**IN THE UNITED STATES DISTRICT COURT**
**FOR THE DISTRICT OF DELAWARE**

| | | |
|---|---|---|
| ONYX THERAPEUTICS, INC., | : | |
| | : | |
| Plaintiff, | : | |
| | : | |
| v. | : | C.A. No. 16-988-LPS |
| | : | CONSOLIDATED |
| CIPLA LIMITED, et al., | : | |
| | : | |
| Defendants. | : | |

Jack B. Blumenfeld, Karen Jacobs, Megan E. Dellinger, MORRIS, NICHOLS, ARSHT & TUNNELL LLP, Wilmington, DE

Lisa B. Pensabene, Hassen Sayeed, Will Autz, Margaret O'Boyle, Caitlin P. Hogan, Carolyn Wall, Eberle Schultz, James Yi Li, Samantha M. Indelicato, Mark A. Hayden, O'MELVENY & MYERS LLP, New York, NY

Meng Xu, O'MELVENY & MYERS LLP, Newport Beach, CA

John R. Labbé, Kevin M. Flowers, Thomas R. Burns, MARSHALL, GERSTEIN & BORUN LLP, Chicago, IL

Wendy A. Whiteford, Brian Kao, C. Nichole Gifford, Joseph E. Lasher, AMGEN, INC., Thousand Oaks, CA

Attorneys for Plaintiff

Benjamin J. Schladweiler, GREENBERG TRAURIG, LLP, Wilmington, DE

Richard G. Greco, RICHARD G. GRECO PC, Rochester, NY

Gurpreet Singh Walia, FISHER BROYLES LLP, New York, NY

Attorneys for Defendants

**OPINION**

May 4, 2020
Wilmington,
Delaware

UNSEALED ON
MAY 7, 2020

## TABLE OF CONTENTS

**STARK, U.S District Judge:**

Onyx Therapeutics, Inc. ("Onyx" or "Plaintiff") sued numerous parties – Apotex Corp., Apotex Inc., Aurobindo Pharma USA Inc., Breckenridge Pharmaceutical Inc., Cipla USA, Inc., Cipla Ltd., Dr. Reddy's Laboratories Inc., Dr. Reddy's Laboratories Ltd., Fresenius Kabi USA LLC, Fresenius Kabi USA Inc., Innopharma, Inc., MSN Laboratories Private Ltd., MSN Pharmaceuticals Inc., Qilu Pharmaceutical Co., Ltd., Qilu Pharma, Inc., and Sagent Pharmaceuticals, Inc. – in this consolidated action brought pursuant to the Hatch-Waxman Act, 35 U.S.C. § 271(e). (*See* D.I. 1, 21) All of the original defendants other than Cipla USA, Inc. and Cipla Ltd. (collectively, hereinafter, "Cipla" or "Defendants") entered into consent judgments with Onyx and were dismissed. (*See* D.I. 114, 504-09, 513-14)

Cipla seeks to market a new drug bioequivalent to Onyx's product KYPROLIS® (carfilzomib) for injection ("Kyprolis"). (D.I. 1 at ¶ 8) Cipla has stipulated that its proposed product (hereinafter, the "Cipla ANDA Product" or "Cipla's ANDA Product") infringes Onyx's U.S. Patent Nos. 7,417,042 ("the '042 Patent") and 8,207,125 ("the '125 Patent") (collectively, "the Compound Patents") as well as Onyx's U.S. Patent No. 7,737,112 ("the '112 Patent" or "the Formulation Patent" and, together with the Compound Patents, "the Asserted Patents"). (*See* D.I. 1; *see also* D.I. 476-1 Ex. 1 (Stipulated Facts) ("SF") ¶ 85; D.I. 218) Cipla contends that the Asserted Patents are invalid. (*See* D.I. 330)

In May 2019, the Court held a five-day bench trial on Cipla's invalidity affirmative defenses and counterclaims. (*See* D.I. 523-29) ("Tr.") Thereafter, the parties submitted post-trial briefing (D.I. 521, 533, 536) and proposed findings of fact (D.I. 522, 532).

Pursuant to Federal Rule of Civil Procedure 52(a), and having considered the entire record in this case and the applicable law, the Court concludes that: (1) claims 23 and 24 of the '042 Patent, claim 1 of the '125 Patent, and claim 31 of the '112 Patent are not invalid for obviousness or double patenting, (2) no challenged claim is invalid due to incorrect inventorship, and (3) claim 32 of the '112 Patent is invalid for double patenting.

The Court's findings of fact and conclusions of law are set forth in detail below.

## FINDINGS OF FACT

This section contains the Court's findings of fact ("FF") on disputes raised by the parties during trial, as well as the facts stipulated to by the parties. (*See* SF) Additional findings of fact are also provided in connection with the Court's conclusions of law later in this Opinion.

### I. Introduction

1. This patent infringement action arises out of Cipla's submission of Abbreviated New Drug Application ("ANDA") No. 209479 to the U.S. Food and Drug Administration ("FDA") under 21 U.S.C. § 355(j), seeking FDA approval of a 60 mg generic carfilzomib injection product. (SF ¶ 81)

2. Onyx is the holder of approved New Drug Application ("NDA") No. 20-2714 on Kyprolis, which was approved by the FDA on July 20, 2012 to treat relapsed or refractory multiple myeloma, which is a type of hematopoietic cancer. (SF ¶¶ 54-55)

3. The '042, '125, and '112 Patents are listed with respect to NDA No. 20-2714 in the FDA's publication, *Approved Drug Products with Therapeutic Equivalence Evaluations*, which is also known as the "Orange Book." (SF ¶ 56) The Asserted Patents together claim the

active ingredient and formulation of Kyprolis. (Bachovchin Tr. 84-85, 293; Amiji Tr. 311; Siegel Tr. 1326, 1344)[1]

4. In its ANDA, Cipla included a certification ("Paragraph IV certification"), pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), that the claims of the Asserted Patents are invalid, unenforceable, and/or will not be infringed by the manufacture, use, importation, sale, or offer for sale of the Cipla ANDA Product. (SF ¶ 82)

5. On October 24, 2016, Onyx sued Cipla pursuant to 35 U.S.C. § 271(a), (b), (c), and (e)(2) for infringement of the '042, '125, and '112 Patents, based on Cipla's ANDA filing and the accompanying Paragraph IV certification Cipla sent to Onyx with respect to Cipla's 60 mg ANDA Product. (SF ¶ 83)

6. On April 20, 2018, Onyx again sued Cipla for infringement of the Asserted Patents based on Cipla's ANDA filing seeking approval to market a 30 mg version of Cipla's ANDA Product. (SF ¶ 84; *see also* C.A. No. 18-598-LPS D.I. 1, 13)

7. Onyx and Cipla thereafter entered into a stipulation that the Cipla ANDA Product, in both the 30 mg and 60 mg dosages, infringes claims 23 and 24 of the '042 Patent, claim 1 of the '125 Patent, and claims 31 and 32 of the '112 Patent. (SF ¶ 85; *see also* D.I. 218)

8. The parties continued to litigate through trial Cipla's affirmative defenses of invalidity due to failure to comply with one or more requirements of patentability under 35 U.S.C. §§ 102 and 103 and due to non-statutory obviousness-type double patenting, as well as Cipla's counterclaims seeking a declaratory judgment that the claims of the Asserted Patents are

[1] Citations to the trial transcript (D.I. 523-29) are in the form: "[Witness last name] Tr. [page number]."

invalid under 35 U.S.C. § 103 as obvious and are invalid for obviousness-type double patenting. (*See* D.I. 1)[2]

## II. Patents-in-Suit

### A. U.S. Patent No. 7,417,042

9. The ’042 Patent issued on August 26, 2008, from U.S. Application Serial No. 11/199,899, which was filed on August 8, 2005. (SF ¶ 22)

10. According to the Orange Book, the ’042 Patent expires on July 20, 2026. (SF ¶ 23)

11. The ’042 Patent lists two inventors: Mark S. Smyth and Guy J. Laidig. (SF ¶ 24)

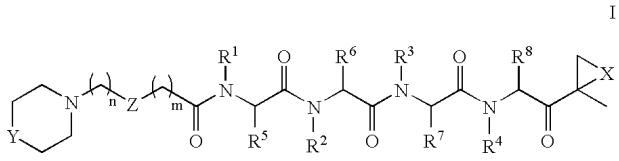
12. On its face, the ’042 Patent is assigned to Proteolix, Inc. It was subsequently assigned to Onyx Therapeutics, Inc., which is the assignee of all right, title, and interest in the ’042 Patent. (SF ¶¶ 25-26)

13. Onyx has asserted claims 23 and 24 of the ’042 Patent. (SF ¶ 27)

14. Claim 23 depends from claim 22, which depends from claim 21, which depends from claim 20, which depends from claim 19, which depends from claim 1. (SF ¶ 28)

15. Claim 1 recites:

> A compound having a structure of formula I or a pharmaceutically acceptable salt thereof,



[2] It was Onyx’s and the Court’s understanding that Cipla voluntarily withdrew its §§ 101 and 112 affirmative defenses. (*See* D.I. 533 Ex. 1)

wherein

X is O, NH, or N-alkyl;

Y is NH, N-alkyl, O, or $C(R^9)_2$;

Z is O or $C(R^9)_2$;

$R^1$, $R^2$, $R^3$, and $R^4$ are all hydrogen;

each $R^5$, $R^6$, $R^7$, $R^8$, and $R^9$ is independently selected from hydrogen, $C_{1-6}$alkyl, $C_{1-6}$hydroxyalkyl, $C_{1-6}$alkoxyalkyl, aryl, and $C_{1-6}$aralkyl, each of which is optionally substituted with a group selected from alkyl, amide, amine, carboxylic acid or a pharmaceutically acceptable salt thereof, carboxyl ester, thiol, and thioether;

m is an integer from 0 to 2; and

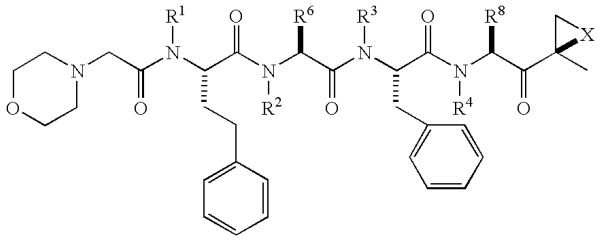
n is an integer from 0 to 2.

(SF ¶ 30)

16. Claim 19 recites:

A compound of claim 1, having a structure of formula IV or a pharmaceutically acceptable salt thereof,

IV



wherein

X is O, NH, or N-alkyl;

$R^1$, $R^2$, $R^3$, and $R^4$ are all hydrogen; and

$R^6$ and $R^8$ are independently selected from hydrogen, $C_{1-6}$alkyl, $C_{1-6}$hydroxyalkyl, $C_{1-6}$alkoxyalkyl, aryl, and $C_{1-6}$aralkyl, each of which is optionally substituted with a group selected from

amide, amine, carboxylic acid or a pharmaceutically acceptable salt thereof, carboxyl ester, thiol, and thioether.

(SF ¶ 31)

17. Claim 20 recites:

A compound of claim 19 or a pharmaceutically acceptable salt thereof, wherein X is O.

(SF ¶ 32)

18. Claim 21 recites:

A compound of claim 20 or a pharmaceutically acceptable salt thereof, wherein $R^6$ and $R^8$ are independently selected from C1-6alkyl, C1-6hydroxyalkyl, and C1-6aralkyl.

(SF ¶ 33)

19. Claim 22 recites:

A compound of claim 21 or a pharmaceutically acceptable salt thereof, wherein $R^6$ and $R^8$ are independently C1-6alkyl.

(SF ¶ 34)

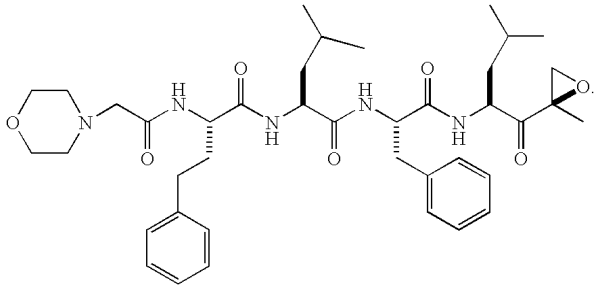
20. Claim 23 recites:

A compound of claim 22 or a pharmaceutically acceptable salt thereof, wherein $R^6$ and $R^8$ are both isobutyl.

(SF ¶ 35)

21. Claim 24 depends from claim 19, which depends from claim 1. Claim 24 recites:

A compound of claim 19 or a pharmaceutically acceptable salt thereof, having the following structure



(SF ¶ 36)

**B. U.S. Patent No. 8,207,125**

22. The ’125 Patent issued on June 26, 2012, from U.S. Application Serial No. 13/334,288, which was filed on December 22, 2011. (SF ¶ 37) The ’125 Patent is a continuation of application No. 11/578,626, filed on April 15, 2005, and several provisional applications with an earliest priority date of April 15, 2004. (JTX-6)

23. According to the Orange Book, the ’125 Patent expires on April 14, 2025. (SF ¶ 38)

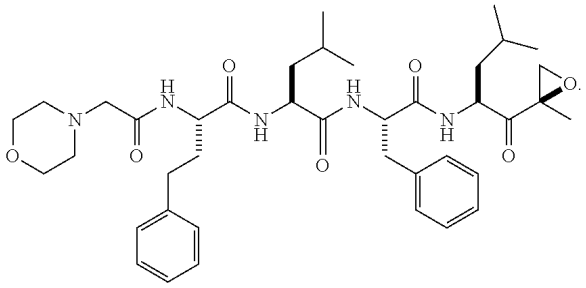
24. The ’125 Patent lists two inventors: Mark S. Smyth and Guy J. Laidig. (SF ¶ 39)

25. On its face, the ’125 Patent is assigned to Onyx Therapeutics, Inc., which is the assignee of all right, title, and interest in the ’125 Patent. (SF ¶¶ 40-41)

26. Onyx has asserted claim 1 of the ’125 patent. (SF ¶ 42)

27. Claim 1 of the ’125 patent recites:

A compound having the formula:



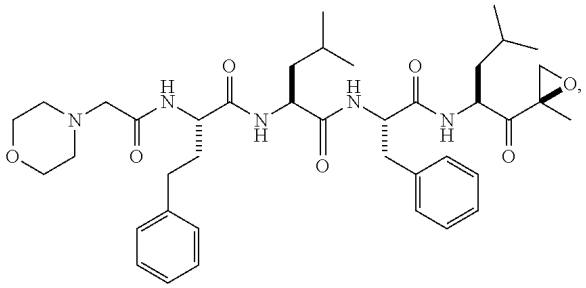
(SF ¶ 43)

28. Also at issue in this case is claim 25, which depends from claim 21, which depends from claim 19.

29. Claim 19 recites:

A composition comprising:

(i) a compound having the formula:



or a pharmaceutically acceptable salt thereof; and

(ii) water.

(JTX-6 at cl. 19)

30. Claim 21 recites:

The composition of claim 19, wherein the composition further comprises one or more other pharmaceutically acceptable carriers.

(JTX-6 at cl. 21)

31. Claim 25 recites:

> The composition of claim 21, wherein at least one of the one or more other pharmaceutically acceptable carriers is a substituted or unsubstituted 3-cyclodextrin.

(JTX-6 at cl. 25)

**C. U.S. Patent No. 7,737,112**

32. The ’112 Patent issued on June 15, 2010, from U.S. Application Serial No. 11/299,265, which was filed on December 7, 2005. (SF ¶ 44)

33. According to the Orange Book, the ’112 Patent expires on December 7, 2027. (SF ¶ 45)

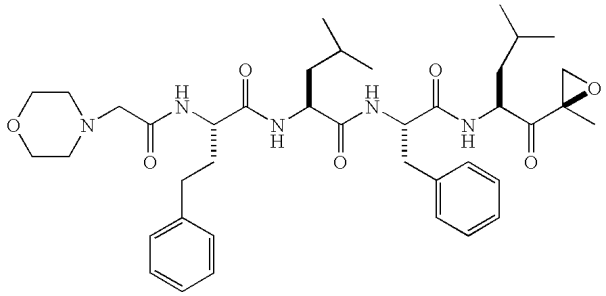
34. The ’112 Patent lists three inventors: Evan R. Lewis, Mark Nguyen Ho, and Fabiana N. Fonseca. (SF ¶ 46)

35. On its face, the ’112 Patent is assigned to Onyx Therapeutics, Inc., which is the assignee of all right, title, and interest in the ’112 Patent. (SF ¶¶ 47-48)

36. Onyx has asserted claims 31 and 32 of the ’112 Patent. (SF ¶ 49)

37. Claim 31 of the ’112 Patent recites:

> A pharmaceutical composition comprising a compound having a structure

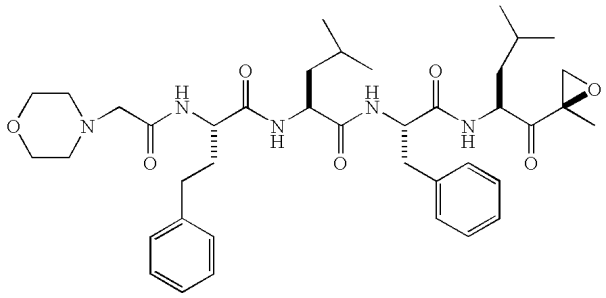


or a pharmaceutically acceptable salt thereof, in an aqueous solution containing 10% (w/v) SBECD and 10 mM citric acid adjusted to pH 3.5.

