PATENT COOPERATION TREATY

PCT

THIRD PARTY OBSERVATION

(PCT Administrative Instructions Part 8)

Applicant's or agent's file reference	
ATAI-01701WO	
International application number	International filing date (day/month/year)
PCT/US2022/043102	09 Sep 2022 (09/09/2022)
Applicant	
ATAI LIFE SCIENCES AG	

Third party observation submitted by	Observation submitted on behalf of
Shahin SHAMS	Porta Sophia
Date of submission(day/month/year)	Language of observation
23 May 2023 (23/05/2023)	English

Basis and contents of observation

1. The observation is made on the basis of the claims in the international application as filed.
2. The observation comprises:
   References to documents: 6
   Uploaded copies of documents: 6
3. Further explanations:
   Uploaded copies of documents: 0

Citation # 1 (Patent/utility model) (# uploaded documents: 1):

Country code:	Publication number:	Document kind code:
WO	2000/059486	A2

Patent Applicant/Patent Owner:	Title of invention:
PFIZER PRODUCTS INC.	USE OF CYP2D6 INHIBITORS IN COMBINATION THERAPIES

Link to document:

Publication Date:	Filing Date:	Priority Date:
12 Oct 2000 (12/10/2000)	20 Mar 2000 (20/03/2000)	07 Apr 1999 (07/04/1999)

Source of Abstract:	Accession number:	Publication Date of Abstract:	Retrieval Date of Abstract:

Most relevant passages or drawings:	Relevant to Claims:
Claims: 1, 4, 5; Pages: 8, 10, 13	1 2 6 7 10 11 12

Brief explanation of relevance:

From claim 1 “A method of administering a drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation, or a pharmaceutically acceptable salt thereof, in combination with a CYP2D6 inhibitor, or a pharmaceutically acceptable salt thereof, to a human in need of the intended pharmaceutical activity of such drug, wherein said drug and said CYP2D6 inhibitor are not the same compound.”; relevant to WO2023039187 claims 1, 2, 6, 7, 10, 11, 12

From claim 4 “A method according to claim 1, wherein the drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation, or pharmaceutically acceptable salt thereof, is selected from the group consisting of mequitazine, tamsulosin, oxybutynin, ritonavir, iloperidone, ibogaine, delavirdine, tolteridine, promethazine, pimozide, epinastine, tramodol, procainamide, methamphetamine, tamoxifen, nicergoline, fluoxetine, alprenolol, amiflamine, amitriptyline, aprindine, brofaromine, buturalol, cinnarizine, clomipramine, codeine, debrisoquine, desipramine, desmethylcitalopram, dexfenfluramine, dextromethorphan, dihydrocodine, dolasetron, encainide, ethylmorphine, flecainide, flunarizine, fluvoxamine, guanoxan, haloperidol, hydrocodone, indoramin, imipramine, maprotiline, methoxyamphetamine, methoxyphenamine, methylenedioxymethamphetamine, metoprolol, mexiletine, mianserin,

minaprine, procodeine, nortriptyline, N-propylajmaline, ondansetron, oxycodone, paroxetine, perhexiline, perphenazine, phenformine, promethazine, propafenone, propanolol, risperidone, sparteine, thioridazine, timolol, tomoxetine, tropisetron, venlafaxine, zuclopenthixol, and pharmaceutically acceptable salts thereof.”; relevant to WO2023039187 claims 1, 2, 6, 7, 10, 11, 12

From claim 5 “A method according to claim 1, wherein the CYP2D6 inhibitor, or pharmaceutically acceptable salt thereof, is selected from the group consisting of quinidine, ajmalacine, sertraline, venlafaxine, dexmedetomidine, tripennelamine, premethazine, hydroxyzine, halofrintane, chloroquine, moclobemide, and pharmaceutically acceptable salts thereof, and St. John's wort, or an extract or component thereof.”; relevant to WO2023039187 claims 7, 10

From page 8, paragraph 3 “This invention also relates to a pharmaceutical composition comprising:

(a) a therapeutically effective amount of a drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation (also referred to throughout this document as a "Therapeutic Drug"), or a pharmaceutically acceptable salt thereof;

(b) an amount of a CYP2D6 inhibitor, or a pharmaceutically acceptable salt thereof, that is effective in treating the disorder or condition for which the Therapeutic Drug referred to in (a) is intended to treat; and

(c) a pharmaceutically acceptable carrier;

wherein said drug and said CYP2D6 inhibitor are not the same compound.”; relevant to WO2023039187 claims 2, 6, 7

From page 10, paragraph 6 “The term "treatment", as used herein, refers to reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such condition or disorder. The term "treatment", as used herein, refers to the act of treating, as "treating" is defined immediately above.”; relevant to WO2023039187 claims 2, 6, 7

