**2018-1804, -1808, -1809**

# United States Court of Appeals for the Federal Circuit

SANOFI-AVENTIS U.S., LLC, AVENTIS PHARMA S.A., SANOFI,

*Plaintiffs-Appellants,*

– v. –

DR. REDDY'S LABORATORIES, INC., DR. REDDY'S LABORATORIES, LTD., SANDOZ, INC.,

*Defendants-Appellees,*

FRESENIUS KABI USA, LLC, ACCORD HEALTHCARE, INC., APOTEX CORP., APOTEX INC., ACTAVIS LLC, ACTAVIS ELIZABETH LLC, MYLAN LABORATORIES LIMITED,

*Defendants-Cross-Appellants.*

*On Appeal from the United States District Court for the District of New Jersey in Case Nos. 3:14-cv-07869-MAS-LHG, 3:14-cv-08079-MAS-LHG, 3:14-cv-08082-MAS-LHG, 3:15-cv-02520-MAS-LHG, 3:15-cv-00287-MAS-LHG, 3:15-cv-01835-MAS-LHG, 3:15-cv-00290-MAS-LHG, 3:15-cv-00776-MAS-LHG, 3:15-cv-03107-MAS-LHG, 3:15-cv-02522-MAS-LHG, 3:16-cv-02259-MAS-LHG, 3:15-cv-03392-MAS-LHG, 3:15-cv-02631-MAS-LHG and 3:16-cv-05678-MAS-LHG, Honorable Michael A. Shipp*

## NON-CONFIDENTIAL BRIEF FOR PLAINTIFFS-APPELLANTS

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JUNE 25, 2018

# CERTIFICATE OF INTEREST

## UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

Sanofi-Aventis U.S. LLC *et al.*, *Appellants* *v.* Fresenius Kabi USA, LLC *et al.* *Appellees*

Case Nos. 2018-1804, 2018-1808, 2018-1809

Counsel for Plaintiffs-Appellants Sanofi-Aventis U.C. LLC, Aventis Pharma S.A., and Sanofi certifies the following:

1. The full name of the party represented by me is:

Sanofi-Aventis U.S. LLC

Aventis Pharma S.A.

Sanofi

2. The name of the real party in interest (only including any real party in interest not identified in Question 3) represented by me is:

Sanofi-Aventis U.S. LLC

Aventis Pharma S.A.

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party represented by me are:

Sanofi U.S. Services Inc.

Aventis, Inc.

Sanofi

sanofi-aventis Amérique du Nord

4. The names of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected

to appear in this court (and who have not or will not enter an appearance in this case) are:

Fitzpatrick, Cella, Harper & Scinto: Joshua I. Rothman, Melinda R. Roberts, Una C. Fan, Jayita Guhaniyogi (no longer with the firm), Cali R. Roth (no longer with the firm)
Walsh Pizzi O'Reilly Falanga LLP: Liza M. Walsh, Katelyn O'Reilly, Tricia O'Reilly
Saul Ewing Arnstein & Lehr LLP: Charles M. Lizza, William C. Baton, David L. Moses

5. The title and number of any case known to counsel to be pending in this or any other court or agency that will directly affect or be directly affected by this court's decision in the pending appeal. *See* Fed. Cir. R. 47.4(a)(5) and 47.5(b).

Aventis Pharma S.A. v. Mylan Laboratories Limited, No. 18-1203

/s/ William E. Solander
Date: June 25, 2018 Signature of counsel

William E. Solander
Cc: Opposing Counsel of Record Printed name of counsel

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**Confidential Material Redacted**

The material omitted on Appx58 and Appx66-67 discloses Plaintiffs-Appellants' proprietary, competitively-sensitive business and financial information, including references to internal documents, which information is not publicly available.

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## STATEMENT OF RELATED CASES

The undersigned counsel for Plaintiffs-Appellants states that the following proceeding in the United States Court of Appeals for the Federal Circuit involves a patent at issue in this appeal, U.S. Patent No. 8,927,592: *Aventis Pharma S.A. v. Mylan Laboratories Limited*, No. 18-1203 from IPR2016-00712.

Counsel for Plaintiffs-Appellants certifies that no other appeal in or from the actions coordinated and/or consolidated in *Sanofi-Aventis U.S. LLC et al. v. Fresenius Kabi USA, LLC et al.*, C.A. No. 14-07869 (MAS)(LHG) (D.N.J.) was previously before this or any other Appellate Court.

Dated: June 25, 2018

*/s/ William E. Solander*

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## STATEMENT OF JURISDICTION

On March 5, 2018, the Honorable Michael A. Shipp entered final judgment for Plaintiffs-Appellants (collectively, "Sanofi") on U.S. Patent No. 5,847,170 ("the '170 patent") and for Defendants-Appellees (collectively, "Defendants") on U.S. Patent No. 8,927,592 ("the '592 patent") consistent with the Order entered on December 17, 2017 and Opinion entered on December 19, 2017. Appx1-99. The district court had jurisdiction pursuant to 28 U.S.C. §§ 1331 and 1338(a). Sanofi timely noticed appeal on April 4, 2018. Appx14540-14541. This Court has jurisdiction pursuant to 28 U.S.C. § 1295(a).

## STATEMENT OF THE ISSUES

1. Whether the district court had subject matter jurisdiction over claims 7, 11, 14-16, and 26 of the '592 patent at the time the court decided those claims were invalid and entered a judgment of invalidity, where those claims had already been disclaimed, and, even before the disclaimer, would inevitably have been cancelled by the United States Patent and Trademark Office.

## STATEMENT OF THE CASE

Sanofi owns the '592 patent, which covers an FDA-approved method of using cabazitaxel to treat patients with prostate cancer whose disease has progressed during or after treatment with docetaxel. Appx5710, Appx11152-

11153. The '592 patent is listed in the Orange Book for Sanofi's Jevtana® (cabazitaxel) product. Appx5710.

Sanofi sued Defendants for infringement of the '592 patent in the District of New Jersey based on Defendants' filing of abbreviated new drug applications ("ANDAs") and/or new drug applications pursuant to 21 U.S.C. § 355(b)(2) ("505(b)(2) NDAs") requesting permission from the Food and Drug Administration ("FDA") to market versions of Jevtana®. Appx14879-14880, Appx14977-14978, Appx15268-15271, Appx15495-15497, Appx15700-15702, Appx15888-15890, Appx16103-16105, Appx16198-16199, Appx16366-16368, Appx16457-16459. Defendants filed counterclaims for a declaratory judgment of invalidity and/or non-infringement of the '592 patent. Appx14938-14940, Appx15027-15029, Appx15317-15319, Appx15562-15564, Appx15748-15750, Appx15949-15950, Appx16158-16160, Appx16254-16256, Appx16417-16419, Appx16543-16546.

The suits against Fresenius Kabi USA, LLC; Accord Healthcare Inc.; Apotex Corp. and Apotex Inc.; Mylan Laboratories Ltd.; and Actavis LLC were consolidated under Civil Action Number 14-07869, and a bench trial was held on September 18-20 and September 25-29, 2017 on validity of the '170 patent, which claims the cabazitaxel molecule, and on validity and infringement of the '592 patent. Appx17, Appx32, Appx80, Appx87, Appx10715-10718, Appx10721,

Appx11123. Defendants BPI Labs, LLC and Belcher Pharmaceuticals, LLC; Breckenridge Pharmaceutical, Inc.; Dr. Reddy's Laboratories, Inc. and Dr. Reddy's Laboratories, Ltd.; Glenmark Pharmaceuticals, Inc. USA and Glenmark Pharmaceuticals, Ltd.; and Sandoz Inc. agreed to be bound by the district court's judgment and did not participate in the trial. Appx15975-15978, Appx16184-16188, Appx16278-16282, Appx16445-16449, Appx16598-16604.

On September 21, 2017, in the middle of trial, the Patent Trial and Appeal Board ("PTAB") issued a final written decision ("FWD") in Mylan's co-pending *inter partes* review (IPR2016-00712) finding invalid the claims of the '592 patent that had been asserted in litigation against Defendants and denying Sanofi's contingent motion to amend. Appx10726-10727, Appx10730. In its Notice of Appeal from the FWD filed on November 17, 2017 (before the time to appeal expired on November 24, 2017), Sanofi did not appeal the PTAB's invalidity finding for claims 7, 11, 14-16, or 26. Appx12182, Appx12185-12187; 35 U.S.C. § 142; 37 C.F.R. § 90.3. On December 8, 2017, Sanofi filed a statutory disclaimer of claims 7, 11, 14-16, and 26 ("the disclaimed claims") at the United States Patent and Trademark Office ("USPTO"). Appx14135-14136.

Sanofi informed the district court that there were no longer any issues to litigate or decide regarding the disclaimed claims because those claims no longer existed. Appx12182-12189, Appx14135-14137. But Defendants nonetheless

insisted that the district court enter judgment of invalidity of the disclaimed claims because Defendants intend in the future to assert a defense of claim preclusion (or res judicata) should the FWD be reversed on appeal and Sanofi's proposed amended claims be granted and asserted against Defendants. Appx14138-14139.

On December 13, 2017, the parties submitted supplemental briefing regarding the district court's subject matter jurisdiction with respect to the disclaimed claims. Appx14140-14142. On December 17, 2017, the district court issued an order finding, among other things, that the disclaimed claims as well as claims 21 and 30 of the '592 patent are invalid. Appx15-16. On December 19, 2017, the district court issued its trial opinion finding that it continued to have subject matter jurisdiction over the disclaimed claims, which the court had found invalid. Appx17, Appx59-62. Final judgment was entered on March 5, 2018. Appx1-14.

Sanofi appeals the district court's determination that a case or controversy existed at the time that it invalidated disclaimed claims 7, 11, 14-16, and 26 of the '592 patent. Accordingly, Sanofi seeks to vacate the district court's finding that those claims are invalid.

Sanofi seeks this relief in view of Defendants' plans to use the district court's invalidity judgment for an ancillary purpose. As noted above, based on the court's invalidity judgment on the disclaimed claims, Defendants will argue that

claim preclusion bars Sanofi from suing them on amended '592 patent claims that may issue in the future once this Court resolves Sanofi's separate appeal from the FWD in the IPR.

## STATEMENT OF THE FACTS

### I. Initial Pleadings and Asserted Claims of the '592 Patent

When the Apotex, Accord, Actavis, Breckenridge, BPI, Belcher, Fresenius, and Mylan Defendants filed their ANDAs and/or 505(b)(2) NDAs with the FDA, the '592 patent had not yet issued and therefore was not listed in the Orange Book for Jevtana®. Appx348, Appx377-378, Appx14727, Appx15062, Appx15171, Appx15355, Appx15591, Appx15782, Appx15986. Initially, Sanofi sued these Defendants for infringement of the Orange Book-listed '170 patent, and later filed separate complaints for infringement of the '592 patent after Defendants amended their ANDAs and/or 505(b)(2) NDAs to include paragraph IV certifications for the '592 patent.[1] Appx348, Appx377-378, Appx14727, Appx14879-14880, Appx14977-14978, Appx15062, Appx15171, Appx15268-15271, Appx15355, Appx15495-15497, Appx15591, Appx15700-15702, Appx15782, Appx15888-15890, Appx15986, Appx16103-16105, Appx16198-16199, Appx16366-16368.

[1] The Glenmark Defendants never filed a paragraph IV certification for the '170 patent, and the Dr. Reddy's Laboratories Defendants filed a paragraph IV certification with respect to the '170 patent only after they had already been sued for infringement of the '592 patent. Appx6, Appx16198-16199, Appx16292.

Accordingly, there was no 30-month stay of regulatory approval connected to the '592 patent.[2] *See* 21 U.S.C. §§ 355(c)(3)(C), 355(j)(5)(B)(iii).

Sanofi's complaints against all Defendants included counts for patent infringement that did not specify any particular patent claims and requested a judgment of infringement of "one or more claims of the '592 patent." Appx14879-14880, Appx14977-14978, Appx15268-15271, Appx15495-15497, Appx15700-15702, Appx15888-15890, Appx16103-16105, Appx16198-16199, Appx16366-16368, Appx16457-16459. Defendants filed counterclaims seeking a declaratory judgment of invalidity of the '592 patent that either did not specify the challenged patent claims or challenged all patent claims. Appx14938-14940, Appx15027-15029, Appx15317-15319, Appx15562-15564, Appx15748-15750, Appx15949-15950, Appx16158-16160, Appx16254-16256, Appx16417-16419, Appx16543-16546. As required by the district court's scheduling orders, Sanofi disclosed the '592 patent claims it was asserting early in the case, but thereafter limited its infringement allegations by the time of trial to claims 7, 11, 14-16, 21, 26, and 30. Appx6748-6752, Appx6929, Appx5728, Appx14179. Defendants did not request judgment on any other claims that Sanofi had previously asserted. *See* Appx14190. None of the parties amended their complaints or counterclaims to

[2] The exception is Sandoz, whose paragraph IV letter regarding its proposed 505(b)(2) NDA for a cabazitaxel product was received in August 2016, much later than the other Defendants' analogous letters. Appx16456.

specify particular patent claims in dispute, and the court-ordered deadline for motions to amend pleadings expired long before trial, on May 4, 2016. Appx14855-14859.

## II. The Timing of Mylan's Delayed IPR and the Denial of a Litigation Stay Resulted in a PTAB Decision During Trial

Ten months after being served with Sanofi's complaint alleging infringement of the '592 patent and more than a year after the '592 patent issued, Mylan filed IPR2016-00712 ("the IPR") requesting cancellation of claims 1-5 and 7-30 of the '592 patent. Appx348, Appx2978, Appx14970, Appx14977-14978. The IPR was instituted on September 22, 2016. Appx15054. By statute, the PTAB was required to issue its FWD concerning validity of the '592 patent by September 22, 2017. 35 U.S.C. § 316(a)(11). When the IPR was instituted, trial in the district court litigation was already scheduled to begin on September 18, 2017. Appx522-524.

On November 16, 2016, having decided to file a contingent motion in the IPR to amend the '592 patent claims if the original claims were found invalid, Sanofi notified Defendants that it intended to seek a stay of the '592 patent litigation pending the outcome of the IPR, while continuing the litigation on the '170 patent. Appx5043. Because Defendants did not agree, Sanofi was compelled to file a motion to stay. Appx4967-4971. Sanofi explained to the district court that

Defendants would not be prejudiced by a litigation stay because there was no 30-month stay of regulatory approval connected to the '592 patent. Appx4982-4983. Also, Sanofi was likely to succeed on the '170 patent, which had already survived an IPR challenge (also filed by Mylan) and did not expire until 2021, thereby allowing time to resolve any remaining issues for the '592 patent after the completion of the IPR. Appx4982-4983. Given the lower burden of proof before the PTAB, Sanofi noted that a stay would not provide Sanofi with a tactical advantage. Appx5215-5217.

Sanofi also explained that a stay would simplify the case, preserve judicial resources, and avoid duplicative trials because: (1) if all the claims of the '592 patent were cancelled during the IPR, the district court would never need to try those claims unless the PTAB decision was overturned on appeal; (2) if the claims were amended, the district court could avoid an unnecessary trial on the original claims followed by a second trial on the amended claims (for which full discovery had not been taken); and (3) if the original claims were upheld, the district court would have the benefit of the PTAB's reasoning. Appx4984-4985, Appx5208-5211. As noted above, because of (a) the 30-month stay, which was associated with the '170 patent only, (b) that patent's 2021 expiration date, and (c) the likelihood that Sanofi could successfully defend the '170 patent's chemical compound claims against allegations of obviousness, there was likely sufficient

time to litigate any '592 patent issues that survived a FWD (due in September 2017) and appeal of that IPR prior to the expiration of the '170 patent. During that time, an injunction based on the successful assertion of the '170 patent would enjoin the FDA from approving Defendants' versions of Jevtana®.

