply to Patent Owner’s Response and the attendant Petitioner’s Exhibits, as well as Dr. Bihovsky’s expert declaration (EX1030), testimony (EX2027, “Bihovsky Dep. Tr.”), and laboratory notebook. Additionally, I have considered the exhibits of record in this case. I have also based my opinions on my professional and academic experiences in the relevant areas of organic and medicinal chemistry.

II. QUALIFICATIONS AND BACKGROUND

3. 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 set out in the April 24, 2024 Expert Declaration of Stephen Graham Davies, D. Phil.

in Support of Patent Owner's Response (EX2020), and by my *curriculum vitae* (EX2013), both of which are hereby incorporated.

4. I understand that the Board adopted Atossa's definition of a POSA in its Institution Decision (Paper 11 at 8-9), which I apply when offering my opinions:

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.

5. I note, however, that Petitioner's Reply now asserts that "[a] POSA . . . should have experience in formulating" dosage forms, which Petitioner contends I lack to provide such opinions. (Paper 16 at 1-2.) However, I have extensive experience in formulation science, including formulation dosage forms using various active pharmaceutical ingredients. (EX2013 at 3, listing the companies I have founded including several focused on the preparation and development of compounds for potential pharmaceutical use.) Accordingly, I meet both the Board's adopted definition of a POSA and Petitioner's new definition of a POSA.

III. Dr. Bihovsky's Laboratory Work

6. I understand Dr. Bihovsky attempted to perform the synthetic and purification methods of Liu (EX1004) in support of Petitioner's position regarding the enablement of Ahmad. (EX1030 at ¶¶ 36-52.) However, none of Dr. Bihovsky's experimental results change my opinions.

7. Dr. Bihovsky alleged both in his declaration and during his deposition that he carried out the procedure of Liu, stating that his "experiments following Liu's procedures provided (Z)-endoxifen with isomeric purities of 93% (recrystallization) and 100% (isomerization followed by recrystallization)." (EX1030 at ¶ 51.) However, Dr. Bihovsky admitted during his deposition that while he recorded his experimental procedures in a laboratory notebook, there was information contained in his laboratory notebook that was not reflected in his expert declaration. (See EX2027 (Bihovsky Dep. Tr.) at 33:17-20; 34:21-35:1.) While Dr. Bihovsky stated that he "tried to follow Liu as precisely as possible" (EX2027 at 40:2-3), he pointed to two steps of Liu's procedure that he modified during his experimental work (see EX2027 at 39:8-21; 40:6-14.)

8. However, in reviewing Dr. Bihovsky's laboratory notebook, it is my opinion that Dr. Bihovsky modified several steps of the Liu procedure that are not described in his expert declaration. I further note that the scale on which Dr. Bihovsky performed his experimental work was one-thousand and two-thousand

times smaller than the scale disclosed by Liu. A POSA would know that reactions on a small scale are not useful models to predict the same reactions on a large scale.

9. For example, Example 2 of Liu describes the synthesis of (4-(2-bromoethoxy)phenyl)(4-hydroxyphenyl)methanone as the first step in the synthetic pathway to endoxifen. (See EX1004 at ¶¶ [0062]–[0063].) Liu provides the following:

Zinc bromide (3.011 kg, 13.1 mol) and polyphosphoric acid (16.5 kg) were charged into a 20-L reaction vessel and stirred well while heated to 45°C. 4-Hydroxybenzoic acid (974 g, 6.98 mol) and 2-phenoxyethyl bromide (1302 g, 6.34 mol) were added. Phosphorus tribromide (2.72 kg, 9.83 mol) was added via an addition funnel over a period of 2.5 hours at a rate as to keep temperature below 50°C. Stirring at 40 - 50°C was continued for 1 hour and overnight (16 hours) without heating. Completion of the reaction was confirmed by NMR.

(EX1004 at ¶ [0062].)

10. By contrast, Dr. Bihovsky's laboratory notebook indicates that when he analyzed the reaction mixture by thin-layer chromatography (TLC), he observed mostly starting material. Dr. Bihovsky then described subsequently heating the reaction mixture to 50 °C for 2.5 hours, followed by 75 °C under a calcium chloride drying tube before proceeding with the reaction workup described in Liu. Finally, Dr. Bihovsky purified the reaction product by chromatography on silica gel using a combination of petroleum ether and ethyl acetate. Liu, however, does not disclose heating the reaction mixture to 75 °C, using a calcium chloride drying tube, or using

silica gel chromatography—let alone chromatography with the specific solvent system used by Dr. Bihovsky.

