

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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|-------------------------|--|-------------------------|------------------|
| Inventor: | QUAY; Steven C. et al. | Group Art Unit: | 1629 |
| Serial Number: | 16/641,985 | Examiner: | Not assigned yet |
| Filing or 371 (c) Date: | 2020-02-25 | CONFIRMATION NO: | 7650 |
| Title: | METHODS FOR MAKING AND USING ENDOXIFEN | | |

FILED ELECTRONICALLY ON: May 29 , 2020

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

INFORMATION DISCLOSURE STATEMENT
UNDER 37 CFR § 1.97

Commissioner for Patents:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP § 609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in § 1.56.

- A. ☒ *37 CFR § 1.97 (b)*. This Information Disclosure Statement should be considered by the Office because:
- ☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under § 1.53 (d);
-- OR --
 - ☐ (2) It is being filed within 3 months of entry of the national stage as set forth in § 1.491 in an international application;
-- OR --
 - ☒ (3) It is being filed before the mailing of a first Office action on the merits;
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 - ☐ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under § 1.114.
- B. ☐ *37 CFR § 1.97(c)*. Although this Information Disclosure Statement is being filed after the period specified in *37 CFR § 1.97(b)*, above, it is filed before the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, this Information Disclosure Statement should be considered because it is accompanied by one of:
- ☐ a statement as specified in §1.97 (e) provided concurrently herewith;
-- OR --
 - ☐ a fee of \$240.00 as set forth in § 1.17 (p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.
- C. ☐ *37 CFR § 1.97 (d)*. Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, it is being filed before payment of the issue fee and should be considered because it is accompanied by:
- i. a statement as specified in § 1.97 (e);
-- AND --
 - ii. a fee of \$240.00 as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.
- D. ☐ *37 CFR §1.97 (e)*. Statement.
- ☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (c);
-- AND/OR --
 - ☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (d);
-- AND/OR --
 - ☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e) (1) as provided for under MPEP 609.04(b) V.

- E. ☐ *Statement Under 37 C.F.R. §1.704(d)*. Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office or is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay.
- F. ☒ *37 CFR §1.98 (a) (2)*. The content of the Information Disclosure Statement is as follows:
- ☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.
- OR --
- ☒ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are not enclosed.
- AND/OR --
- ☒ Copies of Foreign Patent Documents and/or Non Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).
- AND/OR --
- ☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98 (a) (2) (iii).
- G. ☐ *37 CFR §1.98(a)(3)*. The Information Disclosure Statement includes non-English patents and/or references.
- ☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.
- ☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.
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- ☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____
- ☐ Pursuant to 37 CFR §1.98(a) (3) (ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.
- H. ☐ *37 CFR §1.98(d)*. Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:
- ☐ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.
- Application in which the information was submitted: _____
- Information Disclosure Statement(s) filed on: _____
- AND
- ☐ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

- I. ☒ *Fee Authorization.* The Commissioner is hereby authorized to charge the above-referenced fees of \$0.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 23-2415 (Docket No.38602-758.831).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Dated: May 28, 2020

By: /Lisa G Lippert/
Lisa Lippert
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STATEMENT BY APPLICANT**

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|------------------------|------------------|
| Application Number | 16641985 |
| Filing Date | 02-25-2020 |
| First Named Inventor | QUAY; Steven C. |
| Art Unit | 1629 |
| Examiner Name | Not assigned yet |
| Attorney Docket Number | 38602-758.831 |

Sheet 1 of 10

U. S. PATENT DOCUMENTS

| Examiner Initials* | Cite No. ¹ | Document Number | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear |
|--------------------|-----------------------|--|--------------------------------|--|---|
| | | Number-Kind Code ² (if known) | | | |
| | 001 | US-4851433 | 07-25-1989 | KRAUS; Hans A. [De] et al. | |
| | 002 | US-7485623 | 02-03-2009 | BUA; Jay. | |
| | 003 | US-7507769 | 03-24-2009 | NESTOUR; Elisabeth Le. | |
| | 004 | US-7531578 | 05-12-2009 | FORMAN; Barry. et al. | |
| | 005 | US-7704516 | 04-27-2010 | DROUIN; Dominique Salin. et al. | |
| | 006 | US-7786172 | 08-31-2010 | DE LIGNIERES; Bruno. et al. | |
| | 007 | US-7968532 | 06-28-2011 | LE NESTOUR; Elisabeth. et al. | |
| | 008 | US-8048927 | 11-01-2011 | LE NESTOUR; Elisabeth. | |
| | 009 | US-8063249 | 11-22-2011 | KUSHNER; Peter. et al. | |
| | 010 | US-8119695 | 02-21-2012 | FORMAN; Barry. et al. | |
| | 011 | US-9090640 | 07-28-2015 | BIERBACH; Ulrich. et al. | |
| | 012 | US-9200045 | 12-01-2015 | LIU; David R. et al. | |
| | 013 | US-9220680 | 12-29-2015 | PERUMAL; Omathanu P. et al. | |
| | 014 | US-9333190 | 05-10-2016 | AHMAD; Ateeq. et al. | |
| | 015 | US-20070059288 | 03-15-2007 | DINSMORE; Jonathan H. et al. | |
| | 016 | US-20080138391 | 06-12-2008 | CARRARA; Dario Norberto [Ch] et al. | |
| | 017 | US-20090291134 | 11-26-2009 | AHMAD; Ateeq. et al. | |
| | 018 | US-20100112041 | 05-06-2010 | AHMAD; Ateeq. et al. | |
| | 019 | US-20120164075 | 06-28-2012 | AHMAD; Ateeq [Us] et al. | |

Examiner
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| | | | | Application Number | 16641985 |
| | | | | Filing Date | 02-25-2020 |
| | | | | First Named Inventor | QUAY; Steven C. |
| | | | | Art Unit | 1629 |
| | | | | Examiner Name | Not assigned yet |
| Sheet | 2 | of | 10 | Attorney Docket Number | 38602-758.831 |

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|--------------------|-----------------------|--|--------------------------------|--|---|
| | | Number-Kind Code ² (if known) | | | |
| | 020 | US-20140193334 | 07-10-2014 | BIERBACH; Ulrich. et al. | |
| | 021 | US-20140199391 | 07-17-2014 | BIRBARA; Philip J. [Us] et al. | |
| | 022 | US-20150080339 | 03-19-2015 | WANG; Guangdi. et al. | |