In opposition to Sanofi's motion to stay, Defendants noted that PTAB motions to amend are "rarely granted," that it was "extremely unlikely that Plaintiffs' motion to amend the '592 patent claims will succeed," and that "the substance of Sanofi's proposed amendment makes its success even less likely." Appx5096-5097.

On July 20, 2017, more than six months after briefing had been completed, the district court denied Sanofi's request for a stay. Appx5205, Appx5694-5695. The district court found, among other things, that the litigation was in its late stages, with the pretrial conference scheduled for that day. Appx5695. Thus, the parties were required to prepare for and proceed to trial on September 18, 2017 on patent claims that could be invalidated and/or amended at any time prior to September 22, 2017, when the FWD in the IPR was due.

In the IPR, Sanofi's motion to amend proposed substituting claims 31-34 if original claims 27-30 were found invalid. Those original claims and the proposed amended claims are set forth below with deletions in strikethrough and additions in underline. Appx369, Appx10793-10794, Appx14181-14182.

| **Original Claims** | **Proposed Amended Claims** |
|---|---|
| **27.** A method of increasing the survival of a patient with a castration resistant or hormone refractory, metastatic prostate cancer that has progressed during or after treatment with docetaxel, comprising administering a dose of 20 to 25 mg/m$^2$ of cabazitaxel, or hydrate or solvate thereof, to the patient in combination with prednisone or prednisolone. | **31.** A method of increasing ~~the~~ survival ~~of a patient~~ comprising administering to a patient in need thereof (i) an antihistamine, (ii) a corticoid, (iii) an $H_2$ antagonist, and (iv) a dose of 20 to 25 mg/m$^2$ of cabazitaxel, or a hydrate or solvate thereof, wherein said antihistamine, said corticoid, and said $H_2$ antagonist are administered prior to said dose of 20 to 25 mg/m$^2$ of cabazitaxel, or hydrate or solvate thereof, in combination with prednisone or prednisolone, wherein said patient has ~~with a~~ castration resistant or hormone refractory, metastatic prostate cancer that has progressed during or after treatment with docetaxel~~, comprising administering a dose of 20 to 25 mg/m$^2$ of cabazitaxel, or a hydrate or solvate thereof, to the patient in combination with prednisone or prednisolone~~. |
| **28.** The method according to claim 27, where the cabazitaxel, or hydrate or solvate thereof, is administered at a dose of 25 mg/m$^2$. | **32.** The method according to claim 31 ~~27~~, where the cabazitaxel, or hydrate or solvate thereof, is administered at a dose of 25 mg/m$^2$. |
| **29.** The method according to claim 27, comprising repeating the administration of said cabazitaxel, or hydrate or solvate thereof, as a new cycle every 3 weeks. | **33.** The method according to claim 31 ~~27~~, comprising repeating the administration of said antihistamine, said corticoid, said $H_2$ antagonist, and said cabazitaxel, or hydrate or solvate thereof, as a new cycle every 3 weeks. |
| **30.** The method according to claim 27, where the cabazitaxel, or hydrate or solvate thereof, is administered at a dose of 20 mg/m$^2$. | **34.** The method according to claim 31 ~~27~~, where the cabazitaxel, or hydrate or solvate thereof, is administered at a dose of 20 mg/m$^2$. |

## III. Sanofi Reacted Promptly to the PTAB Decision and Narrowed the Issues in Litigation Prior to Conclusion of the Trial

Trial began in the district court on September 18, 2017. Appx10722-10723. On September 21, 2017, while trial was ongoing, the PTAB issued its FWD finding claims 1-5 and 7-30 of the '592 patent invalid for obviousness and denying Sanofi's motion to amend. Appx10726. As of that time, Sanofi's expert on validity of the '592 patent, who was also an expert in the IPR, had not testified and was scheduled to take the stand on September 29, 2017, the last scheduled day of trial. Appx5754-5755, Appx10670-10671, Appx10728, Appx10879.

Thus, Sanofi had one week to evaluate the FWD and determine the best path forward before conclusion of the trial. Instead of continuing to assert infringement of all eight claims that had been held invalid in the FWD, Sanofi narrowed the asserted claims to only two, namely, claims 21 and 30. Defendants were notified of that decision before Sanofi's validity expert for the '592 patent testified. Appx13841. Sanofi also advised the court on the final day of testimony that it was pursuing only these two claims. Appx13841. Accordingly, Sanofi submitted no post-trial briefing on claims 7, 11, 14-16, or 26 of the '592 patent and presented no arguments with respect to infringement or validity of those claims at the closing argument on November 8, 2017. Sanofi thus made clear that, as with the claims it dropped long before trial, claims 7, 11, 14-16, and 26 were no longer being asserted in the case.

## IV. The District Court Found That It Had Subject Matter Jurisdiction Over Patent Claims That No Longer Exist

As of December 8, 2017, when Sanofi filed a statutory disclaimer of claims 7, 11, 14-16 and 26 with the USPTO (Appx14136-14137), those claims ceased having legal power (i.e., could no longer be asserted against any party), and thus ceased to exist. After Sanofi notified the district court that these claims had been disclaimed (Appx14135-14137), the district court ordered simultaneous supplemental briefing on whether it would be appropriate to render a decision with respect to claims 1-5, 7-20, and 22-29 of the '592 patent, which included the disclaimed claims. Appx14140-14142.

In their supplemental briefing, Defendants made two arguments as to why there was a continuing controversy with respect to the disclaimed claims. First, Defendants argued that they needed a final judgment of invalidity of those claims to support a claim preclusion argument they ***might*** have in the future should Sanofi (1) succeed in overturning the FWD and (2) proceed to assert amended patent claims that emerged from the IPR against Defendants. Appx14185-14187. Second, Defendants asserted that the district court retained subject matter jurisdiction to hear their potential request for attorneys' fees on grounds that this is an exceptional case. Appx14188-14190. Defendants argued that Sanofi's continued assertion of claims that were "plainly invalid" and had been held invalid by the PTAB was gamesmanship and vexatious litigation. Appx14188-14190.

Sanofi explained that when claims are cancelled by the USPTO or are disclaimed, litigation on those claims becomes moot, aside from a rare exception to this rule (explained below), which does not apply here. Appx14152-14155. Sanofi also explained that Defendants' speculative claim preclusion scenario—requiring a series of events which have not yet occurred—is too remote to create a present and immediate case or controversy. Appx14156-14157. Sanofi noted in particular that a motion to amend claims in an IPR is not gamesmanship, but rather is explicitly contemplated by statute and legislative history. Appx14155 n.5.

The district court found that it had "good cause to issue a decision" regarding the disclaimed claims, which were at issue during the trial, and that the court had subject matter jurisdiction to decide validity of those claims. Appx60-63. The court based its conclusion on subject matter jurisdiction on two grounds. First, the court relied on Sanofi's failure (a) to object to Defendants' statement at trial that they continued to seek a judgment of invalidity of "all of the claims that have been a part of the case,"[3] and (b) to file a voluntary dismissal of the disclaimed claims prior to conclusion of the trial. Appx61-62. Second, the district court relied on its finding that "the claims at issue have not been cancelled." Appx62. However, the district court did not address (1) whether events that

[3] However, in analyzing infringement of the '592 patent, the district court considered only claims 21 and 30, recognizing that these were the only claims for which Sanofi sought a judgment of infringement. Appx80 n.24.

occurred after trial but before its merits decision was rendered controlled the issue of subject matter jurisdiction, (2) the effect of the statutory disclaimer to cancel the disclaimed claims, or (3) whether a defect in subject matter jurisdiction can be waived. Appx60-62. The district court also did not adopt Defendants' arguments that potential claim preclusion or attorneys' fees disputes supported subject matter jurisdiction.

After the district court issued its trial opinion, Sanofi decided not to appeal the PTAB's (or the district court's) invalidity findings with respect to claims 21 and 30 of the '592 patent. Thus, like disclaimed claims 7, 11, 14-16, and 26 (which Sanofi did not appeal in the IPR), claims 21 and 30 will inevitably be cancelled by the USPTO. All that remains of the '592 patent in these proceedings are proposed substitute claims 31-34 that are the subject of the motion to amend, which was denied by the PTAB in the IPR and is the subject of co-pending Appeal No. 2018-1203.

## SUMMARY OF THE ARGUMENT

In the eyes of the law, disclaimed claims 7, 11, 14-16, and 26 of the '592 patent did not exist and could never be enforced against Defendants or anyone else at the time the district court issued its merits decision in this case. Defendants nonetheless sought a declaratory judgment of invalidity of these disclaimed patent claims for a collateral purpose — to prevent Sanofi on claim preclusion grounds

(i.e., res judicata) from suing Defendants on new amended patent claims that may issue in the future once Sanofi's appeal in the corresponding '592 patent IPR is resolved.

There was no justiciable case or controversy to support subject matter jurisdiction over the disclaimed patent claims. The district court's contrary conclusion that it retained subject matter jurisdiction to invalidate those claims was based on multiple errors of law and should be reversed.

***First,*** the district court incorrectly held that the disclaimed claims had not yet been cancelled when the court reached its merits decision. There is no dispute that claims 7, 11, 14-16, and 26 had been formally disclaimed at that time. The effect of the disclaimer was to immediately cancel those claims such that they ceased to exist.

***Second***, the district court disregarded the axiomatic requirement that subject matter jurisdiction be present at every stage of the case. As a result, the court found a justiciable case or controversy present based on what happened at trial instead of looking at legally controlling post-trial events at the time the courts' merits decision issued, including Sanofi's statutory disclaimer submitted to the USPTO disclaiming claims 7, 11, 14-16, and 26. And, because a subject matter jurisdiction defense cannot be waived, Sanofi's actions at trial on which the court

relied had no effect on the court's obligation to determine whether a case or controversy remained months after the trial when the merits decision was reached.

***Third***, any case or controversy concerning claims 7, 11, 14-16, and 26 was mooted once cancellation of those claims by the USPTO became inevitable in the IPR, and the claims were thereafter disclaimed. The limited exception to the general rule that courts lack subject matter jurisdiction over disclaimed patent disputes recognized by this Court's *Apotex v. Daiichi Sankyo* decision does not apply here. The unique Hatch-Waxman Act market forfeiture provisions that formed the basis for subject matter jurisdiction in *Apotex* are not at issue in this case.

Nor could Defendants meet their burden of demonstrating that a justiciable case or controversy remained when the district court's merits decision was reached after claims 7, 11, 14-16 and 26 were disclaimed. Defendants' efforts to manufacture a case or controversy based on the "ancillary impact" of the invalidity judgment they sought fail as a matter of law.

***First***, the *Senju* case on which Defendants relied does not support a claim preclusion defense to bar Sanofi's future potential suit asserting its proposed amended claims against Defendants. Unlike the circumstances here, the *Senju* patentee sought an improper "second bite at the apple" by means of new reexamined patent claims that it obtained only after the patentee's original claims

were found invalid in an infringement litigation. Here, Sanofi is appropriately pursuing its statutory opportunity to amend its patent claims in an IPR that Mylan initiated. Also, *Senju*'s reasoning predicating a claim preclusion defense on the assumption that a product that infringed new reexamined claims would necessarily infringe the original claims, does not apply here. In this case, the disclaimed claims and the proposed amended claims have different language and scope. And even if *Senju* applied to bar Sanofi's potential future suit on certain of the proposed amended claims, a judgment on the merits as to the disclaimed claims would be superfluous for purposes of Defendants' potential claim preclusion defense since Defendants already have a judgment of invalidity for claims 21 and 30 (which were not disclaimed).

***Second***, even assuming *Senju* could apply here to support Defendants' potential future claim preclusion defense, a dispute over infringement of proposed amended patent claims that do not yet exist was too remote, speculative, and contingent to support a case or controversy in the district court. The proposed amended claims will issue if this Court reverses the FWD in the IPR, an outcome which Defendants have characterized as "unlikely." Indeed, future litigation between the parties on those claims will occur only if a series of potential future events occur, including that the parties do not settle their dispute. Thus, the

"controversy" over the proposed amended claims on which Defendants rely is neither immediate, real, nor ripe for review.

***Third***, Defendants incorrectly allege that there is a controversy over the disclaimed patent claims because a judgment that those claims are invalid will support their potential attorneys' fees request on grounds that this is an "exceptional case." The law is clear that an "exceptional case" based attorneys' fees request does not create a case or controversy as to an otherwise nonjusticiable counterclaim seeking a judgment of patent invalidity. Moreover, a judgment on the disclaimed claims would not afford Defendants the "prevailing party" status they need to recover attorneys' fees because they lost on all issues concerning the '170 compound patent and are currently enjoined based on that patent from launching their versions of Sanofi's Jevtana® product. And, even to the extent that Defendants could be a "prevailing party" on the '592 patent (having obtained a judgment of its invalidity), while losing on the '170 patent, Defendants do not need a judgment of invalidity of the disclaimed claims to recover attorneys' fees because the district court's invalidity judgment of '592 patent claims 21 and 30 (which were not disclaimed) is sufficient for that purpose.

***Lastly***, because there was no case or controversy over the disclaimed claims at the time the district court reached its merits decision, vacatur of the district

court's invalidity finding of claims 7, 11, 14-16, and 26 is the appropriate remedy here.

## STANDARD OF REVIEW

The question of whether an actual controversy exists in a patent case under the Declaratory Judgment Act is one of law subject to *de novo* review. *Prasco, LLC v. Medicis Pharm. Corp*., 537 F.3d 1329, 1335 (Fed. Cir. 2008). A district court's jurisdiction over claims concerning patent infringement is determined under Federal Circuit law. *Microchip Tech. Inc. v. Chamberlain Group*, 441 F.3d 936, 940 (Fed. Cir. 2006).

## ARGUMENT

### I. Principles of Subject Matter Jurisdiction in Declaratory Judgment Actions

Under the Declaratory Judgment Act, a party may seek a declaration of rights in "a case of actual controversy." 28 U.S.C. § 2201(a). An "actual controversy" is one that is justiciable under Article III of the Constitution, namely, that involves a dispute that is "definite and concrete," "real and substantial," and "admit[s] of specific relief through a decree of a conclusive character, as distinguished from an opinion advising what the law would be upon a hypothetical state of facts." *MedImmune, Inc. v. Genentech, Inc*., 549 U.S. 118, 126-27 (2007) (quoting *Aetna Life Ins. Co. v. Haworth*, 300 U.S. 227, 240-41 (1937)). Thus, a

party seeking a declaratory judgment of patent invalidity must demonstrate that "the facts alleged, ***under all the circumstances***, show that there is a substantial controversy, between parties having adverse legal interests, ***of sufficient immediacy and reality*** to warrant the issuance of a declaratory judgment." *MedImmune*, 549 U.S. at 127 (quoting *Md. Cas. Co. v. Pac. Coal & Oil Co.*, 312 U.S. 270, 273 (1941) (emphasis added)). Without such a case or controversy "the court has no discretion to decide the case." *Spectronics Corp. v. H.B. Fuller Co.*, 940 F.2d 631, 633-34 (Fed. Cir. 1991).

In patent cases, subject matter jurisdiction is evaluated on a patent claim by patent claim basis. *Streck, Inc. v. Research & Diagnostic Sys., Inc.*, 665 F.3d 1269, 1281-82 (Fed. Cir. 2012). Thus, "a counterclaimant must show a continuing case or controversy with respect to withdrawn or otherwise unasserted claims." *Id.* at 1283.