From page 13, paragraph 2 “Method: 1. Subjects that are predetermined to be extensive metabolizers (EMs; those individuals with functional CYP2D6 activity) are administered an oral dose of a compound being tested as a CYP2D6 inhibitor. 2. Concomitantly, or at some predetermined time period after the dose of the CYP2D6 inhibitor, these subjects are administered a dose of a drug known to be primarily cleared via CYP2D6 mediated metabolism.”; relevant to WO2023039187 claims 11, 12

Citation # 2 (Patent/utility model) (# uploaded documents: 1):

Country code:	Publication number:	Document kind code:
WO	2001052851	A1

Patent Applicant/Patent Owner:	Title of invention:
SHULMAN, Albert	METHODS FOR THE TREATMENT OF SUBSTANCE ABUSE

Link to document:

Publication Date:	Filing Date:	Priority Date:
26 Jul 2001 (26/07/2001)	22 Jan 2001 (22/01/2001)	22 Jan 2000 (22/01/2000)

Source of Abstract:	Accession number:	Publication Date of Abstract:	Retrieval Date of Abstract:

Most relevant passages or drawings:	Relevant to Claims:
Claims: 1, 4, 31	3, 8

Brief explanation of relevance:

From claim 1 “A method of treating substance addiction in a subject in need thereof, which method comprises administering to said subject a combination of: (i) a μ-opioid receptor antagonist (μORA); (ii) a calcium channel blocker (CCB) which is long-acting or in sustained-release form, or which is nimodipine in rapid release form; and (iii) an NMDA glutamate receptor modulator.”; relevant to WO20230391871 claims 3, 8

From claim 4 “A method according to claim 1 wherein the NMDA glutamate receptor modulator is selected from the group consisting of: CCP, dizocilpine, HA966, ibogaine, memantine,' ifenprodil, eliprodil and acamprosate.”; relevant to WO2023039187 claims 3, 8

From claim 31 “A method according to claim 1 wherein the substance of addiction is nicotine and the combination further comprises at least one of a ganglion nicotinic receptor antagonist, such as mecamylamine; or a nicotinic cholinergic receptor antagonist, such as bupropion; or γ-vinylGABA (vigabactin) or a κ-opioid agonist.”; relevant to WO2023039187 claims 3, 8

Citation # 3 (Patent/utility model) (# uploaded documents: 1):

Country code:	Publication number:	Document kind code:
WO	2023012691	A1

Patent Applicant/Patent Owner:	Title of invention:
PIKE THERAPEUTICS INC.	TRANSDERMAL MICRO-DOSING DELIVERY OF PHARMACEUTICAL AGENTS

Link to document:

Publication Date:	Filing Date:	Priority Date:
09 Feb 2023 (09/02/2023)	03 Aug 2022 (03/08/2022)	03 Aug 2021 (03/08/2021)

Source of Abstract:	Accession number:	Publication Date of Abstract:	Retrieval Date of Abstract:

Most relevant passages or drawings:	Relevant to Claims:
Claims 1, 3, 19, 28	3, 4, 5, 9

Brief explanation of relevance:

ALL CITATIONS ARE FROM THE PRIORITY DOCUMENT OF THIS APPLICATION - WHICH HAS BEEN ATTACHED

From claim 1 “A trasndermal and/or topical pharmaceutical composition comprising: at least one active agent selected from the group consisting of...ibogaine...”; relevant to WO2023039187 claims 3, 4, 5, 9

From claim 3 “A pharmaceutical composition of any one of claims 1 and 2 wherein the pharmaceutical formulation provides a dose of active agent to a patient equal to or greater than.. .10mg/day, or 25 mg/day.”; relevant to WO2023039187 claims 5

From claim 19 “The pharmaceutical composition of any one of claims 1 to 18 further comprising at least one additional active agent selected from the group consisting of...fluoxetine...”; relevant to WO2023039187 claims 3, 4, 5, 9

From claim 28 “The pharmaceutical composition of any one of claims 1 to 27 indicated for the treatment and/or prevention and/or control of chronic pain, multiple sclerosis, severe depression (treatment resistant), major depressive disorder, obsessive-compulsive disorder, post-traumatic stress disorder, quitting smoking, alcohol addiction, cocaine addiction, opioid addiction, anxiety (stress), adult ADHD, cluster headaches, and cancer related or other end-of-life psychological distress in a patient.”; relevant to WO2023039187 claims 3, 4, 5

Citation # 4(Periodical article) (# uploaded documents:1):