FOREIGN PATENT DOCUMENTS

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| | | Country Code ³ Number ⁴ Kind Code ⁵ (if known) | | | | |
| | 001 | WO-2008070463-A2 | 06-12-2008 | JINA PHARMACEUTICA LS INC [US], et al. | | <input type="checkbox"/> |
| | 002 | WO-2009120999-A2 | 10-01-2009 | OLEMA PHARMACEUTICA LS INC [US], et al. | | <input type="checkbox"/> |
| | 003 | WO-2011072244-A1 | 06-16-2011 | SINAI SCHOOL MEDICINE [US], et al. | | <input type="checkbox"/> |
| | 004 | WO-2012050263-A1 | 04-19-2012 | CJ CHEILJEDANG CORP [KR], et al. | | <input type="checkbox"/> |
| | 005 | WO-2014134165-A1 | 09-04-2014 | SLOAN KETTERING INST CANCER [US] | | <input type="checkbox"/> |
| | 006 | WO-2014141292-A2 | 09-18-2014 | INTAS PHARMACEUTICA LS LTD [IN] | | <input type="checkbox"/> |

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| Examiner Signature | | Date Considered | |
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| | | Country Code ³ Number ⁴ Kind Code ⁵ (if known) | | | | |
| | 007 | WO-2016168021-A1 | 10-20-2016 | ATOSSA GENETICS INC [US] | | <input type="checkbox"/> |
| | 008 | WO-2017070651-A1 | 04-27-2017 | US HEALTH [US], et al. | | <input type="checkbox"/> |
| | 009 | WO-2019051416-A1 | 03-14-2019 | ATOSSA GENETICS INC [US] | | <input type="checkbox"/> |

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| Sheet | 4 | of | 10 | | |

| NON-PATENT LITERATURE DOCUMENTS | | | |
|---------------------------------|-----------------------|---|--------------------------|
| Examiner Initials* | Cite No. ¹ | Include name of the author(in CAPITAL LETTERS), title of the article(when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published. | T ² |
| | 001 | ACKERMAN, et al. Contrary view: the breast is not an organ per se, but a distinctive region of skin and subcutaneous tissue. Am J Dermatopathol. 2007 Apr;29(2):211-8. | <input type="checkbox"/> |
| | 002 | Ahmad et al. Endoxifen, a New cornerstone of breast cancer therapy: demonstration of safety, tolerability, and systemic bioavailability in healthy human subjects. Clinical Pharmacology & Therapeutics (2010) 88 6, 814-817. | <input type="checkbox"/> |
| | 003 | AHMAD, et al. Endoxifen, a New Treatment Option for Mania: A Double-Blind, Active-Controlled Trial Demonstrates the Antimanic Efficacy of Endoxifen. Clin Transl Sci. 2016 Oct; 9(5): 252-259. | <input type="checkbox"/> |
| | 004 | AHMAD, et al. Endoxifen for breast cancer: Multiple dose, dose escalation study characterizing pharmacokinetics and safety in metastatic breast cancer patients. J Clin Oncol 30, 2012 (suppl; abstr 3089). | <input type="checkbox"/> |
| | 005 | AHMAD, et al. Orally administered Endoxifen is a new therapeutic agent for breast cancer. Breast Cancer Res Treat. 2010 Jul;122(2):579-84. doi: 10.1007/s10549-009-0704-7. | <input type="checkbox"/> |
| | 006 | Anonymous: "History of Changes for Study: NCT02547961", 10 September 2015 (2015-09-10), XP055669980, Retrieved from the Internet: URL:https://clinicaltrials.gov/ct2/history/NCT02547961?V_1=View#StudyPageTop [retrieved on 2020-02-19]. | <input type="checkbox"/> |
| | 007 | BHATNAGAR, et al. Tumor Lysing Genetically Engineered T Cells Loaded with Multi-Modal Imaging Agents", SCIENTIFIC REPORTS, vol. 4, no. 1, 28 March 2014 (2014-03-28),. | <input type="checkbox"/> |
| | 008 | CABRERA-GALEANA, et al. Ki67 Changes Identify Worse Outcomes in Residual Breast Cancer Tumors After Neoadjuvant Chemotherapy. Oncologist. 2018 Jun;23(6):670-678. | <input type="checkbox"/> |
| | 009 | CHANG, Minsun. Tamoxifen Resistance in Breast Cancer. Biomol. Ther. 20(3), 256-267 (2012). | <input type="checkbox"/> |

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| Sheet | 5 | of | 10 | | |

NON-PATENT LITERATURE DOCUMENTS

| Examiner Initials* | Cite No. ¹ | Include name of the author(in CAPITAL LETTERS),title of the article(when appropriate), title of the item (book,magazine,journal,serial,symposium,catalog,etc.),date,page(s),volume-issue number(s),publisher, city and/or country where published. | T ² |
|--------------------|-----------------------|---|--------------------------|
| | 010 | Clinical Trials Gov. Identifier No. NCT01273168. Endoxifen in Adults With Hormone Receptor Positive Solid Tumors. January 10, 2011. | <input type="checkbox"/> |
| | 011 | Clinical Trials Gov. Identifier No. NCT02311933. Tamoxifen Citrate or Z-Endoxifen Hydrochloride in Treating Patients With Locally Advanced or Metastatic, Estrogen Receptor-Positive, HER2-Negative Breast Cancer. December 9, 2014. | <input type="checkbox"/> |
| | 012 | DICKSCHEN, et al. Physiologically Based Pharmacokinetic Modeling of Tamoxifen and its Metabolites in Women of Different CYP2D6 Phenotypes Provides New Insight into the Tamoxifen Mass Balance. Front Pharmacol. 2012; 3: 92. | <input type="checkbox"/> |
| | 013 | DONNEYONG, et al. Risk of mortality with concomitant use of tamoxifen and selective serotonin reuptake inhibitors: multi-database cohort study. BMJ. 2016 Sep 30;354:i5014. doi: 10.1136/bmj.i5014. | <input type="checkbox"/> |
| | 014 | EP17857260.8 The Extended European Search Report dated March 24, 2020. | <input type="checkbox"/> |
| | 015 | FASCHING, et al. Ki67, chemotherapy response, and prognosis in breast cancer patients receiving neoadjuvant treatment." BMC cancer 11.1 (2011): 486. | <input type="checkbox"/> |
| | 016 | FAUQ et al. A convenient synthesis of (Z)-4-hydroxy-N-desmethyltamoxifen (endoxifen). Bioorg. Med. Chem. Lett. 2010, vol. 20(10), pages 3036-3038. | <input type="checkbox"/> |
| | 017 | GAUTHIER et al. New Highly Stereoselective Synthesis of (Z)-4-Hydroxytamoxifen and (Z)-4-Hydroxytoremifene via McMurry Reaction. J Org Chem. 1996 May 31;61(11):3890-3893. | <input type="checkbox"/> |
| | 018 | GOETZ, et al. A first-in-human phase I study of the Tamoxifen (TAM) metabolite, Z-Endoxifen hydrochloride (Z-Endx) in women with aromatase inhibitor (AI) refractory metastatic breast cancer (MBC) (NCT01327781) San Antonio Breast Conference 2013 [PD3-4]. | <input type="checkbox"/> |