## II. The District Court's Finding That It Had Subject Matter Jurisdiction to Adjudicate the Disclaimed Patent Claims Was Based on Errors of Law

The district court's determination that it retained jurisdiction over the disclaimed claims is incorrect as a matter of law. That conclusion was based on the court's assumptions that: (1) despite Sanofi's statutory disclaimer, the disclaimed claims had not been cancelled, and (2) to object to the court's jurisdiction, Sanofi was required to object to Defendants' unilateral statement that

they would seek a judgment of invalidity of the disclaimed claims and to formally dismiss its assertion of those claims prior to conclusion of trial. Appx61-62.

When the district court issued its trial decision, the statutory disclaimer had effectively cancelled the disclaimed claims. Because subject matter jurisdiction must be present at all stages of the case, the court erred in concluding that the claims had not been cancelled at the relevant time here, namely, when the court's decision was rendered.

Moreover, because a subject matter jurisdiction defense may not be waived, Sanofi's actions at trial on which the court relied did not and cannot control the jurisdictional issue before the court. Rather, post-trial circumstances extant when the court issued its decision, including Sanofi's submission of the statutory disclaimer to the USPTO disclaiming claims 7, 11, 14-16, and 26, are determinative of the jurisdictional issue. The district court's determination that it retained subject matter jurisdiction over the disclaimed claims therefore should be reversed.

### A. The Statutory Disclaimer Cancelled the Claims

It is axiomatic that subject matter jurisdiction must exist at all stages of the litigation. *Streck*, 665 F.3d at 1282. As the party asserting that there was a sufficient case or controversy to issue a declaratory judgment of invalidity, Defendants had the burden to show that the court had subject matter jurisdiction

over the disclaimed claims when the trial decision issued. *See Benitec Austl., Ltd. v. Nucleonics, Inc.*, 495 F.3d 1340, 1344-45 (Fed. Cir. 2007). There is no dispute that Sanofi statutorily disclaimed claims 7, 11, 14-16, and 26 before the district court rendered its decision finding those claims invalid.

"Disclaiming particular claims under [35 U.S.C.] § 253 'effectively eliminate[s] those claims from the original patent.'" *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1299 (Fed. Cir. 2011) (quoting *Vectra Fitness, Inc. v. TNWK Corp.*, 162 F.3d 1379, 1383 (Fed. Cir. 1998)). When a disclaimer is entered, the patent is treated "as though the disclaimed claim(s) had 'never existed.'" *Id.*; *see also Guinn v. Kopf*, 96 F.3d 1419, 1422 (Fed. Cir. 1996) (disclaimer "has the effect of canceling the claims from the patent"). Therefore, because claims 7, 11, 14-16, and 26 of the '592 patent were cancelled by Sanofi's statutory disclaimer, those claims did not exist at the time the district court found them invalid. Thus, the court's conclusion that it retained jurisdiction to invalidate those claims was incorrect as a matter of law.

### B. Sanofi Was Not Required to Formally Remove the Disclaimed Patent Claims from Litigation Prior to the Conclusion of Trial

The district court premised its finding of subject matter jurisdiction in part on Sanofi's failure to formally remove the disclaimed claims from the case before conclusion of trial. Appx61-62. However, a subject matter jurisdiction defense cannot be waived, and can even be addressed for the first time on appeal. Fed. R.

Civ. P. 12(h)(3); *Arbaugh v. Y & H Corp*., 546 U.S. 500, 506-07, 514 (2006); *King Pharms., Inc. v. Eon Labs., Inc*., 616 F.3d 1267, 1282 (Fed. Cir. 2010). Thus, to the extent the district court suggested that Sanofi's actions at trial obviated the court's need to consider whether it had jurisdiction months later when the merits decision was reached, the court was wrong as a matter of law.

The paramount issue here is whether a case or controversy continued to exist at the time the district court rendered its merits decision. Again, because jurisdiction must exist at all stages of the case, the court legally erred by looking at what happened at trial instead of whether jurisdiction was present when the court reached its decision. *See, e.g., Streck*, 665 F.3d at 1282 (jurisdiction must exist at all stages). At that time, Sanofi had filed the statutory disclaimer, and as a result, claims 7, 11, 14-16, and 26 were cancelled and should have been treated as though they had "never existed." *Supra* Argument Section II.A.

Also, even if Sanofi's actions at trial were relevant to subject matter jurisdiction issues here, it was indisputably clear before the district court reached its initial trial decision (on December 17, 2017) that Sanofi was no longer asserting the disclaimed claims. Sanofi informed Defendants and the court during trial that it was no longer asserting those claims and presented no testimony on the validity of those claims. Appx13841. Sanofi presented no post-trial briefing or closing argument regarding those claims, did not appeal the PTAB's invalidity findings

with respect to those claims (such that the USPTO's cancellation of them at the appropriate time was a certainty), and filed a disclaimer of those claims. Appx12182-12187, Appx14135-14136. While the district court found the disclaimed claims had been "fairly placed in issue during the trial," the court also acknowledged that "Plaintiffs appeared to abandon their infringement arguments as to Claims 7, 14, 15, 16, and 26."[4] Appx63, Appx80 n.24. Thus, prior to any merits decision in the case, it was clear to the district court and Defendants that these claims were no longer being asserted and that subject matter jurisdiction was in dispute. In circumstances where it was understood prior to a merits decision that particular claims were not being asserted, even without a formal disclaimer of those claims, this Court has found no case or controversy over those claims. *Fox Group, Inc. v. Cree, Inc.*, 700 F.3d 1300, 1308-09 (Fed. Cir. 2012) (no case or controversy over claims asserted in interrogatory responses where they were not in dispute prior to summary judgment motions); *see also Alcon Res. Ltd. v. Barr Labs., Inc.*, 745 F.3d 1180, 1193 (Fed. Cir. 2014) (the Court does not require a "formal motion or stipulation" to "remove claims from a case," but instead has found an announcement that a patentee is no longer asserting particular claims "coupled with its ceasing to litigate them" to be sufficient).

[4] The district court also did not address infringement of claim 11. Appx80.

The district court relied on *Apple, Inc. v. Samsung Electronics Co*. and *Radware, Ltd. v. A10 Networks, Inc*. (Appx62-63), but both cases are inapposite. Unlike the circumstances here, in those cases, the claims were not facing inevitable cancellation by the USPTO, and had not been disclaimed when the district court's merits decision issued. 67 F. Supp. 3d 1100, 1125-27 (N.D. Cal. 2014); No. 13-02021, 2014 U.S. Dist. LEXIS 81005, at *28-29 (N.D. Cal. June 11, 2014).

## III. Any Dispute over the Disclaimed Patent Claims Was Mooted by the Inevitable Cancellation of Those Claims and the Disclaimer

Jurisdiction for patent infringement in Hatch-Waxman Act litigation is premised on the existence of patent claims. 35 U.S.C. § 271(e)(2) (describing infringement actions for the filing of ANDAs or 505(b)(2) NDAs "for a drug ***claimed in a patent*** or the use of which is ***claimed in a patent***" (emphasis added)). This Court has repeatedly found that cancellation of claims in USPTO proceedings moots district court litigation regarding those claims because the existence of valid claims is "a necessary condition for such an action." *Fresenius USA, Inc. v. Baxter Int'l, Inc*., 721 F.3d 1330, 1340 (Fed. Cir. 2013) (quoting *Slip Track Sys., Inc. v. Metal Lite, Inc*., 159 F.3d 1337, 1340 (Fed. Cir. 1998)); *Target Training Int'l, Ltd. v. Extended Disc. N. Am.*, 645 Fed. App'x 1018, 1023 (Fed. Cir. Apr. 22, 2016); *SHFL Entm't, Inc. v. DigiDeal Corp*., No. 2016-2705, 2018 U.S. App. LEXIS 11656, at *7-8 (Fed. Cir. May 2, 2018). Thus, here, the inevitable USPTO claim

cancellation in the IPR and the actual disclaimer mooted any case or controversy between the parties concerning claims 7, 11, 14-16, and 26.[5] There should be no dispute that the disclaimed claims did not exist when the district court issued its trial decision and, therefore, that those claims could not be enforced against Defendants or anyone else.

Moreover, because Sanofi did not appeal the FWD with respect to claims 7, 11, 14-16, and 26, Sanofi could no longer challenge the PTAB's finding that those claims are invalid. 35 U.S.C. § 142; 37 C.F.R. § 90.3; Fed. Cir. R. 15(a)(1). And, it was not disputed below that those patent claims would inevitably be cancelled by the USPTO once Sanofi's appeal regarding the proposed amended claims was resolved. Appx14187-14188; 35 U.S.C. § 318(b) ("[T]he Director ***shall*** issue and publish a certificate canceling any claim of the patent finally determined to be unpatentable . . . ." (emphasis added)); 37 C.F.R. § 42.80 ("[T]he Office ***will*** issue and publish a certificate canceling any claim of the patent . . . ." (emphasis added)). Thus, the certificate of cancellation for the disclaimed claims was a mere formality that inevitably would occur. By the time the district court reached the merits of the case, it was Mylan's IPR that made cancellation of claims 7, 11, 14-16, and 26

[5] The justiciability requirement of lack of mootness is helpful in applying the *MedImmune* "all circumstances" test for a case or controversy (*supra* Argument Section I) because this doctrine together with standing and ripeness represent the "absolute constitutional minimum." *Prasco*, 537 F.3d at 1336.

inevitable and "extinguished" Sanofi's cause of action with respect to those claims. *See Fresenius USA*, 721 F.3d at 1340. Thus, even before Sanofi filed its statutory disclaimer, the parties' dispute over those claims was moot.

Defendants nonetheless relied below on the fact that cancellation by the USPTO had not yet formally occurred when the district court invalidated the disclaimed claims. Appx14187-14188. But Defendants could not explain how the mere passage of time until that event inevitably occurred created a continuing case or controversy.

Nor could Defendants dispute that, regardless of whether the inevitable USPTO claim cancellation in the IPR mooted the case or controversy here, Sanofi's disclaimer immediately cancelled the disclaimed claims before the district court decided the merits of the case. *Supra* Argument Section II.A. Thus, the general rule that "when a claim is cancelled, the patentee loses any cause of action based on that claim, and any pending litigation in which the claims are asserted becomes moot," applies here. *Fresenius USA*, 721 F.3d at 1340.

Federal courts have repeatedly found that there is no subject matter jurisdiction to adjudicate infringement, invalidity, or enforceability of disclaimed patent claims. *See, e.g.*, *Kruse Tech. P'ship v. Daimler AG*, No. 10-01066, 2012 U.S. Dist. LEXIS 196579, at *10-12 (C.D. Cal. Jan. 23, 2012) (no jurisdiction over declaratory judgment action regarding enforceability of disclaimed patent despite

arguments that the sought-after declaration would be relevant for other patents); *Jacobsen v. Katzer*, 609 F. Supp. 2d 925, 930-32 (N.D. Cal. 2009) (finding a declaratory judgment action relating to enforceability of a disclaimed patent was moot and noting that "any determination regarding patents not yet in suit would render the Court's opinion merely, and impermissibly, advisory"); *Merck & Co. v. Apotex, Inc.*, No. 06-5789, 2007 U.S. Dist. LEXIS 84426, at *15 (D.N.J. Nov. 15, 2007), *aff'd on other grounds*, 292 F. App'x 38 (Fed. Cir. 2008) ("[B]ecause Merck has formally disclaimed the '735 and '443 patents, and can no longer enforce any claims as to these patents, there is no justiciable case or controversy to support jurisdiction in an action for a declaratory judgment here."); *3V, Inc. v. CIBA Specialty Chems. Corp.*, 587 F. Supp. 2d 641, 645-46 (D. Del. 2008) (litigant's wish to establish facts for future cases did not create a case or controversy over a disclaimed patent); *White Mule Co. v. ATC Leasing Co.*, 540 F. Supp. 2d 869, 881 (N.D. Ohio 2008) (the disclaimer "leaves [the court] with no 'actual controversy' to adjudicate"); *Belk, Inc. v. Meyer Corp.*, No. 07-168, 2008 U.S. Dist. LEXIS 57863, at *7-11 (W.D.N.C. July 7, 2008) (dismissing declaratory judgment claim as to a disclaimed patent); *W.L. Gore & Assocs., Inc. v. Oak Materials Group, Inc.*, 424 F. Supp. 700, 702 (D. Del. 1976) (finding there was "no longer a justiciable case or controversy before the Court with respect to the validity of any [disclaimed] claims").

In the district court, Defendants (but not the court) relied in error on a rare exception to the well-established rule that courts lack subject matter jurisdiction to hear disputes over disclaimed patent claims. Appx14184. That exception applies where a later ANDA-filing, generic drug company seeks a declaratory judgment of non-infringement of a disclaimed patent to trigger forfeiture of the first ANDA filer's 180-day market exclusivity. *See, e.g.*, *Apotex Inc. v. Daiichi Sankyo*, 781 F.3d 1356, 1359-63 (Fed. Cir. 2015). In *Apotex*, this Court found that a case or controversy remained despite disclaimer of the entire patent in suit because, under certain Hatch-Waxman Act provisions, a judgment of non-infringement would allow the later-filing generic drug company to enter the market sooner by causing its generic competitor to forfeit its marketing exclusivity. *Id.* at 1359-60, 1362-63. Under these unique circumstances, this Court found that "[t]he stakes . . . are concrete and substantial" because "[i]f the judgment issues, there is ***every likelihood*** that [the innovator/disclaimed patent owner] and [the first ANDA filer] will lose substantial revenues, and [the later ANDA filer] will gain substantial revenues." *Id.* at 1361, 1363 (emphasis added).

There is no dispute that these unique Hatch-Waxman Act market forfeiture provisions are not at issue here. Nor has any Defendant asserted that the disclaimed claims are blocking or delaying market entry of their proposed cabazitaxel products. Thus, the narrow *Apotex* exception to the rule that

jurisdiction is absent to litigate disclaimed patent claims plainly does not apply in this case.

## IV. Defendants Did Not Meet Their Burden of Demonstrating a Continuing Case or Controversy

Because subject matter jurisdiction must exist at all stages of the case, the burden is on the party claiming a right to declaratory relief to establish that such jurisdiction existed at the time the claim for relief was filed and that it has continued since. *Benitec Austl.*, 495 F.3d at 1344-45. Here, recognizing that there is no longer an actual dispute over validity or infringement of the disclaimed claims, Defendants offered two arguments below to the effect that a final judgment on those claims would have an "ancillary impact" on the parties' rights, creating a justiciable controversy. Appx14184. First, Defendants argued that they need such a judgment to support a claim preclusion argument should Sanofi's appeal from the FWD result in the grant of proposed amended claims 31-34 and assertion of those claims against Defendants. Appx14185-14187. Second, Defendants asserted that such a judgment is necessary to support an award of attorneys' fees on grounds that this is an exceptional case under 35 U.S.C. § 285. Appx14188-14190. Neither of Defendants' arguments was adopted by the district court. And, as explained below, both of Defendants' arguments fail as a matter of law.

### A. Defendants' Potential Claim Preclusion Defense Does Not Create a Case or Controversy

Defendants' principal goal in advocating for a continued case or controversy here is to prevent Sanofi from asserting proposed amended claims 31-34 of the '592 patent, should those claims ultimately emerge from the IPR proceeding after Sanofi's appeal is resolved. Defendants rely on *Senju Pharmaceutical Co. v. Apotex Inc*., 746 F.3d 1344 (Fed. Cir. 2014) to argue that the final judgment they seek will preclude Sanofi from asserting those presently non-existent claims against Defendants. Appx14185-14187. But, as explained below, *Senju* does not apply to the circumstances of this case. Moreover, even assuming *Senju* supports Defendants' claim preclusion argument, any dispute over validity and/or infringement of proposed amended claims 31-34, which do not yet exist, is not sufficiently immediate, real, or ripe to create a present case or controversy.

