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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AZURITY PHARMACEUTICALS, INC.
Petitioner,

v.

EXELIXIS, INC.
Patent Owner.

IPR2025-00427
Patent 12,128,039

PETITION FOR INTER PARTES REVIEW OF U.S. PATENT 12,128,039

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1005	CABOMETYX® Product Insert
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1008	U.S. Patent 7,579,473 ("the '473 patent")
1009	Mark Gibson, "Pharmaceutical Preformulation and Formulation: A Practical Guide from Candidate Drug Selection to Commercial Dosage Form," Informa Healthcare USA, Inc. (2009) ("Gibson")
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1053	"Bristol-Myers Squibb and Exelixis collaborate on kinase inhibitors," Nature Reviews Drug Discovery, Volume 8, February 2009, page 1 ("BMS Collaboration")
1054	Prosecution History excerpt for U.S. Application Serial No. 11/753,514, which issued as the '436 patent (Ex. 1040)
1055	Huynh, "Molecularly targeted therapy in hepatocellular carcinoma," *Biochemical Pharmacology*, vol. 80 (2010), 550-560 ("Huynh")
1056	Guiochon, "Preparative liquid chromatography," *Journal of Chromatography A*, 965 (2002), 129-161 ("Guiochon")
1057	Ratain *et al.*, "Phase II Placebo-Controlled Randomized Discontinuation Trial of Sorafenib in Patients with Metastatic Renal Cell Carcinoma," *J. Clin. Oncol.*, vol. 24 (2006), 2505-2512 ("Ratain")
1058	Gotink *et al.*, "Anti-angiogenic tyrosine kinase inhibitors: what is their mechanism of action?" *Angiogenesis*, vol. 13 (2010), 1-14 ("Gotink")
1059	Sherman, "Advances in Chemotherapy of Differentiated Epithelial and Medullary Thyroid Cancers," *J. Clin. Endocrinol. Metab.*, vol. 94(5) (May 2009), 1493-1499 ("Sherman")

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1061	Van Cutsem *et al.*, "Phase 2 study of XL184 (BMS-907351) in a cohort of patients (pts) with hepatocellular carcinoma (HCC)," Thursday, November 18 (2010), Poster 408 ("Van Cutsem")
1062	Eder *et al.*, "Novel Therapeutic Inhibitors of the c-Met Signaling Pathway in Cancer," Clin. Cancer Res., vol. 15(7) (2009), pages 2207-2214 ("Eder")
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1064	Hutson *et al.*, "Novel Therapeutics for Metastatic Renal Cell Carcinoma," *Cancer*, May 15 (2009), pages 2361-2367 ("Hutson")
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Azurity Pharmaceuticals, Inc. ("Azurity"/"Petitioner") requests *inter partes* review ("IPR") of claims 1-22 ("Challenged Claims") of U.S. 12,128,039 ("the '039 patent") (Ex. 1001) purportedly owned by Exelixis, Inc. ("Exelixis"). These claims are obvious in light of the prior art.

I. INTRODUCTION

The independent claims of the '039 patent broadly relate to a tablet or capsule composition of cabozantinib (L)-malate (denoted "Compound IB") containing "100 ppm or less of 6,7-dimethoxy-quinoline-4-ol" or a method of treating cancer using the same composition. Ex. 1001 at 34:2-24 (claim 1), 34:38-61 (claim 6). Additional claims do nothing more than restrict the permissible concentration range for a potentially genotoxic impurity (denoted "6,7-dimethoxy-quinoline-4-ol") that may be present (claims 2-5 and 7-10) or specify a type of cancer (claims 11-22). Ex. 1001 at 34:25-35:30. These claims should never have issued.

Ground 1: Obviousness over Brown in view of Kubo

Each limitation of the Challenged Claims was either expressly disclosed in the prior art or was manifestly obvious. Brown (Ex. 1003) disclosed cabozantinib (L)-malate, its use in treating cancer (including the specific types now claimed), and the idea of formulating it in an oral dosage form (e.g., a tablet or capsule) using pharmaceutically acceptable carriers. Brown also provided a synthetic route for obtaining cabozantinib (L)-malate that Exelixis's experts admitted would afford "de

minimis" levels of the potentially genotoxic impurity now claimed—6,7-dimethoxy-quinoline-4-ol. However, Brown's route to cabozantinib (L)-malate only differs from the '039 patent's disclosure by virtue of an obvious change that Kubo (Ex. 1028) identified as an "alternative" approach—one that was more efficient and would have been expected to further reduce any amount of 6,7-dimethoxy-quinoline-4-ol that was present. Thus, a simple substitution within Brown's synthetic route affords the teachings of the '039 patent—and the reduced amount of 6,7-dimethoxy-quinoline-4-ol in cabozantinib (L)-malate that is associated with the same. From there, it was a matter of applying admittedly "known" formulation techniques from Brown to achieve the claimed compositions for treating the same types of cancer that Brown already identified.

Ground 2: Obviousness over Brown in view of Robinson

It would have been just as obvious to take Brown's cabozantinib (L)-malate, with its "de minimis" level of 6,7-dimethoxy-quinoline-4-ol, and further purify it to reduce the concentration range of 6,7-dimethoxy-quinoline-4-ol that was present. Exelixis's expert admitted that a POSA would have recognized 6,7-dimethoxy-quinoline-4-ol to have an alerting structure and potentially be genotoxic. Robinson (Ex. 1039) explains that such potential would have triggered several obligations and options for developing cabozantinib (L)-malate into a pharmaceutical product. First, determining whether 6,7-dimethoxy-quinoline-4-ol was actually present in Brown's

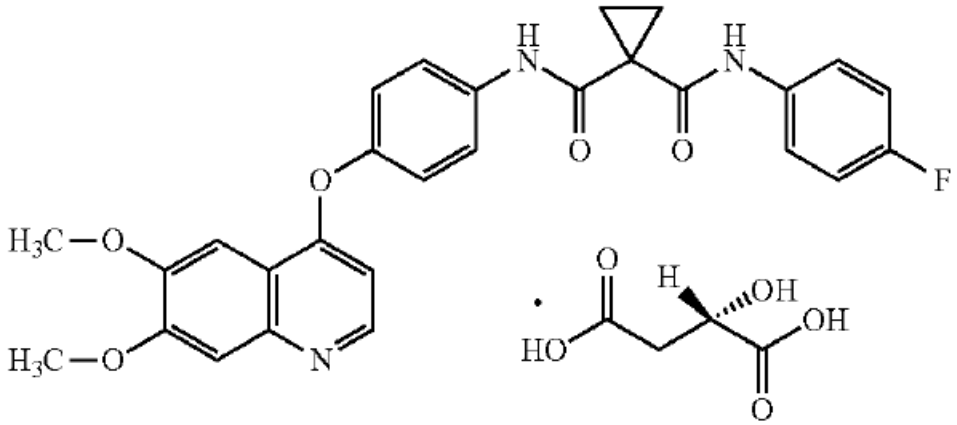
cabozantinib (L)-malate would have been demanded by regulatory authorities. And if it was present, it would have needed to be removed entirely or reduced to a concentration that was no longer of concern (e.g., as low as 1.5 ppm or less). This was an utterly expected result—a variety of control strategies were known.

Accordingly, Azurity respectfully requests that the Board cancel the Challenged Claims under §103.

II. STATE OF THE ART

A. Cabozantinib and Its Malate Salt

Exelixis markets cabozantinib (L)-malate under the tradenames CABOMETYX® and COMETRIQ® for the treatment of certain forms of cancer. Ex. 1005; Ex. 1006; Ex. 1042 ¶36; Ex. 1044 ¶41. Cabozantinib (L)-malate (referred to as "Compound IB" in the '039 patent) has the following structure:



Ex. 1001 at 4:10-24; Ex. 1042 ¶37.

Exelixis first disclosed cabozantinib in a different patent family claiming priority to 2003—well before the '039 patent's alleged priority date. Ex. 1008 at 199 (entry 12); Ex. 1042 ¶39. In that 2003 family, Exelixis admitted that oral administration was "preferable" and that capsules or tablets were suitable dosage forms when admixed with "customary excipients." Ex. 1008 at 273:20-44;[1] Ex. 1042 ¶¶40-41. Exelixis also claimed cabozantinib as the free base "or a pharmaceutically acceptable salt thereof" along with its inclusion in a pharmaceutical composition combined with excipients in this 2003 family. Ex. 1008 at claims 5-7; Ex. 1042 ¶42. Furthermore, in this same 2003 family, Exelixis claimed the use of cabozantinib "or a pharmaceutically acceptable salt thereof" to treat various cancers such as "kidney cancer" and "liver cancer" (Ex. 1051 at claims 69 and 75) while ultimately receiving issuance of claims to treating, *inter alia*, "prostate cancer" (Ex. 1040 at claims 1-4); Ex. 1044 ¶¶44-45. Thus, nothing about cabozantinib or salts thereof, its inclusion in a tablet/capsule composition, or its use to treat the claimed cancers is novel. Ex. 1042 ¶42; Ex. 1044 ¶46.

Cabozantinib (L)-malate was also a known salt form. Ex. 1003 at Abstract; Ex. 1042 ¶43. Exelixis explained how to make this salt and two crystalline forms of

[1] In this family, Ex. 1008 is a 2009 patent, Ex. 1051 is a 2009 application, and Ex. 1040 is a 2011 patent that trace back to the 2003 priority filings.

it in Brown (Ex. 1003), which claims priority to 2009—years before the '039 patent's earliest alleged priority date. Ex. 1003 at (30); Ex. 1042 ¶¶43-47; Ex. 1043 ¶¶37, 49. Indeed, Brown's preparation of cabozantinib (L)-malate's crystalline forms N-1 and N-2 is exactly the same (even to the decimal point) as that provided in the '039 patent. *Compare* Ex. 1003 at [00115]-[00127] *with* Ex. 1001 at 29:54-31:3; Ex. 1043 ¶49. Exelixis's prior experts also admitted that Brown's cabozantinib (L)-malate would contain a "de minimis" amount of a potentially genotoxic impurity—6,7-dimethoxy-quinoline-4-ol (*see* Ex. 1026 at 45, 53).

In this 2009 patent family, Exelixis once again identified capsules and tablets as suitable pharmaceutical compositions for incorporating cabozantinib (L)-malate. Ex. 1003 at [0078]; Ex. 1042 ¶¶44-45. Exelixis also admitted that such pharmaceutical compositions could be prepared by "methods know[n] in the pharmaceutical formulation art." Ex. 1003 at [0082]; Ex. 1042 ¶42. And Exelixis specifically identified the use of cabozantinib (L)-malate for the treatment of kidney, liver, and prostate cancers. Ex. 1008 at [0067]-[0068]; Ex. 1044 ¶¶49-50. Thus, nothing about cabozantinib (L)-malate, its inclusion in a tablet/capsule, or even its use to treat the claimed cancers is novel. Ex. 1042 ¶47; Ex. 1044 ¶51.

B. Orally Administered Tablets and Capsules are Preferred Pharmaceutical Compositions

Active pharmaceutical ingredients (APIs) such as cabozantinib (L)-malate are almost always administered to a subject as part of a pharmaceutical composition.

Ex. 1004 at 889, 891; Ex. 1042 ¶48. Oral administration is the most frequent route. Ex. 1004 at 889; Ex. 1034 at 442; Ex. 1042 ¶49. As compared against an injection, the oral route is simpler, more convenient, and ultimately safer for the patient. Ex. 1009 at 367; Ex. 1042 ¶49.

Tablets and capsules are the two most common oral dosage forms. Ex. 1009 at 367; Ex. 1004 at 889; Ex. 1034 at 442; Ex. 1042 ¶50. In addition to the API, tablets and capsules contain other substances referred to as "excipients" or "carriers." Ex. 1004 at 891; Ex. 1009 at 420; Ex. 1003 at [0087]; Ex. 1042 ¶¶41, 52, 79. Certain classes/categories of excipients are normally incorporated into tablet or capsule formulations, and are discussed briefly below. Ex. 1004 at 891-893; Ex. 1009 at 420; Ex. 1042 ¶55.

1. Fillers

Fillers, which are also referred to as diluents, are a category of excipient that are added to the API in sufficient quantity to make a reasonably sized formulation. Ex. 1004 at 891; Ex. 1034 at 449; Ex. 1009 at 420; Ex. 1042 ¶56. Many excipients may be utilized as a filler. Ex. 1025 at 864; Ex. 1009 at 391 (Table 8); Ex. 1004 at 891; Ex. 1042 ¶¶57-58. However, microcrystalline cellulose is a very popular choice of filler because of its excellent compactibility and high dilution capacity; it also provides some lubricant and disintegrant properties to the formulation. Ex. 1004 at 891; Ex. 1009 at 391 (Table 8); Ex. 1025 at 130; Ex. 1042 ¶59. This is confirmed

by the '039 patent, which selected microcrystalline cellulose when preparing a capsule "according to processes known in the art." Ex. 1001 at 31:5-20; *id*. at 20:41-55.

2. Disintegrants

Disintegrants are a category of excipient that are added to formulations to "facilitate [their] breakup or disintegration after administration." Ex. 1004 at 893; Ex. 1009 at 397; Ex. 1042 ¶60. Inclusion of a disintegrant promotes the rapid release of the API. Ex. 1004 at 893; Ex. 1009 at 397; Ex. 1042 ¶60. Many excipients may function as a disintegrant. Ex. 1025 at 865; Ex. 1009 at 398 (Table 11); Ex. 1004 at 893; Ex. 1042 ¶¶61-62. However, super disintegrants such as croscarmellose sodium, sodium starch glycolate, and crospovidone are now the most commonly used because they "display excellent disintegrant activity at low concentrations and possess better compression properties" than other disintegrants. Ex. 1009 at 396; Ex. 1004 at 893; Ex. 1042 ¶63. This is confirmed by the '039 patent, which selected croscarmellose sodium and sodium starch glycolate when preparing a capsule "according to processes known in the art." Ex. 1001 at 31:5-20; *id*. at 20:41-55.

3. Glidants

Glidants are a category of excipient that are normally added to formulations to enhance the flow of the powder into the manufacturing equipment. Ex. 1009 at 388-89; Ex. 1004 at 893; Ex. 1042 ¶64. Many excipients may function as a glidant.

Ex. 1025 at 868; Ex. 1009 at 389 (Table 7); Ex. 1042 ¶¶65-66. However, fumed silicon dioxide (i.e., colloidal silicon dioxide or fumed silica) is the most commonly used and effective glidant. Ex. 1009 at 390; Ex. 1004 at 893; Ex. 1025 at 185; Ex. 1034 at 452; Ex. 1042 ¶67. This is confirmed by the '039 patent, which selected fumed silica when preparing a capsule "according to processes known in the art." Ex. 1001 at 31:5-20; *id*. at 20:41-55.

4. Lubricants

Lubricants are a category of excipient that are normally added to tablet formulations to prevent adherence of the tablet to the die/punch. Ex. 1009 at 391-92; Ex. 1004 at 892-893; Ex. 1042 ¶68. They are also added to capsule formulations to aid material flow. Ex. 1004 at 921; Ex. 1042 ¶68. Many excipients may function as a lubricant. Ex. 1025 at 873; Ex. 1009 at 392 (Table 9); Ex. 1004 at 892; Ex. 1042 ¶¶69-70. However, magnesium stearate and stearic acid are two of the more widely used lubricants. Ex. 1004 at 892-893; Ex. 1009 at 392; Ex. 1025 at 697; Ex. 1042 ¶71. This is confirmed by the '039 patent, which selected stearic acid when preparing a capsule "according to processes known in the art." Ex. 1001 at 31:5-20; *id*. at 20:41-55.