11. Dr. Bihovsky further described several repetitions of the reaction of Example 2, wherein he heated the reaction mixture to various temperatures for varying amounts of time. Further modifications include using a nitrogen bubbler, oven-drying the zinc bromide starting material at 230 °C, and filtering the reaction mixture over Celite®. These modifications are neither taught nor suggested by Liu.

12. For the synthesis of (4-(2-bromoethoxy)phenyl)(4-hydroxyphenyl)methanone, Dr. Bihovsky reported yields of 33%, 27%, and 46%, while Liu reported an 85% yield. (*See* EX1004 at ¶ [0063].)

13. In Example 3, Liu provides the second step of the synthetic method to prepare 4-[1-[4-(2-bromoethoxy)phenyl]-2-phenyl-1-butenyl]-phenol. (EX1004 at ¶ [0065].) During this step, Liu describes first suspending zinc dust in anhydrous dimethoxyethane under argon gas and cooling to 2 °C. Titanium tetrachloride was then added, and the temperature inside the reactor was kept below 25 °C. The mixture was then heated to reflux and stirred for one hour, and left overnight at ambient temperature. (*Id.*) The reactor was cooled to 5°C, and a solution of propiophenone and (4-(2-bromoethoxy)phenyl)(4-hydroxyphenyl)methanone in anhydrous dimethoxyethane was added to the reaction in one portion. The mixture was stirred and heated at reflux for six hours, then cooled to 60 °C and left overnight

at ambient temperature. The temperature inside the reactor was then cooled to -3 °C and methyl iso-butyl ether was added. A 5% aqueous HCl solution was added via an addition funnel, and the mixture was stirred for two hours before the organic phase was separated. The remaining suspension was then passed through a Celite® pad to remove the remaining excess of zinc dust. The aqueous filtrate was extracted three times with methyl iso-butyl ether, and the combined organic extracts were washed with brine and dried over magnesium sulfate. Separation of magnesium sulfate and removal of solvents *in vacuo* gave a brown oily residue, which was purified by column chromatography on silica gel eluted with methylene chloride. Collected fractions were combined and concentrated *in vacuo* to give a white solid, which was combined with n-heptane and stirred for one hour at 45 °C followed by stirring at ambient temperature for 16 hours. The solid was then separated by filtration and dried *in vacuo* for 72 hours at ambient temperature to provide 4-[1-[4-(2-bromoethoxy)phenyl]-2-phenyl-1-butenyl]-phenol. (See EX1004 at ¶¶ [0065]–[0066].)

14. By contrast to the second synthetic step of Liu, Dr. Bihovsky combined zinc with dimethoxyethane and cooled the reaction mixture under nitrogen, followed by addition of titanium chloride and refluxing for one hour. It is not specified in Dr. Bihovsky's laboratory notebook whether the zinc used was zinc dust (as opposed to zinc turnings or other commercially available forms of elemental zinc), nor whether

the dimethoxyethane used was anhydrous. Dr. Bihovsky then cooled the reaction mixture in an ice bath and added a solution of propiophenone and (4-(2-bromoethoxy)phenyl)(4-hydroxyphenyl)methanone in dimethoxyethane. It is not clear whether Dr. Bihovsky allowed the reaction mixture to stir overnight at ambient temperature prior to addition of the solution of propiophenone and (4-(2-bromoethoxy)phenyl)(4-hydroxyphenyl)methanone in dimethoxyethane, as taught by Liu, in addition to the lack of details regarding the specific reagents used.

15. In Example 4, Liu describes preparing a mixture of (E)-endoxifen and (Z)-endoxifen. Liu describes charging a methylamine solution (33% solution in ethanol) and then 4-[1-[4-(2-bromoethoxy)phenyl]-2-phenyl-1-butenyl]-phenol into a jacketed reactor and heating at 33 °C for 21 hours, and monitoring the reaction progress by TLC. Upon completion of the reaction, the solvent was removed, and the resulting solid was dissolved in methylene chloride and the resultant solution was washed with an aqueous mixture of sodium carbonate and sodium bicarbonate. The aqueous phase was re-extracted once with methylene chloride and the combined organic solution was dried over sodium sulfate, filtered, and evaporated to provide a solid. Acetone was then added to this solid and removed *in vacuo* twice. The solid was then recrystallized in acetone by heating to 65 °C, followed by slow cooling to 20 °C for 19 hours and then kept in a refrigerator at -10 °C for four days. The resulting crystalline material was collected by filtration and dried *in vacuo* to give a

mixture of (E)-endoxifen and (Z)-endoxifen. The filtrate was concentrated to provide an oily residue which was dissolved in boiling acetone and then stored for 4 weeks at -10 °C. Liu describes collecting the resulting crystalline material by filtration and drying it *in vacuo*, while the filtrate of the second crop, containing mostly impurities and E-isomer, was discarded. Liu reported a total yield of 87% and an isomeric ratio (E:Z) of 51:47. (See EX1004 at ¶¶ [0068]–[0070].)