(SF ¶ 50)

38. Claim 32 of the ’112 patent recites:

A pharmaceutical composition in the form of a lyophilizate comprising SBECD and a compound having a structure



or a pharmaceutically acceptable salt thereof.

(SF ¶ 51)

## III. Witnesses

### A. Onyx’s Expert Witnesses

39. Dr. Ross Stein has 36 years of experience in drug discovery, focusing on enzymology and biochemistry. (Stein Tr. 856-57) He has worked on multiple proteasome inhibitors and is an inventor of bortezomib. (*Id*. 860-63) He was a member of the ProScript/Millennium group (*id*. at 860), which Cipla’s expert, Dr. Bachovchin, identified as “the leaders in the field” of proteasome inhibition (Bachovchin Tr. 286).

40. Dr. Christopher Lipinski has more than 30 years of expertise in drug development. (Lipinski Tr. 982) He is a medicinal chemist and member of the Medicinal Chemistry Hall of Fame. (*Id*. 984) Dr. Lipinski is a named inventor on 19 U.S. patents and has

over 275 publications and invited presentations. (*Id*. 982-83) There are over 23,000 total citations to those works. (*Id*. 983)

41. Dr. David Siegel is Chief of the Myeloma Division of the John Theurer Cancer Center, one of the largest myeloma programs in the world, and has been treating myeloma patients for 30 years. (Siegel Tr. 1322-25) He has been involved in clinical trials for every approved myeloma drug since 1997. (*Id*. 1324-25)

42. Dr. Roger Rajewski is a Research Professor in the Department of Pharmaceutical Chemistry at the University of Kansas, where he received his Ph.D. with honors in 1990. (Rajewski Tr. 1086) He is one of the inventors of Captisol® ("Captisol"), a sulferobutylether-β-cyclodextrin ("SBECD"). (*Id*. 1087) He has over 35 years of experience in drug formulation, including formulation of anti-cancer agents and peptides. (*Id*. 1090-91)

**B. Cipla's Expert Witnesses**

43. Dr. William Bachovchin is a professor in the Department of Developmental and Molecular and Chemical Biology at Tufts University School of Medicine. (Bachovchin Tr. 74) He has been a full-time, tenured professor at Tufts since 1989. (*Id*. 76-77) He teaches biochemistry with an emphasis on amino acids and protein biochemistry, enzyme mechanics, and drug design. (*Id*. 75) He also researches the structure and biological function of proteases, including the design of inhibitors as full molecules and therapeutic agents. (*Id*.)

44. Dr. Mansoor Amiji is a professor at Northeastern University, where he teaches Physical Pharmacy and Advanced Delivery Systems. (Amiji Tr. 307) He researches drug formulations for therapeutic delivery, and has experience formulating peptide drug molecules. (*Id*. 307) He is listed on over 300 peer-reviewed publications. (*Id*. 308)

### C. Fact Witnesses

45. Dr. Craig Crews is an academic chemical biologist and a professor at Yale University. (Crews Tr. 592-93) He was responsible for inventing YU-101 – an epoxyketone proteasome inhibitor that served as the precursor to carfilzomib. (Crews Tr. 559, 592-93; Molineaux Tr. 1128) Dr. Crews was a co-founder of, and served as a consultant to, Proteolix. (Crews Tr. 583-84; Molineaux Tr. 1126-27; PTX-27)

46. Gregory Giotta was responsible for Proteolix's intellectual property and related licensing, due diligence with respect to Proteolix's acquisition by Onyx, and the subsequent integration of Proteolix's patent portfolio. (Giotta Tr. 621-22)

47. Dr. Fabiana Novais Fonseca Galea was a scientist at Proteolix who worked on injectable formulations of carfilzomib. (Fonseca Tr. 686-87)

48. Dr. Evan Randall Lewis was a senior/principal scientist at Proteolix who worked on injectable formulations of carfilzomib. (Lewis Tr. 692-94)

49. Dr. John Musser was the vice president of PharmaGensis managing medicinal chemistry, and worked as a consultant with Proteolix to develop proteasome inhibitors. (Musser Tr. 700-01, 707)

50. Dr. Mark Smyth was a medicinal chemist at Proteolix, who participated in research and development of proteasome inhibitors, and is credited as a co-inventor of carfilzomib. (Smyth Tr. 715-17)

51. Dr. Susan Molineaux was a co-founder and Chief Executive Officer of Proteolix, and oversaw the development of Kyprolis. (Molineaux Tr. 1123-25)

## IV. Person Of Ordinary Skill In The Art

52. A person of ordinary skill in the art ("POSA") with regard to the Asserted Patents would be a person having a doctoral degree in a discipline such as organic or medicinal chemistry, pharmacology, enzymology, pharmaceutical sciences, or related disciplines; having at least two years of practical experience in drug discovery and development, drug formulation and delivery, or the clinical treatment of diseases, including cancer, that may benefit from the inhibition of proteasome activity; working together with others, including at least, medicinal chemists, preclinical researchers, formulators, and medical doctors in a multidisciplinary team, to solve a given problem. (Stein Tr. 865-67; Lipinski Tr. 987; Siegel Tr. 1327; *see also* Bachovchin Tr. 88)

53. With respect to the Formulation Patent, a POSA would also include a person with several years of experience in formulation of drug products. (Stein Tr. 865-67)

54. Onyx's and Cipla's experts agreed that their opinions would be the same regardless of whether the Court adopts Onyx's or Cipla's definition of a POSA. (Bachovchin Tr. 88-89; Amiji Tr. 313; Stein Tr. 867; Lipinski Tr. 987-88; Rajewski Tr. 1094) The Court's definition of a POSA is slightly different from those offered by the parties.

55. Onyx's and Cipla's experts further agreed that the problem to be solved at the time of the invention was the need for an improved therapeutic proteasome inhibitor over the FDA-approved bortezomib. (Bachovchin Tr. 226-27; Stein Tr. 874-75) Making a better therapeutic was the only motivation that Cipla's expert, Dr. Bachovchin, identified. (Bachovchin Tr. 94-95 ("for use potentially as an anti-cancer drug"), 100 ("for the treatment of cancer"))

## V. Proteasome And Myeloma

56. The proteasome is a protein complex found within nearly every cell, with the exception of red blood cells. (Bachovchin Tr. 90, 92) Proteasomes cleave peptide bonds to break down proteins – a linear array of amino acids – into smaller fragments. (*Id*. at 90)

57. The proteasome at issue here, 20S, has three relevant sites/types of protease activity: (1) chymotrypsin-like activity ("CT-L"), (2) trypsin-like activity ("TL"), and (3) caspase-like activity ("PGPH"). (*Id*. at 89) These three sites share a similar catalytic mechanism, which involves an N-terminal threonine residue, but each has a different specificity. (*Id*. at 91) Stated simply, each site cleaves a different type of peptide bond. (*Id*.)

58. Proteasomes (or specific active sites) may be inhibited by binding molecules to the active sites, which can produce a biological response. (*Id*. at 92) Inhibitors can bind to one or more sites simultaneously. (*Id*. at 93)

59. Multiple myeloma are cancerous white blood cells that are extremely sensitive to proteasome inhibition. (*Id*.) These cancerous cells produce an enormous number of antibodies (which are proteins), many of which are misfolded or damaged and must be removed from the cell. (*Id*.) Thus, the proteasome serves a vital function in multiple myeloma cells; if the excess proteins are not broken down and removed, the cell dies. (*Id*. at 92-93) It was known in the art that targeting and inhibiting proteasome activity, and, specifically, CT-L activity, would kill multiple myeloma cells. (Bachovchin Tr. 93-95)

60. When inhibiting the proteasome, inhibition can either be on-target (intended) or off-target (unintended). (*Id*. at 93-94) Off-target proteasome inhibitors cross-react to non-

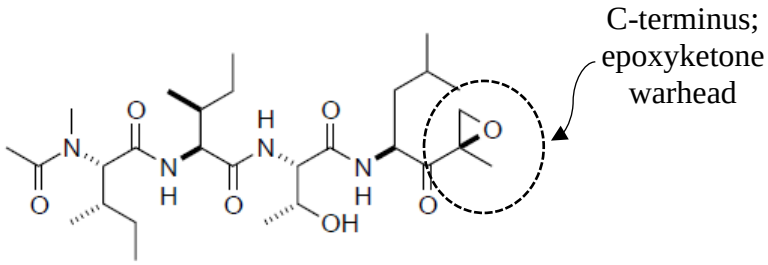
proteasomal proteases. (*Id*. at 94) This is referred to as "non-specific" inhibition, and has the potential to inhibit other critical cellular functions, with toxic effect. (*Id*.)

**VI. YU-101**

61. Dr. Crews, an academic chemical biologist at Yale, had previously worked with epoxomicin, which is a naturally occurring proteasome inhibitor. (Crews Tr. 592-93; Molineaux Tr. 1128-29)

62. Epoxomicin is a potent and highly selective proteasome inhibitor of CT-L activity. (DTX-47; DTX-69; DTX-777; Bachovchin Tr. 124-25; Crews Tr. 547) Specifically, epoxomicin utilizes an epoxyketone "warhead" at the C-terminal carboxylate group to bind with the N-terminal threonine on the CT-L site. (Bachovchin Tr. 95-96, 128-29)

63. Epoxomicin has the following structure:




(DTX-47) (annotations added)

64. Inhibition of CT-L activity alone substantially reduces protein breakdown. (DTX-54 at 9; DTX-77 at 6)

65. While a professor at Yale, Dr. Crews developed a series of compounds that utilize the same epoxyketone warhead as epoxomicin, including a compound labeled "YU-101." (Crews Tr. 590-93; Molineaux Tr. 1128-29, 1135)

66. YU-101 is an irreversible epoxyketone proteasome inhibitor. (Crews Tr. 592-93; Stein Tr. 908; Lipinski Tr. 1010-12; Molineaux Tr. 1135; PTX-508 at 2; *see also infra* FF

¶¶ 127-29) While having the same warhead as epoxomicin, YU-101 has modified side chains to increase specificity and potency. (DTX-47 at 1, 6-7; Bachovchin Tr. 108-10, 125-26) YU-101's high selectivity for CT-L made it a "potent antiproliferative and anti-inflammatory agent." (DTX-47 at 1; *see also* DTX-39 col. 40 ll. 54-57)

67. YU-101, with its modified sidechains, proved to be more potent and specific for CT-L inhibition that all other known inhibitors. (DTX-47 at 6) ("[YU-101] is more powerful and selective for the chymotrypsin-like activity than the previously characterized inhibitors epoxomicin [22], dihydroeponemycin [23], the boronic acid PS-341 [16], *clasto*-lactacystin β-lactone [15] and NLVS [25, 26].") YU-101 was over three times more potent at CT-L (on-target) inhibition than bortezomib and over four times more potent than epoxomicin; it was also 21 and 152 times less potent at TL and PGPH (off-target) inhibition, respectively. (*Id*. at 7; DTX-143 at 11-12 ("YU101 is the best available selective inhibitor of the ChT-L activity . . . with five orders of magnitude lower association constants for the other activities."); Bachovchin Tr. 108-09)

68. Dr. Crews and his lab produced YU-101 to serve as a chemical probe, and considered it "sufficient" for that purpose. (Crews Tr. 592)

69. U.S. Patent No. 6,831,099 ("the '099 Patent") lists Craig Crews, Mikael Elofsson, Ute Splittgerber, Ny Sin, and Kyuong Bo Kim as inventors. (DTX-39)

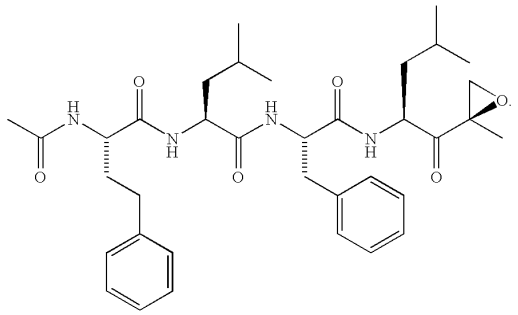
70. The '099 Patent issued on December 14, 2004 from application 09/569,748, which was filed on May 11, 2000. (DTX-39)

71. On its face, the ’099 Patent is assigned to Yale University. (DTX-39) The named inventors assigned their patent rights to Yale, as was required under the Yale Patent Policy. (DTX-39; Crews Tr. 577-79)

72. Claim 15 of the ‘099 Patent embodies YU-101. (DTX-39; Stein Tr. 929)

73. Claim 15 of the ’099 Patent recites:

A compound having the structure:



(DTX-39)

74. Pursuant to the Bayh-Dole Act, 35 U.S.C. § 200 *et seq.*, Yale had an obligation to attempt to commercialize its federally-funded intellectual property, and Yale worked with Dr. Crews to commercialize YU-101. (Crews Tr. 585)

**VII. Proteolix**

75. Dr. Crews and Dr. Raymond Deshaies co-founded Proteolix in 2002 in order to develop commercial proteasome drugs. (Molineaux Tr. 1126-27; PTX-27 at 1) At that time, Dr. Crews ceased work on proteasome inhibitors in his lab at Yale. (Crews Tr. 591-92, 613-14; DTX-677 at 4) Dr. Crews served as a director of, and later as a consultant to, Proteolix. (Molineaux Tr. 1167-69; PTX- 27 at 1; DTX-414 at 3) He remained a full-time professor at Yale throughout his association with Proteolix. (Molineaux Tr. 1128, 1161-62; *see also* Bachovchin Tr. 179)

76. In February 2003, Drs. Crews and Deshaies hired Dr. Susan Molineaux, a biologist with several years of experience in drug development, to serve as the Chief Scientific Officer of Proteolix and to pitch the company to potential investors, including venture capitalists. (Molineaux Tr. 1127-28)

77. Dr. Molineaux and others in the industry knew that another proteasome inhibitor, bortezomib, was close to FDA approval for the treatment of multiple myeloma. (Molineaux Tr. 1129) In May 2003, bortezomib obtained FDA approval to be marketed by Millennium Pharmaceuticals as the active ingredient in Velcade® ("Velcade"). (DTX-73; Molineaux Tr. 1129) Velcade was known to cause irreversible peripheral neuropathy. (Bachovchin Tr. 227; Stein Tr. 872; Molineaux Tr. 1132-33)

78. YU-101 acts on the same CT-L target as bortezomib but is approximately three times more active *in vitro* on CT-L activity. (DTX-47 at 7, Table 4)

79. Dr. Molineaux believed it would be difficult to market a proteasome inhibitor based on YU-101 because (1) normal cells and cancer cells have the proteasome, (2) YU-101 irreversibly bound to the proteasome and, in 2003, "no established pharmaceutical company would want to develop an irreversible inhibitor," and (3) YU-101's warhead was highly reactive and non-selective. (Molineaux Tr. 1129-31; *see also* Lipinski Tr. 1047) Despite these concerns and YU-101's known solubility problems, Dr. Molineaux believed that, in light of Velcade's approval and the fact that Proteolix already had biology and animal efficacy data on YU-101, YU-101 or an analog would be worth exploring. (Molineaux Tr. 1129, 1136)

80. After speaking with numerous venture capitalists, Dr. Molineaux persuaded Larry Lasky – a venture capitalist and biologist, who had spent approximately 30 years at Genentech

Inc. on drug discovery – and Jonathan Root – another venture capitalist, M.D., biologist-neurologist – to build a coalition to invest in Proteolix based on its work with YU-101 and epoxyketones. (Molineaux Tr. 1133-34)

81. Given solubility problems with YU-101, and the fact that YU-101 lacked international patent coverage, Dr. Molineaux and Proteolix's investors believed "it made sense . . . to fund a research plan for [a] backup molecule." (Molineaux Tr. 1136; *see also* Crews Tr. 599-600)

82. Proteolix pursued a license to the '099 Patent from Yale and encountered no competition in seeking such a license. (Molineaux Tr. 1137)

83. Proteolix obtained an exclusive, royalty-bearing license to the '099 Patent from Yale. (DTX-195 at 4) Proteolix was required to pay all maintenance fees associated with the '099 Patent. (*Id*. at 9) Proteolix had "the first right and obligation to defend" the '099 Patent against infringement or interference at its own expense, and had the right to settle such litigation so long as Yale provided written consent. (*Id*. at 11) If Proteolix did not pursue suit within 60 days, Yale reserved the right to pursue an infringement action at its own expense, unilaterally settle such action, and terminate Proteolix's exclusive license in the country where such action took place. (*Id*. at 12) Yale further retained the right to terminate the license agreement if Proteolix failed to pay amounts owed under the agreement, or due to a material breach or insolvency. (*Id.* at 12-13) Proteolix could not transfer its rights under the agreement (except to an affiliate) without Yale's written consent. (*Id.* at 17)

## VIII. Proteolix's 2003 Research Plan

84. After receiving initial funding, and in order to assure investors that any backup molecule would be outside the scope of the '099 Patent, Proteolix endeavored to create a research plan outlining backup molecules for YU-101. (Molineaux Tr. 1144)

85. To develop the research plan, Proteolix hired chemistry consultants, including Dr. Barry Bunin, to generate ideas for possible analogs of YU-101 and epoxomicin that fell outside the scope of the '099 Patent. (Molineaux Tr. 1160)

86. On September 3, 2003, Dr. Bunin emailed Drs. Crews and Molineaux three proposals ("Three Proposals") for creating epoxomicin/YU-101 analogs. (DTX-681; DTX-682; DTX-683) Dr. Bunin first proposed prodrugs of the N-acyl group and provided a figure with a variable-labeled N-terminus comprising a "General Markush." (DTX-682 at 2; Crews Tr. 594) Dr. Bunin stated that an N-terminal modification "[s]hould be rapid to synthesize and test based on availability of analogous intermediate for YU101" and that the total time frame would be "one quarter if done at Yale; two quarters if done at Proteolix." (DTX-682 at 2)

87. Drs. Bunin, Crews, and Molineaux participated in a call on September 4, 2003. (DTX-683) Dr. Bunin thereafter emailed a revised document entitled "Four Proposals to Create New Proteolix IP Outside of YU-101" ("Four Proposals"). (PTX-530/DTX-696) The purpose of the proposals was "to create new IP for Proteolix start[ing] with left side [(N-terminus)] of the YU101 and mov[ing] to the right side [(epoxyketone warhead)]," which corresponds with "the easiest to most challenging" modifications. (PTX-530 at 1) Dr. Bunin first proposed "[m]odify[ing] the acylating agent on the N-terminal end of the tetrapeptide with a solubilizing agent or fragment of Velcade . . . or prodrug acylating agents if needed to retain potency." (*Id.*)

Dr. Bunin elaborated that the proposed "General Markush" on the N-terminus – represented by the variable "R" (*see* FF ¶ 92) – could be one of a "morpholino, 2-pyrazinecarbonyl (from Velcade) and other solubilizing groups like alkyl tertiary amines, etc." (*Id*. at 3) He also proposed that Proteolix "evaluate combinatorial libraries of different acylators of di-, and tri-peptides with less amides." (*Id*.)