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| | | | | Application Number | 16641985 |
| | | | | Filing Date | 02-25-2020 |
| | | | | First Named Inventor | QUAY; Steven C. |
| | | | | Art Unit | 1629 |
| | | | | Examiner Name | Not assigned yet |
| | | | | Attorney Docket Number | 38602-758.831 |
| Sheet | 6 | of | 10 | | |

| NON-PATENT LITERATURE DOCUMENTS | | | |
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| Examiner Initials* | Cite No. ¹ | Include name of the author(in CAPITAL LETTERS),title of the article(when appropriate), title of the item (book,magazine,journal,serial,symposium,catalog,etc.),date,page(s),volume-issue number(s),publisher, city and/or country where published. | T ² |
| | 019 | GOETZ, et al. Final results of a first in human phase I study of the Tamoxifen (TAM) metabolite, Endoxifen hydrochloride in women with aromatase inhibitor (AI) refractory metastatic breast cancer (MBC). (NCT01327781) San Antonio Breast Conference 2015. [PD203]. | <input type="checkbox"/> |
| | 020 | GOETZ, et al., First-in-human phase I study of the Tamoxifen metabolite Z-endoxifen in Women with endocrine-refractory metastatic breast cancer. J. Clin. Oncol. Vol. 35 No. 30, 30 August 2017. | <input type="checkbox"/> |
| | 021 | HAWSE, et al., Endoxifen's molecular mechanisms of action are concentration dependent and different than that of other anti-estrogens. PLOS one, 2013; 8(1): e54613. | <input type="checkbox"/> |
| | 022 | HENDERSON, et al. Profound reduction in tamoxifen active metabolite endoxifen in a breast cancer patient treated with rifampin prior to initiation of an anti-TNF a biologic for ulcerative colitis: a case report, BMC cancer, Vol. 16, 11 May 2016; Pgs. 1-6. | <input type="checkbox"/> |
| | 023 | JOHNSON, et al. Gynecomastia - evaluation and current treatment options. Ther Clin Risk Manag. 2011; 7: 145-148. | <input type="checkbox"/> |
| | 024 | JOHNSON et al. Pharmacological characterization of 4-hydroxy-N-desmethyl tamoxifen, a novel active metabolite of tamoxifen. Breast Cancer Research and Treatment. 85:151-159, 2004. | <input type="checkbox"/> |
| | 025 | JORDAN, C. New insights into the metabolism of tamoxifen and its role in the treatment and prevention of breast cancer. Steroids. 2007 Nov; 72(13): 829-842. | <input type="checkbox"/> |
| | 026 | LAZZERONI, et al. Oral low dose and topical tamoxifen for breast cancer prevention: modern approaches for an old drug. Breast Cancer Res. 2012; 14(5): 214. | <input type="checkbox"/> |
| | 027 | Lee et al., in vitro human skin permeation of endoxifen: potential for local transdermal therapy for primary prevention and carcinoma in situ of the breast, Breast Cancer: Targets and Therapy 2011:3, 61-70. | <input type="checkbox"/> |

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| Examiner Signature | | Date Considered | |
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| | | | | Application Number | 16641985 |
| | | | | Filing Date | 02-25-2020 |
| | | | | First Named Inventor | QUAY; Steven C. |
| | | | | Art Unit | 1629 |
| | | | | Examiner Name | Not assigned yet |
| | | | | Attorney Docket Number | 38602-758.831 |
| Sheet | 7 | of | 10 | | |

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|--------------------|-----------------------|---|--------------------------|
| | 028 | LEE, et al. Local transdermal therapy to the breast for breast cancer prevention and DCIS therapy: preclinical and clinical evaluation. Cancer Chemother Pharmacol. 2015 Dec;76(6):1235-46. doi: 10.1007/s00280-015-2848-y. | <input type="checkbox"/> |
| | 029 | LI, et al. Prognostic values of Ki-67 in neoadjuvant setting for breast cancer: a systematic review and meta-analysis. Future Oncol. 2017 May;13(11):1021-1034. | <input type="checkbox"/> |
| | 030 | MANSEL, et al. A phase II trial of Afimoxifene (4-hydroxyTamoxifen gel) for cyclical mastalgia in premenopausal women. Breast Cancer Res Treat. 2007 Dec;106(3):389-97. | <input type="checkbox"/> |
| | 031 | Maximov et al., Structure-Function Relationships of Estrogenic Triphenylethylenes Related to Endoxifen and 4-Hydroxytamoxifen. J Med. Chem. 22 April 2010; 53(8): 3273-3283. | <input type="checkbox"/> |
| | 032 | MELNIKOW, et al. Preferences of Women Evaluating Risks of Tamoxifen (POWER) study of preferences for Tamoxifen for breast cancer risk reduction. Cancer. 2005 May 15;103(10):1996-2005. | <input type="checkbox"/> |
| | 033 | OGAWA, et al. Synthesis and antiestrogenic activity of the compounds related to the metabolites of (E)-4-[1-[4-[2-(dimethylamino)ethoxy]phenyl]- 2-(4-isopropylphenyl)-1-butenyl]phenyl monophosphate (TAT-59) [corrected]. Chem. Pharm. Bull. 39, 911-916, 1991. | <input type="checkbox"/> |
| | 034 | OKEN, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-655. | <input type="checkbox"/> |
| | 035 | PCT/US2018/050193 International Search Report and Written Opinion dated January 4, 2019. | <input type="checkbox"/> |
| | 036 | PCT/US2018-050272 International Search Report and Written Opinion dated January 3, 2019. | <input type="checkbox"/> |

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| | | Application Number | 16641985 | | |
| | | Filing Date | 02-25-2020 | | |
| | | First Named Inventor | QUAY; Steven C. | | |
| | | Art Unit | 1629 | | |
| | | Examiner Name | Not assigned yet | | |
| Sheet | 8 | of | 10 | Attorney Docket Number | 38602-758.831 |