C. Impurities in APIs and Pharmaceutical Products

When synthesizing APIs and preparing a pharmaceutical product, unwanted impurities "may have deleterious pharmacological and toxicological activities" and,

therefore, "must be removed from the final product." Ex. 1009 at 190; Ex. 1042 ¶72; Ex. 1043 ¶82. Accordingly, the identification of impurities is "a crucial activity in drug substance" research and development. Ex. 1009 at 190. Regulatory authorities publish guidelines concerning various impurities "with the expectation that pharmaceutical companies will comply with them." Ex. 1009 at 314; Ex. 1042 ¶¶73-75; Ex. 1043 ¶82.

Impurities may be classified as organic, inorganic, and residual solvents. Ex. 1009 at 190; Ex. 1041 at 2; Ex. 1043 ¶83. "Organic impurities include, for example, starting materials, by-products, intermediates, degradation products as well as reagents, ligands, and catalysts." Ex. 1009 at 190-91; Ex. 1043 ¶83. These organic, inorganic, and residual solvents are "obvious" impurities in drug substances. Ex. 1009 at 191; Ex. 1043 ¶84.

"[T]he actual and potential impurities most likely to arise during the synthesis, purification, and storage of a new drug substance" should be summarized and provided to regulatory authorities. Ex. 1041 at 3; Ex. 1043 ¶85. This includes the "obvious" impurities previously indicated. Ex. 1041 at 2 (referring to, *inter alia*, starting materials, by-products, and degradation products); Ex. 1043 ¶¶83-84. Furthermore, the laboratory studies used to detect impurities and efforts to identify potential impurities arising during storage (along with the results) should also be summarized and provided to regulatory authorities. *Id*. at 3; Ex. 1043 ¶¶84-85.

Similar work applies to detecting, summarizing, and reporting impurities in drug products. Ex. 1052 at 2-3; Ex. 1042 ¶¶74-75.

Normally, the limit for any particular impurity is 0.15%, which corresponds to 1500 parts per million (ppm). Ex. 1039 at 946; Ex. 1043 ¶86. However, "potentially genotoxic impurities ["PGIs"] have been the subject of increasing regulatory and industry attention since the beginning of the 21st century." Ex. 1039 at 959; Ex. 1043 ¶86. Such impurities are subject to additional restrictions regarding permissible concentration ranges. Ex. 1039 at 947-48, Table 1; Ex. 1037 at 7, 11 (Table 1); Ex. 1038 at 6-7; Ex. 1043 ¶¶86-87. Indeed, using either "existing genotoxicity data or the presence of structural alerts, potential genotoxic impurities should be identified." Ex. 1038 at 4; Ex. 1039 at 947; Ex. 1043 ¶87. If PGIs are present, regulatory guidance indicates that the developer should (1) "alter the route of synthesis so as to remove the PGI entirely;" (2) "reduce the PGI to below a level of concern;" (3) "demonstrate that the PGI will not be present at significant levels;" or (4) "demonstrate that the PGI is not actually harmful at its typical level in the API." Ex. 1039 at 952; Ex. 1043 ¶87. In any event, ignoring a PGI is not an option. Ex. 1042 ¶75; Ex. 1043 ¶87.

III. THE CHALLENGED CLAIMS ARE UNPATENTABLE

Azurity requests cancellation of claims 1-22.

A. Grounds of Challenges

IPR is requested for the following grounds:

Ground	Basis	Challenged Claims
1	Obviousness over WO 2010/083414 ("Brown") in view of U.S. 7,169,789 ("Kubo")	1-22
2	Obviousness over Brown in view of Robinson, "Control of Genotoxic Impurities in Active Pharmaceutical Ingredients: A Review and Perspective" ("Robinson")	1-22

B. The Prior Art

Brown and Robinson are prior art under §102(a) and Kubo is prior art under §102(b).

Reference	Publication	Exhibit No.
1. WO 2010/083414 ("Brown")	2010	Ex. 1003
2. U.S. 7,169,789 ("Kubo")	2007	Ex. 1028
3. Robinson, "Control of Genotoxic Impurities in Active Pharmaceutical Ingredients: A Review and Perspective" ("Robinson")	2010	Ex. 1039

The accompanying declarations of Dr. Graham Buckton (Ex. 1042), Dr. William Dichtel (Ex. 1043), and Dr. Robert Dreicer (Ex. 1044) support this Petition.

IV. LEVEL OF ORDINARY SKILL IN THE ART

Exelixis previously proposed that for the '349 patent (Ex. 1046), which is a parent to the '039 patent, a person of ordinary skill in the art ("POSA") would have had at least a bachelor's degree in chemistry, chemical engineering, pharmaceutical sciences, or a related discipline, along with several years of experience working in pharmaceutical development and/or solid-state chemistry and would also have been part of a team which would have included synthetic organic chemists and process chemists, formulation scientists, analytical scientists and clinicians. Ex. 1010 ¶11. Given the similarity in claim language, Petitioner applied this definition. Ex. 1042 ¶¶24-27; Ex. 1043 ¶¶23-26; Ex. 1044 ¶¶28-31.

V. CLAIM CONSTRUCTION

The Board need only construe claims to the extent necessary to resolve controversy. *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co. Ltd.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017). Considering the closeness of the prior art and the specific arguments herein, Azurity does not believe that any claim terms require construction.

VI. GROUND 1: OBVIOUSNESS OVER BROWN IN VIEW OF KUBO

The Challenged Claims would have been obvious over Brown (Ex. 1003) in view of Kubo (Ex. 1028). The combination of Brown and Kubo teaches the synthetic approach for preparing cabozantinib (L)-malate ("Compound IB") as

disclosed in the '039 patent. Brown further teaches the preparation of tablet/capsule compositions of cabozantinib (L)-malate and describes their use for treating the cancers claimed in the '039 patent. Thus, to the extent the '039 patent discloses tablet/capsule compositions of cabozantinib (L)-malate that satisfy the recited 6,7-dimethoxy-quinoline-4-ol impurity concentration, and methods of treatment using the same, then the combination of Brown and Kubo does so as well. Accordingly, the Challenged Claims would have been obvious.

A. Introduction to Brown

Brown is entitled "Malate Salt of [Cabozantinib], and Crystalline Forms Thereof for the Treatment of Cancer." Brown provides a synthesis for cabozantinib (L)-malate, a quinoline-containing antitumor compound, and describes the preparation of two crystalline forms (denoted N-1 and N-2). Ex. 1003 at [0098]-[00134]; Ex. 1042 ¶78; Ex. 1043 ¶47. Brown also describes the preparation of tablet/capsule compositions of cabozantinib (L)-malate in conjunction with a pharmaceutically acceptable carrier. Ex. 1003 at [0066], [0078], [0082], [0087]; Ex. 1042 ¶¶79-81. Additionally, Brown directs a reader to "known" methods for preparing pharmaceutical compositions as discussed in Remington—just like the '039 patent. *Compare* Ex. 1003 at [0082] *with* Ex. 1001 at 20:41-55; Ex. 1042 ¶82.

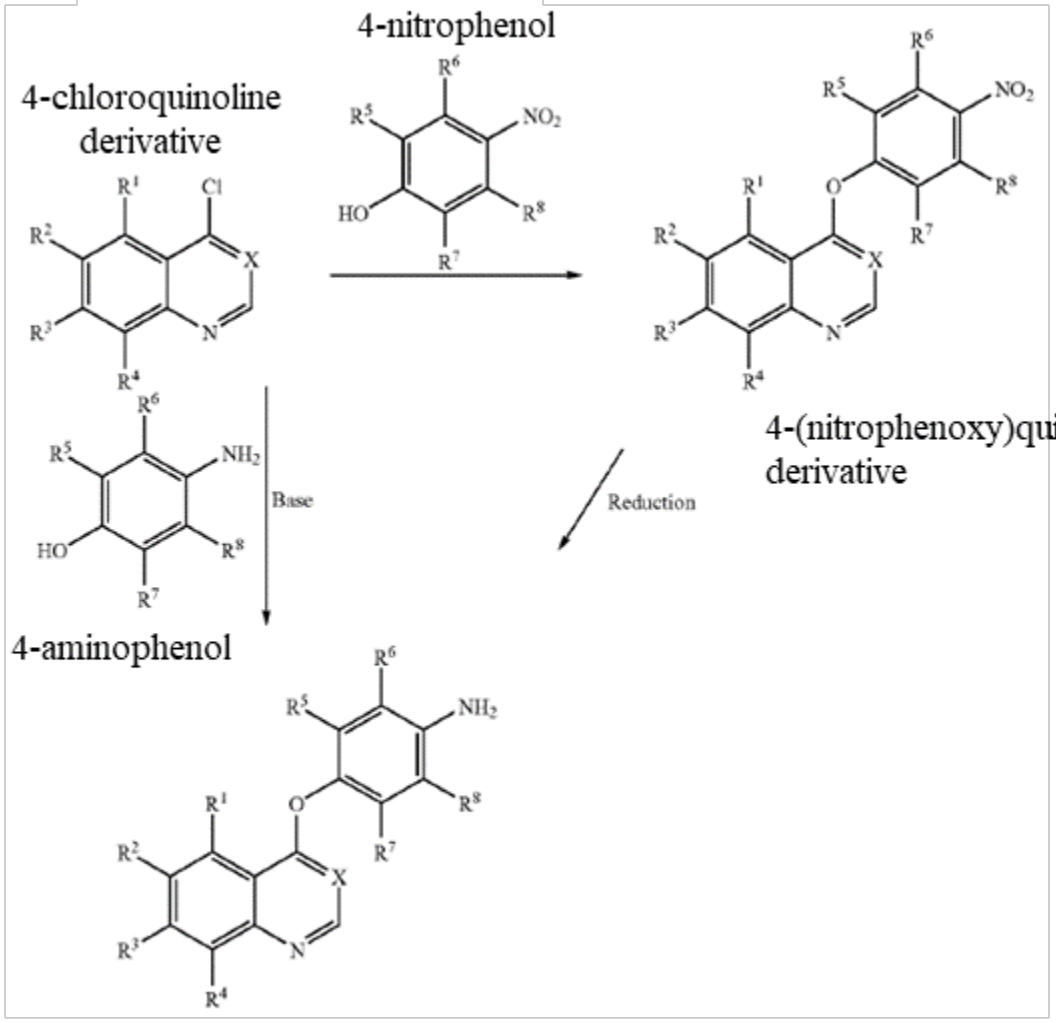
Brown explains that cabozantinib (L)-malate and its pharmaceutical compositions are useful for treating cancer. Ex. 1003 at Title, Abstract, [0004]-

[0005], [0012], [0067]-[0074], claims 12-13; Ex. 1044 ¶49. Brown specifically identifies "kidney cancer," "liver cancer," and "prostate carcinoma" as types of cancer to be treated. Ex. 1003 at [0068]; Ex. 1044 ¶49. And Brown explains why cabozantinib's targeting of kinases would have been expected to treat the claimed types of cancer. Ex. 1003 at [0006]-[0010]; Ex. 1044 ¶87.

B. Introduction to Kubo

Kubo is entitled "Quinoline Derivatives and Quinazoline Derivatives." Kubo relates to the synthesis of antitumor quinoline compounds—just like the cabozantinib (L)-malate of Brown and the '039 patent. Ex. 1028 at 1:7-13 ("[T]he present invention relates to quinoline derivatives and quinazoline derivatives that are useful for the treatment of diseases such as tumor…."); Ex. 1003 at [0010], [0012] (identifying the quinoline derivative cabozantinib and its malate salts for treating "cancer"); Ex. 1001 at 1:34-39 ("More specifically, this disclosure relates to processes for preparing quinolines that are useful for modulating cellular activities such as proliferation, differentiation, programmed cell death…."); Ex. 1043 ¶¶40-41.

Kubo describes two "alternative" approaches for preparing a 4-aminophenoxy-quinoline beginning with a 4-chloroquinoline starting material:



Ex. 1028 at 12:46-14:4 (Annotated); Ex. 1043 ¶43-44. The first alternative is analogous to Brown's synthesis, which utilizes a two-step reaction sequence to afford a 4-(aminophenoxy)quinoline derivative. Ex. 1028 at 12:46-55; Ex. 1043 ¶45. Kubo's second alternative is analogous to the '039 patent, which utilizes a one-step reaction sequence to afford the same 4-(aminophenoxy)quinoline derivative. Ex. 1028 at 12:55-59; Ex. 1043 ¶46.

C. Brown in view of Kubo Renders the Challenged Claims Obvious

1. Claim 1

a. Preamble

Claim 1's preamble recites: "A pharmaceutical composition for oral administration...." Should the Board find that this preamble is limiting, Brown discloses such a "pharmaceutical composition." Ex. 1003 at [0002]-[0003], [0013]-[0014], [0066], [0078], [0082], and [0087]; Ex. 1042 ¶¶87-88.

b. Compound IB

Claim 1's composition requires "Compound IB." Compound IB is cabozantinib (L)-malate. Ex. 1042 ¶37; Ex. 1043 ¶33; Ex. 1044 ¶42. Brown teaches the inclusion of cabozantinib (L)-malate (i.e., "Compound IB") in a pharmaceutical composition. Ex. 1003 at [0002], [0051]-[0052], [0054], [0066], [0077]-[0078], claim 11; Ex. 1042 ¶89. Exelixis cannot contend otherwise—it previously admitted that "Brown discloses a generic pharmaceutical composition of Compound IB…." Ex. 1045 at 90.

A POSA would have been motivated to select cabozantinib (L)-malate for inclusion in a pharmaceutical composition. Ex. 1042 ¶90. Brown explains that cabozantinib (L)-malate "exhibit[ed] beneficial properties over the free base and other salts…." Ex. 1003 at [0053]; Ex. 1042 ¶90. Brown further taught that cabozantinib (L)-malate had "a preferred combination of pharmaceutical properties for development." Ex. 1003 at [0052]; *id*. at [0051]-[0054]; Ex. 1042 ¶90. As such,

it would have been obvious to include cabozantinib (L)-malate in a pharmaceutical composition. Ex. 1042 ¶¶89-90. Exelixis cannot contend otherwise—it previously admitted that a POSA would be so motivated during litigation of the '349 patent. Ex. 1026 at 54 ("The parties agree that a POSA would be motivated to formulate the cabozantinib (L)-malate API as a capsule or tablet….").