88. Dr. Bunin identified each compound in the Four Proposals with the initials of the individual who thought up and proposed that compound. (PTX-530 at 1) All compounds, including the General Markush group, were thought up and proposed by "BAB," Barry A. Bunin, on August 30, 2003, except for one compound thought up and proposed by "BAB/CC," Barry A. Bunin/Craig Crews, on September 4, 2003. (PTX-530 at 1, 6; Molineaux Tr. 1161) The only compound identified as BAB/CC was a modified epoxyketone warhead. (Crews Tr. 612; PTX-530 at 6)

89. A September 5, 2003 revised memo is called "Proteolix YU101 Program: Revised Scientific Plan." ("Revised Plan") (DTX-992B) The Revised Plan emphasized developing YU-101, but also suggested "that, in parallel, [Proteolix] pursue a more intensive back-up analog program than originally planned." (*Id*. at 1) The Revised Plan set forth Dr. Bunin's proposals from the Four Proposals, which could "yield YU101 analogs that will be patent protected internationally and that also may have improved biological properties." (*Id*. at 2) The Revised Plan expanded on Dr. Bunin's proposed modification of the N-terminus, stating:

> Replacement of the acyl group at the N-terminus of the tetrapeptide with either
>
> 1. a solubilizing group that remains in place

> 2. a solubilizing moiety that is cleaved to an N-terminus similar to the acyl group
>
> All molecules in the prior art have unblocked or N-Acyl blocked amino termini. The N terminus is not specified in the Crews or Mundy patents. Current data suggests that modifications to the N-acyl group will be well tolerated (even N-terminally modified biotinylated derivatives still react selectively with the proteasome).

(*Id*. at 2) This description was then followed by the same chemical structure and General Markush group from the Four Proposals. (*Id*. at 3)

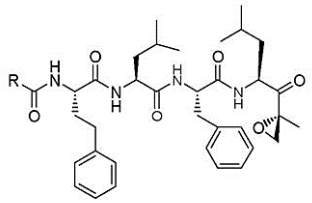
90. On September 20, 2003, Susan Molineaux sent Larry Laskey, Jonathan Root, and others a "revised chemistry plan" ("2003 Research Plan").[3] (DTX-991)

91. The 2003 Research Plan is an unpublished, confidential memorandum outlining a broad plan for the research and development of new proteasome inhibitors, including derivatives of epoxomicin and YU-101, and the identification of other compounds. (Bachovchin Tr. 217; Molineaux Tr. 1159-60, 1164; DTX-991) The 2003 Research Plan lists John Musser, Barry Bunin, Craig Crews, John Schneekloth, Gary Olson (Provid Pharmaceuticals lnc. CEO), and Susan Molineaux as contributors. (DTX-991 Att. at 11) The 2003 Research Plan does not describe the synthesis of any specific compound, but instead lists approaches for potentially modifying epoxomicin and YU-101 at multiple locations. (Bachovchin Tr. 208; Molineaux Tr. 1161, 1163)

[3] The Three Proposals, Four Proposals, Revised Plan, and 2003 Research Plan will be collectively referred to hereinafter as "the September Memoranda."

92. The sixth page of the 2003 Research Plan recites:

**N-Terminus Analogs**



R = morpholino, 2-pyrazinecarbonyl (from Velcade) and other solubiliting groups like alkyl tertiary amines, etc. Substitution of amino acids in the tetrapeptide can include many approaches. One is non-natural amino acids that are outside current patent claims: i.e., N-methyl amino acids such as sarcosine at P4. Alternatives to the P1-P4 residues need to be outside the Chemistry & Biology Crews paper, the revised claims of the Crews patent, the Konishi epoximicin patents, and the published claims of the Mundy patent.

(DTX-991 Att. at 6)

93. The "R=morpholino" subject matter in the 2003 Research Plan (and in earlier portions of the September Memoranda) was contributed by Dr. Bunin. (Crews Tr. 540, 579, 612; Molineaux Tr. 1161-63)

94. The September Memoranda expressly taught a morpholino attached directly to the carbonyl group at the N-terminus of YU-101 with what is called a urea linkage. (Lipinski Tr. 1035-37)

95. U.S. Patent 7,232,818 ("the '818 Patent), which is not asserted in the instant suit, claims a genus of compounds. (JTX-1) Claim 49 of the '818 Patent includes a urea compound with a morpholino carbonyl. (*Id*. at cl. 49) On its face, the '818 Patent lists Mark S. Smyth, Guy J. Laidig, Ronald T. Borchardt, Barry A. Bunin, Craig M. Crews, and John H. Musser as inventors. (JTX-1) On its face, the '818 Patent is assigned to Proteolix. (*Id*.)

96. The 2003 Research Plan also contemplated modifying the epoxyketone warhead to be reversible, rather than irreversible. (Bachovchin Tr. 213-14; DTX-991 Att. at 8)

## IX. Assignments To Proteolix

97. Dr. Bunin signed a Consulting Agreement with Proteolix on August 30, 2003. (DTX-890) ("Consulting Agreement") The Consulting Agreement states that "[a]ll Confidential Information will remain the sole property of the Company and its assigns." (DTX-890 at 2) But it also provides that Dr. Bunin "retain[ed] [his] ownership interest (if any) of all Consultant information, know-how and data contained in the Work Product, but [Proteolix] shall have the right to use the Work Product for all its business purposes." (*Id.*)

98. On September 17, 2003, Dr. Molineux reported to venture capital investor Patrick Latrell that she had asked outside attorneys at Latham & Watkins LLP to prepare new consulting agreements, which she planned to have all of the chemist consultants at Proteolix sign. (DTX-636)

99. Sometime no earlier than September 18, 2003, Dr. Bunin signed a second Consulting Agreement with Proteolix ("Second Consulting Agreement"), which had an effective date of August 30, 2003. (DTX-451/PTX-132 at 1; *see also* Bachovchin Tr. 161; Bunin Tr. 499-500) There is no written date on the Second Consulting Agreement, but a word processing date stamp at the end of the document – "091803" – shows the document was prepared on September 18, 2003. (DTX-451 at 4) The Second Consulting Agreement includes the following provision:

> Consultant hereby assigns to Company any right, title, and interest that Consultant may have in any invention, discovery, improvement, or other intellectual property which Consultant develops as a direct result of performing consulting services for Company under this Agreement.

(DTX-451 at 2) The Second Consulting Agreement also included a provision stating that it "constitutes the entire agreement" between Dr. Bunin and Proteolix, superseding any prior

understandings between the parties, and that those prior agreements "shall not be binding on either party, except to the extent incorporated herein." (*Id.* at 3) Therefore, the Second Consulting Agreement superseded the Consulting Agreement, and created a contractual obligation that Dr. Bunin assign to Proteolix any contribution he had made (or would subsequently make) to the 2003 Research Plan, an obligation that on September 18, 2003 (although not before then) became effective as of August 30, 2003. (DTX-451; DTX-890)

100. Dr. Bunin signed a third consulting agreement with Proteolix on November 15, 2003 that further assigned to Proteolix all IP rights for his consultancy work. (DTX-503; Bunin Tr. 507-09)

101. Dr. Crews was a professor at Yale and had an obligation to assign inventions to Yale. (DTX-439) An exception was made for paid consulting agreements that did not involve activities for which a faculty member was employed by Yale and did not use Yale facilities. (DTX-439 at 3-4)

102. Dr. Crews did not sign a consulting agreement with Proteolix until at least November 2003. (DTX-414) However, Dr. Crews, as a director of Proteolix, owed fiduciary duties to Proteolix, including an obligation to assign it any work he was doing on behalf of the company. (Crews Tr. 583, 612-13; DTX-677 at 2) Dr. Crews did not use Yale's laboratories or resources to contribute to the 2003 Research Plan. (Crews Tr. 613) Furthermore, Dr. Crews informed Yale of his work with Proteolix via his "Conflict of Interest" forms. (Crews Tr. 613-15, 617-18; DTX-677 at 2; DTX-720 at 4; DTX-718 at 7)

## X. The Carfilzomib Compound

103. Drs. Mark Smyth and Guy Laidig led the medicinal chemistry team at Proteolix. (Molineaux Tr. 1143)

104. Drs. Smyth and Laidig had access to, and did access, at least some of the proposals embodied in the 2003 Research Plan. (Smyth Tr. 721-22, 735) ("[T]here were several consultants that the co-founder had consulted to help outline what makes sense to look at and move forward. Based on those proposals from those consultants, we had to formulate a specific plan.")

105. Drs. Smyth and Laidig began by making YU-101 prodrugs, but that approach proved unsuccessful. (Laidig Tr. 477; Molineaux Tr. 1144, 1146-47) Drs. Smyth and Laidig continued their research by making structural modifications all over the molecule. (Molineaux Tr. 1148; Laidig Tr. 464-65)

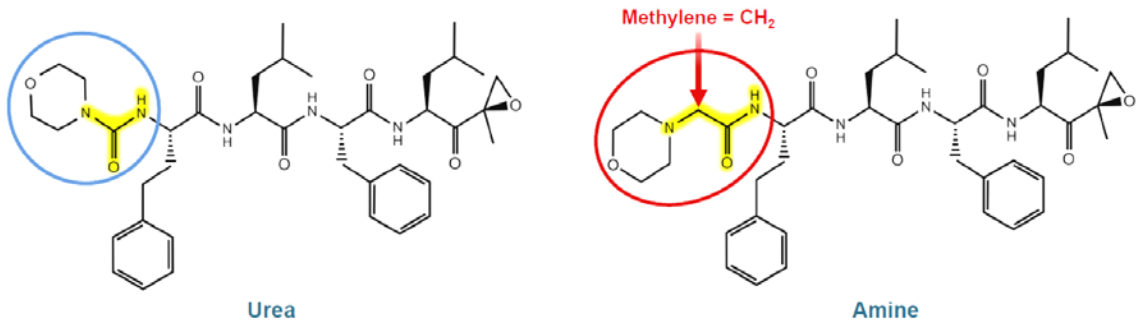
106. As part of a group of molecules intended to be tested, Drs. Smyth and Laidig proposed the carfilzomib compound as early as December 2003, within one month of Dr. Smyth's hiring, and produced a hand-drawn structure of carfilzomib on a whiteboard in January 2004. (Laidig Tr. 465, 468-70, 482-84; Smyth Tr. 721-22, 739-40; Molineaux Tr. 1157-58; PTX-218)

107. Carfilzomib was synthesized for the first time in June 2004. (Smyth Tr. 721; Molineaux Tr. at 1147)

108. Rather than connecting the morpholino to the N-terminus of YU-101 through a urea linkage, as taught expressly by the September Memoranda, carfilzomib comprises a morpholino connected to the N-terminus using a methylene linkage. (Bachovchin Tr. 185-87,

198) A methylene linkage has an additional carbon atom and two hydrogen atoms between the nitrogen of the morpholino substituent and the carbonyl group at the N-terminus of YU-101. (Lipinski Tr. 1036) Hence, as even Cipla's expert agreed at trial, the September Memoranda did not expressly teach carfilzomib. (Bachovchin Tr. 197)

109. Urea and methylene linkers have different chemical properties. A morpholino carbonyl (urea linkage) is neutral and cannot be charged. (Bachovchin Tr. 189; Lipinski Tr. 1036) A morpholino methylene (methylene linkage) has a basic N-terminus with a nitrogen that can be charged. (Bachovchin Tr. 189; Lipinski Tr. 1036-37) The difference in chemical structure is reproduced below:




(*See* PDX-3.72)

110. Cell and animal testing revealed that carfilzomib was the most promising compound, with limited toxicity, high levels of proteasome inhibition, and a 1000-fold increase in solubility over YU-101. (Stein Tr. 912-15; Molineaux Tr. 1154; Siegel Tr. 1334; PTX-234 at 37; PTX-683 at 3, 8)

## XI. The Carfilzomib Formulation

111. In animal studies, the Proteolix team discovered that YU-101 had a substantial solubility problem: the compound would not dissolve in a solvent that animals could tolerate,

meaning the solvents were too toxic for consistent administration. (Laidig Tr. 462; Molineaux Tr. 846, 1145-47)

112. Toxicity was less of a concern when YU-101 was being used as a molecular probe, but was a significant concern for human usage. (Laidig Tr. 462)

113. Carfilzomib was approximately 1,000 times more soluble than YU-101 (Stein Tr. 915), but there were still solubility problems present during formulation (Fonseca Tr. 687).

114. Formulators, including Drs. Lewis and Fonseca, proposed using cyclodextrins to further increase carfilzomib's solubility. (Lewis Tr. 694-96)

## XII. Additional Facts Relating To Obviousness

115. At trial, Cipla contended that the asserted claims of the Compound Patents were invalid as obvious in view of YU-101 (embodied in the '099 Patent) and general knowledge in the prior art that morpholino acts as a solubilizing substituent. (Bachovchin Tr. 140, 155)

116. None of the prior art cited by Cipla, alone or in combination, discloses, teaches, or suggests the compounds described in the asserted claims of the Compound Patents. None of the prior art cited by Cipla teaches a YU-101-based epoxyketone proteasome inhibitor with a morpholino methylene attached to the N-terminus.

117. The purpose of the claimed invention of the Compound Patents was to provide a small molecule proteasome inhibitor with "increased site specificity, improved stability and solubility, and increased potency . . . to allow the exploration of the roles of the proteasome at the cellular and molecular level." (JTX-2 col. 2 ll. 13-17; JTX-6 col. 2 ll. 22-26) According to the patents themselves, the claimed inventions could serve as "unique molecular probes" as well as pharmaceutical compositions "which ameliorate[] the effects of neurodegenerative disease

(such as Alzheimer's disease), muscle-wasting diseases, cancer, chronic infection diseases, fever, muscle disuse, denervation, nerve injury, fasting, and immune-related conditions," and as an "anti-inflammatory." (JTX-2 col. 2 ll. 51-53, col. 3 ll. 9-18; JTX-6 col. 2 ll. 60-62, col. 3. ll. 19-28)

118. None of the prior art cited by Cipla, alone or in combination, would have motivated a POSA in 2004 to make the claimed compound with a morpholino methylene at the N-terminus, with any reasonable expectation of success to produce a drug product or even a better molecular probe. (Stein Tr. 907-08)

119. Cipla's primary prior art reference, the '099 Patent, was considered by the Patent Examiner during prosecution of the Compound Patents and was found to be distinguishable. (*See* JTX-2 at 1; JTX-6 at 1) (citing '099 Patent)

120. None of the prior art cited by Cipla, alone or in combination, discloses, teaches or suggests the formulation described in the asserted claims of the Formulation Patent. None of the prior art cited by Cipla teaches the carfilzomib compound, or a formulation of carfilzomib with 10% w/v SBECD at a pH of 3.5 with 10mM of citric acid that may or may not be lyophilized.

121. The Formulation Patent states that its purpose was to provide workable formulations of peptide epoxyketones that address the "low aqueous solubility of some of these compounds," a problem that had made "it difficult to formulate compositions with optimal bioavailability." (JTX-4 col. 1 ll. 25-27)

122. None of the prior art cited by Cipla, alone or in combination, would have motivated a POSA in 2005 to make the claimed formulation with SBECD and a 10mM citric acid buffer at a pH of 3.5 (with or without lyophilization).

123. The Examiner did not cite the '125 Patent for any purpose in regard to the Formulation Patent. (JTX-4)

### A. Prior Art Compounds

#### 1. Lead Compounds

124. A POSA would have known[4] that proteasome inhibitors could be used for therapeutic purposes and as molecular probes. (JTX-2 col. 1 ll. 15-16, col. 2 ll. 9-17, 51-53; JTX-6 col. 2 ll. 18-26; DTX-39 at 9; DTX-47 at 2; DTX-69 at 2; Bachovchin Tr. 78)

##### a. Drug Product

125. Onyx's and Cipla's experts agreed that the problem to be solved at the time of invention was the need for an improved therapeutic proteasome inhibitor over bortezomib. (Bachovchin Tr. 226-27; Stein Tr. 874-75)

126. If intending to develop a drug product, a POSA would have preferred a lead compound that had human potency data and not just test tube data. (Stein Tr. 883; Lipinski Tr. 994)

127. If intending to develop a drug product, a POSA would have selected a lead compound that balanced safety, efficacy, and deliverability, with a proven mechanism of action and potent *in vitro* and *in vivo* activity. (Stein Tr. 882-83; Lipinski Tr. at 994) A POSA would have considered "drug-like properties," including bioavailability and metabolic stability, which impact a compound's ability to reach the site of action. (Lipinski Tr. 993-94; Stein Tr. 884-85)

[4] All references to what a POSA would have known or done are directed to the time the pertinent invention of the Asserted Patent was made.