NON-PATENT LITERATURE DOCUMENTS

| Examiner Initials* | Cite No. ¹ | Include name of the author(in CAPITAL LETTERS), title of the article(when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published. | T ² |
|--------------------|-----------------------|--|--------------------------|
| | 037 | ROUANET, et al. Neoadjuvant percutaneous 4-hydroxyTamoxifen decreases breast tumoral cell proliferation: a prospective controlled randomized study comparing three doses of 4-hydroxyTamoxifen gel to oral Tamoxifen. J Clin Oncol. 2005 May 1;23(13):2980-7. | <input type="checkbox"/> |
| | 038 | STEARNS, et al. Active tamoxifen metabolite plasma concentrations after coadministration of tamoxifen and the selective serotonin reuptake inhibitor paroxetine. J Natl Cancer Inst. 2003 Dec 3;95(23):1758-64. | <input type="checkbox"/> |
| | 039 | SUN, et al. Construction and evaluation of a novel humanized HER2-specific chimeric receptor. Breast Cancer Research: BCR 16.3 (2014): R61. | <input type="checkbox"/> |
| | 040 | WU, et al. The Tamoxifen metabolite, Endoxifen, is a potent antiestrogen that targets estrogen receptor alpha for degradation in breast cancer cells. Cancer Res. 2009 Mar 1;69(5):1722-7. doi: 10.1158/0008-5472.CAN-08-3933. | <input type="checkbox"/> |
| | 041 | Yang et al., Dendron-Based Micelles for Topical Delivery of Endoxifen: A Potential Chemo-Preventive Medicine for Breast Cancer Adv. Funct. Mater. 2014, 24, 2442-2449. | <input type="checkbox"/> |
| | 042 | ZHAO, et al. A Herceptin-Based Chimeric Antigen Receptor with Modified Signaling Domains Leads to Enhanced Survival of Transduced T Lymphocytes and Antitumor Activity. THE JOURNAL OF IMMUNOLOGY, vol. 183, no. 9, 1 November 2009 (2009-11-01), pages 5563-5574. | <input type="checkbox"/> |

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| | | | | First Named Inventor | QUAY; Steven C. |
| | | | | Art Unit | 1629 |
| | | | | Examiner Name | Not assigned yet |
| | | | | Attorney Docket Number | 38602-758.831 |
| Sheet | 9 | of | 10 | | |

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- ☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

- ☒ A certification statement is not submitted herewith.

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| | | | |
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| Signature | /Lisa G Lippert/ | Date (YYYY-MM-DD) | 2020-05-28 |
| Name/Print | Lisa Lippert | Registration Number | 78332 |

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| EFS ID: | 39574111 |
| Application Number: | 16641985 |
| International Application Number: | |
| Confirmation Number: | 7650 |
| Title of Invention: | METHODS FOR MAKING AND USING ENDOXIFEN |
| First Named Inventor/Applicant Name: | Steven C. Quay |
| Customer Number: | 21971 |
| Filer: | Payal Vrajesh Vyas/Cheuk Hei Ho |
| Filer Authorized By: | Payal Vrajesh Vyas |
| Attorney Docket Number: | 38602-758.831 |
| Receipt Date: | 29-MAY-2020 |
| Filing Date: | 25-FEB-2020 |
| Time Stamp: | 12:55:58 |
| Application Type: | U.S. National Stage under 35 USC 371 |

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| | | | | Filing Date | 02-25-2020 |
| | | | | First Named Inventor | QUAY; Steven C. |
| | | | | Art Unit | 1629 |
| | | | | Examiner Name | Not assigned yet |
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| | | | | Filing Date | 02-25-2020 |
| | | | | First Named Inventor | QUAY; Steven C. |
| | | | | Art Unit | 1629 |
| | | | | Examiner Name | Not assigned yet |
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| | | Art Unit | 1629 | | |
| | | Examiner Name | Not assigned yet | | |
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| | 011 | Clinical Trials Gov. Identifier No. NCT02311933. Tamoxifen Citrate or Z-Endoxifen Hydrochloride in Treating Patients With Locally Advanced or Metastatic, Estrogen Receptor-Positive, HER2-Negative Breast Cancer. December 9, 2014. | <input type="checkbox"/> |
| | 012 | DICKSCHEN, et al. Physiologically Based Pharmacokinetic Modeling of Tamoxifen and its Metabolites in Women of Different CYP2D6 Phenotypes Provides New Insight into the Tamoxifen Mass Balance. Front Pharmacol. 2012; 3: 92. | <input type="checkbox"/> |
| | 013 | DONNEYONG, et al. Risk of mortality with concomitant use of tamoxifen and selective serotonin reuptake inhibitors: multi-database cohort study. BMJ. 2016 Sep 30;354:i5014. doi: 10.1136/bmj.i5014. | <input type="checkbox"/> |
| | 014 | EP17857260.8 The Extended European Search Report dated March 24, 2020. | <input type="checkbox"/> |
| | 015 | FASCHING, et al. Ki67, chemotherapy response, and prognosis in breast cancer patients receiving neoadjuvant treatment." BMC cancer 11.1 (2011): 486. | <input type="checkbox"/> |
| | 016 | FAUQ et al. A convenient synthesis of (Z)-4-hydroxy-N-desmethyltamoxifen (endoxifen). Bioorg. Med. Chem. Lett. 2010, vol. 20(10), pages 3036-3038. | <input type="checkbox"/> |
| | 017 | GAUTHIER et al. New Highly Stereoselective Synthesis of (Z)-4-Hydroxytamoxifen and (Z)-4-Hydroxytoremifene via McMurry Reaction. J Org Chem. 1996 May 31;61(11):3890-3893. | <input type="checkbox"/> |
| | 018 | GOETZ, et al. A first-in-human phase I study of the Tamoxifen (TAM) metabolite, Z-Endoxifen hydrochloride (Z-Endx) in women with aromatase inhibitor (AI) refractory metastatic breast cancer (MBC) (NCT01327781) San Antonio Breast Conference 2013 [PD3-4]. | <input type="checkbox"/> |

| | | | |
|--------------------|-----------------|-----------------|------------|
| Examiner Signature | /BRIAN J DAVIS/ | Date Considered | 08/29/2021 |
|--------------------|-----------------|-----------------|------------|

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| Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary) | | Complete if Known | | | |
| | | Application Number | 16641985 | | |
| | | Filing Date | 02-25-2020 | | |
| | | First Named Inventor | QUAY; Steven C. | | |
| | | Art Unit | 1629 | | |
| | | Examiner Name | Not assigned yet | | |
| Sheet | 6 | of | 10 | Attorney Docket Number | 38602-758.831 |