A POSA would have also had a reasonable expectation of successfully including cabozantinib (L)-malate in a pharmaceutical composition. Ex. 1042 ¶91; Ex. 1026 at 47, 60. Brown expressly described and claimed doing so. Ex. 1003 at [0082], claim 11; Ex. 1042 ¶91. Moreover, Exelixis cannot contend otherwise. *NOF Corp. v. Nektar Therapeutics*, No. IPR2019-01398, 2021 WL 3265737, at *13 (P.T.A.B. July 30, 2021) ("Bentley is Patent Owner's own patent and Patent Owner should not be heard to argue that one of ordinary skill in the art would have had any difficulty in achieving the same molecular weight that is both described *and claimed* in its own patent."). First, Exelixis admitted during prosecution of the '039 patent that Brown disclosed such a composition. Ex. 1045 at 90. Second, the '039 patent expressly relies on "known techniques" for preparing "the pharmaceutical compositions disclosed herein." Ex. 1001 at 20:41-55, 31:5-7. The same "known techniques" were available to a POSA. Indeed, both Brown and the '039 patent cite to the same treatise (i.e., Remington (Ex. 1004)) for describing "[v]arious carriers" and "known" methods/techniques to prepare pharmaceutical compositions of

cabozantinib (L)-malate. *Compare* Ex. 1003 at [0082] *with* Ex. 1001 at 20:41-55. Thus, if novel and non-obvious formulation techniques were required to practice the claimed invention, then Exelixis would have been obligated to describe them. *Trustees of Columbia Univ. in the City of New York v. Illumina, Inc.*, 620 F. App'x. 916, 933 (Fed. Cir. 2015).

c. Carrier

Claim 1's composition requires "a pharmaceutically acceptable carrier." Brown teaches that for solid dosage forms, "at least one inert, pharmaceutically acceptable excipient (also known as a pharmaceutically acceptable carrier)" should be included. Ex. 1003 at [0087]; Ex. 1042 ¶93. Brown also explains that "the pharmaceutically acceptable carrier may be chosen from any one or a combination of carriers known in the art." Ex. 1003 at [0081]; Ex. 1042 ¶93. And Brown identifies particular categories and species of materials for inclusion while explaining that the carrier should be compatible with cabozantinib (L)-malate and other components of the pharmaceutical composition. Ex. 1003 at [0081]-[0082], [0087]; Ex. 1042 ¶93.

A POSA would have been motivated to include "a pharmaceutically acceptable carrier." Ex. 1042 ¶94. Aside from Brown expressly identifying the inclusion of a "pharmaceutically acceptable excipient (also known as a pharmaceutically acceptable carrier)," *see* Ex. 1003 at [0087], it was common

knowledge to include them in tablets and capsules to allow for their manufacturing and impart desirable characteristics to the finished composition. Ex. 1004 at 891; Ex. 1009 at 420; Section II.B., *supra*; Ex. 1042 ¶¶55-71. Indeed, during litigation concerning the '039 patent's predecessor (i.e., the '349 patent (Ex. 1046)), the district court found "that a POSA would be motivated to ensure the formulation is a tablet or capsule that includes a filler, lubricant, disintegrant, and glidant." Ex. 1026 at 54.

A POSA would have had a reasonable expectation of successfully including "a pharmaceutically acceptable carrier" in a composition with cabozantinib (L)-malate. Ex. 1042 ¶95; Ex. 1026 at 47, 60. Brown identifies potential carriers for inclusion and provides criteria for their selection—that they do not have a deleterious effect on other constituents in the composition. Ex. 1003 at [0081], [0087]; Ex. 1042 ¶95. Brown then proceeded to claim just such a composition. Ex. 1003 at claim 11; Ex. 1042 ¶95.

Exelixis cannot contend otherwise. *NOF Corp.*, 2021 WL 3265737, at *13. First, it admitted during prosecution that Brown disclosed such a composition. Ex. 1045 at 90. Second, the '039 patent expressly relies on "known techniques" for preparing "the pharmaceutical compositions disclosed herein." Ex. 1001 at 20:41-55, 31:5-7. The same "known techniques" were available to a POSA. Indeed, both Brown and the '039 patent cite to the same treatise (i.e., Remington) for describing

"[v]arious carriers" and "known" methods/techniques to prepare pharmaceutical compositions of cabozantinib (L)-malate. *Compare* Ex. 1003 at [0082] *with* Ex. 1001 at 20:41-55. Thus, if novel and non-obvious carriers were required to practice the claimed invention, then Exelixis would have been obligated to describe them. *Trustees of Columbia Univ.*, 620 F. App'x. at 933.

d. Tablet/Capsule

Claim 1 further requires that "the pharmaceutical composition is a tablet or capsule." Brown teaches that "[s]olid dosage forms for oral administration, which includes ***capsules***, ***tablets*** pill, powders, and granules, are particularly preferred." Ex. 1003 at [0087]; Ex. 1042 ¶97.

A POSA would have been motivated to prepare a tablet or capsule composition. Ex. 1026 at 54 ("[A] POSA would be motivated to ensure the formulation is a tablet or capsule…."); *id*. at 47 ("A POSA would be motivated to ensure that cabozantinib (L)-malate is formulated as a tablet or capsule…."); Ex. 1042 ¶97. Tablets and capsules are the two most common oral dosage forms. Ex. 1004 at 889 ("Drug substances most frequently are administered orally by means of solid dosage forms such as tablets and capsules."); Ex. 1042 ¶¶49-50; *see also* Section II.B, *supra*. Remington explains that "[t]ablets remain popular as a dosage form because of the advantages afforded both to the manufacturer (eg, simplicity and economy of preparation, stability, and convenience in packaging, shipping, and

dispensing) and the patient (eg, accuracy of dosage, compactness, portability, blandness of taste, and ease of administration)." Ex. 1004 at 889; Ex. 1042 ¶84. Additionally, Remington teaches that capsules are "easily" administered/filled, and that some patients prefer capsules over tablets because they are easier to swallow. Ex. 1004 at 918; Ex. 1042 ¶84. Thus, a POSA would have had ample motivation to prepare a tablet or capsule composition.

A POSA would have also had a reasonable expectation of successfully preparing a tablet or capsule composition. Ex. 1042 ¶98. Brown explains that "known" techniques may be used to formulate cabozantinib (L)-malate. Ex. 1003 at [0078]-[0087]; Ex. 1042 ¶98; Ex. 1026 at 47, 60. Exelixis cannot contend otherwise. *NOF Corp.*, 2021 WL 3265737, at *13. The '039 patent expressly relies on "known techniques" for preparing "the pharmaceutical compositions disclosed herein." Ex. 1001 at 20:41-55, 31:5-7. The same "known techniques" were available to a POSA. Indeed, both Brown and the '039 patent cite to the same treatise (i.e., Remington) for describing "[v]arious carriers" and "known" methods/techniques to prepare pharmaceutical compositions of cabozantinib (L)-malate. *Compare* Ex. 1003 at [0082] *with* Ex. 1001 at 20:41-55. Thus, if novel and non-obvious techniques to prepare tablets/capsules were required to practice the claimed invention, then Exelixis would have been obligated to describe them. *Trustees of Columbia Univ.*, 620 F. App'x. at 933.

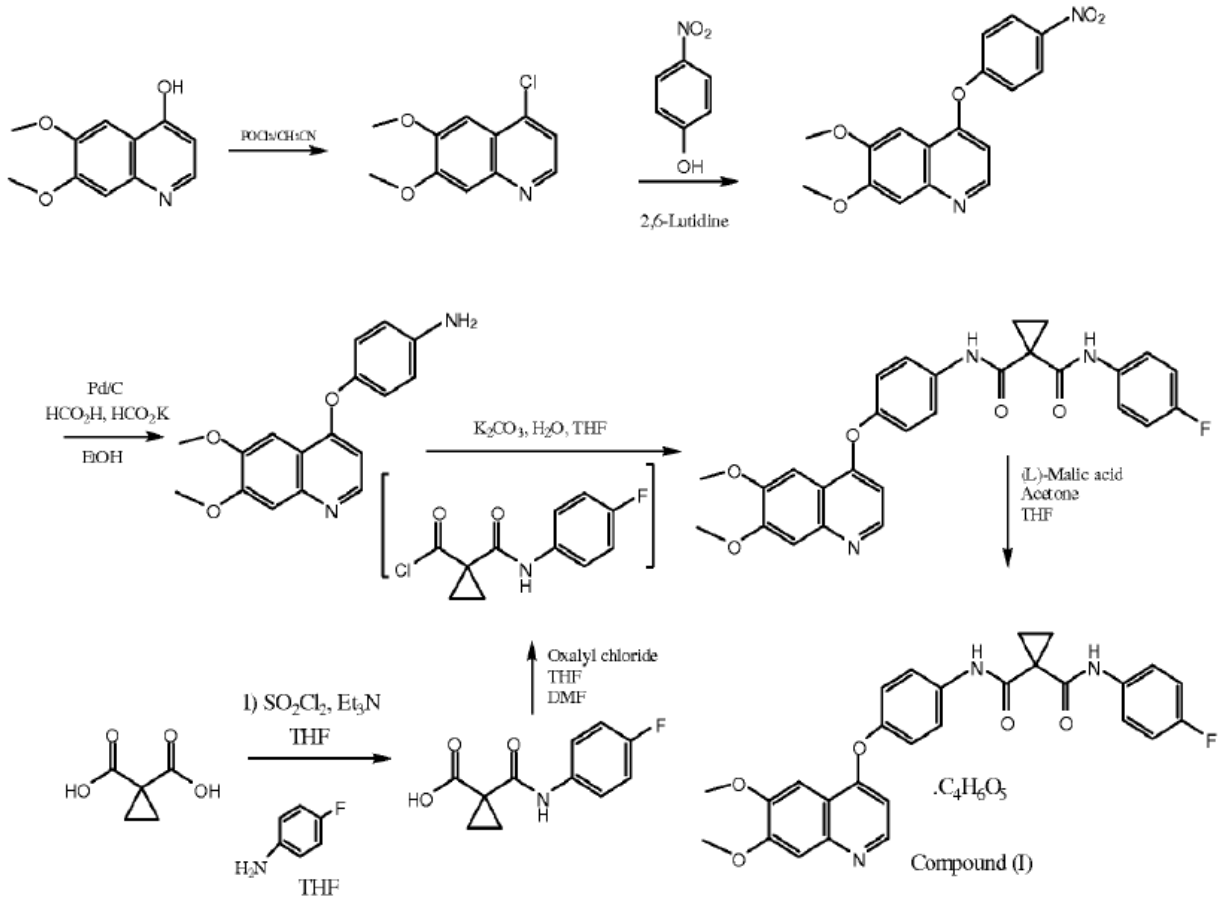
e. A "100 ppm or less" concentration range for "6,7-dimethoxy-quinoline-4-ol" (or any lesser claimed range) would have been obvious

Thus far, there has been no distinction between Brown and the Challenged Claims. Indeed, Exelixis made no effort during prosecution to distinguish the claims on any basis aside from the recited concentration range of 6,7-dimethoxy-quinoline-4-ol. Ex. 1045 at 90. However, it would have been obvious to obtain a composition containing "100 ppm or less of 6,7-dimethoxy-quinoline-4-ol" (or any lesser claimed concentration range). That is the expectation when claiming concentration ranges. *E.I. DuPont De Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1006 (Fed. Cir. 2018) ("[I]t is to be expected that a change in temperature, or in concentration, or in both, would be an unpatentable modification.") (quoting *In re Aller*, 220 F.2d 454, 456 (C.C.P.A. 1955)).

i. API containing 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol (or any lesser claimed range) would have been obvious

Brown describes how to prepare cabozantinib (L)-malate (labeled as "Compound (I)" in Scheme 1):

SCHEME 1



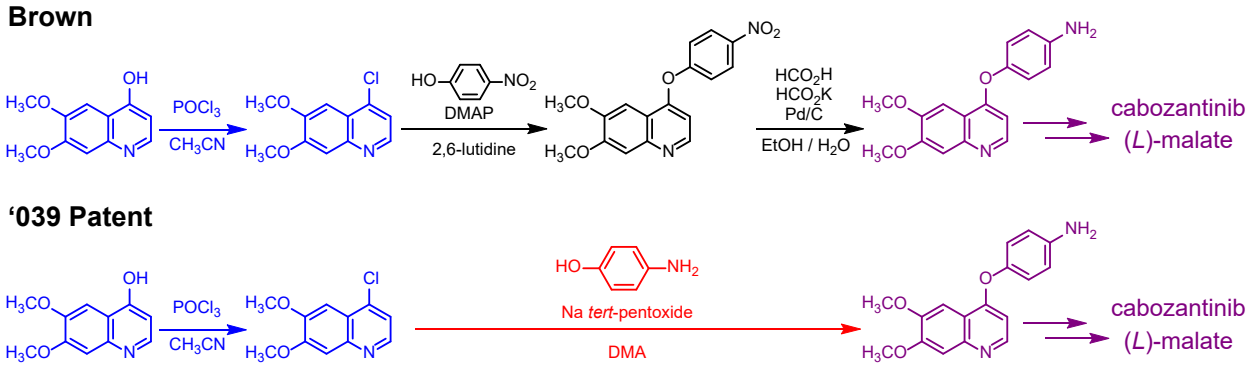
Ex. 1003 at [0099]; Ex. 1043 ¶39. Brown's process utilizes 6,7-dimethoxy-quinoline-4-ol as a starting material. Ex. 1003 at [0099], [00100]-[00102]; Ex. 1043 ¶¶47, 50. Brown also suggests that 6,7-dimethoxy-quinoline-4-ol can remain as a "reaction impurity," whose presence in cabozantinib (L)-malate "may be determined by analytical techniques known in the art." Ex. 1003 at [00102] and [0097]; Ex. 1043 ¶¶51-53.

A POSA would have understood that Brown's 6,7-dimethoxy-quinoline-4-ol starting material, which is the same "byproduct" or "contaminant" identified in the

'039 patent and recited in the Challenged Claims, may be present as a reaction impurity in Brown's cabozantinib (L)-malate. Ex. 1043 ¶¶51-53. Indeed, Brown's cabozantinib (L)-malate was found to contain "at most, de minimis" 6,7-dimethoxy-quinoline-4-ol (indicated in the upper left-hand corner of Scheme 1, *supra*). Ex. 1026 at 46 ("[A] POSA would expect that there is, at most, de minimis impurity left at the end of the Brown process."); *id*. at 52-53. Exelixis cannot contend otherwise. Ex. 1019 at 708:23-709:14 (Exelixis expert stating "we would not expect any significant amount of [6,7-dimethoxy-quinoline-4-ol] to carry through. We just would expect it to be de minimis.").