128. Off-target toxicity occurs when the inhibitor targets enzymes other than the proteasome. (Stein Tr. 873) An irreversible proteasome inhibitor binding to an unrelated target can induce toxic immune responses. (Stein Tr. 878; PTX-146 at 2) On-target, off-tissue toxicity occurs when the intended target (i.e., the proteasome) is inhibited in healthy cells. (Stein Tr. at 873) Because proteasomes are required for cell function, irreversible binding prevents any recovery until the target (e.g., the proteasome) is re-synthesized. (Stein Tr. 873, 877-78; PTX-543 at 3)

129. A POSA would have had concerns with irreversible proteasome inhibitors due to risks of catastrophic and irreparable toxicity. (Stein Tr. 872, 877; Lipinski Tr. 992; *see also* Bachovchin Tr. at 289-90)

130. A POSA would have known that, while certain researchers advocated for irreversible proteasome inhibitors, there was widespread industry aversion to irreversible inhibitors for drug products. (DTX-81 at 100 ("A strong bias against irreversible inhibitors exists in the pharmaceutical industry, and it is an uphill battle to get irreversible inhibitors considered as potential clinical candidates. Even though widely used drugs, such as aspirin and β-lactam antibiotics, are irreversible enzyme inhibitors, the lore in the pharmaceutical industry suggests that irreversible inhibitors will cause immune disorders upon long-term use."); Bachovchin Tr. 262-63; Smyth Tr. 742; Molineaux Tr. 847, 1131; Stein Tr. 876-79; Lipinski Tr. 992) While other irreversible inhibitors (such as aspirin or penicillin) had existed long before 2004, there is no record evidence of their binding mechanism or target, or that their inhibition activity is comparable to that of the proteasome inhibitors at issue in this case. (DTX-81 at 100; Bachovchin Tr. 119-20)

131. A POSA would have known that several classes of proteasome inhibitors were available as potential lead compounds, including aldehydes, boronates, epoxyketones, and vinyl sulphates. (Stein Tr. 965) A POSA would have known that aldehydes and boronates are reversible while epoxyketones are irreversible. (*Id*. 966)

132. A POSA would have known that peptides were known and used as drug products in the prior art. (Lipinski Tr. 1049)

133. A POSA would have known that the interaction between different proteasome subunits (e.g., TL, CT-L, etc.) was not well understood. (Bachovchin Tr. 253-54; DTX-77 at 7)

134. A POSA would have known of the FDA approval of bortezomib, a peptide proteasome inhibitor. (DTX-73) A POSA would have known that bortezomib had an established data package – that is, certain characteristics of its chemistry (such as reversibility, specificity, drug-like nature, and potency) were known. (Lipinski Tr. 989, 999-1000) Bortezomib was the only proteasome inhibitor approved for treating cancer and was the most-clinically advanced proteasome inhibitor at the time. (Lipinski Tr. 997; Stein Tr. 874) Bortezomib, like other boronates, was a reversible inhibitor. (Lipinski Tr. 998; Bachovchin Tr. 225; PTX-38 at 9; PTX-390 at 3) Bortezomib was drug-like, compact, water soluble, and easy to administer. (Lipinski Tr. 999; PTX-391 at 4) A number of research groups pursued boronates. (Bachovchin Tr. 266) The third and only other FDA-approved proteasome inhibitor (besides bortezomib and carfilzomib) is a boronate prodrug (ixazomib). (Bachovchin Tr. 267-68)

135. A POSA would have known that bortezomib was known to cause neurodegeneration, including peripheral neuropathy. (Bachovchin Tr. 227; Stein Tr. 872) Although the cause of bortezomib-associated peripheral neuropathy was not known (Stein Tr.

957), a POSA would have suspected the neuropathy was due to off-target interactions, as the boronic acid warhead was known to have the potential to inhibit the family of serine proteases that exist throughout the body (Bachovchin Tr. 104).

136. A POSA would have known that PS-519, a β-lactone, had an established data package. (Lipinski Tr. 1003-04) There were also known results of its administration in humans. In 2004, PS-519 had demonstrated potency and safety in animal studies and Phase I human clinical trials. (Bachovchin Tr. 288; Stein Tr. 874; Lipinski Tr. 1000-01, 1003-04; PTX-338 at 2, 7) PS-519 was a (slowly) reversible inhibitor, although data on reversibility of β-lactones "lack[ed] clarity." (Bachovchin Tr. 287; *see also* Stein Tr. 879; Lipinski Tr. 1001) Nonetheless, PS-519 had been shown to be specific for the proteasome. (Lipinski Tr. 1001-02; PTX-546 at 3) PS-519 was drug-like, compact, and had been formulated for delivery with saline. (Lipinski Tr. 1002; PTX-338 at 3) Finally, PS-519 was selective for the CT-L site. (Bachovchin Tr. 287; Lipinski Tr. 1003; PTX-546 at 5)

137. A POSA would have known that marizomib, another β-lactone, was potent, specific for the proteasome, drug-like, and compact. (Lipinski Tr. 1004-06; PTX-614 at 1-2; PTX-38 at 10) However, there was no clinical data on marizomib, and its reversibility was unknown. (Lipinski Tr. 1004-05; PTX-643) While it did have an established data package, no data existed regarding the results of its administration in humans. (Lipinski Tr. 1006-07)

138. A POSA would have known that TMC-95A had an established data package, but no results of administration in humans. (Lipinski Tr. 1009-10) TMC-95A is a reversible proteasome inhibitor. (*Id.* 1007-08; PTX-502 at 2, 4; PTX-476 at 1; *see also* Bachovchin Tr. 286-87) It was drug-like and showed potent and specific inhibition for the proteasome.

(Lipinski Tr. 1008-09; PTX-776 at 1-3; PTX-478 at 7-9; PTX-391 at 9) However, no human testing data was available for TMC-95A. (Lipinski Tr. 1009)

139. A POSA would have known that epoxomicin had an established data package. Epoxomicin was known to be a potent and specific proteasome inhibitor for the CT-L activity. (DTX-69; DTX-777; DTX-47) It did not, however, "inhibit papain, chymotrypsin, trypsin, cathepsin B or calpain at concentrations up to 50 μM." (DTX-69 at 5) Epoxomicin was effective *in vivo* as an antitumor and anti-inflammatory agent. (DTX-69; DTX-777; DTX-47 at 9) A POSA would also have known that epoxomicin had increased life expectancy in an *in vivo* B16 xenograft study in mice. (DTX-777; Stein Tr. 967-68)

140. A POSA would have known that YU-101 had a somewhat established data package, but what was known would not have motivated a POSA to use YU-101 as a starting point to develop a drug product. (*See, e.g.*, Lipinski Tr. 1010-14) YU-101 was made by optimizing the side chains of epoxomicin to increase specificity and potency, but it had the same irreversible epoxyketone warhead as epoxomicin. (DTX-47 at 6; Bachovchin Tr. 125-26; Lipinski Tr. 1013) The hydrophobic side chains of YU-101 were responsible for the improved specificity. (DTX-47 at 4-5; Stein Tr. 940-41) A POSA would have known that YU-101 reduced inflammation as part of an *in vivo* mouse ear inflammation study. (DTX-47; Stein Tr. 966-67) YU-101 was designed as a molecular probe to inhibit CT-L activity, but YU-101 was not drug-like and had "not been extensively studied." (Crews Tr. 547; Stein Tr. 891; Lipinski Tr. 1013; PTX-392) There was little data available on YU-101's physical properties, such as solubility, bioavailability, metabolic stability, or cell permeability. (Lipinski Tr. 1011-12) Furthermore, there was little to no data on overall selectivity; YU-101 showed high CT-L

specificity, but that does not equate to proteasome specificity. (Bachovchin Tr. 249-53) There was also no data of results of administration of YU-101 to humans. (Lipinski Tr. 1010) ("[It was] never formulated for delivery to humans. Never entered into clinical trials. Never approved by FDA as a therapeutic. So just no results in humans.")

141. A POSA would not have selected YU-101 as a lead compound for drug development. Although Adams (2003) summarized that "bortezomib, PS-519 and the highly potent, irreversibly inhibiting epoxyketones, such as YU101, epoxomicin and TMC-95, are the most clinically promising of the proteasome inhibitors now in commercial development," he also immediately added that "only a few in vivo studies have examined the effects of proteasome inhibition by agents that permanently and covalently modify their target. Additional studies examining the activities and potential toxicities of irreversible proteasome inhibitors [which would include YU-101] are necessary." (PTX-391 at 9; *see also id.* at 5 ("The future application of these drugs [i.e., YU-101 and TMC-95] for the treatment of human diseases may be possible, although additional in vitro and in vivo studies are necessary to further characterize their in vivo activities and potential toxicities."))

**b. Molecular Probe**

142. A POSA would have known that the CT-L enzymatic (or catalytic) site of the proteasome had been more extensively researched than the physiological importance of the TL or PGPH sites, due at least in part to a lack of molecular probes for the TL and PGPH sites. (Stein Tr. 924-25) However, a POSA would have known the biochemical roles of the TL and PGPH sites had been sufficiently characterized. (*Id.*)

143. A POSA intent on making a molecular probe would have preferred an irreversible inhibitor. (Stein Tr. 960)

144. A POSA would have known that YU-101 was potent and specific to the CT-L site than all other known inhibitors. (*See* FF ¶ 67)

**2. Prior Art Modifications To Lead Compound**

145. At the time of the invention of the Compound Patents, there was no published data on YU-101's solubility. (Smyth Tr. 720; Lipinski Tr. 1018-19; PTX-391 at 9) But a POSA would have suspected that YU-101, like epoxomicin, may have solubility problems. (Bachovchin Tr. 124-26; Smyth Tr. 729-30; Molineaux Tr. at 845-847; DTX-54; DTX-777) If a POSA had selected YU-101 as a compound for further development, such a POSA would have discovered YU-101's solubility problems through routine experimentation. (Laidig Tr. 462; Molineaux Tr. 1145-47)

146. A POSA would have known of several methods to try to improve solubility. (Bachovchin Tr. 129; DTX-56 at 6) A POSA would have known that there is a need for a hydrophilic and hydrophobic balance. (Bachovchin Tr. 130-36; DTX-56 at 6) A weak base allows a balance between the protonated and water-soluble species and the unprotonated neutral species that is not water soluble. (Bachovchin Tr. 130) The hydrophilic-hydrophobic (lipophilic) balance not only allows the drug to get into solution, but also to penetrate the lipid cell membranes and bind to the proteasome. (*Id*.) The CRC Handbook of Chemistry and Physics would have provided a POSA with a few common amines that are weak bases. (*Id.* 133-34)

147. A POSA would have known that molecules can be modified in several ways and at several locations to improve solubility. (Lipinski Tr. 1031-34) In the case of YU-101, such options include modifying the N-terminus or side chains, or the addition of alkyl, acyl, or N-alkyl substituents, varying polar functional groups and aromatic substituents, and prodrugs. (Bachovchin Tr. 233, 235-37; Lipinski Tr. 1020-21, 1032; DTX-56; PTX-610 at 6-7; PTX-662 at 28) Furthermore, a POSA would have known the length, linker, and location of the substituents may affect the chemical properties. (*Id*.) Ultimately, a POSA would have attempted to add any number of acidic, basic, and non-ionizing groups, or otherwise modified YU-101's structure, to improve solubility. (Lipinski Tr. 1023-24; PTX-92)

148. A POSA would have known that certain amine groups, including morpholine, had the potential to increase the solubility of a compound. (Smyth Tr. 731-32, 737-38) However, a POSA would also have known that there are over a thousand amines, and hundreds of heterocyclic weakly basic substituents, although not all possible substituents were well-known or previously used in a commercial drug product. (Lipinski Tr. 1024-26, 1028-29, 1043; PTX-795; PTX-796)

149. A POSA would have known that adding an amine group (and, specifically, a less hydrophobic group) to the N-terminus had the potential to significantly decrease potency. (Bachovchin Tr. 238-39, 242-43, 245, 248, 265, 274-75; Crews Tr. 549; Stein Tr. 900, 902, 905-06; DTX-32; DTX-33 at 33; DTX-47 at 7; DTX-81 at 40) A POSA would have also known, however, that tetrapeptides (such as YU-101) may respond differently to N-terminus modifications than shorter prior art bi- or tri-peptides. (Stein Tr. 940, 945-46) It was known that

the CT-L binding pockets were hydrophobic, but structures outside the pocket could be more freely modified. (*Id.*)

150. The "N-terminus Analogs" section of the 2003 Research Plan referenced "2-pyrazinecarbonyl (from Velcade)." (DTX-991 Att. at 6) A POSA would have known "from Velcade" refers to U.S. Patent 5,780,454 ("Adams" or "the '454 Patent") (DTX-33), which covers the prior art proteasome inhibitor bortezomib (Bachovchin Tr. 194; *see also* Molineaux Tr. 842-43). Every morpholino-containing compound in Adams is a morpholino carbonyl with a urea linkage. (Bachovchin Tr. 193; DTX-33) Adams does not teach a morpholino methylene. (Bachovchin Tr. 193) Moreover, the 2-pyrazinecarbonyl used in Velcade contains nitrogen and oxygen heteroatoms in a morpholino ring, which improves solubility despite being electrically neutral, and the same heteroatoms exist in a morpholino carbonyl. (Bachovchin Tr. at 195-96)

151. A POSA would not attach 2-pyrazinecarbonyl directly to the carbonyl of YU-101. (Lipinski Tr. 1055-56)

**B. Prior Art Formulations**

152. A drug formulation consists of an active ingredient and inactive ingredients called excipients. (Rajewski Tr. 1096) Each formulation is specific to a particular compound. (*Id.* 1099) A POSA designs a pharmaceutical formulation based on the structure and specific properties of the active ingredient. (Amiji Tr. 313, 417-18) Formulators must consider many interrelated factors, including stability, manufacturability, route of administration, patient acceptance, solubility, absorption, and safety. (*Id*. 1097-98) Even when a compound's structure is known, a POSA generally cannot predict all of its physical and chemical properties solely based on its structure. (Rajewski Tr. 1099-100) Without knowledge of a compound's physical

and chemical properties, attempts to formulate are "mostly trial and error." (*Id.* 1100-01; Singh Tr. 1349; PTX-329 at 9)

**1. Carfilzomib Compound**

153. Carfilzomib's structure was not known before December 2003. (FF ¶ 106) This and all the other facts found above in connection with the carfilzomib compound apply equally to the carfilzomib compound portion of formulations containing carfilzomib.

154. Carfilzomib's epoxyketone warhead contains an epoxide consisting of two carbon atoms and an oxygen atom bonded together in a three-membered ring with an adjacent ketone group; a carbon doubled-bonded to an oxygen. (Amiji Tr. 414, 419-20; Rajewski Tr. 1104-07, 1109-10) The epoxyketone warhead of carfilzomib binds to the proteasome to inactivate it – if it degrades, carfilzomib is no longer a drug. (Amiji Tr. 428-29; Rajewski Tr. 1105-06, 1181) Carfilzomib's peptide backbone is part of the compound's guidance system and helps bring the warhead to the right place to bind to the proteasome; without it, carfilzomib is, again, no longer a drug. (Amiji Tr. 433; Rajewski Tr. 1104) Epoxides readily undergo reactions in which the epoxide ring is opened by nucleophiles or basic reagents. (DTX-354) This is because epoxides possess significant angle strain, which creates weaker bonds that are more easily broken. (Amiji Tr. 433; Rajewski Tr. 1105-06) This reactivity provides benefits for therapeutic activity, but is also a source of instability when trying to formulate carfilzomib. (Rajewski Tr. 1106, 1109-10)

155. Chemical bonds are formed by sharing electrons. The oxygen atom in the epoxide ring hoards electrons, drawing them away from the two carbon atoms and weakening those bonds. (Rajewski Tr. 1108-10) This unequal sharing of electrons leaves the nucleus of the

carbon atoms vulnerable to nucleophilic attack by water, which will open the epoxide ring, in a reaction known as hydrolysis. (*Id.* at 1110; PTX-237 at 2; PTX-190 at 4)

156. Hydrolysis can also degrade amide bonds in the peptide backbone of carfilzomib. (Rajewski Tr. 1105; PTX-70 at 6)

157. A POSA would have been aware of the potential stability issues when developing a formulation for carfilzomib. (Rajewski Tr. 1107; DTX-354)

**2. pH of 3.5**

158. pH is a measure of hydrogen ion concentration in an aqueous solution (i.e., in water) on a scale that ranges from 0 (strong acid) to 14 (strong base), with neutral (water) at 7. (Rajewski Tr. 1175-76) The lower the pH the higher the concentration of hydrogen ions and the more acidic the solution. (*Id*.) Because pH is a logarithmic measure, moving up one unit on the pH scale (e.g., from 6 to 7) corresponds to a 10-fold change in hydrogen-ion concentration. (*Id.* at 1176-77)

159. Hydrogen ions catalyze hydrolysis reactions, which can break amide bonds and open epoxide rings. (*Id*. at 1179; PTX-300 at 22)

160. When developing an injectable pharmaceutical formulation, a POSA would have started with a target pH of 7.4, because that is the pH of blood and the pH of maximum physiological acceptability. (Rajewski Tr. 1177-78; PTX-374 at 10) However, the actual final pH selected for a formulation must also consider factors such as solubility and stability, so the final selected pH "is a compromise between the pH of maximum stability, solubility and physiological acceptability." (PTX-374 at 10) "In practice . . . , a reasonably wide pH range can be tolerated, particularly when dosing is via the IV route, and dilution with blood is rapid. In

these circumstances pHs ranging from 2 to 12 can be tolerated (although formulations at the extremes of this range are not recommended)." (*Id*.) "[T]he vast majority of licensed products have a pH between 3 and 9." (*Id*.)