#### 1. *Senju* Claim Preclusion Does Not Apply

In *Senju*, the patentee sought *ex parte* reexamination to amend claims already found invalid by a district court following full trial of a Hatch-Waxman infringement case. 746 F.3d at 1347. After the USPTO allowed amendment of some of the original claims, the patentee filed a second action for a declaratory judgment that the same ANDA product accused in the patentee's earlier case infringed the amended claims that had emerged from reexamination. *Id.* That

ANDA filer then asserted that the doctrine of claim preclusion barred the second suit.

In general, the doctrine of claim preclusion applies where there is a final judgment on the merits in an earlier suit involving the same parties, and a subsequent suit is brought on the same cause of action. *Id*. at 1348 (discussing the elements of claim preclusion in the Third Circuit). In *Senju*, the issue in dispute was whether suit on the newly reexamined patent claims was barred on grounds that those claims were subsumed by the cause of action asserted in the earlier case. *Id*. at 1350. The Court held that new claims emerging from reexamination do not in and of themselves create a new cause of action, reasoning that reexamination is limited in scope, and that new claims cannot be broader than the original claims. *Id*. at 1352. Thus, according to the Court, "a reexamined patent claim cannot contain within its scope any product or process which would not have infringed the original claims." *Id*. at 1352-53. Because the reexamined claims were "essentially the original claims with limiting words added," the court found that the second case was barred because it presented the same cause of action as the first, and that it was unnecessary to make a factually detailed determination as to whether the new claims were "materially different." *Id*. at 1353.[6]

[6] The Court left open the possibility that a reexamination could result in patent claims that were so materially different as to create a new cause of action. *Id.*

Importantly, the circumstances and equities that led to the *Senju* result are not present here. Having pursued reexamination only after losing in the district court, Senju's second infringement case was an attempt at "a do-over" seeking "a second bite at the apple, to assert its patent against the same party, Apotex, and the same product." *Id.* Here, in contrast, Sanofi has engaged in no such conduct. It was Mylan who initiated the IPR relatively late in the litigation, which led to the FWD causing the inevitable cancellation of the disclaimed claims. And it was Mylan and the other Defendants who refused to stay the litigation regarding the '592 patent, thereby forcing Sanofi to pursue litigation during the pendency of the IPR. Thus, unlike in *Senju*, Sanofi's motion to amend its claims in the IPR was not to obtain an improper second bite at the apple, but rather to pursue an opportunity expressly permitted in IPR proceedings. *See, e.g.*, 35 U.S.C. § 316(d).

In fact, rather than gamesmanship, claim amendments are consistent with the legislative purpose of IPR proceedings, namely "to establish a more efficient and streamlined patent system that will ***improve patent quality***." H.R. Rep. No. 112-98, pt. I, at 40 (2011) (emphasis added). In its statement to the Senate Committee on the Judiciary before Congress in 2004, the USPTO explained that amendments are an important feature of post-grant proceedings: "By providing for the possibility of amendment of challenged claims, the proposed system would preserve the merited benefits of patent claims better than the win-all or lose-all

validity contests in district court." *Patent Quality Improvement: Post-Grant Opposition*: *Hearing Before the Subcomm. on Courts, the Internet, and Intellectual Property of the H. Comm. on the Judiciary*, 108th Cong. 10 (2004) (statement of USPTO General Counsel James A. Toupin). And, as this Court recently recognized, "Congress deemed the patent owner's right to amend so important that, in [35 U.S.C.] § 316(d), it mandated that the patent owner be permitted to amend the patent ***as of right*** at least once during the course of an IPR, provided certain specified statutory conditions were met." *Aqua Prods. v. Matal*, 872 F.3d 1290, 1299 (Fed. Cir. 2017) (*en banc*) (emphasis in original).

Thus, there is no basis here to punish Sanofi for seeking valid new claims in response to Mylan's IPR challenge by preventing Sanofi from later asserting those claims against Defendants. In the Hatch-Waxman context, generic drug manufacturers have an incentive to file an ANDA and challenge the innovator's patents as early as possible to receive 180 days of generic marketing exclusivity. 21 U.S.C. § 355(j)(5)(B)(iv); *Janssen Pharmaceutica, N.V. v. Apotex, Inc.*, 540 F.3d 1353, 1361-62 (Fed. Cir. 2008). If *Senju* applied to support claim preclusion any time an ANDA applicant who has been sued for infringement filed an IPR, and the patentee responded with a contingent motion to amend, the amended claims could be asserted only against later ANDA filers who did not participate in the first round of litigation. As a result, there would be little reason for the patentee to

pursue amended claims in an IPR if those claims cannot be asserted against many if not all potential infringers. This outcome is contrary to the statutory scheme and would unjustly prejudice patentees by effectively eliminating much of the benefit in amending patents in an IPR where there is ongoing Hatch-Waxman patent litigation.

Moreover, under this Court's reasoning in *Target Training International, Ltd. v. Extended Disc North America*, Defendants' claim preclusion defense should not apply in the circumstances here. In *Target Training*, new claims emerged from a reexamination proceeding that was commenced after the plaintiff's infringement action was filed. 645 Fed. App'x at 1020-21. After the only claims asserted in litigation were cancelled in reexamination, this Court affirmed dismissal of the infringement case as moot. *Id*. at 1023. Noting that "the claim preclusion principles set forth in *Senju* would not bar a future suit on the facts of this case," this Court explained that claim preclusion "does not apply to bar the assertion of new claims acquired during the pendency of a litigation that could have been, but were not, litigated or adjudicated in the action." *Id.* at 1025-26. Here, the conclusion that *Senju* claim preclusion does not apply is even more compelling since the proposed amended claims do not yet exist and could not have been asserted in the district court.

The circumstances here can be compared to scenarios where a pending

patent application has yet to be allowed. If claim preclusion does not prevent a patentee from asserting patentably distinct claims that issue from a pending application during the course of litigation, claim preclusion should not apply to bar the assertion of new claims that ***have not yet been granted*** in an IPR.[7] *See, e.g.*, *Abbey v. Mercedes Benz of N. Am., Inc*., 138 Fed. App'x 304, 307-08 (Fed. Cir. May 11, 2005) (refusing to apply res judicata to bar litigation on the '977 patent that issued during litigation on other patents); *SimpleAir Inc. v. Google LLC*, 884 F.3d 1160, 1166-67 (Fed. Cir. 2018) (claims issuing from a continuation application create a separate cause of action unless the claims are patentably indistinct or "essentially the same" as previously litigated patent claims); *see also Gillig v. Nike, Inc*., 602 F.3d 1354, 1363 (Fed. Cir. 2010) ("[T]he doctrine of res judicata does not punish a plaintiff for exercising the option not to supplement the pleadings with an after acquired claim.").

Finally, even aside from the foregoing reasons why *Senju* should not apply in any subsequent litigation between the parties here, the reasoning of that case is inapplicable. The *Senju* Court reasoned that the reexamined claims were

[7] Proposed amended claims in an IPR must be patentably distinct from the prior art, including the prior art that was held to render the original claims invalid. *See, e.g.*, *Idle Free Sys., Inc. v. Bergstrom, Inc*., IPR2012-00027, Paper 26 at 6-8 (P.T.A.B. June 11, 2013) (representative).

essentially the same, albeit narrower, than the originally asserted claims, such that if the narrower claims had existed in the first litigation, any accused infringing activity would have been covered by both the original and the reexamined claims. 746 F.3d at 1352-53. Here, in contrast, the disclaimed claims are of a different scope than the proposed amended claims. Further, none of the original claims (including those that were disclaimed) requires the 3-component premedication recited in each proposed amended claim, such that a court would need to do a different invalidity analysis for those amended claims. Appx368-369, Appx14181-14182.

In particular, disclaimed claim 7 is limited to circumstances wherein cabazitaxel "is administered in an amount to provide an AUC of about 991 ng·h/mL (CV 34%)," a condition not required by any of the amended claims. Appx369, Appx14181-14182. Similarly, the method of disclaimed claim 11 includes additional steps not present in any of the proposed amended claims of "monitoring blood counts and measuring neutrophil levels in the patient" and "discontinuing cabazitaxel treatment in a patient with a neutrophil count of ≤1,500 cells/$mm^3$." Appx369, Appx14181-14182. And, disclaimed claims 14-16 are limited to a specific dose of prednisone or prednisolone of 10 mg/day, a condition not required by the amended claims. Appx369, Appx14181-14182. Thus, proposed amended claims 31-34 have different language and scope than the

disclaimed claims, and the use of a product that infringed one or more of the proposed amended claims would not necessarily infringe claims 7, 11, or 14-16. Accordingly, the reasoning of *Senju* does not apply to these disclaimed claims, and Defendants' argument that their potential claim preclusion defense creates a case or controversy here should fail for this reason alone. *See Microsoft Corp. v. DataTern, Inc*., 755 F.3d 899, 904-05 (Fed. Cir. 2014) (in determining whether there is a case or controversy this Court looks to the elements of the potential cause of action, and there must be allegations "that establish at least a reasonable potential that such a claim could be brought").

While disclaimed claim 26 (directed to the specific cabazitaxel dose of 20 $mg/m^2$) is broader than one of the four proposed amended claims (i.e, claim 34), asserted claims 21 and 30 are also broader than proposed amended claim 34 since, like claim 26, asserted claims 21 and 30 recite treating patients with prostate cancer that has progressed during or after treatment with docetaxel by administering 20 $mg/m^2$ of cabazitaxel in combination with either a corticoid or prednisone. Appx369, Appx14181-14182. Therefore, to the extent *Senju* applies here at all, judgment on the merits as to disclaimed claim 26 would be superfluous for Defendants' purposes because claims 21 and 30 already have been adjudged invalid. Thus, a judgment on disclaimed claim 26 would not protect any rights of Defendants that are not already protected by the judgment invalidating claims 21

and 30.

### 2. Even if *Senju* Applied, the Potential for a Claim Preclusion Dispute Is Too Remote, Speculative, and Contingent to Satisfy the Case or Controversy Requirement

As explained above, in the declaratory judgment context, a justiciable case or controversy must, among other things, be of "sufficient immediacy and reality" to warrant relief. *Supra* Argument Section I; *MedImmune*, 549 U.S. at 127. This "immediacy" requirement considers "how far in the future the potential infringement is, whether the passage of time might eliminate or change any dispute, and how much if any harm the potential infringer is experiencing, at the time of the suit, that an adjudication might redress." *Sandoz Inc. v. Amgen*, 773 F.3d 1274, 1278 (Fed. Cir. 2014). The "reality" requirement, which is related to immediacy, considers "uncertainties about whether the plaintiff will take an action that will expose it to potential infringement liability and, if so, exactly what action." *Id*. Similarly, declaratory judgment jurisdiction requires that a claim be ripe for resolution. *Id*. "A claim is not ripe for adjudication if it rests upon contingent future events that may not occur as anticipated, or indeed may not occur at all." *Texas v. United States*, 523 U.S. 296, 300 (1998) (internal quotations omitted) (finding claim not ripe because it was "too speculative whether the problem" presented "will ever need solving"). Here, under these principles, Defendants' theoretical claim preclusion dispute is simply too remote, speculative,

and contingent to meet the immediacy, reality, and ripeness requirements of jurisdiction that are mandated by Supreme Court precedent.

Any actual claim preclusion dispute here may arise only if a number of future contingent events occur, which present two possible scenarios. In the first scenario, (1) this Court reverses the PTAB's finding that the proposed amended claims are invalid, and those claims are granted in the IPR, (2) that decision survives a request for rehearing, (3) Sanofi asserts the proposed amended claims against Defendants, and (4) the parties do not settle their case.[8] In the second scenario, (1) this Court remands Sanofi's motion to amend to the PTAB for further findings, (2) on remand, the PTAB grants Sanofi's motion to amend resulting in issuance of the amended claims, (3) the PTAB decision survives a request for rehearing, (4) the PTAB decision survives an appeal by Mylan, (5) that appeal decision survives a request for rehearing, (6) Sanofi asserts the proposed amended claims against Defendants, and (7) the parties do not settle their case.

Significantly, Defendants already have asserted that neither of these scenarios is likely to occur. Appx5096 (Defendants stating that it is "extremely

[8] Even if this Court reverses the PTAB and finds the proposed amended claims patentable prior to deciding the instant appeal, the jurisdictional question here will still be whether there was a case or controversy over the disclaimed claims at the time the district court issued its decision. *Janssen Pharmaceutica*, 540 F.3d at 1362-63 & n.9 (noting that the Federal Circuit looks at whether jurisdiction exists when the district court issued the final judgment, not when the appeals court is writing its decision).

unlikely" that Sanofi's motion to amend will succeed). At bottom, the case or controversy Defendants advocate here is contingent upon future events that have not occurred, and which Defendants have asserted will not occur.

Thus, where, as here, "it is unclear when any even arguably infringing activity will occur, a dispute will lack the immediacy necessary to support the exercise of declaratory judgment jurisdiction." *Matthew Int'l Corp. v. Biosafe Eng'g, LLC*, 695 F.3d 1322, 1330 (Fed. Cir. 2012); *see also AIDS Healthcare Found., Inc. v. Gilead Sciences, Inc.*, No. 2016-2475, Slip Op. at 7 (Fed. Cir. May 11, 2018) ("The uncertainty of whether future infringement might occur at all weighs against the immediacy and reality requirement of declaratory action."). In *First Data Corp. v. Inselberg*, this Court found that declaratory judgment claims and counterclaims were not ripe because they required the "contingent future event of recovering title to the patents by having a court invalidate the assignment agreement and order that the patents be returned." 870 F.3d 1367, 1374-75 (Fed. Cir. 2017) (internal quotations omitted). Here, like in *First Data*, the proposed amended claims will not exist without the "contingent future event" of this Court's or the PTAB's validity finding after appeal. Therefore, a potential dispute about those currently non-existent claims is not ripe for adjudication now.

In fact, there can be little doubt that if Defendants now sought a declaratory judgment of invalidity of the proposed amended claims, their case would not be

ripe for review. *See, e.g.*, *GAF Bldg. Materials Corp. v. Elk Corp.*, 90 F.3d 479, 482-83 (Fed. Cir. 1996) (finding no justiciable case or controversy over patent that had not yet issued at the time the complaint was filed); *Spectronics Corp.*, 940 F.2d at 636 ("[T]he existence of issued patent claims, presently enforceable against Spectronics, are a requisite to litigation of a declaratory judgment action."). If anything, the "controversy" Defendants have manufactured here is even more remote than a controversy over non-existent patent claims. Defendants effectively seek an advisory opinion on the merits of their potential claim preclusion defense should Sanofi be granted and assert the proposed amended claims in the future. The Supreme Court has repeatedly found such requests to be improper and not justiciable. *See Coffman v. Breeze Corps.*, 323 U.S. 316, 324 (1944) (request for a declaratory judgment that the Royalty Adjustment Act was unconstitutional and for an injunction preventing compliance with that Act was not justiciable because the request was "for an advisory opinion as to the validity of a defense to a suit for the recovery of the royalties," where no such suit had been filed); *Calderon v. Ashmus*, 523 U.S. 740, 747 (1998) (no Article III jurisdiction where the respondent sought "a declaratory judgment as to the validity of a defense the State may, or may not, raise in a habeas proceeding" which was an "attempt[] to gain a litigation advantage by obtaining an advance ruling on an affirmative defense").