Brown's synthesis of cabozantinib (L)-malate and the '039 patent's synthesis of the same material are very similar, as illustrated in Figure 1:

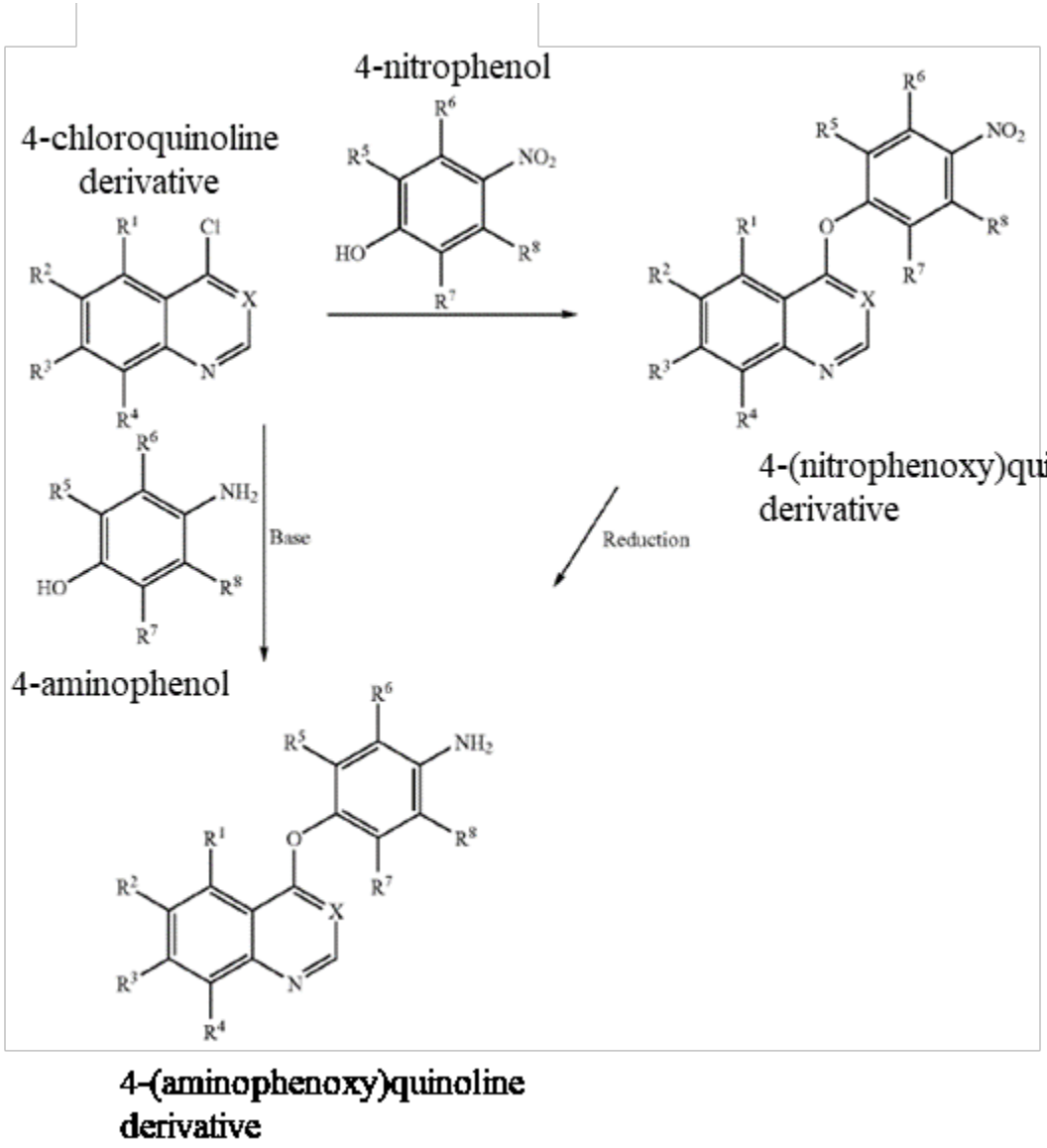
Figure 1—Comparison of synthetic routes in Brown and the '039 patent



Ex. 1043 ¶47. In Figure 1, the steps in **blue** are identical between Brown and the '039 patent's own Figure 1. Ex. 1001 at columns 23-26; Ex. 1043 ¶47. Both Brown and the '039 patent also converge to the same 4-(aminophenoxy)quinoline derivative

(shown in **purple** in Figure 1), which is then subjected to the same chemical transformations to afford cabozantinib (L)-malate. Ex. 1043 ¶48. Indeed, the similarities are so strong with respect to these transformations that the only procedures identified in the '039 patent for obtaining cabozantinib (L)-malate as the crystalline N-1 or N-2 form are copied verbatim from Brown. *Compare* Ex. 1003 at [00115]-[00127] *with* Ex. 1001 at 29:54-31:3; Ex. 1043 ¶49. Thus, the sole, transformative distinction between Brown's synthesis of cabozantinib (L)-malate containing a "de minimis" amount of 6,7-dimethoxy-quinoline-4-ol and that of the '039 patent are the two steps noted in **black** from Brown versus the one step noted in red from the '039 patent (*see* Figure 1, *supra*). Ex. 1043 ¶¶47-49, 57. This distinction would have been obvious.

Kubo teaches that the two steps of Brown (indicated in **black** in Figure 1, *supra*) can "[a]lternatively" be performed in a single step using 4-aminophenol. Ex. 1028 at 12:46-14:4; Ex. 1043 ¶¶58-59. This is illustrated in Kubo's Scheme 1:



Ex. 1028 at 12:46-14:4 (Annotated); Ex. 1043 ¶58.

There is no question as to the relevance of Kubo's teachings regarding antitumor quinoline compounds to Brown's synthesis of cabozantinib (L)-malate, an antitumor quinoline compound. Ex. 1043 ¶¶40-41, 60-62. Kubo uses the same type of starting material as Brown (a "4-chloroquinoline derivative"); Kubo uses the same type of reagents ("4-nitrophenol" and "4-aminophenol"); Kubo forms the same

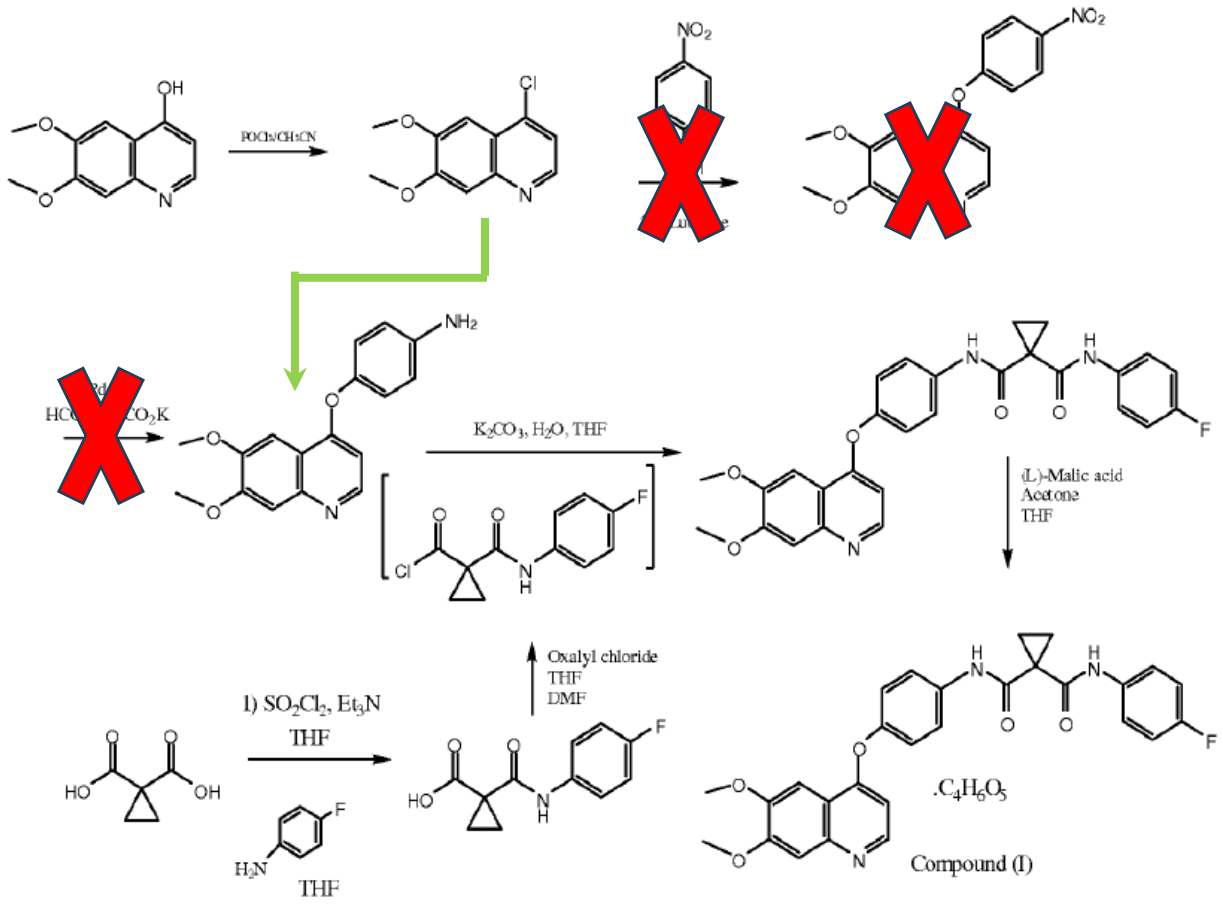
products (a "4-(nitrophenoxy)quinoline derivative" and a "4-(aminophenoxy)quinoline derivative"); and Kubo discusses the separation of "4-(aminophenoxy)quinoline derivative" from the same 4-hydroxyquinoline decompositions products formed in Brown. Ex. 1028 at 12:46-14:4; Ex. 1043 ¶¶60-62. In sum, Kubo involves the same synthetic chemistry as Brown. Ex. 1043 ¶¶45, 60-62. Because a POSA "has good reasons to pursue the known options within his or her technical grasp," utilizing Kubo's alternative, one-step approach would have been obvious. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 417, 421 (2007); *see also ACCO Brands Corp. v. Fellowes, Inc.*, 813 F.3d 1361, 1367 (Fed. Cir. 2016) (explaining that where an "ordinary artisan would … be left with two design choices … [e]ach of these two design choices is an obvious combination"); *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1238 (Fed. Cir. 2010).

Moreover, a POSA would have been motivated to apply Kubo's one-step alternative to Brown's preparation of cabozantinib (L)-malate. Ex. 1043 ¶¶63-72. The single-step approach saves one step in Brown's synthesis of cabozantinib (L)-malate. Ex. 1043 ¶¶64-66. For this reason alone, a POSA would have found the single-step alternative "superior." Ex. 1029 at 133 ("A synthesis that reaches the target in fewer steps than another one is considered superior."); Ex. 1043 ¶¶64-65.

The rationale for eliminating a step is straightforward—doing so improves efficiency. Ex. 1030 at 3012 ("[M]inimising the number of steps leads to an efficient

multistep synthesis in terms of cost and time expended to obtain the desired product."); Ex. 1031 at 2855 ("Minimizing the total number of steps … lays a foundation for achieving overall efficiency."); Ex. 1043 ¶¶64-65. Here, Brown's two-step approach is neither efficient nor economical when compared to Kubo's alternative one-step approach to make the same material that Brown must prepare. Ex. 1043 ¶¶64-66. The gain in efficiency from Kubo is further illustrated below:

SCHEME 1



Ex. 1043 ¶66.

Moreover, Kubo's alternative use of 4-aminophenol to accomplish the desired transformation saves money by eliminating unnecessary chemical usage and waste disposal from the unnecessary reaction. Ex. 1043 ¶67. It saves manpower by eliminating performance of the unnecessary reaction. *Id*. It eliminates a hazardous reagent. Ex. 1035 at 124440; Ex. 1043 ¶67. It also saves in material costs because Brown's two-step approach resulted in a 28% yield of the 4-(aminophenoxy)quinoline derivative while it was known that the one-step approach can afford the same compound in as much as a 92% yield. Ex. 1003 at [00103]-[00106]; Ex. 1001 at 25:61-26:47; Ex. 1033 at 2186 (Scheme 1), 2190; Ex. 1043 ¶¶68-70. Kubo further teaches that the one-step approach can simplify product isolation and improve purity. Ex. 1028 at 12:60-14:2; Ex. 1043 ¶¶71-72. Thus, a POSA would have been motivated to incorporate Kubo's one-step "alternative" in Brown's preparation of cabozantinib (L)-malate for such obvious benefits. Ex. 1043 ¶63. Given the preparation of highly similar quinoline derivatives, for treating the same diseases, and using the same synthetic approach, a POSA interested in preparing cabozantinib (L)-malate would have been well aware of Kubo. Ex. 1043 ¶¶40-46. Exelixis cannot contend otherwise—it cited Kubo during prosecution of the '039 patent. Ex. 1001 at (56). Inexplicably, the Examiner did not reject the Challenged Claims for obviousness over Brown and Kubo. Ex. 1045 at 78-83.

A POSA would have also had a reasonable expectation that applying the one-step approach taught by Kubo to Brown's synthesis of cabozantinib (L)-malate would be successful. Ex. 1043 ¶73. The one-step approach affords the same intermediate that Brown prepared over two steps and subsequently used to prepare cabozantinib (L)-malate. *Id*. Moreover, the '039 patent is itself evidence that this one-step approach would be successful. Ex. 1001 at 8:38-42 ("Unless specified otherwise, the starting materials and ***various intermediates may be*** obtained from commercial sources, prepared from commercially available organic compounds, or ***prepared using well-known synthetic processes***."), 11:1-12:46 (discussing "[n]on-limiting examples of suitable reaction conditions" for the one-step sequence), 17:34-18:21 (disclosing the same 2,6-lutidine base used in Brown's Scheme for the one-step sequence), 33:54-66 (stating "many variations and modifications can be made while remaining within the spirit and scope of the invention"); Ex. 1043 ¶¶78-81.

With respect to the amount of any 6,7-dimethoxy-quinoline-4-ol impurity in cabozantinib (L)-malate, Brown's original synthesis afforded material containing a "de minimis" amount of 6,7-dimethoxy-quinoline-4-ol. Ex. 1026 at 46, 52-53; Ex. 1024 at 668:11-669:14; Ex. 1019 at 708:23-709:19. Applying Kubo's one-step approach to Brown's synthesis of cabozantinib (L)-malate would have been expected to confer an additional benefit of further reducing any amount of 6,7-dimethoxy-quinoline-4-ol in the cabozantinib (L)-malate obtained from the

synthesis. Ex. 1043 ¶¶74-77. Kubo expressly indicates that the one-step approach can be performed under conditions that will separate any 6,7-dimethoxy-quinoline-4-ol from the 4-(aminophenoxy)quinoline intermediate. Ex. 1028 at 12:60-14:2; Ex. 1043 ¶77.

Additionally, both the 4-(nitrophenoxy)quinoline intermediate in Brown's synthesis and the 4-(aminophenoxy)quinoline intermediate in the one-step sequence of Kubo are susceptible to small amounts of degradation by water to afford 6,7-dimethoxy-quinoline-4-ol. Ex. 1043 ¶¶75-76; *see also* Ex. 1024 at 600:10-601:4 (Exelixis inventor admitting that 6,7-dimethoxy-quinoline-4-ol was a degradant forming during "subsequent chemistry steps"). However, the 4-(aminophenoxy)quinoline intermediate is less susceptible to such a degradation reaction than the 4-(nitrophenoxy)quinoline intermediate because the liberation of 4-aminophenol is less likely to occur than the liberation of 4-nitrophenol due to the difference in their stability. Ex. 1032 at 820; Ex. 1043 ¶¶75-76. By applying Kubo's one-step approach with 4-aminophenol to Brown's synthesis of cabozantinib (L)-malate, a POSA would have expected lower amounts of 6,7-dimethoxy-quinoline-4-ol to be present as a result of the difference in hydrolytic stability. Ex. 1043 ¶¶75-76. As a result, cabozantinib (L)-malate containing a "de minimis" amount of 6,7-dimethoxy-quinoline-4-ol as originally produced by Brown would have been expected to contain even lower amounts of 6,7-dimethoxy-quinoline-4-ol as a result

of the change in synthetic process to utilize Kubo's one-step approach. Ex. 1043 ¶77.

Moreover, Kubo's one-step approach combined with Brown must have necessarily afforded cabozantinib (L)-malate containing 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol (or any of the lesser claimed ranges). Ex. 1024 at 694:13-24 (Exelixis expert testifying that the one step sequence controlled for the formation of 6,7-dimethoxy-quinoline-4-ol); Ex. 1019 at 712:1-5 (Exelixis expert testifying that "the first key difference [between Brown and the '039 patent's parent, the '349 patent (Ex. 1046)] is that the '349 patent has a different synthetic process which was designed to minimize the [6,7-dimethoxy-quinoline-4-ol] impurity at very low levels"); Ex. 1043 ¶¶78-81. As previously indicated, the one-step approach is the only transformative difference between Brown's approach to synthesizing cabozantinib (L)-malate and the '039 patent's approach. And the '039 patent indicates that its transformations may be conducted under various conditions and still remain "within the spirit and scope of the invention." Ex. 1001 at 8:38-42, 9:51-56, 11:1-12:46, 17:34-18:21, 24:15-30, 33:54-66; Ex. 1043 ¶¶78-81. Thus, applying the one-step approach of Kubo must necessarily result in cabozantinib (L)-malate containing 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol. *Arbutus Biopharma Corp. v. ModernaTX, Inc.*, 65 F.4th 656, 663-64 (Fed. Cir. 2023); *King Pharms., Inc. v. Eon Labs., Inc.*, 616 F.3d 1267, 1276 (Fed. Cir. 2010); *MEHL/Biophile Int'l*

Corp. v. Milgraum, 192 F.3d 1362, 1366 (Fed. Cir. 1999) ("MEHL/Biophile does not dispute on appeal that the laser operating parameters disclosed in the article substantially coincide with those disclosed in the patent. Accordingly, to the extent the embodiment in the patent achieves hair depilation, so does the Polla method."); Ex. 1043 ¶81.