161. A solution's pH is a major determinant of a compound's stability. (Rajewski Tr. 1179; PTX-300 at 22) Compounds in a solution having a pH below 7 (i.e., acidic solutions) may be susceptible to acid-catalyzed hydrolysis. (Rajewski Tr. 1179; PTX-300 at 22)

162. Epoxides may undergo acid-catalyzed reactions with "extreme ease." (Amiji Tr. 421; PTX-170 at 45) The pH range of maximum stability for carfilzomib's epoxide ring is between 7 and 11, and the area of maximum stability for amide bonds is between pH of 5 and 7. (Rajewski Tr. 1177, 1184; PTX-265 at 2-3; PTX-70 at 6)

163. The Court was not persuaded by Dr. Amiji's opinion that a POSA would have used a purported "rule of thumb" to formulate a compound two pH units below its pKa value. (Amiji Tr. 438) He provided no citation or other support for his so-called "rule." Dr Rajewski testified credibly that he was unaware of such a rule. (Rajewski Tr. 1184-85) The Court was persuaded by Dr. Rajewski's opinion that a POSA would have selected a pH at the point at which the compound was most stable. (*Id.*)

164. Dr. Amiji estimated the pKa of carfilzomib at "about 5," but this estimate was based on Onyx's NDA, which is a confidential document that is not prior art. (Amiji Tr. 438-39)

165. A POSA would not have known, based on the available prior art, the pKa value of carfilzomib. (Amiji Tr. 439; Dr. Rajewski Tr. 1186)

166. Dr. Amiji testified that the Sin reference's (DTX-69) use of neat trifluoracetic acid ("TFA") would have informed a POSA that the epoxide ring in carfilzomib would not open

at a pH of 3.5. (Amiji Tr. 393, 454) The Court was persuaded by the testimony of Dr. Rajewski that neat TFA does not contain any water, and therefore has no pH. (Rajewski Tr. 1189-91) Dr. Rajewski testified that neat TFA is routinely used for the exact purpose of the Sin paper: to remove a protecting group on an intermediate compound having an epoxyketone warhead, and that great lengths are taken to ensure no water is present during such a reaction. (*Id.*) A POSA would not have looked to the Sin reference (DTX-69) to determine an acceptable pH for formulating carfilzomib.

**3. SBECD**

167. A cyclodextrin is a cone-shaped molecule with a hole through the center; the outside is hydrophilic and the inside is hydrophobic. (Rajewski Tr. 1197, 1199) A compound's hydrophobic portions can go in and out of the cavity of a cyclodextrin, potentially increasing the compound's water solubility. (*Id.*; PTX-155 at 3)

168. Unsubstituted β-cyclodextrins have 21 hydroxyl groups around the rim. Hydroxyl groups are "water-like structure[s]" that "can partake in many of the reactions that water can participate in." (Rajewski Tr. 1197; Amiji Tr. 427)

169. SBECDs are specific β-cyclodextrins in which some of the 21 hydroxyl groups on the rim have been substituted with sulfobutylether groups. (Rajewski Tr. 1197-98; Amiji Tr. 426-27)

170. In the decades preceding 2004, interest in cyclodextrin-containing formulations had risen. (PTX-155 at 3; PTX-685 at 16)

171. As of 2003, at least 25 marketed formulations used β-cyclodextrins. (PTX-685 at 10-11) Out of 1200 FDA-approved drug products, only four used β-cyclodextrins, and only two

(Vfend and Geodon) used SBECD. (Rajewski Tr. 1195, 1205-06; DTX-75; PTX-757) There were no FDA-approved peptides that were formulated using cyclodextrin. (Rajewski Tr. 1195-96; PTX 405 at 2)

172. CyDex sells an SBECD under the brand name Captisol. (Amiji Tr. 352; DTX-150) In Captisol, seven of the 21 hydroxyl groups are substituted, leaving 14 hydroxyl groups around the rim. (Amiji Tr. 427) Captisol is advertised as being capable of complexing with peptides. (DTX-150 at 3)

173. A POSA would have known that SBECD may be used to improve the solubility of a drug product. As of July 2003, CyDex provided an FAQ ("CyDex's FAQ") for formulators on how to complex a drug product with SBECD to improve solubility. (DTX-150 at 3) CyDex's FAQ recommends performing a phase solubility analysis where solutions of 0, 2.5, 5, 10, 20, and 40% w/v SBECD are mixed with a drug product, and the results are plotted "to develop formulations where a required solubility must be maintained." (*Id*. at 7)

174. In 2004, some research existed that cyclodextrins could catalyze the opening of an epoxide ring (in the synthesis of α-hydroxyketone) through hydrogen bonding between hydroxyl groups on the rim of cyclodextrins and the oxygen atom in the epoxide ring. (Rajewski Tr. 1199-1201, 1251-52; PTX-598 at 1-2; PTX-682 at 1-2) Dr. Amiji testified that, based on how cyclodextrin will complex with carfilzomib, the cyclodextrin will have no impact on the epoxide structure. (Amiji Tr. 347-48) While a POSA may have had concerns that SBECD may open the epoxide ring, that would not have prevented a POSA from trying to formulate carfilzomib with SBECD. (Amiji Tr. 358, 364-65)

175. In 2004, some research existed that cyclodextrins would catalyze the breaking of amide bonds by hydrolysis. (Rajewski Tr. 1201-03; PTX-34 at 1) Dr. Rajewski testified that if the cyclodextrin complexed with the hydrophobic side chains of the amino-acid residues in carfilzomib, the hydroxyl groups on the outside rim of the cyclodextrin would be adjacent to an amide bond. (Rajewski Tr. 1201-03) Dr. Amiji testified that cyclodextrin would have no impact on the peptide bonds because cyclodextrin interacts only with the non-polar side chains and aromatic ring structures. (Amiji Tr. 348-49) While a POSA may have had concerns that SBECD may break carfilzomib's amide bonds, that would not have prevented a POSA from trying to formulate carfilzomib with SBECD. (Amiji Tr. 358, 364-65)

176. A POSA would have known that other solubilizing technologies existed, including cosolvents, emulsions, suspensions, small particle size, solid dispersions, surfactants, salts, and polymorphs. (Rajewski Tr. 1314-16; PTX-300 at 16-21; PTX-775 at 10; DTX-53 at 14-24) A POSA would also have known that YU-101 required a near-toxic amount of co-solvent in order to solubilize. (Molineaux Tr. 846)

**4. Lyophilization**

177. Lyophilization is a well-known freeze-drying process in which water is sublimed from a pharmaceutical product after it is frozen. (Amiji Tr. 368-69; DTX-364 at 25) "The particular advantages of this process are that biologicals and pharmaceuticals that are relatively unstable in aqueous solution can be processed and filled into dosage containers in the liquid state . . . and stored in the dry state, in which there are relatively few stability problems." (DTX-364 at 25)

178. Bortezomib (Velcade), a prior art injectable drug, is lyophilized. (DTX-73)

179. Vfend, a prior art injectable drug formulated with SBECD (Captisol), was lyophilized. (Amiji Tr. 373; DTX-74)

180. Geodon, a prior art injectable drug formulated with SBECD (Captisol), was lyophilized. (Amiji Tr. at 374; DTX-75)

181. A POSA would have known to at least try to lyophilize a formulation of a compound with known stability problems. (Amiji Tr. 371-75)

**5. Citric Acid**

182. Citric acid is a known buffer commonly used in parenteral products. (DTX-209 at 7)

**6. Combination Of Elements**

183. CyDex's FAQ recommends adjusting the pH to create a positive charge on the drug product to attract and retain the compound in Captisol's hydrophobic cavity. (DTX-150 at 7; Amiji Tr. 361-62)

184. In 1999, Dr. Rajewski gave a presentation discussing the "synergistic effect" of complexation with SBECD and pH controlled by citric acid. (Rajewski Tr. 1307-08) Dr. Rajewski testified that the presentation concerned solid formulations (e.g., tablets), not aqueous formulations (*id*. at 1308-10), but did not testify specifically as to how this would affect a POSA's consideration of SBECD and pH control using citric acid.

## LEGAL STANDARDS

### I. Presumption Of Validity

An issued patent is presumed to be valid. *See* 35 U.S.C. § 282. Therefore, to invalidate a patent, a party must carry its burden of proof by "clear and convincing evidence." *See Procter &*

*Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009). Clear and convincing evidence is evidence that "proves in the mind of the trier of fact an abiding conviction that the truth of [the] factual contentions [is] highly probable." *Intel Corp. v. U.S. Int'l Trade Comm'n*, 946 F.2d 821, 830 (Fed. Cir. 1991) (internal quotation marks omitted; first alteration in original). A defendant's burden to prove invalidity based on prior art (e.g., anticipation or obviousness) is "especially difficult when the prior art [on which it relies] was before the PTO examiner during prosecution of the application." *Hewlett-Packard Co. v. Bausch & Lomb Inc.*, 909 F.2d 1464, 1467 (Fed. Cir. 1990).

## II. Obviousness

A patent may not issue "if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains." 35 U.S.C. § 103(a). Obviousness is a question of law based on underlying factual findings concerning: (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the art; and (4) objective considerations of non-obviousness. *See Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18 (1966).

To prove that a patent is obvious, a party must demonstrate "that a skilled artisan would have had reason to combine the teaching of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success from doing so." *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1069 (Fed. Cir. 2012) (internal citation and quotation marks omitted); *see also*

*Amgen, Inc. v. F. Hoffman-La Roche Ltd.*, 580 F.3d 1340, 1362 (Fed. Cir. 2009) ("An obviousness determination requires that a skilled artisan would have perceived a reasonable expectation of success in making the invention in light of the prior art."). While an analysis of any teaching, suggestion, or motivation to combine known elements is useful to an obviousness analysis, the overall obviousness inquiry must be expansive and flexible. *See KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 415, 419 (2007).

The use of hindsight is not permitted when determining whether a claim would have been obvious to one having ordinary skill in the art. *See id.* at 421 (cautioning against "the distortion caused by hindsight bias" and obviousness "arguments reliant upon ex post reasoning"). To protect against the improper use of hindsight in a determination that an invention would have been obvious, the Court is required to consider objective (or "secondary") considerations of non-obviousness, such as commercial success, failure of others, unexpected results, and long-felt but unmet need. *See, e.g., Leo Pharm. Prods., Ltd v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013). Objective considerations "may often be the most probative and cogent evidence in the record" relating to obviousness. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983).

## III. Incorrect Inventorship

Pursuant to the applicable (pre-America Invents Act) version of the statute, a person shall be entitled to a patent "unless he did not himself invent the subject matter sought to be patented." 35 U.S.C. § 102(f). To prove improper derivation under § 102(f), the patent challenger must show, by clear and convincing evidence: (1) prior conception by another; and (2) communication

of that conception to a named inventor. *See Cumberland Pharm. Inc. v. Mylan Institutional LLC*, 846 F.3d 1213, 1217-18 (Fed. Cir. 2017).

Conception, including the date of conception, is a question of law based on underlying findings of fact. *See NFC Tech., LLC v. Matal*, 871 F.3d 1367, 1371 (Fed. Cir. 2017); *Taurus IP, LLC v. DaimlerChrysler Corp.*, 726 F.3d 1306, 1322-23 (Fed. Cir. 2013). "[T]he test for conception is whether the inventor had an idea that was definite and permanent enough that one skilled in the art could understand the invention . . . . An idea is definite and permanent when the inventor has a specific, settled idea, a particular solution to the problem at hand, not just a general goal or research plan he hopes to pursue." *Burroughs Wellcome Co. v. Barr Labs., Inc.*, 40 F.3d 1223, 1228 (Fed. Cir. 1994). "[C]onception is not complete if the subsequent course of experimentation, especially experimental failures, reveals uncertainty that so undermines the specificity of the inventor's idea that it is not yet a definite and permanent reflection of the complete invention as it will be used in practice." *Id.* at 1228-29.

## IV. Obviousness-Type Double Patenting

Obviousness-type double patenting ("OTDP") is a judicially-created doctrine designed to "prevent claims in separate applications or patents that do not recite the 'same' invention, but nonetheless claim inventions so alike that granting both exclusive rights would effectively extend the life of patent protection." *Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1373 (Fed. Cir. 2005) (internal citation omitted). OTDP prohibits the issuance of claims in a second patent that are "not patentably distinct from the claims of the first patent." *In re Longi*, 759 F.2d 887, 892 (Fed. Cir. 1985) (internal citations omitted). A later patent claim "is not patentably distinct from an earlier claim if the later claim is obvious over, or anticipated by, the earlier claim." *Eli*

*Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 968 (Fed. Cir. 2001) (internal citations omitted). OTDP is a question of law based on underlying factual findings. *See In re Hubbell*, 709 F.3d 1140, 1145 (Fed. Cir. 2013).

An obviousness-type double patenting analysis entails two steps. "First, as a matter of law, a court construes the claim in the earlier patent and the claim in the later patent and determines the differences. Second, the court determines whether the differences in subject matter between the two claims render the claims patentably distinct." *Eli Lilly*, 251 F.3d at 968.

## DISCUSSION

### I. Obviousness: Compound Patents

Cipla seeks to invalidate the asserted claims of the Compound Patents as obvious in view of YU-101 (embodied in the '099 Patent) and knowledge in the art that morpholino acts as a solubilizing substituent. The Court concludes, for the reasons below, that Cipla has failed to prove obviousness of the Compound Patents by clear and convincing evidence.

#### A. Lead Compound Analysis

In determining the obviousness of a new chemical compound, the Federal Circuit applies a "lead compound" analysis. *Otsuka Pharm. Co., Ltd. v. Sandoz, Inc.*, 678 F.3d 1280, 1291 (Fed. Cir. 2012). Lead compound analysis requires a court determining "whether a new chemical compound would have been prima facie obvious over particular prior art compounds" ordinarily to undertake a two-part inquiry and assess: (1) "whether a chemist of ordinary skill would have selected the asserted prior art compounds as lead compounds, or starting points, for further development," and (2) "whether the prior art would have supplied one of ordinary skill in the art

with a reason or motivation to modify a lead compound to make the claimed compound with a reasonable expectation of success." *Id*. at 1291-92.[5]

A lead compound is a compound in the prior art that would be "most promising to modify in order to improve upon its [] activity and obtain a compound with better activity." *Takeda Chem.*, 492 F.3d at 1357. The analysis "focuses on those proposed lead compounds that the alleged infringer has attempted to prove, by clear and convincing evidence, that the skilled artisan would have had a reason to select from the panoply of known compounds in the prior art." *Otsuka*, 678 F.3d at 1292. A lead compound is a compound that is "a natural choice for further development efforts." *Altana Pharma AG v. Teva Pharm. USA, Inc.*, 566 F.3d 999, 1008 (Fed. Cir. 2009). In any particular case, there may be more than one prior art compound that a chemist of ordinary skill would have considered for further development. *See id.* (explaining that limiting lead compound test to single compound "would present a rigid test similar to the teaching-suggestion-motivation test that the Supreme Court explicitly rejected in *KSR*").

In determining whether a chemist would have selected a prior art compound as a lead, the analysis is guided by evidence of the compound's pertinent properties, such as activity, potency, toxicity, and other relevant characteristics. *See Otsuka*, 678 F.3d at 1292. "Absent a reason or

[5] Cipla contends the Federal Circuit's "lead compound" theory conflicts with the Supreme Court's standards for obviousness set out in *KSR*. (*See* D.I. 521 at 3; D.I. 536 at 7 n.4) This Court is not persuaded. *See UCB, Inc. v. Accord Healthcare, Inc.*, 201 F. Supp.3d 491 (D. Del. 2016), *aff'd*, 890 F.3d 1313, 1328-29 (Fed. Cir. 2018) (applying lead compound analysis), *cert. denied*, 139 S. Ct. 574 (Nov. 19, 2018); *see also Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007). Accordingly, the Court will follow the direction of the Federal Circuit and apply the lead compound analysis.

motivation based on such prior art evidence, mere structural similarity between a prior art compound and the claimed compound does not inform the lead compound selection." *Id*.

Once a lead compound has been identified, a party seeking to invalidate a patent must then show the reason or motivation for modifying the lead compound, which "may come from any number of sources and need not necessarily be explicit in the prior art." *Id*. Again, the pertinent properties of the lead are relevant, for "it is the possession of promising useful properties in a lead compound that motivates a chemist to make structurally similar compounds." *Id*. at 1292-93 (internal quotation marks omitted). "[I]t is sufficient to show that the claimed and prior art compounds possess a sufficiently close relationship . . . to create an expectation, in light of the totality of the prior art, that the new compound will have similar properties to the old." *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1301 (Fed. Cir. 2007) (internal quotation marks omitted).

**B. YU-101 Is Not A Lead Compound For Development Of A Drug Product**

It is Cipla's burden to prove that a POSA would have viewed YU-101 as a lead compound for developing a drug product. Cipla has not met its burden. To the contrary, the Court is persuaded that it is far more likely a POSA would have viewed bortezomib as a lead compound.