16. Dr. Bihovsky modified the procedure of Liu's Example 4 by using centrifugation to separate the liquids and solids, rather than filtration—as noted in his expert declaration. (See EX1030 at 28 n.2.) Dr. Bihovsky's expert declaration reports an E:Z ratio of 67:33 by nuclear magnetic resonance (NMR) spectroscopy. (See *id.* at ¶ 40.)

17. Example 5 of Liu provides a recrystallization procedure to obtain (Z)-endoxifen from an approximately 50:50 mixture of (E)-endoxifen and (Z)-endoxifen. Liu describes dissolving endoxifen in hot isopropyl acetate at 88 °C and cooling the solution to 23 °C for six hours. The resulting crystalline material was collected by filtration, washed with isopropyl acetate, and dried *in vacuo* to provide a material with an E:Z ratio of 68:30. The filtrate was concentrated to provide a material having an E:Z ratio of 19:77. (See EX1004 at ¶ [0072].)

18. Example 6 of Liu further describes isomerizing endoxifen having an E:Z ratio of 70:30 to approximately 70% (Z)-endoxifen by heating the initial

material in isopropyl acetate at 85 °C for 2 hours. The solution was cooled slowly to 15 °C, resulting in the preferential crystallization of the (E)-isomer. The mother liquor was removed, concentrated, and dried at 35 °C to provide endoxifen having approximately 70% (Z)-isomer. (See EX1004 at ¶¶ [[0073]–[0074].])

19. In Example 7, Liu then dissolves endoxifen having an E:Z ratio of 30:70 in acetone followed by heating to reflux. The resulting solution was cooled and stirred for 40 hours at 1 to 5 °C, after which the mother liquor was removed. The remaining crystalline material was re-dissolved in boiling acetone and then stirred for 50 hours at 1 to 5 °C, and the mother liquor removed again. The remaining crystalline material was again dissolved in boiling acetone, and this hot solution was filtered and kept at 1 to 5 °C for 22 hours. The crystalline material that precipitated was collected by filtration and washed with ice-cooled acetone, then dried *in vacuo* at 35 °C to provide 99% (Z)-endoxifen. (See EX1004 at ¶ [0076].)

20. Notably, Dr. Bihovsky attempted to repeat the crystallization experiments of Examples 5, 6, and 7 of Liu over 15 times, often using conditions not described in Liu (e.g., varying temperatures and times). For example, Dr. Bihovsky took the crude material he obtained by the methods of Example 4 of Liu and dissolved this crude endoxifen in isopropyl acetate at reflux, cooled the solution to 40 °C for one hour, followed by stepwise cooling to 25 °C and then 15 °C over one and a half hours. Dr. Bihovsky filtered the material, rinsed with cold isopropyl

acetate at 15 °C, and collected the filtrate. Liu, by contrast, teaches dissolving the crude material in isopropyl acetate at 88 °C and cooling the solution to 23 °C for six hours, followed by washing with isopropyl acetate of an unspecified temperature. (See EX1004 at ¶ [0072].) In a subsequent repetition of this procedure, Dr. Bihovsky deviated from the temperature and cooling times disclosed in Example 5 of Liu by cooling the solution to 21 °C for 16 hours. (*Id.*)

21. While Dr. Bihovsky purports that he obtained “(Z)-endoxifen with 100% isomeric purity” (see EX1030 at ¶ 43), I note that his methodology deviated from the methods disclosed by Liu. Notably, Liu recrystallizes the crude endoxifen by:

- (1) Recrystallizing in acetone by heating to 65 °C, followed by slow cooling to 20 °C for 19 hours, and then -10 °C for four days,
- (2) Recrystallizing the material of (1) in isopropyl acetate at 85 °C for 2 hours, followed by cooling slowly to 15 °C, and
- (3) Recrystallizing the material of (2) three times in acetone, first in acetone at reflux followed by cooling for 40 hours at 1 to 5 °C and removal of the mother liquor, second in acetone followed by cooling for 50 hours at 1 to 5 °C and removal of the mother liquor, and third in acetone, followed by filtering the hot solution and cooling at 1 to 5 °C for 22 hours.