NON-PATENT LITERATURE DOCUMENTS

| Examiner Initials* | Cite No. ¹ | Include name of the author(in CAPITAL LETTERS), title of the article(when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published. | T ² |
|--------------------|-----------------------|---|--------------------------|
| | 019 | GOETZ, et al. Final results of a first in human phase I study of the Tamoxifen (TAM) metabolite, Endoxifen hydrochloride in women with aromatase inhibitor (AI) refractory metastatic breast cancer (MBC). (NCT01327781) San Antonio Breast Conference 2015. [PD203]. | <input type="checkbox"/> |
| | 020 | GOETZ, et al., First-in-human phase I study of the Tamoxifen metabolite Z-endoxifen in Women with endocrine-refractory metastatic breast cancer. J. Clin. Oncol. Vol. 35 No. 30, 30 August 2017. | <input type="checkbox"/> |
| | 021 | HAWSE, et al., Endoxifen's molecular mechanisms of action are concentration dependent and different than that of other anti-estrogens. PLOS one, 2013; 8(1): e54613. | <input type="checkbox"/> |
| | 022 | HENDERSON, et al. Profound reduction in tamoxifen active metabolite endoxifen in a breast cancer patient treated with rifampin prior to initiation of an anti-TNF a biologic for ulcerative colitis: a case report, BMC cancer, Vol. 16, 11 May 2016; Pgs. 1-6. | <input type="checkbox"/> |
| | 023 | JOHNSON, et al. Gynecomastia - evaluation and current treatment options. Ther Clin Risk Manag. 2011; 7: 145-148. | <input type="checkbox"/> |
| | 024 | JOHNSON et al. Pharmacological characterization of 4-hydroxy-N-desmethyl tamoxifen, a novel active metabolite of tamoxifen. Breast Cancer Research and Treatment. 85:151-159, 2004. | <input type="checkbox"/> |
| | 025 | JORDAN, C. New insights into the metabolism of tamoxifen and its role in the treatment and prevention of breast cancer. Steroids. 2007 Nov; 72(13): 829-842. | <input type="checkbox"/> |
| | 026 | LAZZERONI, et al. Oral low dose and topical tamoxifen for breast cancer prevention: modern approaches for an old drug. Breast Cancer Res. 2012; 14(5): 214. | <input type="checkbox"/> |
| | 027 | Lee et al., in vitro human skin permeation of endoxifen: potential for local transdermal therapy for primary prevention and carcinoma in situ of the breast, Breast Cancer: Targets and Therapy 2011:3, 61-70. | <input type="checkbox"/> |

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|--------------------|-----------------|-----------------|------------|
| Examiner Signature | /BRIAN J DAVIS/ | Date Considered | 08/29/2021 |
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| INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary) | | Application Number | 16641985 | | |
| | | Filing Date | 02-25-2020 | | |
| | | First Named Inventor | QUAY; Steven C. | | |
| | | Art Unit | 1629 | | |
| | | Examiner Name | Not assigned yet | | |
| Sheet | 7 | of | 10 | Attorney Docket Number | 38602-758.831 |

NON-PATENT LITERATURE DOCUMENTS

| Examiner Initials* | Cite No. ¹ | Include name of the author(in CAPITAL LETTERS),title of the article(when appropriate), title of the item (book,magazine,journal,serial,symposium,catalog,etc.),date,page(s),volume-issue number(s),publisher, city and/or country where published. | T ² |
|--------------------|-----------------------|---|--------------------------|
| | 028 | LEE, et al. Local transdermal therapy to the breast for breast cancer prevention and DCIS therapy: preclinical and clinical evaluation. Cancer Chemother Pharmacol. 2015 Dec;76(6):1235-46. doi: 10.1007/s00280-015-2848-y. | <input type="checkbox"/> |
| | 029 | LI, et al. Prognostic values of Ki-67 in neoadjuvant setting for breast cancer: a systematic review and meta-analysis. Future Oncol. 2017 May;13(11):1021-1034. | <input type="checkbox"/> |
| | 030 | MANSEL, et al. A phase II trial of Afimoxifene (4-hydroxy-Tamoxifen-gel) for cyclical mastalgia in premenopausal women. Breast Cancer Res Treat. 2007 Dec;106(3):389-97. | <input type="checkbox"/> |
| | 031 | Maximov et al., Structure-Function Relationships of Estrogenic Triphenylethylenes Related to Endoxifen and 4-Hydroxytamoxifen. J Med. Chem. 22 April 2010; 53(8): 3273-3283. | <input type="checkbox"/> |
| | 032 | MELNIKOW, et al. Preferences of Women Evaluating Risks of Tamoxifen (POWER) study of preferences for Tamoxifen for breast cancer risk reduction. Cancer. 2005 May 15;103(10):1996-2005. | <input type="checkbox"/> |
| | 033 | OGAWA, et al. Synthesis and antiestrogenic activity of the compounds related to the metabolites of (E)-4-[1-[4-[2-(dimethylamino)ethoxy]phenyl]- 2-(4-isopropylphenyl)-1-butenyl]phenyl monophosphate (TAT-59) [corrected]. Chem. Pharm. Bull. 39, 911-916, 1991. | <input type="checkbox"/> |
| | 034 | OKEN, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group.Am J Clin Oncol. 1982;5:649-655. | <input type="checkbox"/> |
| | 035 | PCT/US2018/050193 International Search Report and Written Opinion dated January 4, 2019. | <input type="checkbox"/> |
| | 036 | PCT/US2018-050272 International Search Report and Written Opinion dated January 3, 2019. | <input type="checkbox"/> |

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| | | Application Number | 16641985 | | |
| | | Filing Date | 02-25-2020 | | |
| | | First Named Inventor | QUAY; Steven C. | | |
| | | Art Unit | 1629 | | |
| | | Examiner Name | Not assigned yet | | |
| Sheet | 8 | of | 10 | Attorney Docket Number | 38602-758.831 |

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| | 037 | ROUANET, et al. Neoadjuvant percutaneous 4-hydroxyTamoxifen decreases breast tumoral cell proliferation: a prospective controlled randomized study comparing three doses of 4-hydroxyTamoxifen gel to oral Tamoxifen. J Clin Oncol. 2005 May 1;23(13):2980-7. | <input type="checkbox"/> |
| | 038 | STEARNS, et al. Active tamoxifen metabolite plasma concentrations after coadministration of tamoxifen and the selective serotonin reuptake inhibitor paroxetine. J Natl Cancer Inst. 2003 Dec 3;95(23):1758-64. | <input type="checkbox"/> |
| | 039 | SUN, et al. Construction and evaluation of a novel humanized HER2-specific chimeric receptor. Breast Cancer Research: BCR 16.3 (2014): R61. | <input type="checkbox"/> |
| | 040 | WU, et al. The Tamoxifen metabolite, Endoxifen, is a potent antiestrogen that targets estrogen receptor alpha for degradation in breast cancer cells. Cancer Res. 2009 Mar 1;69(5):1722-7. doi: 10.1158/0008-5472.CAN-08-3933. | <input type="checkbox"/> |
| | 041 | Yang et al., Dendron-Based Micelles for Topical Delivery of Endoxifen: A Potential Chemo-Preventive Medicine for Breast Cancer Adv. Funct. Mater. 2014, 24, 2442-2449. | <input type="checkbox"/> |
| | 042 | ZHAO, et al. A Herceptin-Based Chimeric Antigen Receptor with Modified Signaling Domains Leads to Enhanced Survival of Transduced T Lymphocytes and Antitumor Activity. THE JOURNAL OF IMMUNOLOGY, vol. 183, no. 9, 1 November 2009 (2009-11-01), pages 5563-5574. | <input type="checkbox"/> |