In the context of the instant case, a POSA looking for a lead compound to try to develop into a drug product would have preferred a compound that had human potency data and not just test tube data. (*See, e.g.*, FF ¶ 126) A POSA would also have chosen as a lead a compound that balanced safety, efficacy, and deliverability, with a proven mechanism of action and potent *in vitro* and *in vivo* activity. (*See, e.g.*, FF ¶ 127) A POSA would also have known of the FDA

approval of bortezomib, a boronate, which was the only proteasome inhibitor approved for treating cancer. (*See, e.g.*, FF ¶ 134) Such a POSA would also have known that bortezomib had an established data package, had been safely and effectively administered to humans, and was the most clinically-advanced proteasome inhibitor at the pertinent time. (*See id.*)

In the early 2000s, proteasome inhibitors were not new (JTX-2 col. 2 ll. 9-10; DTX-47 at 2), but they were also not well-understood. Generally speaking, given only an inhibitor's chemical structure, chemists had difficulty predicting (1) its biological properties, such as specificity, stability, potency, and toxicity, and (2) its impact on other biological functions in the human body. (JTX-2 col. 2 ll. 10-13; FF ¶¶ 142, 127-128, 134-135, 136-140) Despite this unpredictability, there was a desire in the art to develop proteasome inhibitors to serve as drug products (and molecular probes), especially after the FDA approval of bortezomib, which was the first proteasome inhibitor approved for cancer treatment. (Bachovchin Tr. 78; JTX-6 col. 2 ll. 18-26; JTX-2 col. 2 ll. 9-17; DTX-39 col. 2 ll. 26-32) In the pursuit of a lead compound to be used as a proteasome inhibitor, a POSA would have looked for a molecule that displayed the best balance of specificity, stability, potency, toxicity (safety), deliverability, and efficacy.

The FDA approval of bortezomib not only validated the CT-L site as a therapeutic target, but also proved to the industry that proteasome inhibition could provide high-impact therapeutic uses. (Bachovchin Tr. 100; Bunin Tr. 490; Stein Tr. 862, 922) A POSA would have been aware, though, that bortezomib caused peripheral neuropathy (a degradation of certain nervous functions), likely due to bortezomib's non-specificity and off-target toxicity. (FF ¶ 135) Thus, there was a need in the art to create a safer proteasome inhibitor that was more specific to the CT-L site, having minimal off-target and off-tissue toxicity. (JTX-2 col. 2 ll. 13-17; FF ¶ 135)

While YU-101 showed promise with respect to these criteria, it was an irreversible inhibitor, and the early 2000s were a period of strong industry aversion to irreversible inhibitors. (FF ¶ 1300) Its irreversibility means that once YU-101 binds to its target site, that bond cannot be broken. (*See, e.g.*, FF ¶¶ 128-29) If an irreversible inhibitor like YU-101 inadvertently binds to an off-target site, a patient may suffer catastrophic side effects that cannot be alleviated. (*See id.*; Stein Tr. 872; Bachovchin Tr. 104) Thus, there was significant pressure in the industry to focus only on reversible inhibitors. *See generally Neptune Generics, LLC v. Eli Lilly & Co.*, 921 F.3d 1372, 1377 (Fed. Cir. 2019) ("Evidence of industry skepticism is a question of fact that weighs in favor of non-obviousness."); *see also* FF ¶ 130.

Cipla contends that YU-101's CT-L specificity was so overwhelming that it would have outweighed general industry concerns of off-site toxicity. (D.I. 521 at 14) This contention is not supported by the record evidence. Cipla has not shown that POSAs in the industry would have correlated proven CT-L site specificity with increased safety. Nor has Cipla proven that a POSA would have believed YU-101 would not bind off-tissue and would not cause an adverse immune response. (*See* Molineaux Tr. 847-48; DTX-81 at 100 ("The specificity of many new inhibitors is usually not examined with many other proteases, and yet the inhibitor is often claimed to be 'specific'.")) The record contains no significant evidence that anyone in the industry (other than the inventors of the Compound Patents) was pursuing irreversible proteasome inhibitors (generally, or YU-101, specifically) as a drug product.[6] The Court has not been presented with

[6] The '099 Patent specification, which states broadly that it describes compositions for treating cancers and other diseases, would not have impacted a POSA's choice of lead compound. (*See* D.I. 521 at 15) The '099 Patent does not state that YU-101, in particular, may treat all of the listed diseases, including cancer. (DTX-39 col 4 ll. 9-17) Moreover, a POSA choosing a lead compound would have looked to real-world safety and efficacy data, rather than self-proclaimed

clear and convincing evidence that a POSA would have selected an irreversible inhibitor such as YU-101 as a lead compound for a drug product in 2003.

It may be that pioneering, non-"ordinary" chemists may have seen great potential in YU-101 as a compound to be researched for further development into a drug product. (*See* Stein Tr. 958-59 (noting academics may have been intrigued though industry was not); Lipinski Tr. 1047-48 (acknowledging that, in 2004, there were compounds approved by the FDA that bound irreversibly)) But a POSA is "presumed to be one who thinks along the line of conventional wisdom in the art and is not one who undertakes to innovate, whether by patient, and often expensive, systematic research or by extraordinary insights." *Standard Oil Co. v. Am. Cyanamid Co.*, 774 F.2d 448, 454 (Fed. Cir. 1985).

For at least the same reasons, the fact that Proteolix treated YU-101 as a lead compound for trying to develop a drug product does not satisfy Cipla's burden to prove that a ***POSA*** would have done so. Notably, Proteolix also had substantial skepticism about the prospect of developing YU-101 into a drug product and also pursued numerous other molecules as back-ups. (*See, e.g.*, FF ¶ 89) Nobody competed with Proteolix when it sought and obtained a license to YU-101 from Yale. (*See* FF ¶ 82) Proteolix, co-founded by Yale's Dr. Crews, may have been idiosyncratically motivated to pursue YU-101 by, in part, Yale's obligation to attempt to commercialize its federally-funded intellectual property. (FF ¶ 74)

A POSA looking to develop a new drug product would have much more likely pursued modifying other known reversible inhibitors, such as boronates, and especially bortezomib –

---

descriptions in a patent. (Lipinski Tr. 989-90) Such data was lacking for YU-101, while it was available for bortezomib, which was FDA-approved for treatment of multiple myeloma.

which was FDA approved and for which much necessary data was already available – while (at best, for Cipla) waiting for research on irreversible inhibitors to mature and industry aversion to them to abate. Other potential lead compounds identified by Onyx (which has no burden of proof on this issue) – including PS-519, marizomib, and TMC-95A – were also more promising starting points than YU-101, for reasons including their established data packages, their specificity and potency and drug-like structure, as well as (for some of them) their reversibility (TMC-95A) and evidence of results of administration in humans (PS-519). (*See, e.g.*, FF ¶¶ 136-41)

In sum, Cipla has failed to prove that a POSA would have viewed YU-101 to be a lead compound for a POSA looking to develop a drug product.

### C. Cipla Has Failed To Meet Its Burden With Respect To Its Newfound Focus On Development Of A Molecular Probe

Surprisingly, much of Cipla's obviousness argumentation, during closing argument at trial and again in the post-trial briefing, is not directed to showing that carfilzomib would have been obvious to a POSA developing a drug product to treat multiple myeloma. Instead, Cipla has tried to shift the focus to its purported proof that carfilzomib would have been obvious to a POSA developing an improved molecular probe. Cipla's molecular probe contentions are untimely and unfairly prejudiced Onyx at and after trial. Consequently, the Court would not invalidate the Compound Patents based on Cipla's molecular probe theory even if Cipla had produced sufficient evidence to support it. But Cipla's theory additionally fails for lack of proof.

The Court agrees with Onyx that Cipla's "argument about a search for a better molecular probe is flawed" and "untimely." (D.I. 533 at 1-2) In defense of the timing, Cipla points to three disputed facts it indicated in the pretrial order ("PTO") it intended to prove at trial. (*See* D.I. 476

Ex. 3 at 61; *see also* D.I. 521 at 5-6) However, as Onyx correctly observes, these paragraphs appeared under the sub-heading, "A POSA Would Have Been Motivated to Investigate Peptide α', β' Epoxyketone Proteasome Inhibitors ***As A Therapeutic Agent for Cancer***." (D.I. 476 Ex. 3 at 61) (emphasis added) Nothing about these statements in the pretrial order (or anything else Cipla has identified from prior to trial) put Onyx on notice that at trial Cipla was going to pursue (as one of its theories of invalidity) that the patents were obvious based solely on molecular probe evidence, independent of any motivation relating to the development of a drug product.

Cipla also points to a statement in Onyx's Daubert briefing, that "Proteolix was originally founded to develop a compound called YU-101 – a research tool used in an academic laboratory – into a drug." (D.I. 521 at 5) (quoting D.I. 462 at 4) This statement merely reflects the reality that some of the compounds involved in this case could be used as molecular probes. At most it indicates that Onyx was aware that some researchers may have been motivated to use YU-101 to develop an improved probe. But nothing in Onyx's own briefing could (or did) give Onyx notice that Cipla intended at trial to seek to invalidate Onyx's Compound Patents based on a molecular probe theory.

According to Cipla, "[t]he issue was plainly identified repeatedly in the Defendants' Statement of Contested Issues of Fact (Final Pretrial Order, Exhibit 3, ¶¶ 159-162), in the Defendants' opening statement (Tr. 14-15), in the direct testimony of Dr. Bachovchin (Tr. 78), in cross examination of Plaintiff's expert (Tr. (Stein) 960-961), and in Defendant's closing argument (Tr. 1379-1380)." (D.I. 521 at 6) (internal footnote omitted and internal grammar modified) As is apparent, the only pretrial notice Cipla even contends it provided Onyx (and the Court) was the three facts in the PTO, which the Court already addressed above. Cipla is correct

that it increasingly emphasized a molecular probe theory as trial progressed. Obviously, however, nothing that occurred during trial could have given Onyx pretrial notice of Cipla's probe-related contentions.

In any event, even had Cipla adequately disclosed its probe theory prior to trial, the record the parties created at trial does not persuade the Court, by clear and convincing evidence, that a POSA developing a probe would have viewed YU-101 as a lead compound. Instead, there is a failure of proof on this point.

***Both parties' experts*** agreed that the problem to be solved at the time of the invention was the need for an improved ***therapeutic*** proteasome inhibitor over the FDA-approved bortezomib. (Bachovchin Tr. 226-27; Stein Tr. 874-75; FF ¶¶ 55, 125) Making a better therapeutic was the only motivation that Cipla's expert, Dr. Bachovchin, identified. (Bachovchin Tr. 94-95 ("for use potentially as an anti-cancer drug"), 100 ("for the treatment of cancer")) Relatedly, even Cipla's definition of a POSA was limited to drug development. (*See* Bachovchin Tr. 87-88) (explaining that POSA collaborates with those in design and synthesis of peptides as drug molecules, formulation of drug products, and other professionals in drug development field) Therefore, evidence relating to a POSA's motivation to make a molecular probe, starting with (or without) YU-101, is lacking.

As Onyx correctly points out:

> No expert testified about any motivation to modify YU-101 to make a molecular probe. The only purported motivation for modifying YU-101 that Cipla offers is improving YU-101's solubility as an injectable therapeutic. That motivation is inapplicable to probes.

(D.I. 533 at 16; *see also* Crews Tr. 565-66, 592-93 (stating that YU-101 had sufficient solubility for use as probe and was already optimized for such use))

The Court acknowledges that the facts and the law suggest that Cipla perhaps ***could have proven*** that YU-101 was a lead compound for the development of a molecular probe. It is also true, as Cipla emphasizes (D.I. 521 at 4), that the Compound Patents suggest that one of the goals of these patents is to make proteasome inhibitors as molecular probes and research tools.[7] Some of the prior art similarly noted the molecular probe goal.[8] Also, the most important considerations for a molecular probe are specificity and potency, and irreversibility is not a problem, all of which would have likely made YU-101 more attractive to a POSA trying to make a molecular probe than one who was trying to make a drug product.[9]

Furthermore, as Cipla notes (*see* D.I. 521 at 3-4) and as the Supreme Court explained in *KSR*, 550 U.S. at 419: "In determining whether the subject matter of a patent claim is obvious, neither the particular motivation nor the avowed purpose of the patentee controls." (D.I. 521 at 3-4) It follows that, even though the inventors of the Compound Patents were motivated to create a drug product, any motivation (and not just the desire to create a drug product) might

[7] *See* JTX-6 col. 2 ll. 18-26; JTX-2 col. 2 ll. 9-17.

[8] *See* DTX-55 at 1 ("A number of small molecule inhibitors of the 20S proteasome have been developed for use as molecular probes of proteasome function and potential therapeutics; however, many lack specificity for the proteasome, thus compromising their utility."); DTX-39 col. 2 ll. 26-32 ("Enzyme inhibitors are valuable tools that enable the elucidation of details of cellular events that are regulated by these enzymes."); DTX-47 at 1 ("The strong *in vivo* and *in vitro* activities suggest that this class of proteasome inhibitors could be both molecular probes and therapeutic agents."); DTX-69 (Sin) at 2).

[9] *See* FF ¶¶ 68, 112, 117, 140, 143-44; DTX-47 at 1; DTX-39 col. 40. ll. 54-57; Crews Tr. 566; Stein Tr. 960, 973-74.

render the Compound Patent claims invalid as obvious. (*See id.* at 4) The Court agrees with Cipla that, as stated in *KSR*, any motivation might supply the motivation to combine necessary to render a patent claim invalid due to obviousness.

The problems with Cipla's contentions about molecular probes is not, then, the law or the evidence it might have brought to bear on the point. Instead, the problems are that Cipla did not provide adequate notice to Onyx that the motivation to develop an improved probe was a basis on which it was going to try to invalidate the Compound Patents and (likely relatedly, given the untimeliness of the theory) the record does not contain clear and convincing evidence that YU-101 would have been a lead compound even for developing a probe.[10]

Accordingly, Cipla has failed to prove that a POSA would have viewed YU-101 as a lead compound for developing a molecular probe.

**D. The Morpholino Methylene Modification Would Not Have Been Obvious**

Because the Court must apply a lead compound analysis, and because Cipla has failed to prove that YU-101 would have been a lead compound, Cipla cannot prevail in its attempt to prove that the Compound Patents are invalid as obvious. *See generally In re Cyclobenzaprine*,

[10] To the extent Cipla is now contending that the selection of YU-101 as a lead compound for developing an improved molecular probe is self-evident – from facts such as the historical reality that YU-101 was developed as a molecular probe, the '099 Patent's description of YU-101's benefits as a molecular probe, and the Compound Patents' references to molecular probes – Cipla has not persuaded the Court of this proposition by clear and convincing evidence. In fact, the ease with which Cipla suggests one could find that YU-101 was the lead compound for developing a molecular probe makes all the more striking Cipla's failure to disclose this theory of invalidity in a timely manner prior to trial. In any event, even if the Court viewed YU-101 as a lead compound for developing an improved molecular probe, Cipla's new theory fails, as the record is devoid of evidence that a POSA would have been motivated to modify it – at all, given that it was already an adequate probe; and specifically with a morpholino methylene at the N-terminus, as explained further below.

676 F.3d at 1069 (noting party asserting obviousness bears burden of persuasion).[11] Nonetheless, the Court will address an additional failing in Cipla's obviousness case with respect to the Compound Patents. Even assuming that a POSA would have selected YU-101 as a lead compound, Cipla has not proven by clear and convincing evidence that a POSA would have modified YU-101's N-terminus with a morpholino methylene.

The primary theory proffered by Cipla is that a morpholino methylene would have been an obvious modification to improve YU-101's solubility. (D.I. 521 at 10-14) It is undisputed, and the Court finds, that YU-101's solubility problems were either known in the art or could have been discovered through routine experimentation. (FF ¶ 145; *see also id.* ¶¶ 79, 81, 111) It is also undisputed, and the Court finds, that adding morpholino moieties was one of many known options for potentially increasing solubility. (FF ¶¶ 147-50)

Cipla's contention that a POSA designing a drug product would have been motivated to increase YU-101's solubility improperly rests on hindsight reasoning.

> Where a skilled artisan merely pursues "known options" from "a finite number of identified, predictable solutions," the resulting invention is obvious under Section 103. *KSR*, 550 U.S. at 421, 127 S.Ct. 1727. Where, however, a defendant urges an obviousness finding by "merely throw[ing] metaphorical darts at a board" in hopes of arriving at a successful result, but "the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful," courts should reject "hindsight claims of obviousness." *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009).

[11] Additionally, YU-101 was considered by the Examiner during prosecution of the '042 Patent (in the form of the '099 Patent), who expressly found that carfilzomib is not obvious or anticipated by it. (*See* Lipinski Tr. 1030-31; JTX-11 at 337; FF ¶ 119) Cipla's burden to prove invalidity based on prior art is "especially difficult when th[at] prior art was before the PTO examiner during prosecution," *Hewlett-Packard*, 909 F.2d at 1467, and Cipla has not met this difficult challenge.