22. By contrast, Dr. Bihovsky recrystallized the crude endoxifen by:

- (1) Recrystallizing in acetone as described above,

- (2) Recrystallizing the material of (1) in isopropyl acetate at reflux for an unspecified amount of time, followed by cooling to 23 °C for one hour and allowing the solution to stand at 23 °C for six hours, and
- (3) Recrystallizing the material of (2) two times in acetone, first in acetone at reflux, followed by cooling at 4 °C for a total of 64 hours, filtration and washing of the solid with cold acetone, and second in acetone, followed by cooling at 4 °C for a total of 50 hours and filtering and drying the solid.

23. Accordingly, I disagree that Dr. Bihovsky “tried to follow Liu as precisely as possible” (*see* EX2027 at 40:2–3), because, as described above, Dr. Bihovsky made several modifications beyond the scope of the methods disclosed by Liu.

24. I further note that in several instances, Dr. Bihovsky’s laboratory notebook referenced X-ray powder diffraction (XRPD) and identified the product as “Form I” or “not Form I.” Importantly, Liu does not utilize XRPD to characterize (Z)-endoxifen or any crystal forms thereof, nor do any of the other references relied upon by Petitioner. The characterization of crystal forms of (Z)-endoxifen, including Form I, comes directly from the ’334 Patent. (*See, e.g.*, EX1001 at 3:21-34; 31:28-35.) It is my opinion that Dr. Bihovsky was only able to identify the product he obtained as “Form I” or “not Form I” based on the teachings of the ’334 Patent.

25. Dr. Bihovsky's modifications to the methods taught by Liu, and the various repetitions of these procedures that he performed, indicate that achieving greater than 90% (Z)-endoxifen was not a matter of simply following the methods of Liu as written. It is my opinion that a POSA would expect that variations in synthetic procedure can lead to different outcomes. Therefore, because Dr. Bihovsky's experimental work does not replicate the methods of Liu, I disagree with Dr. Bihovsky's conclusions based on this work.

26. It is my opinion that Dr. Bihovsky's experimental work on the methods of Liu, regardless of the modifications he made, does not cure the deficiencies in Petitioner's enablement argument. At no point did Dr. Bihovsky perform any of the synthetic methods of Ahmad. (*See* EX2027 at 33:10-16). Dr. Bihovsky's laboratory work, therefore, provides no evidence as to the isomeric ratio of the endoxifen produced by Ahmad's methods, nor how the endoxifen of Ahmad could be successfully purified to at least 90% (Z)-endoxifen. Critically, Dr. Bihovsky did not begin with the crude endoxifen of Ahmad's synthetic procedure and apply the purification methods of Liu, as Petitioner suggests a POSA would have done at the time of the '334 Patent's filing. (*See* Paper 16 at 4-5.) Instead, Dr. Bihovsky carried out the methods of Liu alone, stating that he "rejected some of the [other references] as being not as good as Liu because I found them to be less practical or possibly not having sufficient detail." (EX2027 at 66:1-4).

27. As a POSA would readily understand, synthetic chemistry and chemical purification are inherently unpredictable endeavors and even slight changes in methodology can lead to different results (as evidenced by Dr. Bihovsky's own experimental work). As I stated in my previous declaration, (EX2020 at ¶¶ 87-88), and as Dr. Bihovsky agreed during his deposition, (*see* EX2027 at 84:2-6), different synthetic pathways can result in different stability and impurity profiles.

28. It is therefore my opinion that following the synthetic method of Ahmad and subsequently applying the purification method of Liu would lead to a different isomeric ratio than following the synthetic and purification methods of Liu. Because of the different impurity profiles and different residual solvent contents in the synthetic product of Ahmad and the synthetic product of Liu, a POSA would not have a reasonable expectation of success in combining the methods of these references as Petitioner suggests. Dr. Bihovsky's laboratory work does not contradict my opinion. Indeed, Dr. Bihovsky's laboratory work confirms my opinion, because Dr. Bihovsky himself had to modify several aspects of the methods disclosed in Liu in order to achieve the results reported in his expert declaration.

IV. CONCLUSION

29. For at least the reasons I discuss above, it is my opinion that Dr. Bihovsky's laboratory notebook contradicts his opinions and testimony that he reproduced the teachings of Liu to obtain 93% and 100% (Z)-endoxifen. Dr.

Bihovsky's experimental work does not demonstrate that a POSA at the time of the '334 Patent's filing would be able to combine the teachings of Ahmad and Liu to achieve greater than 90% (Z)-endoxifen as Petitioner alleges. Accordingly, my opinion remains that Ahmad is not enabled and does not anticipate or render obvious the claims of the '334 Patent.

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

Respectfully submitted,

Dated: September 6, 2024

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

Stephen Graham Davies, D. Phil.