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|--------------------|-----------------|-----------------|------------|
| Examiner Signature | /BRIAN J DAVIS/ | Date Considered | 08/29/2021 |
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Doc code: IDS

PTO/SB/08a (02-18)

Doc description: Information Disclosure Statement (IDS) Filed

Approved for use through 11/30/2020. OMB 0651-0031

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| | Filing Date | 2020-02-25 |
| | First Named Inventor | STEVEN; C. Quay |
| | Art Unit | 1629 |
| | Examiner Name | - |
| | Attorney Docket Number | 109559-669805 |

| U.S.PATENTS | | | | | | Remove |
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| | |
|------------------------|-----------------|
| Application Number | 16641985 |
| Filing Date | 2020-02-25 |
| First Named Inventor | STEVEN; C. Quay |
| Art Unit | 1629 |
| Examiner Name | - |
| Attorney Docket Number | 109559-669805 |

| | |
|---|---|
| 1 | Extended European Search Report for European Application No. EP18853361.6, dated May 28, 2021, 5 pages. |
| 2 | FOREFRONT., "Endoxifen Shows Promise As Breast Cancer Treatment", Mayo Clinic Cancer Center's Online Magazine, Vol. 3, Issue 1, 2014, 3 pages. |
| 3 | LOVE et al., "A Feasibility Study of the Intraductal Administration of Chemotherapy", Cancer Prevention Research, Vol. 6, No. 1, January 2013, pp. 51-58. |
| 4 | Search Report and Written Opinion for Singapore Patent Application No. SG11202002105W mailed April 21, 2021, 8 pages. |

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

| | | | |
|-------------------------|--|-------------------------|----------------|
| Inventor: | Steven C. Quay | Group Art Unit: | 1612 |
| Serial Number: | 16/641,985 | Examiner: | Brian J. Davis |
| Filing or 371 (c) Date: | February 25, 2020 | CONFIRMATION NO: | 7650 |
| Title: | METHODS FOR MAKING AND USING ENDOXIFEN | CUST. NO.: | 27148 |

FILED ELECTRONICALLY ON October 15, 2021

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

INFORMATION DISCLOSURE STATEMENT
UNDER 37 CFR § 1.97

Commissioner for Patents:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP § 609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in § 1.56.

A. ☐ 37 CFR § 1.97 (b). This Information Disclosure Statement should be considered by the Office because:

☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under § 1.53 (d);

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☐ (3) It is being filed before the mailing of a first Office action on the merits;

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☐ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under § 1.114.

B. ☒ 37 CFR § 1.97(c). Although this Information Disclosure Statement is being filed after the period specified in 37 CFR § 1.97(b), above, it is filed before the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, this Information Disclosure Statement should be considered because it is accompanied by one of:

☐ a statement as specified in §1.97 (e) provided concurrently herewith;

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☒ a fee of \$130.00 as set forth in § 1.17 (p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.

C. ☐ 37 CFR § 1.97 (d). Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, it is being filed before payment of the issue fee and should be considered because it is accompanied by:

i. a statement as specified in § 1.97 (e);

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ii. a fee of \$260.00 as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.

D. ☐ 37 CFR §1.97 (e). Statement.

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (c);

-- AND/OR --

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (d);

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☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e) (1) as provided for under MPEP 609.04(b) V.

E. ☐ *Statement Under 37 C.F.R. §1.704(d).* Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office or is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay.

F. ☒ *37 CFR §1.98 (a) (2).* The content of the Information Disclosure Statement is as follows:

☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.

-- OR --

☐ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are not enclosed.

-- AND/OR --

☒ Copies of Foreign Patent Documents and/or Non Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).

-- AND/OR --

☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98 (a) (2) (iii).

G. ☐ *37 CFR §1.98(a)(3).* The Information Disclosure Statement includes non-English patents and/or references.

☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.

☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.

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☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____

☐ Pursuant to 37 CFR §1.98(a) (3) (ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.

H. ☐ *37 CFR §1.98(d).* Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:

☐ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.

Application in which the information was submitted: _____

Information Disclosure Statement(s) filed on: _____

AND

☐ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

- I. ☒ *Fee Authorization.* The Commissioner is hereby authorized to charge the above-referenced fees of \$130.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 501662 (Docket No. 50-1662).

Respectfully submitted,

Dated: October 15, 2021,

/Lisa G Lippert/
Lisa G. Lippert, Ph.D.
Registration No. 78,332

POLSINELLI PC
900 W. 48th Place, Suite 900
Kansas City, MO 64112
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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| Application Number | 16/641,985 |
| Filing Date | 02-25-2020 |
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| Examiner Initials* | Cite No. ¹ | Document Number | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear |
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| Application Number | 16/641,985 |
| Filing Date | 02-25-2020 |
| First Named Inventor | STEVEN; C. Quay |
| Art Unit | 1612 |
| Examiner Name | DAVIS, BRIAN J |
| Attorney Docket Number | 109559-669805 |

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| Sheet | 2 | of | 8 |
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| | 035 | US-20160346230 | 12-01-2016 | AHMAD; Ateeq et al. | |
| | 036 | US-20160375234 | 12-29-2016 | STEVEN; C. Quay | |
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| | | Country Code ³ Number ⁴ Kind Code ⁵ (if known) | | | | |
| | 001 | CN-104230723-B | 08-24-2016 | ASYMCHEM LAB TIANJIN CO LTD. | | <input checked="" type="checkbox"/> |
| | 002 | EP-1709062-B9 | 02-13-2013 | CEDARBURG PHARMACEUTICALS INC [US] | | <input type="checkbox"/> |
| | 003 | EP-2350111-A1 | 08-03-2011 | SYNTHON BV [NL] | | <input type="checkbox"/> |

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| Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary) | | | | Complete if Known | |
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| Sheet | 3 | of | 8 | Attorney Docket Number | 109559-669805 |

| FOREIGN PATENT DOCUMENTS | | | | | | |
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| | | Country Code ³ Number ⁴ Kind Code ⁵ (if known) | | | | |
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| | 008 | WO-2009069140-A1 | 06-04-2009 | DABUR PHARMA LTD [IN], et al. | | <input type="checkbox"/> |
| | 009 | WO-2013050280-A1 | 04-11-2013 | COMMISSARIAT ENERGIE ATOMIQUE [FR] | | <input type="checkbox"/> |
| | 010 | WO-2013134230-A1 | 09-12-2013 | XAVIER UNIVERSITY [US] | | <input type="checkbox"/> |
| | 011 | WO-2014060640-A8 | 05-07-2015 | FERMION OY [FI] | | <input type="checkbox"/> |
| | 012 | WO-2015106094-A1 | 07-16-2015 | ATOSSA GENETICS INC [US] | | <input type="checkbox"/> |
| | 013 | WO-2015138340-A1 | 09-17-2015 | REPROS THERAPEUTICS INC [US] | | <input type="checkbox"/> |
| | 014 | WO-2017011623-A1 | 01-19-2017 | ATOSSA GENETICS INC [US] | | <input type="checkbox"/> |