For the same reasons, applying the one-step approach of Kubo must also result in API having 6,7-dimethoxy-quinoline-4-ol impurity concentration ranges of "50 ppm or less," "25 ppm or less," "10 ppm or less," and "5 ppm or less" as recited in the Challenged Claims. *Id*. Exelixis's prior litigation experts admitted as much. Ex. 1019 at 712:1-5, 773:7-24; Ex. 1024 at 694:13-24. Accordingly, the claimed concentration ranges are an inherent property of an otherwise obvious compound afforded by the combination of Brown and Kubo as previously explained. "If a property of a composition is in fact inherent, there is no question of a reasonable expectation of success in achieving it." *Hospira, Inc. v. Fresenius Kabi USA, LLC*, 946 F.3d 1322, 1332 (Fed. Cir. 2020); *see also Cytiva BioProcess R&D AB v. JSR Corp.*, No. 2023-2074, 2024 WL 4960327, at *9 (Fed. Cir. Dec. 4, 2024) (holding that "[a]ny separate analysis on this point is unnecessary").

Additionally, nothing in the '039 patent instructs a POSA as to what must actually be done to obtain cabozantinib (L)-malate containing 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol. Ex. 1043 ¶¶78-81. There is no measurement of the

levels of 6,7-dimethoxy-quinoline-4-ol in the pre-formulated API. *Id*. There is no discussion of what conditions do or do not result in the formation of 6,7-dimethoxy-quinoline-4-ol. *Id*. The '039 patent simply leaves it to a POSA to figure out on its own what variables afford API having 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol. *Id*. Even then, the '039 patent only contains "non-limiting examples" while proclaiming that "many variations and modifications can be made." Ex. 1001 at 7:43-48, 8:36-43, 9:33-56, 11:34-12:46, 12:64-13:10, 13:57-14:5, 24:14-30, 33:50-66; *id*. Thus, to the extent that the '039 patent describes and enables the production of cabozantinib (L)-malate that satisfies the claimed impurity limitations, then Brown in view of Kubo must necessarily do so as well.

ii. A pharmaceutical composition containing 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol (or any lesser claimed range) would have been obvious

Section VI.C.1.e.i, *supra*, explained why cabozantinib (L)-malate containing less than 100 ppm of 6,7-dimethoxy-quinoline-4-ol (as well as each of the concentration ranges in the Challenged Claims) would have been obvious. Formulating such material into a tablet or capsule containing a pharmaceutically acceptable carrier and not exceeding the claimed impurity thresholds would have also been obvious. Ex. 1042 ¶¶100-109. This conclusion is fully supported by the district court's findings from a prior litigation concerning the parent of the '039 patent. Ex. 1026 at 47 ("A POSA would be motivated to ensure that cabozantinib

(L)-malate is formulated as a tablet or capsule that include a filler, lubricant, disintegrant, and glidant."); *id*. ("It was not unexpected that cabozantinib (L)-malate could be formulated and stay essentially free of the [6,7-dimethoxy-quinoline-4-ol] impurity. A POSA would have expected that cabozantinib (L)-malate that is essentially free of the [6,7-dimethoxy-quinoline-4-ol] impurity could be formulated into a capsule or tablet that is essentially free of the [6,7-dimethoxy-quinoline-4-ol] impurity."). It is a conclusion that Exelixis did not dispute. *Id*. at 54. And it is the normal expectation for such concentration ranges. *E.I. DuPont*, 904 F.3d at 1006.

Exelixis cannot now contend otherwise. Its litigation expert admitted that there is nothing in the parent of the '039 patent other than the synthetic process for cabozantinib (L)-malate that would control the amount of 6,7-dimethoxy-quinoline-4-ol in the resulting pharmaceutical composition. Ex. 1019 at 773:7-24. The '039 patent admits that preparing "the pharmaceutical compositions disclosed herein" requires nothing more than "known techniques." Ex. 1001 at 20:40-55, 31:5-7; Ex. 1042 ¶¶107-109. Brown teaches the same. Ex. 1003 at [0082]; Ex. 1042 ¶¶107-109. Thus, if the cabozantinib (L)-malate contains less than 100 ppm of 6,7-dimethoxy-quinoline-4-ol (or any of the thresholds recited in the dependent claims) before formulation as a tablet or capsule, and only "known techniques" are required to prepare a capsule/tablet, then nothing more is needed to establish obviousness. *Persion Pharm. LLC v. Alvogen Malta Operations Ltd.*, 945 F.3d 1184, 1190 (Fed.

Cir. 2019) ("It is long settled that in the context of obviousness, the mere recitation of a newly discovered function or property, inherently possessed by things in the prior art, does not distinguish a claim drawn to those things from the prior art.") (internal quotation marks omitted); *Purdue Pharma L.P. v. Epic Pharma, LLC*, 811 F.3d 1345, 1353 (Fed. Cir. 2016) ("Purdue claimed the end product; it did not claim a particular method for creating that product."); *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1376 (Fed. Cir. 2001); *see also Trustees of Columbia Univ.*, 620 F. App'x. at 933.

Indeed, there is no basis to dispute that Brown would afford a reasonable expectation of successfully formulating cabozantinib (L)-malate as a tablet/capsule with "a pharmaceutically acceptable carrier" without violating any of the claimed concentration ranges for 6,7-dimethoxy-quinoline-4-ol that may be present. Brown explains that the carrier should not be "incompatible with the form of the active compound(s)" and should not "otherwise interact[] in a deleterious manner with any other component(s) of the pharmaceutical composition." Ex. 1003 at [0081]. Brown then proceeds to identify carriers that may be utilized. Ex. 1003 at [0082]. This is considerably more disclosure than provided in the '039 patent.

It would also not have been unexpected to identify an acceptable "carrier" in view of Brown's teachings, *see* Ex. 1026 at 47, particularly if cabozantinib (L)-malate is a "very, very, very, stable compound" as Exelixis's expert previously

alleged. Ex. 1024 at 661:9-663:11. Obvious choices of pharmaceutically acceptable carriers existed, *see* Section II.B.1-4, *supra*; Ex. 1042 ¶¶107-108, and such obvious choices were the same ones ultimately used by Exelixis to prepare a capsule composition that purportedly met the claimed concentration threshold. Ex. 1001 at 31:5-20 and Table 7A. This was purportedly done using "known" processes and techniques. Ex. 1001 at 20:41-55, 31:5-20; Ex. 1042 ¶108. Accordingly, such obvious choices and known methods must necessarily afford a composition that meets the claimed concentration threshold. *Arbutus*, 65 F.4th at 663-64; *King Pharms.*, 616 F.3d at 1276; *MEHL*, 192 F.3d at 1366. Indeed, "if novel and nonobvious chemistry was needed to practice the claimed inventions, [Exelixis] would have been obligated to disclose this chemistry in the patent." *Trustees of Columbia Univ.*, 620 F. App'x. at 933.

In sum, maintaining any of the claimed concentration ranges for the 6,7-dimethoxy-quinoline-4-ol impurity upon formulation must necessarily result from utilizing any one or more of the obvious choices of acceptable carriers. As such, the Board need not even reach the issue of reasonable expectation of success. *Hospira*, 946 F.3d at 1332; *see also Cytiva*, 2024 WL 4960327, at *9. "To hold otherwise would allow any formulation—no matter how obvious—to become patentable merely by testing and claiming an inherent property." *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012).

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Thus, a POSA would have had ample motivation and expectation of success to have utilized the express teachings of Brown and Kubo to prepare a tablet/capsule for oral administration that included "Compound IB" (cabozantinib (L)-malate) and a pharmaceutically acceptable carrier while containing less than 100 ppm "6,7-dimethoxy-quinoline-4-ol." As such, claim 1 would would have been obvious.

2. Claims 2-5 recite obvious concentrations of 6,7-dimethoxy-quinoline-4-ol

Claims 2-5 each depend from the immediately preceding claim and only limit the amount of 6,7-dimethoxy-quinoline-4-ol that may be present in the composition. Ex. 1001 at claim 2 (reciting "50 ppm or less"), claim 3 (reciting "25 ppm or less"), claim 4 (reciting "10 ppm or less"), claim 5 (reciting "5 ppm or less"); Ex. 1042 ¶¶110-112. Reciting various thresholds for the 6,7-dimethoxy-quinoline-4-ol impurity does not distinguish the claimed compositions from Brown in view of Kubo. *See* Section VI.C.1.e, *supra*.

As previously indicated, Brown and Kubo render obvious the synthesis of cabozantinib (L)-malate as described by the '039 patent. *See* Section VI.C.1.e.i, *supra*. Accordingly, to the extent that the '039 patent enables the production of cabozantinib (L)-malate that satisfies the claimed thresholds of 6,7-dimethoxy-quinoline-4-ol, then Brown in view of Kubo must do so as well. *Id*. With respect to the formulation of this API so as to not exceed the claimed thresholds, such

compositions would have been obvious for the reasons previously discussed. *See* Section VI.C.1.e.ii, *supra*; Ex. 1042 ¶¶110-112.

3. Claim 6

Claim 6 of the '039 patent recites "[a] method of treating cancer, comprising administering to a subject in need thereof" the pharmaceutical composition as specified in claim 1. Ex. 1001 at 34:38-61; Ex. 1044 ¶60. For the reasons discussed above in Section VI.C.1, *supra*, a POSA would have found the pharmaceutical composition recited in claim 6 to be obvious.

Regarding the use of such a pharmaceutical composition to treat cancer, Brown teaches that the administration of pharmaceutical compositions of cabozantinib (L)-malate to a subject is useful for treating cancer. Ex. 1003 at Title, Abstract, [0004]-[0005], [0012], [0067]-[0077], [0079], claims 12-15; Ex. 1044 ¶¶62-66; *see also* Section II.A, *supra*. Accordingly, a POSA would have been motivated to administer the claimed pharmaceutical composition to a subject for the treatment of cancer. Ex. 1044 ¶¶62-66. Exelixis cannot contend otherwise—it admitted during prosecution that "Brown discloses a generic pharmaceutical composition of Compound IB ***and treatment of cancer***…." Ex. 1045 at 90.

A POSA would have had a reasonable expectation of successfully using such an obvious composition of cabozantinib (L)-malate for the treatment of cancer. Ex. 1044 ¶¶67-72. Exelixis was actively promoting its agreement with Bristol-Myers

Squibb ("BMS") to co-develop XL184 for the treatment of cancer, which was in Phase III clinical trials. Ex. 1053 at 1; Ex. 1044 ¶68. Brown was jointly filed naming both Exelixis and BMS as applicants. Ex. 1003 at (71); Ex. 1044 ¶47. Because Exelixis and BMS were only co-developing two kinase inhibitors for treating cancer (Ex. 1053 at 1), and only XL184 matched the kinase targets provided for cabozantinib (L)-malate, it would have been reasonable to believe that XL184 is cabozantinib (L)-malate and that it was in Phase III clinical trials for such a use. Ex. 1044 ¶¶55-57.

However, any question concerning the identity of XL184 as cabozantinib (L)-malate was dispelled by the earliest possible priority date of the '039 patent. During prosecution of the '436 patent (Ex. 1040), Exelixis linked the identity of XL184 with that of cabozantinib in a response dated November 11, 2010. Ex. 1054 at 413-414 (providing data from posters presented at an ASCO conference for the compound of claim 111, which is cabozantinib, under the filename "XL184"); Ex. 1044 ¶¶55-57. Accordingly, at least by the earliest alleged priority date of the '039 patent, a POSA would have known that XL184 was cabozantinib. Ex. 1044 ¶¶55-57.

Moreover, even in the absence of Exelixis inadvertently disclosing the identity of XL184, Brown's explanation of cabozantinib's mechanism of action would have provided a reasonable expectation that the administration of a

pharmaceutical composition containing cabozantinib (L)-malate to a subject would be useful for treating cancer. Ex. 1003 at [0006]-[0011], [0079]; Ex. 1044 ¶¶56, 69-70. Brown indicates that cabozantinib inhibits, regulates, and/or modules Ret, c-Met and VEGFR2. Ex. 1003 at [0010]; Ex. 1044 ¶¶56, 69-70. These are the same targets that several pharmaceutical companies were successfully using kinase inhibitors to treat a variety of cancers. Ex. 1053 at 1, Table 1; Ex. 1058 at 1, Abstract, 4 (Table 1); Ex. 1059 at 1493; Ex. 1055 at 551, Table 1; Ex. 1060 at Abstract; Ex. 1061 at 408; Ex. 1062 at 2207 (Abstract); Ex. 1063 at Poster 104; Ex. 1044 ¶69-70.

Exelixis cannot contend there would be no reasonable expectation of success in view of Brown. *NOF Corp.*, 2021 WL 3265737, at *13 ("In any event, Bentley is presumptively enabled and this presumption may be applied against Patent Owner in this case to demonstrate a reasonable expectation of success in achieving the disclosed and claimed molecular weight ranges.") (citing *Abbott Labs. v. Andrx Pharms., Inc.*, 452 F.3d 1331, 1341-42 (Fed. Cir. 2006)); *see also Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1325-26 (Fed. Cir. 2005). First, the '039 patent contains no description of any testing of cabozantinib (L)-malate for the treatment of any form of cancer. Ex. 1044 ¶¶50, 71. The '039 patent never even refers to "cancer," "treatment," or any method concerning the treatment of renal cancer, prostate cancer, or hepatocellular carcinoma in the "Summary" or "Detailed Description" sections. Ex. 1044 ¶71. The only reference to any "cancer" is in the

"Background of the Invention"—which is substantively identical to Brown's disclosure. *Compare* Ex. 1003 at [0006]-[0011] *with* Ex. 1001 at 1:41-3:34; Ex. 1044 ¶71. Accordingly, there is nothing in the '039 patent regarding treating cancer that is not also present in Brown. *Liquidia Techs., Inc. v. United Therapeutics Corp.*, No. IPR2021-00406, 2022 WL 2820717, at *14 (P.T.A.B. July 19, 2022); Ex. 1044 ¶71.

Moreover, the Patent Office issued several claims to methods of treating cancer from applications in Brown's patent family. Ex. 1047 at claims 3-5; Ex. 1048 at claims 1-3; Ex. 1044 ¶88. Exelixis clearly believed that it had enabled the use of cabozantinib to treat a wide variety of cancers, having claimed just such a use in its patent family claiming priority back to 2003. Ex. 1051 at claims 69 (identifying cabozantinib) and 75 (claiming the treating of, *inter alia*, "kidney cancer," "liver cancer," and "prostate carcinoma"); Ex. 1044 ¶¶44-45; *NOF Corp.*, 2021 WL 3265737, at *13; *Liquidia Techs.*, 2022 WL 2820717, at *14. Thus, to the extent the '039 patent describes and enables the claimed treatment methods, then Brown must afford a reasonable expectation of success in the same. Ex. 1044 ¶72.