Defendants' reliance below (Appx14184) on *Teva Pharmaceuticals USA*,

*Inc. v. Novartis Pharmaceuticals Corp*., 482 F.3d 1330 (Fed. Cir. 2007) was misplaced. In that case, which Defendants cited to argue that the threat of a future suit creates a justiciable controversy, the patent claims in dispute already had issued, and the patentee had chosen not to assert them. 482 F.3d at 1340-41. Here, of course, the proposed amended claims do not yet exist. Where the existence of patent claims is uncertain, courts have repeatedly found that no immediate or real case or controversy exists. *See, e.g.*, *Amana Refrigeration, Inc. v. Quadlux, Inc.*, 172 F.3d 852, 856 (Fed. Cir. 1999) (risk of further litigation on the potential grant of a reissue patent was "wholly speculative" and, therefore, insufficient to establish a present controversy); *Spectronics Corp.*, 940 F.2d at 636-37 (no jurisdiction over potential infringement of claims in reissue that did not yet exist); *Visto Corp. v. Sprogit Techs., Inc*., No. 04-0651, 2006 U.S. Dist. LEXIS 96173, at *12 (N.D. Cal. Oct. 4, 2006) (risk of infringement action on claims in reexamination too speculative to create a case or controversy). Accordingly, the mere "possibility of future infringement does not meet the immediacy and reality criteria" of the case or controversy requirement for jurisdiction. *AIDS Healthcare Found*., Slip. Op. at 7.

Finally, because the injunction based on the '170 patent prevents Defendants from launching their proposed cabazitaxel products until 2021 (Appx1-13), Defendants are not currently suffering any harm based on the disclaimed claims or the potential future amended claims. Rather, Defendants' asserted injury is the

mere ***potential*** to return to the district court and participate in litigation over the proposed amended claims, an event which may never happen. Appx14186-14187.[9]

### B. Defendants' Potential Request for Attorneys' Fees Does Not Create a Case or Controversy

Defendants asserted below that there continues to be a case or controversy with respect to the disclaimed claims because Defendants allegedly need a final judgment on those claims to support an award of attorneys' fees. Appx14188-14190. By statute, to pursue such an award, Defendants must show that they are "the prevailing party" and that this is an "exceptional case[]." 35 U.S.C. § 285.

There are two reasons why Defendants' potential attorneys' fees request fails to create a case or controversy among the parties here. First, subject matter jurisdiction to hear an attorneys' fees request does not confer jurisdiction to decide patent validity. In *Highway Equipment Co. v. FECO, Ltd*. (cited by Defendants below), after the patent owner provided a covenant not to sue, the parties stipulated to dismissal of patent infringement claims and declaratory judgment counterclaims for non-infringement and invalidity. 469 F.3d 1027, 1030 (Fed. Cir. 2006). The district court dismissed the entire action, but retained subject matter jurisdiction to decide the attorneys' fees request. *Id*. at 1031. This Court noted that the covenant

[9] Defendants would be in the same situation if Sanofi had instead pursued the proposed amended claims in a continuation application that issued after the initial litigation was commenced.

not to sue "may have eliminated the case or controversy pled in the patent-related counterclaims and deprived the district court of Article III jurisdiction with respect to those counterclaims," but the covenant did "not deprive the district court of jurisdiction to determine . . . the request for attorney[s'] fees under 35 U.S.C. § 285." *Id*. at 1032 n.1. Thus, the Court recognized that jurisdiction to decide the merits of the declaratory judgment claims was separate and independent from jurisdiction to consider a request for attorneys' fees based on litigation conduct, and that jurisdiction over the latter request does not support jurisdiction over the former claim.

Similarly, in *H.R. Technologies, Inc. v. Astechnologies, Inc*., where the plaintiff was found not to own the patent in suit, patent infringement claims and counterclaims for a declaratory judgment of non-infringement were properly dismissed by the district court for lack of standing. 275 F.3d 1378, 1381, 1386 (Fed. Cir. 2002). However, this Court recognized that the district court improperly dismissed defendant's counterclaim for attorneys' fees under Section 285. *Id*. at 1386. Thus, a pending attorneys' fees dispute does not create subject matter jurisdiction over invalidity counterclaims that are otherwise not justiciable. Put differently, an attorneys' fees dispute cannot be used to manufacture a controversy regarding patent invalidity counterclaims. *See Sony Elecs., Inc. v. Soundview Techs. Inc*., 359 F. Supp. 2d 173, 176-77 (D. Conn. 2005) (finding that a party "is

entitled to seek attorneys fees on the underlying litigation on which [it] has prevailed, but [that the party] cannot create more litigation that is otherwise moot merely to create an alternative basis for attorneys fees").

Second, under the attorneys' fees statute, Defendants should not be the "prevailing party" in the district court because they lost in all respects on the '170 patent. There can be only one prevailing party (*Shum v. Intel Corp.*, 629 F.3d 1360, 1367 (Fed. Cir. 2010)),[10] who must receive "at least some relief on the merits" and "that relief must materially alter the legal relationship between the parties by modifying one party's behavior in a way that directly benefits the opposing party." *SSL Servs., LLC v. Citrix Sys.*, 769 F.3d 1073, 1086 (Fed. Cir. 2014) (internal quotations omitted). Here, Sanofi obtained an injunction keeping Defendants' cabazitaxel products off the market until at least 2021, when the '170 patent expires. Thus, Sanofi should be the prevailing party here because the injunction Sanofi obtained altered Defendants' behavior in a way that benefits Sanofi. *See id.* at 1086-87 (finding patentee who recovered damages for willful infringement on one patent to be the prevailing party even though another patent

[10] While *Shum* addressed a Fed. R. Civ. P. 54(d)(1) award of litigation costs, the Court's reasoning was based on use of "the" in the rule, which "unambiguously limits the number of prevailing parties in a given case to one," similar to the use of "the prevailing party" in 35 U.S.C. § 285. 629 F.3d 1367; *see also Tech. Innovations, LLC v. Amazon.com, Inc.*, No. 11-690, 2013 U.S. Dist. LEXIS 115352, at *10-11 (D. Del. Aug. 15, 2013) (applying this single prevailing party rule to Section 285).

was found not infringed). Thus, a judgment on the disclaimed claims of the '592 patent would not make Defendants the prevailing party here.

Moreover, even if Defendants could be the prevailing party (having invalidated the '592 patent claims despite being enjoined by the '170 patent), contrary to their assertions below, Defendants do not need a judgment on the disclaimed claims to pursue an attorneys' fees request. Rather, the district court's final judgment of invalidity of the sole asserted claims 21 and 30 of the '592 patent should be sufficient for that purpose.

Lastly, even a cursory review of Defendants' potential claim of "exceptional case" reveals serious flaws, suggesting that it is unlikely that Defendants' attorneys' fees claim will proceed. Defendants fault Sanofi for continuing to assert patent claims after they were found invalid by the PTAB, while simultaneously accusing Sanofi of gamesmanship for dropping claims 7, 11, 14-16 and 26 from litigation after the FWD issued. Appx14188-14189 (Defendants arguing that allegations of exceptional case are "made all the worse" by Sanofi "persist[ing]" with claims "even after the IPR decision"). If continued assertion of claims found invalid by the PTAB makes this an exceptional case, then Sanofi's decision to drop all but two of those claims from litigation after the PTAB's invalidity finding

cannot also support an allegation of gamesmanship.[11] Plainly, Sanofi's narrowing of the issues in dispute does not make this an exceptional case. *See, e.g.*, *Stickle v. Heublein, Inc.*, 716 F.2d 1550, 1564-65 (Fed. Cir. 1983) (finding that withdrawal of defenses shortly before trial was not sufficient to support bad faith for exceptional case purposes without evidence the defenses were a sham and used for vexatious or dilatory tactics); *Power Integrations, Inc. v. Fairchild Semiconductor Int'l, Inc.*, No. 09-5235, 2017 U.S. Dist. LEXIS 5561, at *20 (N.D. Cal. Jan. 13, 2017) (finding the losing party to be "well within reason to assert a broader range of [counter]claims and then narrow them" (quoting *Chiron Corp. v. Sourcecf Inc.*, No. 05-1938, 2006 U.S. Dist. LEXIS 52589, at *7 (N.D. Cal. June 16, 2006))). Indeed, it was not gamesmanship by Sanofi, but rather Mylan's delayed IPR and Defendants' refusal to stay the litigation that led to the PTAB invalidating claims in litigation in the middle of trial and to the inevitable cancellation of claims 7, 11, 14-16, and 26.

[11] It was neither improper nor exceptional for Sanofi to continue asserting claims 21 and 30 in litigation since Sanofi had the right to pursue an appeal from the FWD concerning those claims, and Defendants' burden of proof before the district court to prove invalidity was higher than Mylan's burden before the PTAB. Appx12185-12187; *compare* 35 U.S.C. § 316(e) (preponderance of the evidence before the PTAB) *with Microsoft Corp. v. i4i Ltd.*, 564 U.S. 91, 100 (2011) (clear and convincing evidence in litigation).

## V. The District Court's Judgment of Invalidity of the Disclaimed Patent Claims Should Be Vacated

Appellate courts have broad statutory power to "affirm, modify, vacate, set aside or reverse any judgment, decree, or order of a court lawfully brought before [them] for review." 28 U.S.C. § 2106. When it is determined that a district court did not have jurisdiction over particular patent claims prior to issuing a decision on the merits, the invalidity judgment for those claims should be vacated. *See, e.g.*, *Fox Group*, 700 F.3d at 1308-09; *Creative Compounds, LLC v. Starmark Labs.*, 651 F.3d 1303, 1317 (Fed. Cir. 2011); *King Pharms.*, 616 F.3d at 1283. Thus, here, because there was no longer a justiciable case or controversy over the disclaimed claims by the time the district court issued its decision, vacatur of the district court's invalidity finding of those claims is the appropriate remedy.

## CONCLUSION AND RELIEF SOUGHT

For the foregoing reasons, this Court should reverse the district court's finding that there was subject matter jurisdiction over claims 7, 11, 14-16, and 26 of the '592 patent and vacate the judgment of invalidity of those claims.

Respectfully submitted,

Date: June 25, 2018

*/s/ William E. Solander*

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# ADDENDUM

**UNITED STATES DISTRICT COURT**
**DISTRICT OF NEW JERSEY**

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| SANOFI-AVENTIS U.S. LLC, AVENTIS PHARMA S.A. and SANOFI<br><br>Plaintiffs,<br><br>v.<br><br>FRESENIUS KABI USA, LLC,<br><br>Defendant. | Consolidated Civil Action No. 14-07869(MAS)(LHG)<br><br>Civil Action No. 14-8082(MAS)(LHG)<br>Civil Action No. 15-2631(MAS)(LHG)<br><br>**FINAL JUDGMENT** |
| SANOFI-AVENTIS U.S. LLC, AVENTIS PHARMA S.A. and SANOFI<br><br>Plaintiffs,<br><br>v.<br><br>ACCORD HEALTHCARE, INC.,<br><br>Defendant. | Civil Action No. 14-08079(MAS)(LHG)<br>Civil Action No. 15-02520(MAS)(LHG) |
| SANOFI-AVENTIS U.S. LLC, AVENTIS PHARMA S.A. and SANOFI<br><br>Plaintiffs,<br><br>v.<br><br>BPI LABS, LLC AND BELCHER PHARMACEUTICALS, LLC,<br><br>Defendants. | Civil Action No. 14-08081(MAS)(LHG)<br>Civil Action No. 15-02521(MAS)(LHG) |

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| SANOFI-AVENTIS U.S. LLC, AVENTIS PHARMA S.A. and SANOFI<br><br>Plaintiffs,<br><br>v.<br><br>APOTEX CORP. AND APOTEX INC.,<br><br>Defendants. | Civil Action No. 15-00287(MAS)(LHG)<br>Civil Action No. 15-01835(MAS)(LHG) |
| SANOFI-AVENTIS U.S. LLC, AVENTIS PHARMA S.A. and SANOFI<br><br>Plaintiffs,<br><br>v.<br><br>BRECKENRIDGE PHARMACEUTICAL, INC.,<br><br>Defendant. | Civil Action No. 15-00289(MAS)(LHG)<br>Civil Action No. 15-01836(MAS)(LHG) |
| SANOFI-AVENTIS U.S. LLC, AVENTIS PHARMA S.A. and SANOFI<br><br>Plaintiffs,<br><br>v.<br><br>MYLAN LABORATORIES LTD.,<br><br>Defendant. | Civil Action No. 15-00290(MAS)(LHG)<br>Civil Action No. 15-03392(MAS)(LHG) |

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| SANOFI-AVENTIS U.S. LLC, AVENTIS PHARMA S.A. and SANOFI<br><br>Plaintiffs,<br><br>v.<br><br>ACTAVIS LLC AND ACTAVIS ELIZABETH LLC,<br><br>Defendants. | Civil Action No. 15-00776(MAS)(LHG)<br>Civil Action No. 15-03107(MAS)(LHG) |
| SANOFI-AVENTIS U.S. LLC, AVENTIS PHARMA S.A. and SANOFI<br><br>Plaintiffs,<br><br>v.<br><br>DR. REDDY'S LABORATORIES, INC. AND DR. REDDY'S LABORATORIES, LTD.,<br><br>Defendants. | Civil Action No. 15-02522(MAS)(LHG)<br>Civil Action No. 16-02259(MAS)(LHG) |
| SANOFI-AVENTIS U.S. LLC, AVENTIS PHARMA S.A. and SANOFI<br><br>Plaintiffs,<br><br>v.<br><br>GLENMARK PHARMACEUTICALS INC., USA AND GLENMARK PHARMACEUTICALS LTD.,<br><br>Defendants. | Civil Action No. 15-02523(MAS)(LHG) |

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| SANOFI-AVENTIS U.S. LLC, AVENTIS PHARMA S.A. and SANOFI<br><br>Plaintiffs,<br><br>v.<br><br>SANDOZ INC.,<br><br>Defendant. | Civil Action No. 16-05678(MAS)(LHG) |

This consolidated patent infringement action was brought by Plaintiffs Sanofi Aventis U.S. LLC, Aventis Pharma S.A., and Sanofi ("Plaintiffs") against Defendants Fresenius Kabi USA, LLC ("Fresenius"), Accord Healthcare, Inc. ("Accord"), BPI Labs and Belcher Pharmaceuticals, LLC (collectively, "BPI"), Apotex Corp. and Apotex Inc. (collectively, Apotex"), Breckenridge Pharmaceutical, Inc. ("Breckenridge"), Mylan Laboratories Ltd. ("Mylan"), Actavis LLC and Actavis Elizabeth LLC (collectively, "Actavis"), Dr. Reddy's Laboratories, Inc. and Dr. Reddy's Laboratories, Ltd. (collectively, "Dr. Reddy's"), Glenmark Pharmaceuticals Inc., USA and Glenmark Pharmaceuticals Ltd. (collectively, "Glenmark"), and Sandoz Inc. ("Sandoz") (all collectively, "Defendants"), alleging infringement of U.S. Patent Nos. 5,847,170 ("the '170 patent") and/or 8,927,592 ("the '592 patent").

On September 15, 2017, the Court consolidated for trial the above-captioned suits pending against Fresenius, Accord, Apotex, Mylan, and Actavis in *Sanofi-Aventis U.S. LLC et al. v. Fresenius Kabi USA, LLC, et al.*, No. 3:14-cv-7869-MAS-LHG (D.N.J.) (hereinafter, "Consolidated Lead Case"). Civil Action No. 14-7869, D.I. 232, ¶ 2. On or before September 15, 2017, the Court entered stipulations between Plaintiffs and each of BPI, Glenmark, Dr. Reddy's, Breckenridge, and Sandoz, under which the parties to these other actions agreed, *inter alia*, to be bound by particular aspects of any final judgment in the Consolidated Lead Case.