Author:	Title of article:	Title of Periodical:	Publication Date:
Paul Glue	Influence of CYP2D6 activity on the pharmacokinetics and pharmacodynamics of a single 20 mg dose of ibogaine in healthy volunteers	The Journal of Clinical Pharmacology	04 Feb 2015 (04/02/2015)

Issue Number of Periodical:	Publisher of Periodical:	Place of publication:
Vol 55 / Issue 6		

Page range of article within periodical:	ISBN:	ISSN:
DOI:		

Most relevant passages or drawings:	Relevant to Claims:
Pages: 680, 681, 682, 686 Figures: 1 Tables: 1	See below

Brief explanation of relevance:

Relevant to claims 1, 7, 11, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22

From page 680 “Conversion of ibogaine to its active metabolite noribogaine appears to be mediated primarily by CYP2D6. We compared 168 hours pharmacokinetic profiles of both analytes after a single oral 20 mg dose of ibogaine in 21 healthy subjects who had been pretreated for 6 days with placebo or the CYP2D6 inhibitor paroxetine. In placebo-pretreated subjects, ibogaine was rapidly converted to noribogaine. Median peak noribogaine concentrations occurred at 4 hours. Compared with placebo-pretreated subjects, paroxetine-pretreated subjects had rapid (Tmax¼1.5 hours) and substantial absorption of ibogaine, with detectable levels out to 72 hours, and an elimination half-life of 10.2 hours.”; relevant to WO2023039187 claims 1, 7, 11, 13, 14, 15, 16, 17, 18, 19, 20, 21, and 22

From page 681 “Subjects were randomized to receive double blind capsules containing paroxetine or placebo between days 2 and 15 (10 mg on days 2–3 and 20 mg/day on days 4–15, according to a computer-generated random code). On day 7, subjects were given a single 30 mg dose of dextromethorphan, and urine was collected for the next 5 hours, for repeated CYP2D6 phenotyping. On day 8, a single 20 mg dose of ibogaine was administered to all subjects, and 8 mL blood samples collected pre-dose and at 0.5, 1.0, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, and 168 hours post dose.”; relevant to WO2023039187 claims 11 and 16

From page 682 “Although mean noribogaine AUC0–t values were similar in both groups, mean Cmax was lower (12.7 vs. 18.7 ng/mL;P¼.05) and t1/2 longer (20.1 vs. 13.0 hours;P¼.07) in paroxetine-pretreated compared with placebo-pretreated subjects (Table 1).”; relevant to WO2023039187 claim 21

From page 686 “In placebo-pretreated subjects, ibogaine was rapidly converted to noribogaine, with undetectable ibogaine levels in all subjects by 4 hours post dose. Median peak noribogaine concentrations occurred by 4 hours. Compared with placebo-pretreated subjects, subjects who had reduced CYP2D6 activity from paroxetine pretreatment had rapid (median Tmax¼1.5 hours) and substantial absorption of ibogaine, with detectable levels out to72 hours, and an elimination half-life of 10.2 hours.”; relevant to WO2023039187 claim 20

From Figure 1, page 681; relevant to WO2023039187 claim 16

From Table 1, page 684; relevant to WO2023039187 claims 20 and 21

Citation # 5(Book) (# uploaded documents:1):

Title:	Author:	Subtitle:
Introduction to Basics of Pharmacology and Toxicology	Abialbon Paul	
Place of publication:	Publisher: Springer	Year of Publication:
Number of edition:	ISBN: 978-981-32-9779-1	
DOI:		
Most relevant passages or drawings: page 81	Relevant to Claims: 22	

Brief explanation of relevance:

From chapter titled "Drug Absorption and Bioavailability", which is attached here

From page 81 “Drug absorption is quantified in terms of bioavailability. Bioavailability is the extent to which absorption occurs. In other words, bioavailability is the fraction of the administered drug that reaches the systemic circulation in the unchanged form.”; relevant to WO2023039187 claim 22

Citation # 6(Periodical article) (# uploaded documents:1):

Author:	Title of article:	Title of Periodical:	Publication Date:
Marieke Henstra	Toxicokinetics of ibogaine and noribogaine in a patient with prolonged multiple cardiac arrhythmias after ingestion of internet purchased ibogaine	Clinical Toxicology	09 Feb 2017 (09/02/2017)
Issue Number of Periodical: Volume 55 / Issue 6	Publisher of Periodical:	Place of publication:	
Page range of article within periodical:	ISBN:	ISSN:	
DOI:			
Most relevant passages or drawings: Page 600	Relevant to Claims: 1		

Brief explanation of relevance:

From page 600 “QTc-prolongation remained present until 12 days after ingestion, several days after ibogaine plasma-levels were low, implicating clinically relevant noribogaine concentrations long after ibogaine had been cleared from the plasma."; relevant to WO2023039187 claim 1