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| Sheet | 4 | of | 8 |
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NON-PATENT LITERATURE DOCUMENTS

| Examiner Initials* | Cite No. ¹ | Include name of the author(in CAPITAL LETTERS), title of the article(when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published. | T ² |
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| Sheet | 6 | of | 8 |
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| | 029 | ROBERTSON, et al., "Fulvestrant: Pharmacokinetics and Pharmacology," British Journal of Cancer, 2004, Vol. 90, pp. S7-S10. | <input type="checkbox"/> |
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| Sheet | 8 | of | 8 |
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CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

- ☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

- ☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).
- ☐ See attached certification statement.
- ☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.
- ☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

| | | | |
|------------|------------------|---------------------|------------|
| Signature | /Lisa G Lippert/ | Date (YYYY-MM-DD) | 2021-10-15 |
| Name/Print | Lisa G. Lippert | Registration Number | 78332 |

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| EFS ID: | 44045115 |
| Application Number: | 16641985 |
| International Application Number: | |
| Confirmation Number: | 7650 |
| Title of Invention: | METHODS FOR MAKING AND USING ENDOXIFEN |
| First Named Inventor/Applicant Name: | Steven C. Quay |
| Customer Number: | 27148 |
| Filer: | Lisa Gail Lippert/Megan Thornton |
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| Attorney Docket Number: | 109559-669805 |
| Receipt Date: | 15-OCT-2021 |
| Filing Date: | 25-FEB-2020 |
| Time Stamp: | 17:51:03 |
| Application Type: | U.S. National Stage under 35 USC 371 |

Payment information:

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| Submitted with Payment | yes |
| Payment Type | DA |
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| RAM confirmation Number | E20210EH51562474 |
| Deposit Account | 501662 |
| Authorized User | Megan Thornton |

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PGR2023-00043 – Atossa

Ex. 2004 - Page 46

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| | | | | Filing Date | 02-25-2020 |
| | | | | First Named Inventor | STEVEN; C. Quay |
| | | | | Art Unit | 1612 |
| | | | | Examiner Name | DAVIS, BRIAN J |
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PGR2023-00043 - Atossa

Ex. 2004 - Page 56

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| | | | | Filing Date | 02-25-2020 |
| | | | | First Named Inventor | STEVEN; C. Quay |
| | | | | Art Unit | 1612 |
| | | | | Examiner Name | DAVIS, BRIAN J |
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| | 038 | US-20180049999 | 02-22-2018 | QUAY; Steven C. | |
| | 039 | US-20180200206 | 07-19-2018 | QUAY; Steven C. | |

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|--------------------|-----------------------|---|--------------------------------|--|---|-------------------------------------|
| | | Country Code ³ Number ⁴ Kind Code ⁵ (if known) | | | | |
| | 001 | CN-104230723-B | 08-24-2016 | ASYMCHEM LAB TIANJIN CO LTD. | | <input checked="" type="checkbox"/> |
| | 002 | EP-1709062-B9 | 02-13-2013 | CEDARBURG PHARMACEUTICALS INC [US] | | <input type="checkbox"/> |
| | 003 | EP-2350111-A1 | 08-03-2011 | SYNTHON BV [NL] | | <input type="checkbox"/> |

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| Examiner Signature | /BRIAN J DAVIS/ | Date Considered | 10/22/2021 |
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PGR2023-00043 - Atossa

Ex. 2004 - Page 57

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| Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary) | | | | Complete if Known | |
| | | | | Application Number | 16/641,985 |
| | | | | Filing Date | 02-25-2020 |
| | | | | First Named Inventor | STEVEN; C. Quay |
| | | | | Art Unit | 1612 |
| | | | | Examiner Name | DAVIS, BRIAN J |
| Sheet | 3 | of | 8 | Attorney Docket Number | 109559-669805 |

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|-----------------------|--------------------------|---|-----------------------------------|--|---|--------------------------|
| | | Country Code ³ Number ⁴ Kind Code ⁵ (if known) | | | | |
| | 004 | EP-3202420-A1 | 08-09-2017 | BESINS HEALTHCARE LU SARL [LU] | | <input type="checkbox"/> |
| | 005 | WO-0064416-A3 | 03-08-2001 | LILLY CO ELI [US], et al. | | <input type="checkbox"/> |
| | 006 | WO-0174366-A1 | 10-11-2001 | ASTRAZENECA AB [SE], et al. | | <input type="checkbox"/> |
| | 007 | WO-2009032699-A1 | 03-12-2009 | DRUGTECH CORP [US], et al. | | <input type="checkbox"/> |
| | 008 | WO-2009069140-A1 | 06-04-2009 | DABUR PHARMA LTD [IN], et al. | | <input type="checkbox"/> |
| | 009 | WO-2013050280-A1 | 04-11-2013 | COMMISSARIAT ENERGIE ATOMIQUE [FR] | | <input type="checkbox"/> |
| | 010 | WO-2013134230-A1 | 09-12-2013 | XAVIER UNIVERSITY [US] | | <input type="checkbox"/> |
| | 011 | WO-2014060640-A8 | 05-07-2015 | FERMION OY [FI] | | <input type="checkbox"/> |
| | 012 | WO-2015106094-A1 | 07-16-2015 | ATOSSA GENETICS INC [US] | | <input type="checkbox"/> |
| | 013 | WO-2015138340-A1 | 09-17-2015 | REPROS THERAPEUTICS INC [US] | | <input type="checkbox"/> |
| | 014 | WO-2017011623-A1 | 01-19-2017 | ATOSSA GENETICS INC [US] | | <input type="checkbox"/> |

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PGR2023-00043 - Atossa

Ex. 2004 - Page 58

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| Sheet | 4 | of | 8 | Attorney Docket Number | 109559-669805 |