More specifically, BPI, Dr. Reddy's, Breckenridge, and Sandoz agreed to be bound by any judgment as to the infringement and validity of the '170 and '592 patents entered in the Consolidated Lead Case. *Sanofi-Aventis U.S. LLC et al. v. BPI Labs, LLC, et al.*, Nos. 3:14-cv-8081 (D.N.J.), D.I. 58, Stipulation ¶ 2, 3:15-cv-2521 (D.N.J.), D.I. 48, Stipulation ¶ 2; *Sanofi-Aventis U.S. LLC et al. v. Dr. Reddy's Labs., Inc. et al.*, No. 3:15-cv-2522 (D.N.J.), D.I. 48, Stipulation ¶ 2, 3:16-cv-2259 (D.N.J.), D.I. 24, Stipulation ¶ 2; *Sanofi-Aventis U.S. LLC et al. v. Breckenridge Pharmaceutical, Inc.*, Nos. 15-cv-289 (D.N.J.), D.I. 79, Stipulation ¶ 2, 15-cv-1836 (D.N.J.), D.I. 56, Stipulation ¶ 2; *Sanofi-Aventis U.S. LLC et al. v. Sandoz Inc.*, No. 16-cv-5678 (D.N.J.), D.I. 32, Stipulation ¶ 2. Glenmark agreed to be bound by any judgment as to the infringement and validity of the '592 patent entered in the Consolidated Lead Case. *Sanofi-Aventis U.S. LLC et al. v. Glenmark Pharmaceuticals, Inc., USA et al.*, No. 15-cv-2523 (D.N.J.), D.I. 56, Stipulation ¶ 1. Prior to trial, Plaintiffs notified Defendants that Claims 1-6, 8-10, 12-13, 17-20, 22-25, and 27-29 of the '592 patent were not asserted.

The Court conducted an eight-day bench trial on September 18-20 and September 25-29, 2017 in the Consolidated Lead Case. The parties in the Consolidated Lead Case submitted post-trial briefs on October 31, 2017, and the Court heard closing arguments on November 8, 2017. The parties filed supplemental correspondence on November 17, 2017, December 4, 2017, and December 11, 2017. Pursuant to Court order, the parties filed supplemental legal briefs on December 13, 2017. The Court issued an Order in the Consolidated Lead Case on December 17, 2017 (D.I. 306).

In the Consolidated Lead Case, the Court has set forth its Findings of Fact and Conclusions of Law in an accompanying Opinion. Having considered the documentary evidence

and testimony, and having reviewed the parties' post-trial briefs and supplemental legal briefs, for the reasons set forth in the Court's Opinion dated December 19, 2017 (D.I. 308),

**IT IS HEREBY ORDERED AND ADJUDGED** that:

1. Final judgment is entered in favor of Plaintiffs and against Defendants (except for Glenmark, which did not challenge the '170 patent) that Claims 1 and 2 of the '170 patent are not invalid due to obviousness and obviousness-type double patenting.

2. Final judgment is entered in favor of Plaintiffs and against Fresenius Kabi USA, LLC that the commercial manufacture, use, sale, or offer for sale within the United States or importation into the United States of the Cabazitaxel Injection, 60 mg/1.5 mL solution that is the subject of Abbreviated New Drug Application ("ANDA") No. 207591 would infringe Claims 1 and 2 of the '170 patent.

3. Pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any final approval by the United States Food and Drug Administration of ANDA No. 207591 under § 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355(j)) shall be a date not earlier than the date of expiration of the '170 patent together with the period of Pediatric Exclusivity awarded to Plaintiffs. Currently the '170 patent together with the period of Pediatric Exclusivity expires on September 26, 2021.

4. Pursuant to 35 U.S.C. § 271(e)(4)(B), Fresenius Kabi USA, LLC and its officers, agents, attorneys, and employees, and those acting in privity or concert therewith, are hereby enjoined from commercial manufacture, use, sale, or offer for sale within the United States or importation into the United States of the product that is the subject of ANDA No. 207591 until the expiration date of the '170 patent, which is currently March 26, 2021.

5. Final judgment is entered in favor of Plaintiffs and against Fresenius Kabi USA, LLC that the commercial manufacture, use, sale, or offer for sale within the United States or importation into the United States of the Cabazitaxel Injection, 60 mg/3 mL (20 mg/mL) solution that is the subject of New Drug Application ("NDA") No. 207937 would infringe Claims 1 and 2 of the '170 patent.

6. Pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any final approval by the United States Food and Drug Administration of NDA No. 207937 under § 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355(b)(2)) shall be a date not earlier than the date of expiration of the '170 patent together with the period of Pediatric Exclusivity awarded to Plaintiffs. Currently the '170 patent together with the period of Pediatric Exclusivity expires on September 26, 2021.

7. Pursuant to 35 U.S.C. § 271(e)(4)(B), Fresenius Kabi USA, LLC and its officers, agents, attorneys, and employees, and those acting in privity or concert therewith, are hereby enjoined from commercial manufacture, use, sale, or offer for sale within the United States or importation into the United States of the product that is the subject of NDA No. 207937 until the expiration date of the '170 patent, which is currently March 26, 2021.

8. Final judgment is entered in favor of Plaintiffs and against Accord Healthcare, Inc. that the commercial manufacture, use, sale, or offer for sale within the United States or importation into the United States of the Cabazitaxel Injection, 60 mg/1.5 mL product that is the subject of ANDA No. 207693 would infringe Claims 1 and 2 of the '170 patent.

9. Pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any final approval by the United States Food and Drug Administration of ANDA No. 207693 under § 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355(j)) shall be a date not

earlier than the date of expiration of the '170 patent together with the period of Pediatric Exclusivity awarded to Plaintiffs. Currently the '170 patent together with the period of Pediatric Exclusivity expires on September 26, 2021.

10. Pursuant to 35 U.S.C. § 271(e)(4)(B), Accord Healthcare, Inc. and its officers, agents, attorneys, and employees, and those acting in privity or concert therewith, are hereby enjoined from commercial manufacture, use, sale, or offer for sale within the United States or importation into the United States of the product that is the subject of ANDA No. 207693 until the expiration date of the '170 patent, which is currently March 26, 2021.

11. Final judgment is entered in favor of Plaintiffs and against Accord Healthcare, Inc. that the commercial manufacture, use, sale, or offer for sale within the United States or importation into the United States of the Cabazitaxel Injection, 20 mg/mL, 3mL product that is the subject of NDA No. 207949 would infringe Claims 1 and 2 of the '170 patent.

12. Pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any final approval by the United States Food and Drug Administration of NDA No. 207949 under § 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355(b)(2)) shall be a date not earlier than the date of expiration of the '170 patent together with the period of Pediatric Exclusivity awarded to Plaintiffs. Currently the '170 patent together with the period of Pediatric Exclusivity expires on September 26, 2021.

13. Pursuant to 35 U.S.C. § 271(e)(4)(B), Accord Healthcare, Inc. and its officers, agents, attorneys, and employees, and those acting in privity or concert therewith, are hereby enjoined from commercial manufacture, use, sale, or offer for sale within the United States or importation into the United States of the product that is the subject of NDA No. 207949 until the expiration date of the '170 patent, which is currently March 26, 2021.

14. Final judgment is entered in favor of Plaintiffs and against BPI Labs, LLC and Belcher Pharmaceuticals, LLC that the commercial manufacture, use, sale, or offer for sale within the United States or importation into the United States of the Cabazitaxel 60 mg/1.5 mL solution for intravenous infusion that is the subject of ANDA No. 207735 would infringe Claims 1 and 2 of the '170 patent.

15. Pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any final approval by the United States Food and Drug Administration of ANDA No. 207735 under § 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355(j)) shall be a date not earlier than the date of expiration of the '170 patent together with the period of Pediatric Exclusivity awarded to Plaintiffs. Currently the '170 patent together with the period of Pediatric Exclusivity expires on September 26, 2021.

16. Pursuant to 35 U.S.C. § 271(e)(4)(B), BPI Labs, LLC and Belcher Pharmaceuticals, LLC and their officers, agents, attorneys, and employees, and those acting in privity or concert therewith, are hereby enjoined from commercial manufacture, use, sale, or offer for sale within the United States or importation into the United States of the product that is the subject of ANDA No. 207735 until the expiration date of the '170 patent, which is currently March 26, 2021.

17. Final judgment is entered in favor of Plaintiffs and against Apotex Corp. and Apotex Inc. that the commercial manufacture, use, sale, or offer for sale within the United States or importation into the United States of the Cabazitaxel Injection, 60 mg/1.5 mL product that is the subject of ANDA No. 207736 would infringe Claims 1 and 2 of the '170 patent.

18. Pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any final approval by the United States Food and Drug Administration of ANDA No. 207736 under

§ 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355(j)) shall be a date not earlier than the date of expiration of the '170 patent together with the period of Pediatric Exclusivity awarded to Plaintiffs. Currently the '170 patent together with the period of Pediatric Exclusivity expires on September 26, 2021.

19. Pursuant to 35 U.S.C. § 271(e)(4)(B), Apotex Corp. and Apotex, Inc. and their officers, agents, attorneys, and employees, and those acting in privity or concert therewith, are hereby enjoined from commercial manufacture, use, sale, or offer for sale within the United States or importation into the United States of the product that is the subject of ANDA No. 207736 until the expiration date of the '170 patent, which is currently March 26, 2021.

20. Final judgment is entered in favor of Plaintiffs and against Breckenridge Pharmaceutical, Inc. that the commercial manufacture, use, sale, or offer for sale within the United States or importation into the United States of the Cabazitaxel Solution, IV, 60 mg/1.5 mL (40 mg/mL) product that is the subject of ANDA No. 207619 would infringe Claims 1 and 2 of the '170 patent.

21. Pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any final approval by the United States Food and Drug Administration of ANDA No. 207619 under § 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355(j)) shall be a date not earlier than the date of expiration of the '170 patent together with the period of Pediatric Exclusivity awarded to Plaintiffs. Currently the '170 patent together with the period of Pediatric Exclusivity expires on September 26, 2021.

22. Pursuant to 35 U.S.C. § 271(e)(4)(B), Breckenridge Pharmaceutical, Inc. and its officers, agents, attorneys, and employees, and those acting in privity or concert therewith, are hereby enjoined from commercial manufacture, use, sale, or offer for sale within

the United States or importation into the United States of the product that is the subject of ANDA No. 207619 until the expiration date of the '170 patent, which is currently March 26, 2021.

23. Final judgment is entered in favor of Plaintiffs and against Mylan Laboratories Ltd. that the commercial manufacture, use, sale, or offer for sale within the United States or importation into the United States of the Cabazitaxel Injection [60 mg/1.5 mL] [40 mg/mL] product that is the subject of ANDA No. 207381 would infringe Claims 1 and 2 of the '170 patent.

24. Pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any final approval by the United States Food and Drug Administration of ANDA No. 207381 under § 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355(j)) shall be a date not earlier than the date of expiration of the '170 patent together with the period of Pediatric Exclusivity awarded to Plaintiffs. Currently the '170 patent together with the period of Pediatric Exclusivity expires on September 26, 2021.

25. Pursuant to 35 U.S.C. § 271(e)(4)(B), Mylan Laboratories Ltd. and its officers, agents, attorneys, and employees, and those acting in privity or concert therewith, are hereby enjoined from commercial manufacture, use, sale, or offer for sale within the United States or importation into the United States of the product that is the subject of ANDA No. 207381 until the expiration date of the '170 patent, which is currently March 26, 2021.

26. Final judgment is entered in favor of Plaintiffs and against Actavis LLC and Actavis Elizabeth LLC that the commercial manufacture, use, sale, or offer for sale within the United States or importation into the United States of the Cabazitaxel Injection, 10 mg/mL product that is the subject of NDA No. 207970 would infringe Claims 1 and 2 of the '170 patent.

27. Pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any final approval by the United States Food and Drug Administration of NDA No. 207970 under § 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355(b)(2)) shall be a date not earlier than the date of expiration of the '170 patent together with the period of Pediatric Exclusivity awarded to Plaintiffs. Currently the '170 patent together with the period of Pediatric Exclusivity expires on September 26, 2021.

28. Pursuant to 35 U.S.C. § 271(e)(4)(B), Actavis LLC and Actavis Elizabeth LLC and their officers, agents, attorneys, and employees, and those acting in privity or concert therewith, are hereby enjoined from commercial manufacture, use, sale, or offer for sale within the United States or importation into the United States of the product that is the subject of NDA No. 207970 until the expiration date of the '170 patent, which is currently March 26, 2021.

29. Final judgment is entered in favor of Plaintiffs and against Dr. Reddy's Laboratories, Inc. and Dr. Reddy's Laboratories, Ltd. that the commercial manufacture, use, sale, or offer for sale within the United States or importation into the United States of the Cabazitaxel, 60 mg/1.5 mL product that is the subject of ANDA No. 207718 would infringe Claims 1 and 2 of the '170 patent.

30. Pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any final approval by the United States Food and Drug Administration of ANDA No. 207718 under § 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355(j)) shall be a date not earlier than the date of expiration of the '170 patent together with the period of Pediatric Exclusivity awarded to Plaintiffs. Currently the '170 patent together with the period of Pediatric Exclusivity expires on September 26, 2021.

31. Pursuant to 35 U.S.C. § 271(e)(4)(B), Dr. Reddy's Laboratories, Inc. and Dr. Reddy's Laboratories, Ltd. and their officers, agents, attorneys, and employees, and those acting in privity or concert therewith, are hereby enjoined from commercial manufacture, use, sale, or offer for sale within the United States or importation into the United States of the product that is the subject of ANDA No. 207718 until the expiration date of the '170 patent, which is currently March 26, 2021.

32. Final judgment is entered in favor of Plaintiffs and against Sandoz Inc. that the commercial manufacture, use, sale, or offer for sale within the United States or importation into the United States of the Cabazitaxel Injection (10 mg/mL), 45 mg/4.5 mL and 60 mg/6 mL product that is the subject of NDA No. 208715 would infringe Claims 1 and 2 of the '170 patent.

33. Pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any final approval by the United States Food and Drug Administration of NDA No. 208715 under § 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355(b)(2)) shall be a date not earlier than the date of expiration of the '170 patent together with the period of Pediatric Exclusivity awarded to Plaintiffs. Currently the '170 patent together with the period of Pediatric Exclusivity expires on September 26, 2021.

34. Pursuant to 35 U.S.C. § 271(e)(4)(B), Sandoz Inc. and its officers, agents, attorneys, and employees, and those acting in privity or concert therewith, are hereby enjoined from the commercial manufacture, use, sale, or offer for sale within the United States or importation into the United States of the product that is the subject of NDA No. 208715 until the expiration date of the '170 patent, which is currently March 26, 2021.

35. Final judgment is entered in favor of Defendants and against Plaintiffs that claims 7, 11, 14, 15, 16, 21, 26, and 30 of the '592 patent are invalid due to obviousness.

36. In the event that any portion of this Final Judgment is appealed, any motion for attorneys' fees and/or costs under Fed. R. Civ. P. 54(d) and/or Local Rules 54.1 and/or 54.2, including any motion that this case is exceptional under 35 U.S.C. § 285, shall be considered timely if filed and served within thirty (30) days after final disposition of any such appeal.

37. In the event that no portion of this Final Judgment is appealed, any motion for attorneys' fees and/or costs under Fed. R. Civ. P. 54(d) and/or Local Rules 54.1 and/or 54.2, including any motion that this case is exceptional under 35 U.S.C. § 285, shall be considered timely if filed and served within thirty (30) days after the expiration of the time for filing a notice of appeal under Fed. R. App. P. 3 and 4.