4. Claims 7-10 recite the same obvious concentration ranges for 6,7-dimethoxy-quinoline-4-ol as in Claims 2-5

Claims 7-10 each depend from the immediately preceding claim and only limit the method by the amount of 6,7-dimethoxy-quinoline-4-ol that may be present. Ex. 1001 at claim 7 (reciting "50 ppm or less"), claim 8 (reciting "25 ppm

or less"), claim 9 (reciting "10 ppm or less"), claim 10 (reciting "5 ppm or less"); Ex. 1042 ¶115. Section VI.C.2, *supra*, explained why such pharmaceutical compositions would have been obvious. Ex. 1042 ¶116. Nothing about these impurity levels would have been expected to affect the claimed treatment of cancer. Ex. 1044 ¶¶73-75. That is because the efficacy of a composition is attributable to the active ingredient rather than the impurity. Ex. 1044 ¶74. For those reasons, and the reasons provided above with respect to the method recited in claim 6 (*see* Section VI.C.3, *supra*), a POSA would have found claims 7-10 obvious. Ex. 1044 ¶¶73-75.

5. Claims 11-22

Claims 11-22 depend from the methods of claims 6-9 and limit the broadly claimed treatment of "cancer" to either "renal cancer," "prostate cancer," or "hepatocellular carcinoma." For the reasons discussed above with respect to claims 6-9, a method of treating cancer with the claimed pharmaceutical compositions would have been obvious. *See* Sections VI.C.3-4, *supra*. Using such compositions to treat "renal cancer," "prostate cancer," and "hepatocellular cancer" would have also been obvious. Ex. 1044 ¶¶76-78.

a. Brown disclosed treating renal cancer

Regarding the treatment of "renal cancer" (claims 11, 14, 17, and 20), Brown teaches that a pharmaceutical composition of cabozantinib (L)-malate is to be administered to a subject as a method of treating kidney cancer. Ex. 1003 at [0067],

[0068] ("Another aspect of this disclosure relates to a method of treating cancer, as discussed above, where the cancer treated is … kidney cancer…."); Ex. 1044 ¶79. A POSA would have understood that "kidney cancer" and "renal cancer" are synonymous forms of cancer. Ex. 1044 ¶79. Thus, Brown teaches treating "renal cancer."

b. Brown disclosed treating prostate cancer

Regarding the treatment of "prostate cancer" (claims 12, 15, 18, and 21), Brown teaches that a pharmaceutical composition of cabozantinib (L)-malate is to be administered to a subject as a method of treating prostate carcinoma. Ex. 1003 at [0068] ("Another aspect of this disclosure relates to a method of treating cancer, as discussed above, where the cancer treated is … prostate carcinoma…."); Ex. 1044 ¶80. A POSA would have understood that "prostate carcinoma" and "prostate cancer" are synonymous forms of cancer. Ex. 1044 ¶80. Thus, Brown teaches treating "prostate cancer."

c. Brown taught treating hepatocellular carcinoma

Regarding the treatment of "hepatocellular carcinoma" (claims 13, 16, 19, and 22), Brown teaches that a pharmaceutical composition of cabozantinib (L)-malate is to be administered to a subject as a method of treating liver cancer. Ex. 1003 at [0067], [0068] ("Another aspect of this disclosure relates to a method of treating cancer, as discussed above, where the cancer treated is … liver cancer…."); Ex. 1044

¶81. A POSA would have understood that "hepatocellular carcinoma" is a type of "liver cancer." Ex. 1044 ¶81. Moreover, Brown taught that cabozantinib inhibits Ret, c-Met, and VEGFR2 while explaining that c-MET regulates "hepatocyte growth factor," which affects liver cells. Ex. 1003 at [0008], [0010]; Ex. 1044 ¶81-82. Inhibition of these kinases was known to be useful for treating hepatocellular carcinoma. Ex. 1053 at 1; Ex. 1055 at 551 (Table 1); Ex. 1061 at 408; Ex. 1062 at 2212; Ex. 1044 ¶81-82. Thus, Brown's teachings would have motivated a POSA to treat "hepatocellular carcinoma."

d. There would have been a reasonable expectation of successfully treating the specified cancers

A POSA would have had a reasonable expectation of successfully treating renal cancer, prostate cancer, and hepatocellular carcinoma as claimed. *See* Section VI.C.3, *supra*; Ex. 1044 ¶¶84-89. Even if XL184 was not known to be cabozantinib, it was known that hepatocellular carcinoma, renal cell carcinoma, and prostate cancer could be treated by targeting the same kinases that cabozantinib was targeting. Ex. 1053 at 1, Table 1; Ex. 1055 at 551 (Table 1); Ex. 1057 at 2505, 2510; Ex. 1058 at 1, 4 (Table 1); Ex. 1060 at Abstract; Ex. 1061 at 408, Conclusions; Ex. 1062 (Eder) 2209 (Table 1), 2212 (Conclusions); Ex. 1064 at 2361, 2363 (Table 2); Ex. 1044 ¶85-87.

Moreover, leaving aside the fact that Brown instructs a POSA to do so (*see* Ex. 1003 at [0068]), Brown contains more description regarding such treatment

methods than is present in the '039 patent. *See* Section VI.C.3, *supra*; Ex. 1044 ¶87. Indeed, the Patent Office issued several claims to methods of treating cancer, including kidney and liver cancer, from applications in Brown's patent family. Ex. 1047 at claims 3-5; Ex. 1048 at claims 1-3; Ex. 1044 ¶88. Exelixis also clearly believed that it had enabled the use of cabozantinib to treat "kidney cancer," "liver cancer," and "prostate carcinoma/cancer" as early as 2003—8 years prior to the earliest possible priority date of the Challenged Claims. Ex. 1051 at claims 69 and 75; Ex. 1040 at claims 1, 4; Ex. 1044 ¶88. Such claims, as well as Brown itself, are presumptively enabled. *In re Antor Media Corp.*, 689 F.3d 1282, 1288 (Fed. Cir. 2012); *Amgen Inv. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1355 (Fed. Cir. 2003). To the extent there is any connection between a reasonable expectation of success and enablement, it should apply to Exelixis's own disclosures. *Compare Abbott*, 452 F.3d at 1341-42 *with UCB, Inc. v. Accord Healthcare, Inc.*, 890 F.3d 1313, 1327 (Fed. Cir. 2018).

Indeed, Exelixis cannot contend there would be no reasonable expectation of successfully treating these specific cancers—the '039 patent contains no description of any such testing or use. *Trustees of Columbia Univ.*, 620 F. App'x. at 933; Ex. 1044 ¶71. The only possible support for such claims is in the '039 patent's "Background," which identifies the mechanism of action of cabozantinib. *In re Fout*, 675 F.2d 297, 300 (C.C.P.A. 1982) ("Valid prior art may be created by the

admissions of the parties."). But Brown provides an equivalent description. *Compare* Ex. 1003 at [0006]-[0011] *with* Ex. 1001 at 1:41-3:34; Ex. 1044 ¶¶71, 87. Thus, to the extent the '039 patent describes and enables the treatment of renal cancer, prostate cancer, and hepatocellular carcinoma with a pharmaceutical composition of cabozantinib (L)-malate, then Brown must also afford a reasonable expectation of success. *NOF Corp.*, 2021 WL 3265737, at *13; *Liquidia Techs.*, 2022 WL 2820717, at *14.

VII. GROUND 2: OBVIOUSNESS OVER BROWN IN VIEW OF ROBINSON

The Challenged Claims would have also been obvious over Brown (Ex. 1003) in view of Robinson (Ex. 1039). As previously explained, Brown teaches the preparation of cabozantinib (L)-malate ("Compound IB"), the preparation of tablet/capsule compositions, and the treatment of cancer—including the specific types claimed by the '039 patent. Moreover, Exelixis's litigation experts admitted that Brown's cabozantinib (L)-malate contained a "de minimis" amount of a potentially genotoxic impurity—6,7-dimethoxy-quinoline-4-ol. Robinson explains that such an impurity must be entirely removed or reduced to within the concentration ranges recited in the Challenged Claims. Robinson further cites to industry examples where similar removal/reductions were successfully accomplished. Accordingly, the Challenged Claims would have been obvious.

A. Introduction to Robinson

Robinson is entitled "Control of Genotoxic Impurities in Active Pharmaceutical Ingredients: A Review and Perspective." Robinson explains that "[r]ecent guidelines from drug regulatory authorities in Europe and the United States of America (USA) ***require the control of*** genotoxic and ***potentially genotoxic impurities at parts per million levels*** in drug substances." Ex. 1039 at Abstract. Moreover, Robinson teaches that "[a] drug substance will typically contain a range of low-level impurity compounds, for example arising as residues of starting materials … or degradation reactions; these need to be understood and controlled within tight limits." *Id*. at 946. "Manufacturers must therefore eliminate [impurities] (or at least mitigate the risk associated with them) to the greatest extent possible." *Id*.

Robinson further explains that the European Medicines Agency (EMEA) "recommends that any potentially genotoxic impurities (PGIs) in the drug substance should be identified" from existing data or the presence of "structural alerts." *Id*. at 947. Once identified, there are four courses of action:

> (1) alter the route of synthesis so as to remove the PGI entirely; (2) alter relevant process parameters to reduce the PGI to below a level of concern; (3) deploy chemical and mechanistic arguments, ideally backed with experimental evidence, to demonstrate that the PGI will not be present at significant levels; (4) conduct testing to demonstrate that the PGI is not actually harmful at its typical level in the API.

Id. at 952. With respect to the "level of concern," Robinson indicates that authorities have set a limit of 1.5 micrograms per day "for most known and all suspect carcinogens, unless experimental evidence can justify higher limits." *Id*. at 969, 948 (Table 1). Robinson then provides examples of how the pharmaceutical industry has utilized each of the above-indicated options to satisfy regulatory authorities. *Id*. at 952-969.

B. Brown in view of Robinson Renders the Challenged Claims Obvious

1. Claim 1

a. Preamble

Brown alone renders obvious "[a] pharmaceutical composition for oral administration...." *See* Section VI.C.1.a, *supra*.

b. Compound IB

Brown alone renders obvious a composition that includes "Compound IB." *See* Section VI.C.1.b, *supra*.

c. Carrier

Brown alone renders obvious a composition that includes "a pharmaceutically acceptable carrier." *See* Section VI.C.1.c, *supra*.

d. Tablet/Capsule

Brown alone renders obvious a "tablet or capsule" composition. *See* Section VI.C.1.d, *supra*.

e. A "100 ppm or less" threshold for "6,7-dimethoxy-quinoline-4-ol" (or any lesser claimed range) would have been obvious

Claim 1 further requires that the composition contain "100 ppm or less of 6,7-dimethoxy-quinoline-4-ol." Brown in view of Robinson renders obvious the claimed concentration range or any lesser claimed concentration range.

i. API containing 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol (or any lesser claimed range) would have been obvious

Section VI.C.1.e.i, *supra*, explained that Brown prepared cabozantinib (L)-malate using 6,7-dimethoxy-quinoline-4-ol as a starting material. Exelixis's litigation expert admitted that Brown's cabozantinib (L)-malate contained a "de minimis" amount of 6,7-dimethoxy-quinoline-4-ol. Ex. 1019 at 708:23-709:19; Ex. 1026 at 52-53. This was not surprising—Robinson explains that "[a] drug substance will typically contain a range of low-level impurity compounds, for example arising as ***residues of starting materials***, reagents, intermediates, or as ***side-products generated by the synthetic processes*** or ***degradation reactions***…." Ex. 1039 at 946; Ex. 1043 ¶90. Here, 6,7-dimethoxy-quinoline-4-ol was the starting material and an expected degradant of an intermediate in Brown's synthesis. Ex. 1043 ¶¶98-100. It is of no moment that Brown does not expressly report its presence or absence in the synthesized cabozantinib (L)-malate. Ex. 1043 ¶¶101-102.

Brown specifically identified cabozantinib (L)-malate for development as a pharmaceutical. Ex. 1003 at [0052]; Ex. 1042 ¶79; Ex. 1043 ¶101. As such, a POSA would have been motivated to ensure that this pharmaceutical product would comply with regulatory guidances. Ex. 1042 ¶¶72-75, 102-105; Ex. 1043 ¶¶101-102. Robinson reviews guidelines applicable to cabozantinib (L)-malate's pharmaceutical development, discusses strategies for complying with these requirements, and provides examples of the pharmaceutical industry's compliance. Ex. 1039 at Abstract; Ex. 1043 ¶¶91-94. Thus, a POSA would have been motivated to apply Robinson's teachings to the development of cabozantinib (L)-malate. Ex. 1043 ¶¶89-90, 102-103. Failure to do so would be unlikely to lead to a marketable pharmaceutical product. *Id*.

A POSA would not have ignored the uncertainty surrounding the presence or absence of 6,7-dimethoxy-quinoline-4-ol in view of Robinson. Ex. 1043 ¶¶102-105. Even "low-level impurity compounds … need to be understood and controlled within tight limits." Ex. 1039 at 946; Ex. 1043 ¶100. This is particularly true for known or suspected genotoxic impurities—especially when it involves a "starting material" or "may be expected based on the synthetic pathway." Ex. 1037 at 1 ("***This guidance provides specific recommendations regarding*** the safety qualification of ***impurities with known or suspected genotoxic or carcinogenic potential***…. This guidance also applies to ***known starting materials*** or anticipated reaction

products."); *id*. at 6 ("However, in cases where the presence of an impurity with genotoxic or carcinogenic potential is identified ***or where such an impurity may be expected based on the synthetic pathway***, steps should be taken during the clinical development stage to address safety concerns associated with these impurities."); Ex. 1042 ¶¶104-105; Ex. 1043 ¶¶102-103. "[A]ny potentially genotoxic impurities (PGIs) in the drug substance should be identified, either from existing genotoxicity data or through the presence of 'structural alerts.'" Ex. 1039 at 947; Ex. 1019 at 764:17-25 (Exelixis expert admitting that a POSA would have been motivated to determine whether any impurities were genotoxic and control them within certain limits); Ex. 1043 ¶104.

Quinoline was known to be genotoxic. Ex. 1036 at 11-13; Ex. 1042 ¶103. Both quinoline and 6,7-dimethoxy-quinoline-4-ol share a common structure—that of a "quinoline." Ex. 1019 at 771:9-20 (Exelixis expert admission); Ex. 1043 ¶103. Thus, a POSA would have suspected that 6,7-dimethoxy-quinoline-4-ol is potentially genotoxic. *Id*.; Ex. 1019 at 769:5-770:11 (Exelixis expert admitting that the quinoline structure of 6,7-dimethoxy-quinoline-4-ol was a "structural alert" requiring further evaluation). This structural alert would have motivated a POSA to evaluate Brown's cabozantinib (L)-malate, identify the presence of 6,7-dimethoxy-quinoline-4-ol (even if "de minimis"), and follow the regulatory guidances described in Robinson regarding the treatment of this potentially genotoxic impurity (PGI)—

such as removing it entirely or reducing it to a concentration below a level of concern. Ex. 1039 at 952; Ex. 1037 at 11; *id*. at 12 (Table 2) (specifying that when a PGI is present, then options are to "[m]odify synthetic pathway to eliminate the impurity, if possible" or "[c]onduct genotoxicity assays to characterize the genotoxic potential if not already known" and/or "[s]et specification to that associated with a potential daily impurity exposure supported by compound-specific risk assessment or relevant qualification threshold (see Table 1)"); Ex. 1043 ¶105; Ex. 1042 ¶¶104-105. Applying these options would have been obvious. *KSR*, 550 U.S. at 417, 421; *ACCO Brands*, 813 F.3d at 1367.