*In re Cyclobenzaprine*, 676 F.3d at 1070-71. In this case, Cipla has shown that numerous potential modifications were available to a POSA who desired to increase YU-101's solubility, but the record does not demonstrate that a POSA would have been motivated specifically to place a morpholino methylene on the N-terminus. Cipla's oft-repeated contention that YU-101 "had a simple solution to its one real shortcoming of poor solubility" has simply not been proven. (D.I. 536 at 5; *see also* Tr. 21, 31 (Cipla claiming in opening statement that YU-101's solubility problem was "easier to solve," as it was a "simple" to improve compound), 1405 (reiterating in closing argument that YU-101's problems were "easily" solved))

Cipla has not proven even that the N-terminus was the obvious location to modify YU-101 to increase solubility. As support for this component of its defense, Cipla points to the YU-101 biotinylation experiment (which modified the N-terminus) and presumes that "Dr. Barry Bunin[] clearly understood the significance of the experiments with biotinylation as showing that even very large substituents at the N-terminus were well tolerated," adding that Dr. Bunin's insights reflect "what real people of skill thought." (D.I. 521 at 13) Cipla's heavy reliance on Dr. Bunin only makes more striking Cipla's failure to show that Dr. Bunin was a POSA – as opposed to a person of extraordinary skill in the art or a person especially tasked with solving a problem a POSA would not have confronted. *See Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1138 (Fed. Cir. 1985) ("The invention must be evaluated not through the eyes of the inventor, who may have been of exceptional skill, but as by one of 'ordinary skill.'"); *Envtl. Designs, Ltd. v. Union Oil Co. of California*, 713 F.2d 693, 697 (Fed. Cir. 1983) ("The important consideration [is whether] an invention would or would not have been obvious, as a whole, when it was made, to a person of 'ordinary skill in the art' – not to the judge, or to a layman, or to

those skilled in remote arts, or to geniuses in the art at hand."). Further, even assuming (without deciding) that a POSA would have understood that the N-terminus sits outside of the hydrophobic CT-L pocket – making the N-terminus an attractive location for modification – Cipla did not prove that the N-terminus would, therefore, have been the sole or even primary location a POSA would have looked to modify to increase the solubility of YU-101. (*See* FF ¶ 147)

Cipla points to the Sin reference, but Sin does not conclude that the N-terminus is an obvious location to modify YU-101 for a drug product. Instead, the Sin researchers used biotinylation, a well-known labeling/identification process (DTX-69 at 2), to "understand[] the mode of action of epoxomicin" and observe whether it bound to the same proteasome sites as eponemycin (*id*. at 4). Although the results showed that biotinylated epoxomicin still selectively bound to the same site as non-biotinylated epoxomicin (and eponemycin), Dr. Crews presented unrebutted testimony that potency decreased "over 90 percent" because biotinylation made the epoxomicin less membrane permeable. (Crews Tr. at 549) While a POSA could deduce that modifying the N-terminus may not significantly affect selectivity of the CT-L site, the Sin reference says nothing about any modification's effects on potency (or any other property), which would have been (giving Cipla the benefit of the doubt for the sake of argument) a primary reason for having selected YU-101 as a lead compound in the first place.

Furthermore, even assuming the N-terminus was chosen by a POSA as the location to modify, Cipla has failed to show why a POSA would have arrived at a morpholino methylene as the right modification, or even as one of multiple obvious (or inevitably-discovered through repeated routine experimentation) modifications. Onyx presented unrebutted evidence that a

POSA would have had numerous options, including prodrugs or other sidechain or N-terminal modifications, at her disposal as mechanisms for trying to increase solubility. (*See, e.g.*, FF ¶ 147)[12] Further, while adding a morpholino methylene to the N-terminus may have increased solubility (Smyth Tr. at 723-24), it is undisputed that substantial uncertainty surrounded the biological implications of any modification to YU-101, and it was unknown whether the morpholino methylene N-terminus modification would actually produce a better drug product (or molecular probe). (Bachovchin Tr. 276; Crews Tr. 557-58; Smyth Tr. 724, 731-33; Molineaux Tr. 780-81, 786-87; Stein Tr. 902; Lipinski Tr. 1036-37) Hence, even if adding a morpholino (or, specifically, a morpholino methylene) were obvious to try as part of an effort to solve the problem of solubility, it does not follow – and Cipla has failed to prove – that there was a reasonable expectation of success that this modification would work for its intended result. (*See, e.g.*, Bunin Tr. 492)

Given the uncertainty and relative lack of data surrounding YU-101 as a whole, the Court is persuaded by Onyx's expert, Dr. Lipinski (*see, e.g.*, Tr. 1024-25), and not by Cipla's expert, Dr. Bachovchin (*see, e.g.*, Tr. 155-56), that modifying the N-terminus of YU-101 with a

[12] Cipla cites *Merck & Co. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989), for the proposition that "other possible solutions do[] not make use of morpholine less obvious." (D.I. 536 at 10; *see also* D.I. 521 at 11) In *Merck*, a prior art patent expressly disclosed a genus compound with over 1,200 chemical combinations (all of which would have produced the formulation of the patent being challenged as obvious) as well as numerous obvious species of modifications a POSA would have been motivated to try with a reasonable expectation of success. Here, by contrast, while the prior art may have taught some form of the proposed modification (i.e., a morpholino moiety as a solubilizing substituent), the prior art did not provide any specific motivation to modify the genus or any reasonable expectation of success from the particular modification (i.e., modifying YU-101 with a morpholino methylene to be a drug product or improved probe).

morpholino methylene was not obvious. *See generally KSR*, 550 U.S. at 401. Cipla has failed to prove, by clear and convincing evidence, that a POSA would have selected a morpholino methylene from the plethora of known options available with any reasonable expectation of success to produce a better drug product.

For pretty much all of the same reasons, Cipla has likewise failed to prove that a POSA seeking to develop an improved molecular probe would have modified YU-101's N-terminus with a morpholino methylene. Further, the record does not establish that a POSA would have even been motivated to make a YU-101-based molecular probe more soluble. To the contrary, Dr. Crews had solubilized YU-101 using solvents, and considered YU-101 a "sufficient" molecular probe without further modification. (FF ¶ 68) Even Cipla concedes that solvent toxicity is not as material a consideration for a molecular probe as it is for a drug product. (D.I. 521 at 17; D.I. 522 ¶ 75)

Again, Cipla has failed to prove, by the requisite clear and convincing evidence, necessary components of its obviousness case.

**E. Objective Indicia Of Nonobviousness**

Even though Cipla has failed to meet its burden with respect to identifying a lead compound and with respect to the modifications that would need to be made to its purported lead compound, and even though the parties devoted very little attention to objective indicia of nonobviousness (just four of 216 pages of combined briefing and proposed findings of fact), the

Court has considered the limited evidence of objective indicia and find that these indicia do not alter the conclusion of nonobviousness.[13]

As best as the Court can discern, Onyx contends that it proved the following objective indicia: long-felt unmet need and industry skepticism. (D.I. 533 at 39-40) Onyx proved that its FDA-approved drug product, Kyprolis, embodies the asserted claims of the Compound Patents and Formulation Patent. (*See, e.g.*, FF ¶ 3) The Court was persuaded by the evidence, especially the testimony of Dr. Siegel, that Kyprolis met the longstanding needs of many patients with relapsed or refractory multiple myeloma for an improved treatment, often extending their lives by months. (*See, e.g.*, Siegel Tr. 1338-40) This conclusion is further supported by the FDA's decision to grant fast-track designation to Kyprolis. (*See id.* 1335-36; *see also generally Ferring B.V. v. Watson Labs., Inc.*, 764 F.3d 1401, 1407 (Fed. Cir. 2014)) The Court was also persuaded that the inventors and Proteolix encountered skepticism from other industry participants as they pursued an irreversible proteasome inhibitor as a therapeutic option. (*See, e.g.*, Stein Tr. 916-17; Molineaux Tr. 1132-34; *see also generally WBIP, LLC*, 829 F.3d at 1329)

Onyx's proof of secondary considerations of nonobviousness further strengthens the Court's conclusion that the Compound Patents have not been proven to be invalid as obvious.

[13] *See generally Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 666-67 (Fed. Cir. 2000) ("[S]econdary considerations, when present, must be considered in determining obviousness."); *Cephalon, Inc. v. Slayback Pharma Ltd. Liability Co.*, 2020 WL 1983730, at *3 (D. Del. Apr. 27, 2020) ("[T]he safer course for a district court faced with an obviousness challenge (and looking to avoid reversal by the Federal Circuit) is to treat *Graham*'s 'invitation' to look at secondary considerations like a subpoena."); *but see Otsuka*, 678 F.3d at 1299 ("Because we agree with the district court that the prior art would not have provided one of ordinary skill with a reason or motivation to make aripiprazole from the unsubstituted butoxy compound, we need not examine Otsuka's evidence of secondary considerations of nonobviousness.").

### F. Conclusion

In sum, Cipla has not proven that the Compound Patents are invalid due to obviousness, for at least two reasons. First, Cipla failed to meet its burden to prove that YU-101 would have been an obvious lead compound to develop as a drug product or improved molecular probe. Second, even if YU-101 were a lead compound, Cipla failed to meet its burden to show any motivation to modify YU-101's N-terminus with a morpholino methylene with any reasonable likelihood of success. Having additionally considered Onyx's evidence of objective indicia of nonobviousness, the Court will not invalidate the Compound Patents due to obviousness.[14]

## II. Incorrect Inventorship: Compound Patents

Cipla seeks to invalidate the asserted claims of the '042 and '125 Patents as being invented by another, pursuant to 35 U.S.C. § 112(f). (D.I. 521 at 21) To prevail on this defense,

---

[14] Although Cipla dropped its enablement defense prior to trial (*see* D.I. 533-1 Ex. 1), it makes numerous arguments relating to enablement. For instance, Cipla contends:

> Plaintiff's expert, Dr. Stein, was firm in testifying that a person of ordinary skill in the art considering the disclosure of the patents in suit would not believe that carfilzomib would be a successful cancer drug, but would rather believe it would not be. (Tr. (Stein) 937-939) If Dr. Stein is correct, the patents are not enabled for a therapeutic use, and it is not necessary to prove the claims are obvious for a use that is not enabled by the patents.

(D.I. 521 at 21) Onyx responds that "the utility of the claimed compounds is disclosed and the claims are enabled because of pharmacological data in the patent specifications' description." (D.I. 533 at 2)

The Court is not persuaded that any of Cipla's enablement-related arguments provide a meritorious basis to invalidate Onyx's asserted claims. The Compound Patents disclose experimental test data on proteasome inhibitory activity, which show the claimed compounds' utility that is not in the prior art. (*See* JTX2 col. 44 ll. 49-67) Experimental data of pharmacological activity, even without clinical data, can be sufficient to support a patent's assertion of therapeutic utility. *See In re Brana*, 51 F.3d 1560, 1567 (Fed. Cir. 1995).

Cipla must prove, by clear and convincing evidence, that the invention it seeks to invalidate was conceived by someone other than the named inventors, and that the person who truly conceived of the invention communicated that conception to a named inventor. *See Cumberland Pharm.*, 846 F.3d at 1217-18. The Court concludes, for the reasons below, that Cipla has failed to prove either of these elements of its claim.

**A. Conception By Another**

Cipla has failed to prove by clear and convincing evidence that Barry Bunin, or anyone other than the named inventors, Drs. Smyth and Laidig, conceived of carfilzomib.

As evidence of Dr. Bunin's purported conception of carfilzomib, Cipla relies on the September Memoranda, in which he proposed a Markush group in which "R=morpholino." (D.I. 521 at 22; *see also, e.g.*, FF ¶¶ 87, 92-93) It is undisputed, however, and the Court finds, that Dr. Bunin's proposal of "R=morpholino" is (at best for Cipla) ambiguous. The Court is persuaded by Onyx's expert, Dr. Lipinski, that a POSA would interpret "R=morpholino" in the September Memoranda as referring literally to a urea linkage (a morpholino carbonyl), and not carfilzomib (a morpholino methylene). (*See, e.g.*, Lipinski Tr. 1035-36; Bachovchin Tr. 198 (agreeing that R=morpholino literally refers to urea linkage)) Cipla's competing evidence – that Dr. Bunin sought to address YU-101's solubility issues, that a POSA would have known a urea linkage would not substantially improve solubility, and so a POSA would read "R=morpholino" as implicitly referring to a methylene linkage (or a morpholino methylene) (*see* Bachovchin Tr. 155-56, 193-98) – is not implausible. But it is also not the clear and convincing evidence required to demonstrate that Dr. Bunin had the idea for carfilzomib "that was definite and

permanent enough" that a POSA could have understood it. *Burroughs Wellcome*, 40 F.3d at 1228.

To the contrary, the September Memoranda show merely that Dr. Bunin had "just a general goal or research plan" he (and Proteolix) hoped to pursue, which is insufficient to constitute conception. *Id.* The documents and associated communications repeatedly refer to the September Memoranda as research plans or proposals. (*See* DTX-682 at 1 ("Three Proposals for New Proteolix IP Outside YU101"); DTX-696 ("Four Proposals to Create New Proteolix IP Outside of YU101 and Epoximicin"); DTX-992B at 1 ("Proteolix YU101 Program: Revised Scientific Plan"); DTX-991 at 1 ("Here is a revised chemistry plan")) The lack of the required "specific, settled idea" or "a particular solution to the problem at hand" is further evidenced by the undisputed fact that the September Memoranda's "R=morpholino" was one among thousands of proposed modifications for YU-101. (PTX-530; DTX-991 Att. at 6; DTX-992B at 2-3; Molineaux Tr. 788 ("[H]e's basically saying, there is a million different ways to make a soluble compound. There's no data on any of those compounds. You could take some groups from the Velcade world. You could put any other number of solubilizing groups on. Or you could actually just make a library of di- and tripeptides and cut the compound down and try to find a more soluble compound that way."))

At the time of the September Memoranda, Dr. Bunin had conducted no testing and had no particular expectation of success. There existed substantial uncertainty around the entirety of Proteolix's YU-101 endeavor. (*See* Bunin Tr. 492 ("I was involved more in sort of the theory and concepts and ideas, but really the hard work is actually proving it in the real world that something works . . . ."); *id.* (testifying it was Dr. Smyth who "[made] the compound that

became the drug in the laboratory, and [did] the experimental trial and error work to figure out the derivative STEL [(short-term exposure limit)] for solubility and other drug-like properties"))

For at least these reasons, Cipla has failed to prove that Dr. Bunin conceived of every modification he proposed, and, most pertinently, has failed to prove, by clear and convincing evidence, that he conceived of carfilzomib.

**B. Communication To Named Inventor**

Because Dr. Bunin did not conceive of carfilzomib, Cipla cannot prove that he communicated that conception to a named inventor. Cipla's showing at this second prong of the incorrect inventorship analysis fails for the additional reason that Cipla failed to present clear and convincing evidence that the Research Plan was shared with Dr. Smyth (and Cipla has never alleged that it was shared with Dr. Laidig). Dr. Smyth testified (Tr. 735) that it was "possible" he received a copy of the final Research Plan (DTX-167), but a mere possibility is insufficient to meet Cipla's burden of proof. Nor does speculation based on how quickly Drs. Smyth and Laidig developed carfilzomib constitute clear and convincing evidence, alone or in combination with Cipla's other evidence. Again, Cipla's defense fails.

**C. Section 102(f) Prior Art**

In the alternative, Cipla argues the 2003 Research Plan constitutes § 102(f) prior art and may be used to prove that the Compound Patents are invalid as obvious. That is, if (as the Court has found) the 2003 Research Plan teaches a urea linkage (morpholino carbonyl), those teachings may nonetheless render obvious a methylene linkage (morpholino methylene) and, therefore, make carfilzomib obvious. (D.I. 521 at 24; *see also* D.I. 536 at 12 ("Any person of ordinary skill would know that the attachment of the morpholine could not be with a urea linkage, as Plaintiff

contends, if the goal were to add solubility to YU-101, and the correct method of attachment was both obvious and easily done."))

Prior art under § 102(f) can be used to show obviousness. *See OddzOn Prods., Inc. v. Just Toys, Inc.*, 122 F.3d 1396, 1401 (Fed Cir 1997) ("[A] fair reading of § 103, as amended in 1984, leads to the conclusion that § 102(f) is a prior art provision for purposes of § 103."). However, § 103(c)(1) precludes the use of § 102(f) prior art "where the subject matter [constituting § 102(f) prior art] and the claimed invention were, ***at the time the claimed invention was made***, owned by the same person or subject to an obligation of assignment to the same person." 35 U.S.C. § 103(c)(1) (emphasis added). Thus, the § 103(c)(1) exception for § 102(f) prior art turns on the relationship between the prior art and the claimed invention ***at the time the claimed invention was made***.

Here, the claimed invention, carfilzomib, was not made until June 2004, when Drs. Smyth and Laidig synthesized carfilzomib and appreciated its properties. (*See* FF ¶ 107) Carfilzomib was not even conceived until at least December 2003, when Drs. Smith and Laidig designed and proposed the molecule; they produced a hand-drawn structure of carfilzomib on a whiteboard in January 2004. (*See* FF ¶ 106) As of December 2003 (and thereafter), Dr. Bunin, Dr. Crews, and anyone else associated with the Research Memoranda had all signed consulting agreements that, indisputably, required them to assign any invention connected to their work for Proteolix to Proteolix. (*See* FF ¶¶ 99-102; *see also* D.I. 521 at 27) Thus, none of the Research Memoranda constitute § 102(f) prior art.[15]

[15] It follows that, even assuming Dr. Bunin did not have an obligation to assign his inventions to Proteolix on September 4, 2003, when he contributed the "R=morpholino" concept to the Research Memoranda, and even if he only undertook such an obligation with his September 18

Even if all of this were not the case, and the Research Plan is treated as prior art to the Compound Patents, Cipla has still failed to prove the Research Plan renders carfilzomib obvious. The Research Plan discloses hundreds of compounds and does not call out modifying YU-101 at the N-terminus as a preferred modification to a lead compound. Further, as Onyx persuasive argues:

> Cipla failed to prove that a POSA would have been motivated to select the urea-linked morpholino carbonyl compound out of the Research Plan from all of the prior art – including more promising leads – to then modify. . . . [T]he Research Plan itself taught that other compounds were more promising candidates. Cipla skips the question of ***why*** a POSA would have selected the "R=morpholino" structure for modification, and jumps instead into modifying the urea-linked morpholino carbonyl into a morpholino methylene.