38. This Judgment is final and appealable, as all other claims, counterclaims, and defenses have been finally adjudicated.

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Hon. Michael A. Shipp
United States District Judge

Dated: 3/5/18

**UNITED STATES DISTRICT COURT**
**DISTRICT OF NEW JERSEY**

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| SANOFI-AVENTIS U.S. LLC, et al.,<br><br>Plaintiffs,<br><br>v.<br><br>FRESENIUS KABI USA, LLC, et al.,<br><br>Defendants. | Civil Action No. 14-7869 (MAS) (LHG)<br><br>**ORDER** |

This consolidated action arises under the patent laws of the United States. The Court conducted an eight-day bench trial on September 18-20 and September 25-29, 2017. The parties submitted post-trial briefs on October 31, 2017 and the Court heard closing arguments on November 8, 2017. The parties filed supplemental correspondence on November 17, 2017, December 4, 2017, and December 11, 2017. Pursuant to Court order, the parties filed supplemental legal briefs on December 13, 2017. The Court has set forth its Findings of Fact and Conclusions of Law in an accompanying Opinion pursuant to Federal Rule of Civil Procedure 52(a)(1). For the reasons set forth in the accompanying Opinion, and for other good cause shown,

**IT IS** on this 17th day of December 2017 **ORDERED** that:

1. Claims 1 and 2 of U.S. Patent No. 5,847,170 are valid and are infringed by Defendants' proposed generic products.
2. Claims 7, 11, 14, 15, 16, 21, 26, and 30 of U.S. Patent No. 8,927,592 are invalid.
3. The parties shall meet and confer and shall provide to the Court a proposed form of judgment for each of the underlying cases by **December 27, 2017**.
4. The Clerk is directed to file the accompanying Opinion under temporary seal until further order of the Court.

5. To the extent that any party believes that portions of the Court's Opinion should be permanently sealed, that party shall file (or the parties may jointly file) a formal motion to seal. Any motion to seal shall be filed by **January 17, 2018**.

s/ Michael A. Shipp
**MICHAEL A. SHIPP**
**UNITED STATES DISTRICT JUDGE**

**NOT FOR PUBLICATION**

**UNITED STATES DISTRICT COURT**
**DISTRICT OF NEW JERSEY**

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| SANOFI-AVENTIS U.S. LLC, et al.,<br><br>Plaintiffs,<br><br>v.<br><br>FRESENIUS KABI USA, LLC, et al.,<br><br>Defendants. | Civil Action No. 14-7869 (MAS) (LHG)<br><br>**OPINION**<br><br>**SEALED** |

**SHIPP, District Judge**

This consolidated action[1] arises under the patent laws of the United States. The Court has subject matter jurisdiction pursuant to 28 U.S.C. §§ 1331 and 1338(a). The Court conducted an eight-day bench trial on September 18-20 and September 25-29, 2017.[2] The parties submitted

[1] On September 15, 2017, upon consent of the parties, the Court consolidated the following cases for trial: *Sanofi-Aventis U.S., LLC, et al. v. Fresenius Kabi USA, LLC*, 14-7869, 14-8082, 15-2631; *Sanofi-Aventis U.S., LLC, et al. v. Accord Healthcare, Inc.*, 14-8079, 15-2520; *Sanofi-Aventis U.S., LLC, et al. v. Apotex Corp., et al.*, 15-287, 15-1835; *Sanofi-Aventis U.S., LLC, et al. v. Mylan Labs.*, 15-290, 15-3392; and *Sanofi-Aventis U.S., LLC, et al. v. Actavis LLC*, 15-776, 16-3107.

On September 11, 2017, the Court entered the Stipulation to be Bound between Plaintiffs and Defendants Glenmark Pharmaceuticals, Inc., USA and Glenmark Pharmaceuticals Ltd. (15-2523, ECF No. 56.) On September 12, 2017, the Court entered the Stipulation to be Bound between Plaintiffs and Defendants BPI Labs, LLC and Belcher Pharmaceuticals, LLC. (14-8081, ECF No. 58; 15-2521, ECF No. 48.) On September 13, 2017, the Court entered the Stipulation to be Bound between Plaintiffs and Breckenridge Pharmaceutical, Inc. (15-289, ECF No. 79; 15-1836, ECF No. 56.) On September 15, 2017, the Court entered the Stipulation to be Bound between Plaintiffs and Defendants Dr. Reddy's Laboratories, Inc. and Dr. Reddy's Laboratories, Ltd. (15-2522, ECF No. 48; 16-2259, ECF No. 24.) The Defendants in these cases, therefore, did not participate in the bench trial.

[2] The trial transcript is docketed at ECF numbers 286 through 297.

post-trial briefs on October 31, 2017 and the Court heard closing arguments on November 8, 2017. (ECF No. 284.) The Court has considered the evidence presented at trial and the parties' related arguments and herein sets forth its Findings of Fact and Conclusions of Law pursuant to Federal Rule of Civil Procedure 52(a)(1).[3]

## I. BACKGROUND

### A. The Parties

Sanofi ("Sanofi") is a corporation organized and existing under the laws of France, having its principal place of business at 54 rue La Boétie, 75008 Paris, France. (SF 1.)[4] Sanofi-Aventis U.S. LLC ("Sanofi U.S.") is an indirectly, wholly-owned U.S. subsidiary of Sanofi and is a company organized and existing under the laws of the State of Delaware, having commercial headquarters at 55 Corporate Drive, Bridgewater, New Jersey 08807. (SF 2.) Aventis Pharma S.A. ("Aventis") is a corporation organized and existing under the laws of France, having its principal place of business at 20 avenue Raymond Aron, 92160 Antony, France. (SF 3.) Rhône-Poulenc Rorer ("RPR") was a predecessor company to Sanofi. (SF 4.)

Fresenius Kabi USA, LLC ("Fresenius") is a corporation organized and existing under the laws of Delaware, with corporate headquarters at Three Corporate Drive, Lake Zurich, Illinois 60047. (SF 6.) Accord Healthcare, Inc. ("Accord") is a corporation organized and existing under

[3] To the extent that any Finding of Fact represents a Conclusion of Law, it is hereby adopted as a Conclusion of Law and vice versa. In evaluating the testimony of the witnesses appearing at trial, and after the Court had the opportunity to hear their testimony and to observe their demeanor, the Court undertook an individualized credibility assessment of each witness and assigned the appropriate weight to the testimony based on the Court's conclusions with respect to credibility. Such determinations are reflected in the Court's factual findings.

[4] The parties stipulated to a number of facts in the Joint Final Pretrial Order. These Stipulated Facts ("SF") required no proof at trial. (Joint Final Pretrial Order, ECF No. 167.) The Court will reference the paragraph number of each Stipulated Fact, not the corresponding page number of the Joint Final Pretrial Order.

the laws of North Carolina, having its principal place of business as 1009 Slater Road, Suite 210B, Durham, North Carolina 27703. (SF 7.) Belcher Pharmaceuticals, LLC is a Florida corporation having a place of business at 6911 Bryan Dairy Road, Suite 210, Largo, Florida 33777. (SF 8.) BPI Labs, LLC ("BPI") is a Florida corporation that has a place of business at 4400 Route 9 South, Suite 1000, Freehold, New Jersey 07728. (SF 9.) BPI is a wholly-owned subsidiary of Belcher Pharmaceuticals, LLC. (*Id.*) Apotex Inc. is a corporation organized and existing under the laws of Canada, with a place of business at 150 Signet Drive, Toronto, Ontario, Canada M9L 1T9. (SF 10.) Apotex Corp. is a corporation organized and existing under the laws of Delaware, with a place of business at 2400 North Commerce Parkway, Suite 400, Weston, Florida 33326. (SF 11.)

Breckenridge Pharmaceutical, Inc. ("Breckenridge") is a corporation organized and existing under the laws of Florida with a place of business at 6111 Broken Sound Parkway, NW, Suite 170, Boca Raton, Florida 33487. (SF 12.) Mylan Laboratories Limited ("Mylan") is a corporation organized and existing under the laws of India, having its principal place of business at Opp. IIM, Bilekahalli, Bannerghatta Road, Bangalore, Karnataka 560076, India. (SF 13.) Mylan was formerly known as Onco Therapies Limited. (SF 13.) Actavis LLC ("Actavis") is a Delaware corporation with a place of business at Morris Corporate Center III, 400 Interpace Parkway, Parsippany, New Jersey 07054. (SF 14.) Actavis was formerly known as Actavis Inc. (SF 14.)

Dr. Reddy's Laboratories, Inc. is a corporation organized and existing under the laws of New Jersey, having its principal place of business at 107 College Road East, Princeton, New Jersey 08540. (SF 15.) Dr. Reddy's Laboratories, Ltd. is a company organized and existing under the laws of India, having its principal place of business at 8-2-337 Road No. 3, Banjara Hills, Hyderabad 500034, India. (SF 16.) Dr. Reddy's Laboratories, Inc. is a subsidiary of Dr. Reddy's Laboratories, Ltd. (SF 16.)

Glenmark Pharmaceutical Inc., USA is a Delaware corporation, having its principal place of business at 750 Corporate Drive, Mahwah, New Jersey 07430. (SF 17.) Glenmark Pharmaceuticals Inc., USA was formerly known as Glenmark Generics, Inc., USA, and is the North American Division of Glenmark Pharmaceuticals Ltd. (SF 17.) Glenmark Pharmaceuticals Ltd. is a company organized and existing under the laws of India, having its principal place of business at Glenmark House, B D S Marg, Chakala, Off Western Express Highway, Andheri (East), Membai 400099, Maharashtra, India. (SF 18.)

**B. The '170 Patent**

United States Patent No. 5,847,170 ("the '170 patent") is entitled "Taxoids, Their Preparation And Pharmaceutical Compositions Containing Them." (SF 19.) Hervé Bouchard, Jean-Dominique Bourzat, and Alain Commerçon are listed as the named inventors of the '170 patent. (SF 20.) The '170 patent issued from U.S. Patent Application Serial No. 08/622,011, filed on March 26, 1996, and claims priority from U.S. Provisional Application No. 60/010,144, filed January 17, 1996; French Application No. 9503545, filed March 27, 1995; and French Application No. 9515381, filed December 22, 1995. (SF 21.) On December 8, 1998, the United States Patent and Trademark Office issued the '170 patent. (SF 22.) When it issued in 1998, the '170 patent was assigned to RPR. (SF 23.) The '170 patent is now assigned to Aventis Pharma S.A. (SF 24.) The priority date for Claims 1-2 of the '170 patent is March 27, 1995 and the effective U.S. filing date for these claims is January 17, 1996. (SF 24.) The '170 patent is listed in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations ("the Orange Book") for JEVTANA® (hereinafter JEVTANA® or "Jevtana") (NDA No. 201023). (SF 25.) The '170 patent expires on March 6, 2021, and the Orange Book states that it has a period of pediatric exclusivity until September 26, 2021. (SF 26.)

C. **The '592 Patent**

United States Patent No. 8,927,592 ("the '592 patent") is entitled "Antitumoral Use Of Cabazitaxel." (SF 27.) Sunil Gupta is the named inventor of the '592 patent. (SF 28.) The '592 patent issued from U.S. Patent Application Number 13/456,720 ("the '720 application"), filed April 26, 2012, and the '720 application is a continuation of International Application No. PCT/IB2010/054866, filed October 27, 2010. (SF 29-30.) International Application No. PCT/IB2010/054866 claims priority to seven U.S. provisional patent applications: Provisional Application No. 61/256,160, filed October 29, 2009; Provisional Application No. 61/293,903, filed January 11, 2010; Provisional Application No. 61/355,834, filed June 17, 2010; Provisional Application No. 61/355,888, filed June 17, 2010; Provisional Application No. 61/369,929, filed August 2, 2010; Provisional Application No. 61/383,933, filed September 17, 2010; and Provisional Application No. 61/389,969, filed October 5, 2010. (SF 31.)

The priority date for Claims 10, 14-16, 21, 26, and 30 of the '592 patent is October 29, 2009. (SF 32.) The effective U.S. filing date for these claims is October 29, 2009. (SF 32.) The priority date and effective filing date for Claim 11 of the '592 patent is January 11, 2010. (SF 33.) The priority date and effective U.S. filing date for Claims 7 and 8 of the '592 patent is June 17, 2010. (SF 34.) The '592 patent is owned by Aventis and issued on January 6, 2015. (SF 35-36.) The '592 patent is listed in the Orange Book for Jevtana (NDA No. 201023). (SF 37.) The '592 patent expires on October 27, 2030, and the Orange Book states that it has a period of pediatric exclusivity until April 27, 2031. (SF 38.)

D. **Sanofi's JEVTANA® Product**

Sanofi U.S. holds approved New Drug Application ("NDA") No. 201023 for cabazitaxel injection, 60 mg/1.5 mL (40 mg/mL), which is prescribed and sold in the United States under the

trademark JEVTANA®. (SF 39.) The United States Food and Drug Administration ("FDA") approved NDA No. 201023 on June 17, 2010. (SF 39.)

**E. Defendants' Proposed Products**

Defendants' proposed products are set forth in the chart below.[5]

| Application with FDA | Proposed Product | Date of Notice Letter | Patent Challenged | Basis for Certification filed with FDA |
|---|---|---|---|---|
| **Fresenius** | | | | |
| B2 NDA No. 207937 | Cabazitaxel Injection, 60 mg/3 mL solution (20 mg/mL) | Nov. 3, 2014 | '170 patent | Certification pursuant to 21 U.S.C. § 355(b)(2)(A)(iv) the '170 patent is invalid, unenforceable and/or will not be infringed by the commercial manufacture, use, or sale of Fresenius's proposed product. (SF 44.) |
| B2 NDA No. 207937 | Cabazitaxel Injection, 60 mg/3 mL solution (20 mg/mL) | Apr. 2, 2015 | '592 patent | Certification pursuant to 21 U.S.C. § 355(b)(2)(A)(iv): the '592 patent is invalid, unenforceable and/or will not be infringed by the commercial manufacture, use, and/or sale of Fresenius's proposed product. (SF 46.) |
| ANDA No. 207591 | Cabazitaxel Injection, 60 mg/1.5 mL | Nov. 18, 2014 | '170 patent | Certification pursuant to 21 U.S.C. § 355 (j)(2)(A)(vii)(IV): the '170 patent is invalid, unenforceable and/or will not be infringed by the commercial manufacture, use, or sale of Fresenius's proposed ANDA product. (SF 51.) |
| ANDA No. 207591 | Cabazitaxel Injection, 60 mg/1.5 mL | Apr. 2, 2015 | '592 patent | Certification pursuant to 21 U.S.C. § 355 (j)(2)(A)(vii)(IV): the '592 patent is invalid, unenforceable and/or will not be infringed by the commercial manufacture, use, or sale of Fresenius's Proposed ANDA Product. (SF 53.) |

[5] All of the submissions to the FDA include reference to Sanofi U.S.'s NDA No. 201023. In addition, every proposed product sought approval for use in combination with prednisone for treatment of patients with hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing treatment regimen.