NON-PATENT LITERATURE DOCUMENTS

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| | 002 | AYDINER, et al., "Meta-Analysis of Trials Comparing Anastrozole and Tamoxifen for Adjuvant Treatment of Oostmenopausal Women with Early Breast Cancer," Trials, Vol. 9 (47), 29 July 2008, pp. 1-9. | <input type="checkbox"/> |
| | 003 | BAO, et al., "The Clinical Pharmacology of Anastrozole," European Oncology and Hematology, Vol. 7 (2), 2011, pp. 106-108. | <input type="checkbox"/> |
| | 004 | BATH, et al., "An Improved Synthesis of Raloxifene Hydrochloride: A Selective Estrogen Receptor Modulator," Heteroletters, Vol. 4 (4), 2014, pp. 515-518. | <input type="checkbox"/> |
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| | 006 | DOWSETT, et al., "The Effect of Anastrozole on the Pharmacokinetics of Tamoxifen in Post-Menopausal Women with Early Breast Cancer," British Journal of Cancer, Vol. 79 (2), 1999, pp. 311-315. | <input type="checkbox"/> |
| | 007 | FORBES, et al., "Anastrozole Versus Tamoxifen for the Prevention of Locoregional and Contralateral Breast Cancer in Postmenopausal Women with Locally Excised Ductal Carcinoma in Situ (IBIS-II DCIS): A Double-Blind," Randomised Controlled trial Lancet, Vol. 387, 2016, pp. 866-873. | <input type="checkbox"/> |
| | 008 | GAUTHIER S., et al., "New Highly Stereoselective Synthesis of (Z)-4-Hydroxytamoxifen and (Z)-4-Hydroxytoremifene via McMurry Reaction," The Journal of Organic Chemistry, Vol. 61(11), 31 May 1996, pp. 3890-3893. | <input type="checkbox"/> |
| | 009 | GELMON, et al., "Targeting Triple-Negative Breast Cancer: Optimizing Therapeutic Outcomes," Annals of Oncology, Vol. 23 (9), September 2012, pp. 2223-2234. | <input type="checkbox"/> |

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| | | Examiner Name | DAVIS, BRIAN J | | |
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| | 010 | HERSHMAN, et al., "Early Discontinuation and Non-adherence to Adjuvant Hormonal Therapy in a Cohort of 8, 769 early Stage Breast Cancer Patients," Journal of Clinical Oncology, Vol. 26(27), 20 September 2010. | <input type="checkbox"/> |
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| | 015 | KAUR, et al., "Design, Synthesis and Evaluation of Ospemifene Analogs as Anti-Breast Cancer Agents," European Journal of Medicinal Chemistry, Vol. 86, 30 October 2014, pp. 211-218. | <input type="checkbox"/> |
| | 016 | KEBAMO., et al., "The Role of Biotransformation in Drug Discovery and Development," Journal of Drug Metabolism and Toxicology, Vol. 6 (5), 2015, pp. 1-13. | <input type="checkbox"/> |
| | 017 | LANCET, "Aromatase Inhibitors Versus Tamoxifen in Early Breast Cancer: Patient-Level Meta-Analysis of the Randomised Trials," Vol. 386, 2015, pp. 1341-1352. | <input type="checkbox"/> |
| | 018 | LARI, et al., "Biological Markers in DCIS and Risk of Breast Recurrence: A Systematic Review," Journal of Cancer, Vol. 2, 2011, pp. 232- 261. | <input type="checkbox"/> |
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PGR2023-00043 - Atossa

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| | | Examiner Name | DAVIS, BRIAN J | | |
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| | 024 | MANNI, et al., "Combination of Antiestrogens and Omega-3 Fatty Acids for Breast Cancer Prevention," Biomed Research International, 1 January 2015, 10 pages. | <input type="checkbox"/> |
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| | 026 | MILLER, et al., "Stereospecific Synthesis of (Z)-Tamoxifen via Carbometallation of Alkynylsilanes," The Journal of Organic Chemistry, Vol. 50 (12), 1985, pp. 2121-2123. | <input type="checkbox"/> |
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| | 028 | PARTRIDGE, et al., "Nonadherence to Adjuvant Tamoxifen Therapy in Women with Primary Breast Cancer," Journal of Clinical Oncology, 15 Febuary 2003, Vol. 21. | <input type="checkbox"/> |
| | 029 | ROBERTSON, et al., "Fulvestrant: Pharmacokinetics and Pharmacology," British Journal of Cancer, 2004, Vol. 90, pp. S7-S10. | <input type="checkbox"/> |
| | 030 | ROBERTSON, et al., "Pharmacokinetic Profile of Intramuscular Fulvestrant in Advanced Breast Cancer," Clinical Pharmacokinetics, 2004, Vol. 43 (8), pp. 529-538. | <input type="checkbox"/> |

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| | 032 | UMAREDDY, et al., "Improved Process for Centchroman, A Selective Estrogen Receptor Modulator (SERM)," Journal of Chemical and Pharmaceutical Research, 2015, Vol. 7 (7), pp. 736-741. | <input type="checkbox"/> |
| | 033 | UMAREDDY, et al., "Total Synthesis of Lasofoxifene and Nafoxidine," An International Journal for Rapid Communication of Synthetic Organic Chemistry, 2016, Vol. 46 (4), pp. 309-313. | <input type="checkbox"/> |
| | 034 | VERGOTE, et al., "Fulvestrant is an Effective and Well-Tolerated Endocrine Therapy for Postmenopausal Women with Advanced Breast Cancer," Results from Clinical Trials, British Journal of Cancer, 90 (Suppl), 2004, pp. S11-S14. | <input type="checkbox"/> |
| | 035 | WELSH J., "Induction of Apoptosis in Breast Cancer Cells in Response to Vitamin D and Antiestrogens," Biochemistry and Cell Biology, 1994, Vol. 72 (11-12), pp. 537-545. | <input type="checkbox"/> |
| | 036 | YAO, et al., "Synthesis and Reactivity of Potential Toxic Metabolites of Tamoxifen Analogues: Droloxifene and Toremifene a-Quinones," Chemical Research in Toxicology, 2001, Vol. 14 (12), pp. 1643-1653. | <input type="checkbox"/> |
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| | 038 | ZHANG B., et al., "The Safety Parameters of the Study on Intraductal Cytotoxic Agent Delivery to the Breast Before Mastectomy," http://dx.doi.org/10.3978/j.issn.1000-9604.2014.10.06 , September 09, 2014, Chinese Journal of Cancer Research, Vol. 26(5), pp: 579-587. | <input type="checkbox"/> |

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| | | Examiner Name | DAVIS, BRIAN J | | |
| Sheet | 8 | of | 8 | Attorney Docket Number | 109559-669805 |

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

- ☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

- ☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).
- ☐ See attached certification statement.
- ☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.
- ☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

| | | | |
|------------|------------------|---------------------|------------|
| Signature | /Lisa G Lippert/ | Date (YYYY-MM-DD) | 2021-10-15 |
| Name/Print | Lisa G. Lippert | Registration Number | 78332 |