For a PGI such as 6,7-dimethoxy-quinoline-4-ol, regulatory guidance indicates that the concentration may be limited such that it remains below a level of concern (the threshold of toxicological concern or "TTC"). Ex. 1039 at 952; Ex. 1037 at 7, 11 (Table 1); Ex. 1038 at 6-7; Ex. 1043 ¶106. Such guidance teaches that the permissible concentration should range from less than 120 μg/day to less than 1.5 μg/day depending upon the duration of treatment. Ex. 1039 at 948 (Table 1); Ex. 1037 at 7, 11 (Table 1); Ex. 1038 at 6-7; Ex. 1043 ¶106; Ex. 1042 ¶105. As applied to cabozantinib, a POSA would have known from Exelixis's earlier disclosures that the amount of API intended to be administered was "about 0.1 to about 1,000 mg per day." Ex. 1008 at 274:52-57; Ex. 1043 ¶107; Ex. 1042 ¶105. Thus, a POSA could readily calculate the permissible concentration range of a PGI

such as 6,7-dimethoxy-quinoline-4-ol. Ex. 1043 ¶107; Ex. 1042 ¶105. For the 1000 mg per day dosage for cabozantinib that Exelixis disclosed, the limit for 6,7-dimethoxy-quinoline-4-ol would have been 120 ppm or less to as low as 1.5 ppm or less. *See* Ex. 1039 at 948 (Table 1); Ex. 1037 at 7, 11 (Table 1), 12 (Table 2); Ex. 1038 at 6 (Eq. 1) (substituting 1000 mg or 1 g as the dose and either 120 μg/day or 1.5 μg/day as the Threshold of Toxicological Concern); Ex. 1043 ¶107; Ex. 1042 ¶105.

Thus, it would have been obvious to limit the concentration of 6,7-dimethoxy-quinoline-4-ol to less than 100 ppm per regulatory guidance (indeed, it would have been obvious for each of the concentration ranges of "50 ppm or less," "25 ppm or less," "10 ppm or less," and "5 ppm or less" recited in the Challenged Claims). The claimed concentration ranges overlap with, fall within, or are met by the concentration ranges recommended by regulatory guidance. Ex. 1043 ¶107; Ex. 1042 ¶¶105-109. Decades of Federal Circuit precedent have recognized that such concentration ranges are obvious. *Valeant Pharms. Int'l, Inc. v. Mylan Pharms. Inc.*, 955 F.3d 25, 32 (Fed. Cir. 2020); *E.I. DuPont*, 904 F.3d at 1006; *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 736-41 (Fed. Cir. 2013); *Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1322 (Fed. Cir. 2004); *In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003) ("A *prima facie* case of obviousness typically exists when the ranges of a claimed composition overlap the ranges disclosed in the prior

art.") (collecting cases); *id*. at 1330 ("[W]hen, as here, the claimed ranges are completely encompassed by the prior art, the conclusion is even more compelling than in cases of mere overlap.").

Moreover, a POSA would have had a reasonable expectation of successfully reducing the "de minimis" concentration of 6,7-dimethoxy-quinoline-4-ol in Brown's cabozantinib (L)-malate to the threshold of 100 ppm or less (or even each of the "50 ppm or less," "25 ppm or less," "10 ppm or less," and "5 ppm or less" ranges recited in the Challenged Claims). The pharmaceutical industry was already successfully following the regulatory authorities' recommendations. Ex. 1039 at 952-59, 959 ("[I]t is clear that the control of PGIs at levels well below those of other impurities is here to stay. Indeed, industry has risen to the challenge of meeting the ppm levels with a variety of control strategies…."); Ex. 1043 ¶¶108-117; *see also* Ex. 1042 ¶¶110-112.

Indeed, Robinson provides examples where PGIs were controlled. Ex. 1039 at 951-959. For example, "[i]n many cases, PGIs have been successfully reduced below the TTC simply by altering appropriate conditions in either the reaction or workup stages." Ex. 1039 at 954; Ex. 1043 ¶110. One particular example Robinson identified used chromatography to purify the API. Ex. 1039 at 955 (citing Maddula (Ex. 1049)); Ex. 1043 ¶¶110-111. This was a known solution: "In many cases, preparative chromatography is the method needed to satisfy the purity specifications

required [by regulatory authorities] on a routine basis." Ex. 1056 at 131; Ex. 1043 ¶¶112-113. For that reason, the pharmaceutical industry has adopted it as a "general separation method for the purification of" intermediates and APIs. *Id*.

Turning to Robinson's example, Maddula developed a procedure for the "removal of structurally related impurities from synthetic API using low-pressure preparative chromatography on commercially available adsorbants." Ex. 1049 at 689; Ex. 1043 ¶¶114-115. In one experiment, Maddula's procedure reduced an impurity's concentration to as little as 10 ppm (0.001%). Ex. 1049 at 688; Ex. 1043 ¶114. In another experiment, the impurity was reduced to non-detectable levels (ND), which was described as "less than 1 ppm." Ex. 1049 at 689, Table 3 (entry 3, "% of b (after elution)"); Ex. 1043 ¶115. Accordingly, a POSA would have had a reasonable expectation that preparative chromatography would successfully reduce the concentration of a PGI such as 6,7-dimethoxy-quinoline-4-ol to the ranges recommended by regulatory authorities and claimed by the '039 patent. Ex. 1043 ¶¶116-117.

Obviously, cabozantinib (L)-malate and 6,7-dimethoxy-quinoline-4-ol are not the same API and structurally related impurity that Maddula successfully removed using chromatography. *Id*. at ¶116. This, however, would not negate the reasonable expectation of success afforded by either Robinson or Maddula. *Id*. at ¶¶116; *Pfizer Inc. v. Sanofi Pasteur Inc.*, 94 F.4th 1341, 1349 (Fed. Cir. 2024) ("The Board

correctly explained that a prior art reference is not limited to its specific working examples."); *PAR Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1198 (Fed. Cir. 2014) (holding that technology of general applicability afforded a reasonable expectation of success); *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007) ("[T]he expectation of success need only be reasonable, not absolute."). Brown explicitly identified "chromatography" for monitoring reactions and processing impurities. Ex. 1003 at [0097]; Ex. 1043 ¶112. Brown even used chromatography to monitor for the presence of 6,7-dimethoxy-quinoline-4-ol during the initial reaction in cabozantinib (L)-malate's synthesis. Ex. 1003 at [00102]; Ex. 1043 ¶112. It would be reasonable to expect that chromatography could be used to purify cabozantinib (L)-malate to within the claimed concentration ranges given Brown's use of chromatography to monitor for 6,7-dimethoxy-quinoline-4-ol—particularly in view of Guiochon and Maddula. Ex. 1065 at 9; Ex. 1043 ¶112.

ii. A pharmaceutical composition containing 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol would have been obvious

Section VII.B.1.e.i, *supra*, explained why cabozantinib (L)-malate containing less than 100 ppm of 6,7-dimethoxy-quinoline-4-ol (or even each of the "50 ppm or less," "25 ppm or less," "10 ppm or less," and "5 ppm or less" ranges recited in the Challenged Claims) would have been obvious. Formulating such material as a tablet or capsule containing a pharmaceutically acceptable carrier while maintaining the

claimed amount of 6,7-dimethoxy-quinoline-4-ol would have also been obvious in view of Brown. *See* Section VI.C.1.e.ii, *supra*. Indeed, if novel and nonobvious formulation methods were needed to practice the claimed inventions, Exelixis would have been obligated to disclose this in the '039 patent. *Trustees of Columbia Univ.*, 620 F. App'x. at 933.

***

Thus, a POSA would have had ample motivation and expectation of success to have utilized the express teachings of Brown and Robinson to prepare a tablet or capsule for oral administration that included "Compound IB" (cabozantinib (L)-malate) and a pharmaceutically acceptable carrier while containing less than 100 ppm "6,7-dimethoxy-quinoline-4-ol" (or any lesser claimed range). As such, claim 1 would have been obvious.

2. Claims 2-5 recite obvious concentrations of 6,7-dimethoxy-quinoline-4-ol

Section VII.B.1, *supra*, explained why it would have been obvious to prepare the claimed pharmaceutical composition containing a concentration of the potentially genotoxic 6,7-dimethoxy-quinoline-4-ol impurity of 120 ppm or less to as low as 1.5 ppm or less. Claims 2-5 recite nothing more than narrower concentration ranges for 6,7-dimethoxy-quinoline-4-ol. Ex. 1001 at claim 2 (reciting "50 ppm or less"), claim 3 (reciting "25 ppm or less"), claim 4 (reciting "10 ppm or less"), claim 5 (reciting "5 ppm or less"); Ex. 1043 ¶95; Ex. 1042 ¶¶110-

112. However, "'it is to be expected that a change ... in concentration ... would be an unpatentable modification.'" *DuPont*, 904 F.3d at 1006. This is particularly so when the claimed concentrations overlap with, fall within, and/or are met by the recommendations of regulatory guidances for a PGI such as 6,7-dimethoxy-quinoline-4-ol. *See* Sections VII.B.1.e.i-ii. Especially when the pharmaceutical industry had successfully demonstrated that such recommendations could be met by using chromatographic methods. *Id*. For the same reasons as previously indicated, claims 2-5 would have been obvious.

3. Claim 6

Claim 6 recites "[a] method of treating cancer, comprising administering to a subject in need thereof" the pharmaceutical composition containing limitations as specified in claim 1. Ex. 1001 at 34:38-61. As discussed above in Section VII.B.1, *supra*, the composition recited in claim 6 would have been obvious. Moreover, the broadly claimed "method of treating cancer" would have been obvious over Brown for reasons previously indicated. *See* Section VI.C.3, *supra*.

4. Claims 7-10 recite the same obvious concentrations of 6,7-dimethoxy-quinoline-4-ol as in Claims 2-5

Claims 7-10 only limit the recited treatment method by narrowing the concentration range of 6,7-dimethoxy-quinoline-4-ol that may be present in the composition. Ex. 1001 at claim 7 (reciting "50 ppm or less"), claim 8 (reciting "25 ppm or less"), claim 9 (reciting "10 ppm or less"), claim 10 (reciting "5 ppm or

less"); Section VI.C.4, *supra*. Such compositions would have been obvious over Brown in view of Robinson. *See* Section VII.B.2, *supra*. Moreover, it would have been obvious to administer such compositions for the claimed treatment of cancer for the reasons previously indicated. *See* Sections VI.C.3 and VII.B.3, *supra*.

5. Claims 11-22

Claims 11-22 depend from the methods of claims 6-9 and narrow the broadly claimed treatment of "cancer" to either "renal cancer" (claims 11, 14, 17, and 20), "prostate cancer" (claims 12, 15, 18, and 21), or hepatocellular carcinoma (claims 13, 16, 19, and 22). For the reasons discussed above with respect to claims 6-9, treating "cancer" as claimed would have been obvious. *See* Sections VII.B.3-4, *supra*. Likewise, using such compositions to treat "renal cancer," "prostate cancer," and "hepatocellular cancer" would have been obvious in view of Brown for the reasons previously indicated. *See* Sections VI.C.3 and VI.C.5, *supra*.

VIII. SECONDARY CONSIDERATIONS

Exelixis previously argued that commercial success, long-felt need, and unexpected results were secondary considerations of nonobviousness with respect to a family member of the '039 patent. Ex. 1026 at 56. The district court rejected Exelixis's arguments of long-felt need and unexpected results. *Id*. at 57-60. It further found that a blocking patent diminished the strength of any commercial success. *Id*. at 60-65. Accordingly, Azurity is not presently aware of any allegations

that would support a conclusion of nonobviousness. *See Leapfrog v. Fisher-Price*, 485 F.3d 1157, 1162 (Fed. Cir. 2007).

IX. INSTITUTION IS WARRANTED

This petition should not be subject to discretionary denial under the Board's §314(a) or §325(d) tests.

A. *Fintiv* Does Not Favor Denial

In certain circumstances that are not applicable here, the PTAB has not instituted an otherwise justified IPR where a parallel federal court litigation was addressing the same issues. 35 U.S.C. § 314(a); *Apple, Inc. v. Fintiv, Inc.*, IPR2020-00019, Paper 11 at 5-6 (PTAB Mar. 20, 2020). Such discretion should not be exercised here. There has been no litigation over the '039 patent—the only potentially relevant litigation concerned claim 3 of the '349 patent (Ex. 1046), did not involve Petitioner, and did not involve the same grounds of invalidity/evidence raised here. The IPR of a different patent/claims should not be denied based upon such other litigation.

1. Factor 1 Disfavors Denial

There is currently no pending litigation, or an opportunity for a stay, between Exelixis and Azurity. Accordingly, Factor 1 disfavors discretionary denial because it is presently inapplicable.

Even if, hypothetically, Exelixis did sue Azurity in the future, the likelihood of a stay is low. Exelixis would almost certainly assert additional patents against Azurity—just as it has done in other litigations over cabozantinib. Thus, there will be no reason to stay proceedings in view of this IPR proceeding. Accordingly, under this hypothetical scenario, Factor 1 would be neutral.

2. Factor 2 Disfavors Denial

The Board's projected statutory deadline for a final written decision is approximately 18 months from the filing of this petition. With no present parallel district court proceeding, the projected statutory deadline should be well-before any hypothetical trial date. Accordingly, Factor 2 disfavors discretionary denial.

3. Factors 3 and 4 Disfavor Denial

There is no parallel district court proceeding between Azurity and Exelixis. Accordingly, neither party nor a district court has invested any resources. Thus,

Assuming, *arguendo*, that the Board were to consider the district court proceeding between MSN and Exelixis concerning the '349 patent as a "parallel proceeding" for the purposes of evaluating the *Fintiv* Factors, discretionary denial would still be disfavored. There are several differences between this petition's arguments and those tried between MSN and Exelixis. First, a different patent/claims are at issue. Second, the petition's Ground 1 relies upon a secondary reference ("Kubo") that, when combined with Brown, explains why it would have

been obvious to obtain cabozantinib (L)-malate containing the claimed concentration ranges for 6,7-dimethoxy-quinoline-4-ol. Lastly, Ground 2 relies upon a secondary reference ("Robinson") that, when combined with Brown, explains why it would have been obvious to identify the presence of a PGI such as 6,7-dimethoxy-quinoline-4-ol and then follow regulatory guidance to reduce the concentration of this impurity to below the claimed thresholds. Accordingly, any overlap between this petition and the MSN/Exelixis litigation is either a consequence of Exelixis's admissions or the closeness of the prior art. Thus, Factors 3 and 4 disfavor discretionary denial.

4. Factor 5 Disfavors Denial

Azurity was not a party to the MSN/Exelixis litigation. Accordingly, Factor 5 should disfavor discretionary denial. Even so, as an unrelated petitioner, Azurity explained the disparate issues between this petition and the MSN/Exelixis litigation regarding the '349 patent when discussing Factors 3 and 4, *supra*. Thus, Factor 5 disfavors discretionary denial.

5. Factor 6 Disfavors Denial

As indicated above, Factors 1-5 disfavor discretionary denial. Accordingly, the Board need not consider *Fintiv* Factor 6. *Commscope Tech. LLC v. Dali Wireless, Inc.*, IPR2022-01242, Paper 23 (PTAB Feb. 27, 2023). However, should the Board do so, Factor 6 also disfavors discretionary denial.