(D.I. 533 at 26-27)

## III. Double Patenting: Compound Patents

Cipla seeks to invalidate claims 23 and 24 of the '042 Patent and claim 1 of the '125 Patent – that is, the asserted claims of the Compound Patents, which claim the compound carfilzomib – as being an obvious double-patenting ("OTDP") of claim 15 of the '099 Patent, which claims YU-101. (D.I. 521 at 28-30) Cipla's contention fails.

As an initial matter, for the same reasons that the Court has already held that the Compound Patents are not invalid due to obviousness in light of YU-101, Cipla's OTDP claim must also fail. To prevail on its OTDP defense, Cipla would have to demonstrate that a POSA

---

execution of the Second Consulting Agreement (effective retroactively to August 30), these facts would not be dispositive, since carfilzomib was not conceived of – and, most importantly, was not "made" – until months later. Hence, even though the Court agrees with Cipla that "Plaintiff cannot retroactively remove prior art by a private agreement" (D.I. 536 at 13), this does nothing to alter the outcome here.

would have been motivated to modify YU-101 (claim 15 of the '099 Patent) to arrive at the structure of carfilzomib. *See Otsuka*, 678 F.3d at 1298 (equating OTDP analysis to § 103 obviousness: "whether one of ordinary skill in the art would have had reason or motivation to modify the earlier claimed compound to make the compound of the asserted claim with a reasonable expectation of success"). As the Court has explained at length, Cipla has failed to prove that carfilzomib was obvious.

The Court will briefly address another deficiency in Cipla's OTDP defense.

While double patenting does not *per se* require a complete overlap of inventors or common ownership, there must be some commonality between the earlier and later patents. *See In re Hubbell*, 709 F.3d at 1148. In *Hubbell*, the Federal Circuit noted that "the MPEP [Manual of Patent Examining Procedure] provides that obviousness-type double patenting may exist between an issued patent and an application filed by 'the same inventive entity, ***or by a different inventive entity*** having a common inventor, and/or by a common assignee/owner.'" *Id*. at 1146-48 (quoting MPEP § 804) (emphasis added). The Federal Circuit further stated that "the MPEP standard is consistent with the rationale we have used to support application of obviousness-type double patenting rejections." *Id.*

It is undisputed, and the Court finds, that the '099 Patent does not share any common inventors with the Compound Patents. (FF ¶¶ 11, 24) Nor does Onyx own the '099 Patent; Yale does. (DTX-195; FF ¶ 71)

Cipla argues, nonetheless, that Onyx's[16] exclusive license with Yale gave Onyx "all substantial rights" to the '099 Patent, such that Onyx is effectively an owner of the '099 Patent. (D.I. 521 at 29-30) Specifically, Cipla points to Onyx's "first right to sue for infringement" as evidence of Onyx's effective ownership. (*Id*.) In essence, Cipla is asking the Court to extend the effective ownership doctrine from the realm of standing to non-statutory double patenting. The Court is not persuaded to do so, as Cipla's position ignores the fundamental nature and purpose of the non-statutory double patenting doctrine.

"There are two justifications for obviousness-type double patenting." *In re Hubbell*, 709 F.3d at 1145. The first is "to prevent unjustified timewise extension of the right to exclude granted by a patent no matter how the extension is brought about." *In re Van Ornum*, 686 F.2d 937, 943-44 (C.C.P.A. 1982) (internal quotation marks and citation omitted). The second is to prevent multiple infringement suits by different assignees asserting essentially the same patented invention. *See In re Fallaux*, 564 F.3d 1313, 1319 (Fed. Cir. 2009). Neither of these purposes is served by extending the effective ownership doctrine to double patenting.

There is a statutory prohibition on a certain type of double patenting. Specifically, 35 U.S.C. § 101 limits inventors to a single patent for an invention, so an inventor is statutorily barred from obtaining a second patent on the same invention. *Application of Braithwaite*, 379 F.2d 594, 602 (C.C.P.A. 1967) (Smith, J., concurring). The OTDP doctrine being considered in this case is non-statutory (obviousness-type) double patenting, which is a judicial creation, aimed at barring specific patent claims that statutes, including especially § 102, fail to reach. *Id*.; *see*

[16] The license agreement is between Yale and Onyx's predecessor-in-interest to the Patents-in-Suit, Proteolix. (DTX-195 at 1)

*also Sun Pharm. Indus., Ltd. v. Eli Lilly & Co.*, 625 F.3d 719, 721 (Fed. Cir. 2010) (Newman, J., dissenting) ("A double patenting analysis occurs only when the earlier patent is not prior art against the later patent."). Without the judicial doctrine of OTDP, an inventor's prior invention that has neither been in the public domain for more than a year (*see* § 102(b)) nor abandoned (*see* § 102(c)) could not serve as prior art to bar a second, obvious patent by the same inventor (*see* §§ 102(a), (d)-(g)), thereby allowing an inventor to effectively extend the term of her patent monopoly.[17]

A licensee to a patent, even one who may be considered the effective owner of a licensed patent, cannot take advantage of this gap in § 102, so long as the licensee does not also own a patent sharing any assignees, owners, or inventors with the patent to which it is obtaining a license. In other words, the licensed patent will always be made by ***another*** who is not the licensee (e.g., the licensor) and the licensed patent will, therefore, constitute § 102 prior art to the licensee's patent. *See* §§ 102(a), (d)-(g). The licensee cannot take advantage of the gap which OTDP is directed at filling, so there is no reason to extend OTDP in the manner Cipla proposes.

[17] The pre-AIA version of § 102, which is applicable here, did not treat an inventor's own work as prior art (which could invalidate an inventor's subsequent patent) unless that inventor's own work had been in existence more than a year before a patent application is filed (§ 102(b)) or unless the inventor had abandoned the prior work (§ 102(c)). All other potentially-invalidating prior art had to be created by someone other than the inventor. *See* 35 U.S.C. § 102 ("A person shall not be entitled to a patent unless – (a) the invention was known or used ***by others*** . . . (e) the invention was described in – (1) an application for patent . . . ***by another*** . . . or (2) a patent granted on an application for patent ***by another*** . . . (f) he did not himself invent the subject matter . . . (g) (1) during the course of an interference . . . the invention was made by such ***other inventor*** . . . [or] (2) . . . the invention was made in this country ***by another*** inventor. . . .") (emphasis added).

Hence, Cipla's OTDP claim fails as a matter of law. The '099 Patent lists different inventors and different assignees/owners than the Compound Patents and, thus, will always constitute § 102 prior art, even without invoking the doctrine of OTDP. The Compound Patents are not invalid based on OTDP.

## IV. Obviousness: Formulation Patent

Given the conclusions already stated above in connection with the Compound Patents, it follows that Cipla's contention that the '112 Patent, the Formulation Patent, is invalid due to obviousness must also fail. This is because both asserted claims of the Formulation Patent, claims 31 and 32, have as a claim limitation that the active ingredient of the claimed formulation is carfilzomib.[18] Because carfilzomib was not obvious, for the reasons explained above, a formulation containing carfilzomib also cannot have been obvious.

The Court further agrees with Onyx on the following points:

> There were no prior art formulations of ***any*** drug using the combination of 10% (w/v) SBECD and 10 mM citric acid, adjusted to pH 3.5. It was this unique combination that allowed Proteolix to formulate carfilzomib in a pharmaceutical composition. To argue otherwise, Cipla [improperly] relies on hindsight . . . .

(D.I. 533 at 29)

Therefore, Cipla has failed to prove that claims 31 and 32 of the '112 Patent are invalid due to obviousness.

[18] In addition, because YU-101 was considered during the prosecution of the Formulation Patent (*see* DTX-39 at 34; JTX-13 at 139), Cipla's burden of proving obviousness based on YU-101 is greater than it would otherwise be. *See Minn. Mining*, 976 F.3d at 1572.

## V. Double Patenting: Formulation Patent

Finally, Cipla also seeks to invalidate claims 31 and 32 of the '112 Patent as being an obvious double-patenting of claim 25 of the '125 Patent. (D.I. 521 at 36-37) The '125 Patent expires earlier than the '112 Patent and is commonly owned (FF ¶¶ 23, 25, 33, 35) – therefore, the '125 Patent qualifies as a reference for double patenting. *See In re Hubbell*, 709 F.3d at 1148. Claim 25 of the '125 Patent claims a composition of carfilzomib in water with a substituted or unsubstituted beta cyclodextrin. (FF ¶¶ 28-31)[19]

### A. Claim 31

The substantive differences between claim 31 of the '112 Patent and claim 25 of the '125 Patent are that the carfilzomib of claim 31 is: (1) complexed with a specific cyclodextrin, SBECD, at 10% w/v, (2) at a pH of 3.5, (3) with 10mM citric acid, (4) in a single formulation.

**10% w/v SBECD**. There is no patentably distinct difference between claiming substituted or unsubstituted beta cyclodextrin, as claim 25 of the '125 Patent does, and claiming 10% w/v SBECD, as claim 31 of the Formulation Patent does. Of the "thousands" of cyclodextrins covered by the '125 Patent, and the hundreds that were commercially available (Rajewski Tr. 1223, 1229, 1231), fewer than a handful had been used in FDA-approved drugs, two of which were forms of Captisol, an SBECD (FF ¶ 171). It would have been obvious to a POSA formulator at least to start with SBECD, given its proven track record with the FDA.

[19] The nonobviousness of carfilzomib does not preclude Cipla from potentially prevailing on its effort to invalidate formulations containing carfilzomib based on OTDP because the double patenting analysis looks at whether there are patentable differences between claims of two commonly owned or invented patents. *See generally Otsuka*, 678 F.3d at 1297 ("The patent principally underlying the double patenting rejection need not be prior art.").

Furthermore, Captisol was sold for the express purpose of increasing solubility of relatively insoluble molecules, including peptides, and its manufacturer, CyDex, directed in its FAQ that a POSA mix SBECD at several concentrations, including 10% w/v, and choose the concentration that performed best under a routine test. (*See, e.g.*, FF ¶¶ 172-75, 179-80; *see also* Amiji Tr. 378). Thus, to a POSA, formulating carfilzomib with SBECD at 10% w/v was an obvious and patentably indistinct choice from the cyclodextrins claimed in the '125 Patent.

**pH of 3.5**. There is a patentably distinct difference between claiming carfilzomib in a formulation with no specific pH, as does claim 25 of the '125 Patent, and a formulation with carfilzomib with a pH of 3.5. Cipla's pH contentions are largely premised on a "rule of thumb" that a drug product's pH should be approximately two pH units below its pKa value. (D.I. 521 at 34; Amiji Tr. 326-27) Other than the testimony of one of Cipla's experts, Dr. Amiji (*see* Amiji Tr. 438), there is no evidence in the record to support this purported rule or its applicability here. Nor has Cipla proven by clear and convincing evidence that a POSA would even be able to calculate or measure the pKa of carfilzomib, a prerequisite to applying the purported rule of thumb. (*Compare* Amiji Tr. 439 *with* Rajewski Tr. 1186) The record also contains substantial evidence that a POSA would have had concerns with whether carfilzomib could be stable at a pH of 3.5. (*See, e.g.*, FF ¶¶ 158-66)

**10mM of Citric Acid**. There is also a patentably distinct difference between claiming carfilzomib and claiming a specific formulation with 10mM of citric acid. Cipla contends that the 10mM concentration of citric acid was a routine adjustment to reach a pH of 3.5. (D.I. 522 at ¶ 227) While using citric acid as a buffer may have been obvious, using the concentration of

citric acid to reach a pH of 3.5 could only have been obvious if the pH value of 3.5 was obvious, which it was not (as already explained).

**Combination**. Even if all the elements of claim 31 of the Formulation Patent were obvious and patentably indistinct from the elements of claim 25 of the '125 Patent (which they were not), Cipla has not shown that the combination as a whole was obvious. Although claim 25 of the '125 Patent directs a POSA to use a β-cyclodextrin, the record does not establish that a POSA would have viewed the use of 10% w/v SBECD combined with a pH of 3.5 and 10mM of citric acid as resulting in a working formulation. Cipla has failed to present clear and convincing evidence that a POSA would have arrived at the exact arrangement of the claimed formulation. *See Prolitec, Inc. v. Scentair Techs., Inc.*, 807 F.3d 1353, 1371 (Fed. Cir. 2015), *overruled in part by Aqua Products, Inc. v. Matal*, 872 F.3d 1290 (Fed. Cir. 2017).

In sum, the formulation of claim 31 is a non-obvious and patentably distinct modification of both the carfilzomib compound and of claim 25 of the '125 Patent.

**B. Claim 32**

The only substantive differences between claim 32 of the '112 Patent and claim 25 of the '125 Patent are that claim 32: (1) is directed at a "pharmaceutical composition" (rather than just a "composition"); (2) recites SBECD instead of substantiated or unsubstantiated β-cyclodextrin; and (3) requires lyophilization.

Onyx does not argue that there is a difference between the claimed "pharmaceutical composition" of claim 32 and the "composition" of claim 25 of the '125 Patent. (D.I. 533 at 37-38) The Court has also found in connection with claim 31 that there is no patentably distinct difference between claiming substantiated or unsubstantiated beta cyclodextrin and SBECD. So

all that is left as potentially patentably distinct between claim 32 of the Formulation Patent and claim 25 of the earlier '125 Patent is lyophilization.

It is undisputed that lyophilization was a well-known process especially intended to be used with unstable compounds. (FF ¶¶ 177, 181; Amiji Tr. 394-95) Carfilzomib was unstable (Molineaux Tr. 1131), rendering it a candidate for lyophilization (FF ¶ 181). Cipla has also shown that a POSA would have had a reasonable expectation of success in lyophilizing proteasome inhibitors, as evidenced by bortezomib's FDA-approved, lyophilized formulation – FDA approval being considered the "gold standard" by POSAs. (*See, e,g.*, FF ¶ 177-81; Lipinski Tr. 990) Cipla has further proven that a POSA would have had a reasonable expectation of success that SBECD complexes may be lyophilized, as evidenced by Vfend and Geodon, two FDA-approved formulations containing SBECD. (FF ¶¶ 179-80) Therefore, Cipla has proven, by clear and convincing evidence, that a POSA would have been motivated to formulate carfilzomib with SBECD as a lyophilized formulation and would have had a reasonable expectation of success in doing so.

Onyx presented expert testimony that the lyophilization process was energy-intensive, complex, and expensive. (*See* Rajewski Tr. 1227-28; Singh Tr. 1353-54) This does not mean, however, that these factors would have rendered the lyophilization aspect of claim 32 patentably distinct from the earlier-claimed composition of claim 25 of the '125 Patent. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1367-68 (Fed. Cir. 2007) ("[M]any techniques that require extensive time, money, and effort to carry out may nevertheless be arguably "routine" to one of ordinary skill in the art.").

For these reasons, claim 32 of the ’112 Patent is invalid due to obviousness-type double patenting, in view of claim 25 of the ’125 Patent.

## CONCLUSION

Cipla has not proven by clear and convincing evidence that any of the asserted claims are obvious in light of the prior art or that they were invented by someone other than the named inventors. With respect to obviousness-type double patenting, Cipla has met its burden only for claim 32 of the ’112 Patent.

An appropriate Order follows.

**IN THE UNITED STATES DISTRICT COURT**
**FOR THE DISTRICT OF DELAWARE**

| | | |
|---|---|---|
| ONYX THERAPEUTICS, INC., | : | |
| | : | |
| Plaintiff, | : | |
| | : | |
| v. | : | C.A. No. 16-988-LPS |
| | : | CONSOLIDATED |
| CIPLA LIMITED, et al., | : | |
| | : | |
| Defendants. | : | |

**ORDER**

At Wilmington this **4th** day of **May, 2020**, for the reasons set forth in the Opinion issued this same date, **IT IS HEREBY ORDERED** that:

1. Defendants have not proven by clear and convincing evidence that any of claims 23 and 24 of U.S. Patent No. 7,417,042 ("the '042 Patent"), claim 1 of U.S. Patent No. 8,207,125 ("the '125 Patent"), and claims 31 and 32 of U.S. Patent No. 7,737,112 ("the '112 Patent") are invalid for obviousness.

2. Defendants have not proven by clear and convincing evidence that any of claims 23 and 24 of the '042 Patent or claim 1 of the '125 Patent are invalid due to incorrect inventorship or obviousness-type double patenting ("OTDP").

3. Defendants have not proven by clear and convincing evidence that claim 31 of the '112 Patent is invalid for OTDP but they have proven by clear and convincing evidence that claim 32 of the '112 Patent is invalid due to OTDP in light of claim 25 of the '125 Patent.

4. The parties shall meet and confer and submit, no later than **May 8, 2020**, a proposed order consistent with the Opinion, to enter final judgment **FOR** Plaintiffs and **AGAINST** Defendants with respect to the valid, asserted claims of the '042, '125, and '112

Patents, and final judgment **FOR** Defendants and **AGAINST** Plaintiff with respect to claim 32 of the ’112 Patent. By the same date, the parties shall submit a joint status report, providing their position(s) as to whether any further proceedings are required.

5. Because the Opinion has been issued under seal, the parties shall meet and confer and, no later than **May 6, 2020**, submit a proposed redacted version, should they believe they can make the necessary showing for any such redactions. Thereafter, the Court will issue a public version of its Opinion.

HONORABLE LEONARD P. STARK
UNITED STATES DISTRICT JUDGE