"[W]hen determining whether there is a compelling unpatentability challenge, the Board evaluates whether the Petition presents challenges 'in which the evidence, if unrebutted in trial, would plainly lead to a conclusion that one or more claims are unpatentable by a preponderance of the evidence.'" *Commscope*, Paper 23 at 3. That is the present situation. When one scrutinizes the'039 patent in view of Brown and Kubo and compares it against the breadth of the claims as the petition has done in Ground 1, there is no daylight left to conclude that the Challenged Claims are nonobvious. Moreover, Robinson inexplicably requires a POSA to identify the presence of 6,7-dimethoxy-quinoline-4-ol in Brown's API and composition and ensure that the levels of this PGI are reduced to those that overlap or fall within the claimed limits. Such claims are *prima facie* obvious. Thus, Ground 2 also disfavors discretionary denial.

B. *Advanced Bionics* Does Not Favor Denial

In determining whether to exercise discretion to deny institution under §325(d), the Board applies *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469 (PTAB Feb. 13, 2020) (Paper 6) (precedential) ("(1) whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office; and (2) if either condition of first part of the framework is satisfied,

whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims.").

1. Step 1 is largely inapplicable

There were only two rejections of record during prosecution of the '039 patent. *See* Ex. 1045 at 77-83. The first concerned anticipation by U.S. 8,877,776 (Ex. 1047), which is the national phase entry of Brown (Ex. 1003). The second concerned obviousness-type double patenting. Ex. 1045 at 80-82. Accordingly, the obviousness arguments in this petition's Grounds 1 and 2 were not "the same or substantially the same arguments previously were presented to the Office." Moreover, Robinson (Ex. 1039) was never presented to the Office. So the Examiner never had a chance to consider the obviousness arguments in Ground 2. Similarly, although Brown (Ex. 1003) and Kubo (Ex. 1028) were cited in an IDS, the PTAB has rejected arguments that an Examiner's acknowledgement of an IDS is a sufficient basis for discretionary denial. *Bowtech, Inc. v. Mcp Ip, LLC*, IPR2019-00382 Paper 12 at 12 (P.T.A.B. Aug. 6, 2019) ("*Becton, Dickinson* expressly distinguished the situation 'where the prior art was simply listed in an IDS during prosecution.'").

2. *Advanced Bionics* favors institution

Upon considering Grounds 1 and 2, the Examiner plainly erred by relying solely on a theory of anticipation. When addressing this rejection, Exelixis admitted

that "Brown discloses a generic pharmaceutical composition of Compound IB and treatment of cancer." Ex. 1045 at 90. As explained in Ground 1, the Examiner failed to appreciate that the combination of Brown and Kubo teaches the preparation of cabozantinib (L)-malate as broadly described in the '039 patent. Given the '039 patent's reliance on "known" formulation methods, the prior art combination must necessarily afford the claimed compositions. Moreover, for Ground 2, the Examiner did not have the benefit of Exelixis's admissions and expert's statements regarding the potential genotoxicity of 6,7-dimethoxy-quinoline-4-ol or Robinson's discussion regarding the pharmaceutical industries' obligations to identify and address the concentration of these impurities.

According, the two-step *Advanced Bionics* test does not disfavor institution.

X. MANDATORY NOTICES PURSUANT TO 37 C.F.R. §42.8(A)(1)

Pursuant to 37 C.F.R. §42.8(a)(1), the mandatory notices identified in 37 C.F.R. §42.8(b) are provided below as part of this Petition.

A. Real Party-In-Interest (37 C.F.R. §42.8(b)(1))

Azurity Pharmaceuticals, Inc. is the Petitioner and real-party-in-interest. Slayback Pharma LLC is a wholly-owned subsidiary of Azurity Pharmaceuticals, Inc.

B. Related Matters (37 C.F.R. §42.8(b)(2))

Petitioner is aware of the following judicial or administrative matters that would affect, or be affected by, a decision in the proceeding:

IPR2025-00210

Exelixis, Inc. v. Cipla Ltd. et al., 1-24-cv-00565 (DDE)

Exelixis, Inc. v. Cipla Ltd. et al., 1-23-cv-00287 (DDE)

Exelixis, Inc. v. Teva Pharmaceutical Industries Ltd. et al., 1-22-cv-01168 (DDE)

Exelixis, Inc. v. MSN Laboratories Private Limited et al., 1-22-cv-00945 (DDE)

Exelixis, Inc. v. MSN Laboratories Private Limited et al., 1-22-cv-00228 (DDE), which has been appealed to the U.S. Court of Appeals for the Federal Circuit, Appeal Nos. 2025-1236, 2025-1241 (Fed. Cir.)

Exelixis, Inc. v. Sun Pharmaceutical Industries Ltd. et al., 1-24-cv-01208 (DDE)

Petitioner is aware of the following patents and patent applications related to the ’039 patent: U.S. 9,717,720; U.S. 10,123,999; U.S. 10,543,206; U.S. 11,298,349; U.S. Application Serial No. 16/706,323; U.S. Application Serial No. 17/152,394; U.S. Application Serial No. 17/497,201; U.S. Application Serial No. 17/957,505; U.S. Application Serial No. 18/462,739; U.S. Application Serial No. 17/679,634;

U.S. Application Serial No. 18/899,774; PCT/US2012/024591; U.S. Provisional Application No. 61/441,520; U.S. Provisional Application No. 61/441,527.

C. Lead and Backup Counsel (37 C.F.R. §42.8(b)(3))

Azurity provides the following designation of counsel, all of whom are identified in Azurity's Power of Attorney.

Lead Counsel	Back-up Counsel
Andrew E. Morrell (Reg. No. 63,737) amorrell@windelsmarx.com WINDELS MARX LANE & MITTENDORF, LLP One Giralda Farms Madison, NJ 07940 Tel.: 973-966-3200	Ajay Kayal (Reg. No. 66,691) akayal@windelsmarx.com Leah Digby (Reg. No. 82,956) lkuhn@windelsmarx.com WINDELS MARX LANE & MITTENDORF, LLP One Giralda Farms Madison, NJ 07940 Tel.: 973-966-3200

D. Service Information (37 C.F.R. §42.8(b)(4))

Please direct all correspondence to lead counsel and back-up counsel at the addresses shown above. Petitioner also consents to electronic service by email to AzurityIPRs@windelsmarx.com.

XI. PAYMENT OF FEES

The undersigned authorize the Office to charge the §42.15(a) review fee and any additional fees to Deposit Account No. 603243. Review of 22 claims is requested.

XII. ADDITIONAL REQUIREMENTS UNDER 37 C.F.R. §42.104

Azurity certifies that the '039 patent is available for IPR and is not barred or estopped from requesting IPR challenging the claims on the identified grounds.

XIII. CONCLUSION

Claims 1-22 of the '039 patent are unpatentable and should be canceled.

Respectfully submitted,

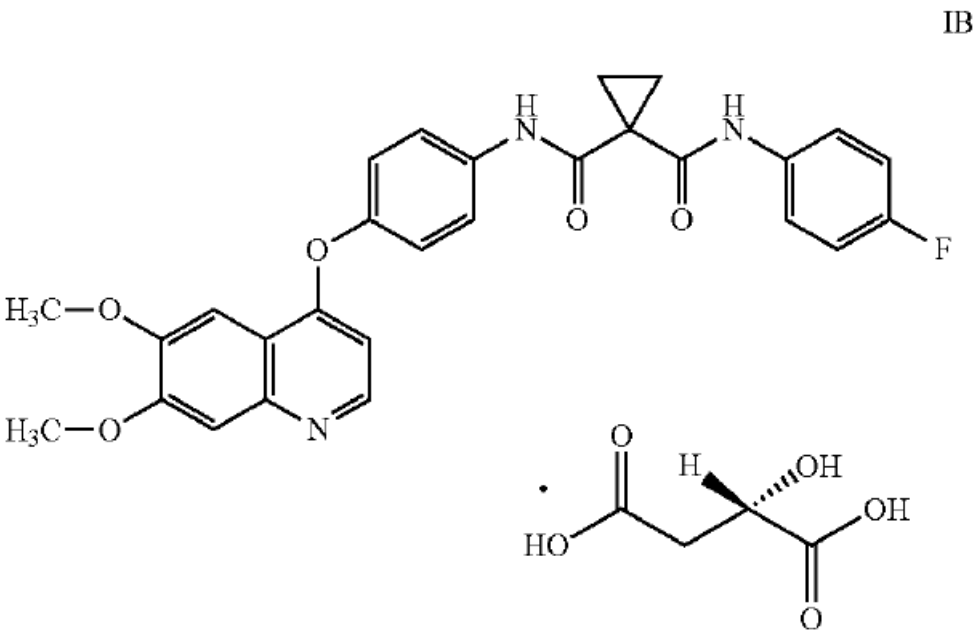
WINDELS MARX LANE & MITTENDORF, LLP

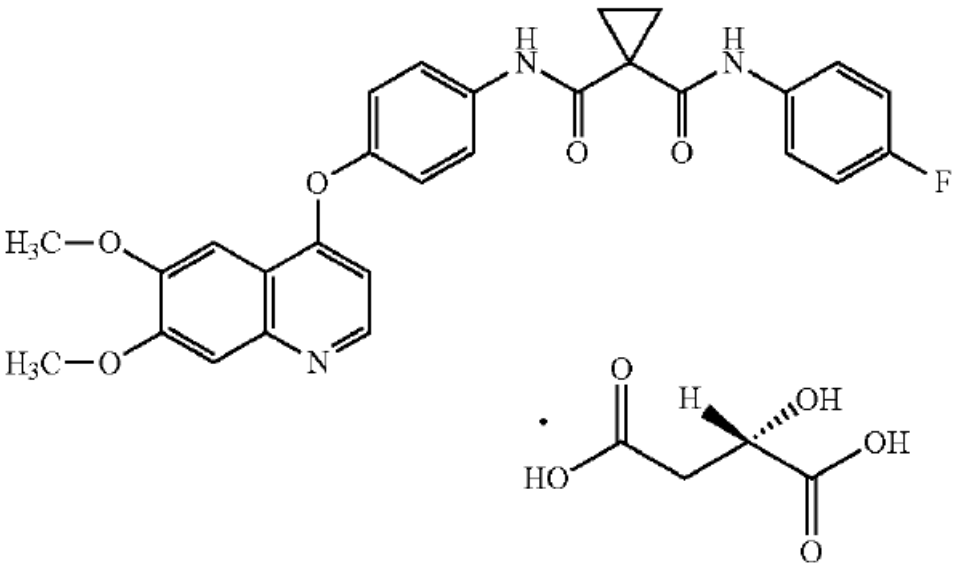
Dated: January 9, 2025 By: /Andrew E. Morrell/

Andrew E. Morrell (Reg. No. 63,737)
Ajay Kayal (Reg. No. 66,691)
Leah Digby (Reg. No. 82,956)

Attorneys/Practitioners for Petitioner
Azurity Pharmaceuticals, Inc.

APPENDIX 1

Listing of claims from U.S. 12,128,039
Claim 1
1. A pharmaceutical composition for oral administration comprising Compound IB:    and a pharmaceutically acceptable carrier, wherein the pharmaceutical composition is a tablet or a capsule, and wherein the pharmaceutical composition contains 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol.
Claim 2
2. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition contains 50 ppm or less of 6,7-dimethoxy-quinoline-4-ol.
Claim 3

3. The pharmaceutical composition of claim 2, wherein the pharmaceutical composition contains 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol.
Claim 4
4. The pharmaceutical composition of claim 3, wherein the pharmaceutical composition contains 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol.
Claim 5
5. The pharmaceutical composition of claim 4, wherein the pharmaceutical composition contains 5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.
Claim 6
6. A method of treating cancer, comprising administering to a subject in need thereof a pharmaceutical composition comprising Compound IB: IB  and a pharmaceutically acceptable carrier, wherein the pharmaceutical composition is a tablet or a capsule, and wherein the pharmaceutical composition contains 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

Claim 7
7. The method of claim 6, wherein the pharmaceutical composition contains 50 ppm or less of 6,7-dimethoxy-quinoline-4-ol.
Claim 8
8. The method of claim 7, wherein the pharmaceutical composition contains 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol.
Claim 9
9. The method of claim 8, wherein the pharmaceutical composition contains 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol.
Claim 10
10. The method of claim 9, wherein the pharmaceutical composition contains 5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.
Claim 11
11. The method of claim 6, wherein the cancer is renal cancer.
Claim 12
12. The method of claim 6, wherein the cancer is prostate cancer.
Claim 13
13. The method of claim 6, wherein the cancer is hepatocellular carcinoma.
Claim 14
14. The method of claim 7, wherein the cancer is renal cancer.
Claim 15
15. The method of claim 7, wherein the cancer is prostate cancer.

Claim 16
16. The method of claim 7, wherein the cancer is hepatocellular carcinoma.
Claim 17
17. The method of claim 8, wherein the cancer is renal cancer.
Claim 18
18. The method of claim 8, wherein the cancer is prostate cancer.
Claim 19
19. The method of claim 8, wherein the cancer is hepatocellular carcinoma.
Claim 20
20. The method of claim 9, wherein the cancer is renal cancer.
Claim 21
21. The method of claim 9, wherein the cancer is prostate cancer.
Claim 22
22. The method of claim 9, wherein the cancer is hepatocellular carcinoma.

CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. §42.24(d), the undersigned certifies that foregoing **PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT 12,128,039** complies with the type-volume limitation of 37 C.F.R. §42.24(a)(1). According to Microsoft Office Word 2016's word count, this Petition contains 13,849 words, exclusive of the parts exempted as provided in 37 C.F.R. §42.24(a).

Respectfully submitted,

WINDELS MARX LANE & MITTENDORF, LLP

Dated: January 9, 2025

By: /Andrew E. Morrell/

Andrew E. Morrell (Reg. No. 63,737)
Ajay Kayal (Reg. No. 66,691)
Leah Digby (Reg. No. 82,956)

Attorneys/Practitioners for Petitioner
Azurity Pharmaceuticals, Inc.

CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of the foregoing **PETITION FOR INTER PARTES REVIEW OF U.S. PATENT 12,128,039** and **EXHIBITS 1001, 1003-1006, 1008-1010, 1013, 1018-1019, 1024-1026, 1028-1049, and 1051-1065** are being served on January 9, 2025, via Federal Express overnight delivery at the correspondence address for U.S. 12,128,039 as identified in Patent Center:

Jonathan P. O'Brien, Ph.D./Exelixis
Honigman LLP
650 Trade Centre Way
Suite 200
Kalamazoo, MI 49002-0402

Service is also being effected by sending a true and correct copy of the foregoing **PETITION FOR INTER PARTES REVIEW OF U.S. PATENT 12,128,039** and **EXHIBITS 1001, 1003-1006, 1008-1010, 1013, 1018-1019, 1024-1026, 1028-1049, and 1051-1065**, via Federal Express overnight delivery to the address of Exelixis, Inc.:

Jeffrey J. Hessekiel, J.D.
Exelixis, Inc.
1851 Harbor Bay Parkway
Alameda, CA 94502

A courtesy copy of the foregoing **PETITION FOR INTER PARTES REVIEW OF U.S. PATENT 12,128,039** and **EXHIBITS 1001, 1003-1006, 1008-1010, 1013, 1018-1019, 1024-1026, 1028-1049, and 1051-1065** are being sent via Federal Express overnight delivery to the address of Exelixis, Inc.'s counsel of record in IPR2025-00210:

Emily R. Whelan
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Dated: January 9, 2025 By: /Andrew E. Morrell/

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