| Application with FDA | Proposed Product | Date of Notice Letter | Patent Challenged | Basis for Certification filed with FDA |
|---|---|---|---|---|
| **Accord** | | | | |
| B2 NDA No. 207949 | Cabazitaxel Injection, 20 mg/mL, 3 mL (SF 54.) | Nov. 25, 2014 | '170 patent | Certification pursuant to 21 U.S.C. § 355(b)(2)(A)(iv): the '170 patent is invalid, unenforceable and/or will not be infringed by the commercial manufacture, use, offer for sale, sale, and/or importation of Accord's Proposed B2 NDA Product. (SF 58.) |
| B2 NDA No. 207949 | Cabazitaxel Injection, 20 mg/mL, 3 mL (SF 54.) | Mar. 11, 2015 | '592 patent | Certification pursuant to 21 U.S.C. § 355(b)(2)(A)(iv): the '592 patent is invalid, unenforceable and/or will not be infringed by the commercial manufacture, use, offer for sale, sale, and/or importation of Accord's Proposed B2 NDA Product. (SF 60.) On June 25, 2015, Accord received tentative approval from the FDA for the Accord B2 NDA. (SF 61.) |
| ANDA No. 207693 | Cabazitaxel Injection, 60 mg/1.5 mL (SF 62) | Nov. 24, 2014 | '170 patent | Certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV): the '170 patent is invalid, unenforceable and/or will not be infringed by the commercial manufacture, use, offer for sale, sale, and/or importation of Accord's Proposed ANDA Product. (SF 66.) |
| ANDA No. 207693 | Cabazitaxel Injection, 60 mg/1.5 mL (SF 62) | Mar. 11, 2015 | '592 patent | Certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV): the '592 patent is invalid, unenforceable and/or will not be infringed by the commercial manufacture, use, offer for sale, sale, and/or importation of Accords' Proposed ANDA Product. (SF 68.) On October 24, 2016, Accord received tentative approval from the FDA for the Accord ANDA. (SF 69.) |
| **BPI** | | | | |
| ANDA No. 207735 | Cabazitaxel 60 mg/1.5 mL solution for | Nov. 19, 2014 | '170 patent | Certification pursuant to 23 U.S.C. § 355(j)(2)(A)(vii)(IV): the '170 patent is invalid, unenforceable and/or will not be infringed by the commercial manufacture, use, offer for sale, sale, |

| Application with FDA | Proposed Product | Date of Notice Letter | Patent Challenged | Basis for Certification filed with FDA |
|---|---|---|---|---|
| | intravenous infusion (SF 70.) | | | and/or importation of BPI's Proposed ANDA Product. (SF 74.) |
| ANDA No. 207735 | Cabazitaxel 60 mg/1.5 mL solution for intravenous infusion (SF 70.) | Dec. 9, 2014 | '170 patent | Certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV): the '170 patent is invalid, unenforceable and/or will not be infringed by the commercial manufacture, use, offer for sale, sale, and/or importation of BPI's Proposed ANDA Product. (SF 76.) |
| ANDA No. 207735 | Cabazitaxel 60 mg/1.5 mL solution for intravenous infusion (SF 70.) | Mar. 12, 2015 | '592 patent | Certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV): the '592 patent is invalid, unenforceable and/or will not be infringed by the commercial manufacture, use, offer for sale, sale, and/or importation of BPI's Proposed ANDA Product. (SF 78.) |
| **Apotex** | | | | |
| ANDA No. 207736 | Cabazitaxel injection, 60 mg/1.5 mL (SF 79.) | Dec. 4, 2014 | '170 patent | Certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV): the '170 patent is invalid, unenforceable and/or will not be infringed by the commercial manufacture, use, offer for sale, sale, and/or importation of Apotex's Proposed ANDA Product. (SF 83.) |
| ANDA No. 207736 | Cabazitaxel injection, 60 mg/1.5 mL (SF 79.) | Jan. 28, 2015 | '592 patent | Certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV): the '592 patent is invalid, unenforceable and/or will not be infringed by the commercial manufacture, use, offer for sale, sale, and/or importation of Apotex's Proposed ANDA Product. (SF 85.)<br>On January 26, 2017, Apotex received tentative approval from the FDA for the Apotex ANDA. (SF 86.) |
| **Breckenridge** | | | | |
| ANDA No. 207619 | Cabazitaxel solution, IV, 60 mg/1.5 mL (40 | Dec. 2, 2014 | '170 patent | Certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV): the '170 patent is invalid, unenforceable and/or will not be infringed by the commercial manufacture, use, offer for sale, sale, |

| Application with FDA | Proposed Product | Date of Notice Letter | Patent Challenged | Basis for Certification filed with FDA |
|---|---|---|---|---|
| | mg/mL) (SF 87.) | | | and/or importation of Breckenridge's Proposed ANDA Product. (SF 91.) |
| ANDA No. 207619 | Cabazitaxel solution, IV, 60 mg/1.5 mL (40 mg/mL) (SF 87.) | Jan. 26, 2015 | '592 patent | Certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV): the '592 patent is invalid, unenforceable and/or will not be infringed by the commercial manufacture, use, offer for sale, sale, and/or importation of Breckenridge's Proposed ANDA Product. (SF 93.) |
| **Mylan** | | | | |
| ANDA No. 207381 | Cabazitaxel injection [60 mg/1.5 mL] [40 mg/mL] (SF 94.) | Dec. 4, 2014 | '170 patent | Certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV): the '170 patent is invalid, unenforceable and/or will not be infringed by the commercial manufacture, use, and/or sale of Mylan's Proposed ANDA Product. (SF 98.) |
| ANDA No. 207381 | Cabazitaxel injection [60 mg/1.5 mL] [40 mg/mL] (SF 94.) | May 5, 2015 | '592 patent | Certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV): the '592 patent is invalid, unenforceable and/or will not be infringed by the commercial manufacture, use, and/or sale of Mylan's Proposed ANDA Product. (SF 100.) |
| **Actavis** | | | | |
| ANDA No. 207970 | Cabazitaxel Injection, 10 mg/mL. (SF 101.) | Dec. 22, 2014 | '170 patent | Certification pursuant to 21 U.S.C. § 355(b)(2)(A)(iv): the '170 patent is invalid, unenforceable and/or will not be infringed by the commercial manufacture, use, or sale of Actavis's Proposed B2 NDA Product. (SF 105.) |
| ANDA No. 207970 | Cabazitaxel Injection, 10 mg/mL. (SF 101.) | Apr. 23, 2015 | '592 patent | Certification pursuant to 21 U.S.C. § 355(b)(2)(A)(iv): the '592 patent is invalid, unenforceable and/or will not be infringed by the commercial manufacture, use, or sale of Actavis's Proposed B2 NDA Product. (SF 107.)<br><br>Actavis received tentative approval from the FDA for the Actavis B2 NDA. (SF 108.) |

| Application with FDA | Proposed Product | Date of Notice Letter | Patent Challenged | Basis for Certification filed with FDA |
|---|---|---|---|---|
| **DRL** | | | | |
| ANDA No. 207718 | Cabazitaxel, 60 mg/1.5 mL. (SF 109.) | Mar. 18, 2015 | '592 patent | Certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV): the '592 patent is invalid, unenforceable and/or will not be infringed by the commercial manufacture, use, offer for sale, sale, and/or importation of DRL's Proposed ANDA Product. (SF 113.) |
| ANDA No. 207718 | Cabazitaxel, 60 mg/1.5 mL. (SF 109.) | Mar. 10, 2016 | '170 patent | Certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV): the '170 patent is invalid, unenforceable and/or will not be infringed by the commercial manufacture, use, offer for sale, sale, and/or importation of DRL's Proposed ANDA Product. (SF 115.) |
| **Glenmark** | | | | |
| ANDA No. 207784 | 60 mg/1.5 mL (40 mg/mL) cabazitaxel for injection. (SF 116.) | Mar. 27, 2015 | '592 patent | Certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV): the '592 patent is invalid, unenforceable and/or will not be infringed by the commercial manufacture, use, offer for sale, sale, and/or importation of Glenmark's Proposed ANDA Product. (SF 120.) |

### F. Defendants' Proposed Product Labels

| Product | Label Comparison |
|---|---|
| Fresenius's Proposed ANDA Product | *See* FCAB00345193-235. (SF 121.) |
| Fresenius's Proposed B2 NDA Product | *See* FCAB00011220-260. (SF 124.) |
| Accord's Proposed ANDA Product | Except for the corporate identity and product information, the product label for Accord's Proposed ANDA Product is identical to the label for Sanofi's JEVTANA® product. (SF 127.) |
| Accord's Proposed B2 NDA Product | Except for the corporate identity, product information, inactive ingredients, and number of dilutions, the product label for Accord's Proposed B2 NDA Product is identical to the label for Sanofi's JEVTANA® product. (SF 130.) |

| Product | Label Comparison |
|---|---|
| BPI's Proposed ANDA Product | Except for the corporate identity and product information, the product label for BPI's Proposed ANDA Product is identical to the label for Sanofi's JEVTANA® product. (SF 133.) |
| Apotex's Proposed ANDA Product | *See* AAPO-CAB00013976-4027. (SF 135.) |
| Breckenridge's Proposed ANDA Product | *See* at BRKCAB-00088842-889. (SF 137.) |
| Mylan's Proposed ANDA Product | *See* MYL_CAB0000039-094. (SF 139.) |
| Actavis's Proposed B2 NDA Product Prescribing and Patient Information | *See* ACT_CABAZ_00012190-225. (SF 141.) |
| DRL's Proposed ANDA Product | Except for the corporate identity, product information, and inactive ingredients, the product label for DRL's Proposed ANDA Product is identical to the label for Sanofi's JEVTANA® product. (SF 144.) |
| Glenmark's Proposed ANDA Product | Except for the corporate identity and product information, the product label for Glenmark's Proposed ANDA Product is identical to the label for Sanofi's JEVTANA® product. (SF 147.) |

## II. LEGAL STANDARDS

Plaintiffs must prove infringement by a preponderance of the evidence. *See Medtronic, Inc. v. Mirowski Family Ventures, LLC*, 134 S. Ct. 843, 846 (2014); *Integrated Tech. Corp. v. Rudolph Techs., Inc.*, 734 F.3d 1352, 1356 (Fed. Cir. 2013); *Siemens Med. Sols. USA, Inc. v. Saint-Gobain Ceramics & Plastics, Inc.*, 637 F.3d 1269, 1279, 1283 (Fed. Cir. 2011); *Mannesmann Demag Corp. v. Engineered Metal Prods. Co.*, 793 F.2d 1279, 1282 (Fed. Cir. 1986); *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 758 (Fed. Cir. 1984); *Curlin Med. Inc. v. Acta Med., LLC*, 228 F. Supp. 3d 355, 358 (D.N.J. 2017) (citing *Tech. Licensing Corp. v. Videotek, Inc.*, 545 F.3d 1316, 1327 (Fed. Cir. 2008)).

Defendants must prove invalidity by clear and convincing evidence. *See* 35 U.S.C. § 282 ("The burden of establishing invalidity of a patent or any claim thereof shall rest on the party

asserting such invalidity."); *Microsoft Corp. v. i4i Ltd. P'ship*, 564 U.S. 91, 102 (2011); *Amgen Inc. v. F. Hoffman-La Roche Ltd.*, 580 F.3d 1340, 1362 (Fed. Cir. 2009) (quoting *PharmaStem Therapeutics, Inc. v. Viacell, Inc.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007)); *Tech. Licensing Corp.*, 545 F.3d at 1327; *Purdue Pharm. Prods. L.P. v. Actavis Elizabeth LLC*, No. 12-5311, 2015 WL 5032650, at *10 (D.N.J. Aug. 25, 2015) (quoting *Linear Tech Corp. v. Int'l Trade Comm'n*, 566 F.3d 1049, 1066 (Fed. Cir. 2009)). Obviousness must be considered against the totality of the prior art. *Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 752 F.3d 967, 973 (Fed. Cir. 2014). In making an obviousness determination, courts must consider secondary considerations or objective indicia of non-obviousness. *See id.* "[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007); *see also Senju Pharm. Co. v. Lupin Ltd.*, 780 F.3d 1337, 1341 (Fed. Cir. 2015). "Thus, a defendant asserting obviousness in view of a combination of references has the burden to show by clear and convincing evidence that a person of ordinary skill in the [art] . . . had reason to combine the elements in the manner claimed." *Senju Pharm. Co.*, 780 F.3d at 1341 (citing *KSR Int'l Co.*, 550 U.S. at 418-19). Additionally, "a defendant must also demonstrate that a person of ordinary skill in the art [("POSA")] would have [had] a reasonable expectation of success in combining the elements." *Id.* (citing *PharmaStem Therapeutics, Inc.*, 491 F.3d at 1360).

Furthermore, in making an obviousness determination, courts must avoid hindsight analysis. *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1070-71 (Fed. Cir. 2012) (holding that courts should reject "hindsight claims of obviousness" where "a defendant urges an obviousness finding by merely throwing metaphorical darts at a board in hopes of arriving at a successful result, but the prior art gave either no indication

of which parameters were critical or no direction as to which of many possible choices is likely to be successful." (internal quotations omitted) (quoting *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009))); *see also Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012); *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008) (hindsight is "always inappropriate for an obviousness test").

The longstanding prohibition of the doctrine of obviousness-type double patenting "prohibits an inventor from extending his right to exclude through claims in a later-expiring patent that are not patentably distinct from the claims of the inventor's earlier-expiring patent." *Gilead Scis., Inc. v. Natco Pharma Ltd.*, 753 F.3d 1208, 1210 (Fed. Cir. 2014); *see, e.g.*, *Singer Mfg. Co. v. June Mfg. Co.*, 163 U.S. 169, 185 (1896) ("It is self-evident that on the expiration of a patent the monopoly created by it ceases to exist, and the right to make the thing formerly covered by the patent becomes public property. It is upon this condition that the patent is granted."); *Miller v. Eagle Mfg. Co.*, 151 U.S. 186, 197-98 (1894); *Suffolk Co. v. Hayden*, 70 U.S. 315, 317 (1865); *Boehringer Ingelheim Int'l GmbH v. Barr Labs., Inc.*, 592 F.3d 1340, 1346 (Fed. Cir. 2010); *In re Longi*, 759 F.2d 887, 892 (Fed. Cir. 1985). The obviousness-type double patenting analysis involves a two-step process. First, the Court "construes the claims in the earlier patent and the claims in the later patent and determines the differences." *Abbvie Inc. v. Mathilda & Terence Kennedy Inst. of Rheumatology Tr.*, 764 F.3d 1366, 1374 (Fed. Cir. 2014) (internal quotations and citations omitted). Second, the Court "determines whether those differences render the claims patentably distinct. A later claim that is not patentably distinct from, *i.e.*, is obvious over or anticipated by, an earlier claim is invalid for obviousness-type double patenting." *Id.* (internal quotations and citations omitted).

## III. '170 PATENT

### A. Invention Story

Around 1989, Sanofi launched a medicinal chemistry program to search for taxane analogs to treat cancers. (Tr. (Bouchard) 1017:4-6; Tr. (Vrignaud) 1108:10-20.) The program used existing taxanes, docetaxel, which was then under development by Sanofi, and paclitaxel, as reference compounds. (Tr. (Bouchard) 1018:5-8; Tr. (Vrignaud) 1113:6-14.) The program's goal was to identify taxane analogs that worked at least as well as docetaxel in sensitive tumors, but had greater activity than docetaxel in resistant tumors, and to improve water solubility. (Tr. (Vrignaud) 1108:14-20; Tr. (Bouchard) 1035:13-20.)

Over the next seven years, Sanofi researchers, including Dr. Hervé Bouchard, explored "almost every part" of the taxane structure, including modifications to the side chain and modifications to the core at C-2, C-4, C-5, C-6, C-7, C-9 and C-10. (Tr. (Bouchard) 1027:3-23; Tr. (Vrignaud) 1109:4-9.) The modifications varied, and included the addition of different functional groups and changes in the stereochemistry of different portions of the molecule. (*Id.* at 1027:3-1029:6; *see generally* JTX-133; JTX-153; JTX-154; JTX-155.) Certain compounds were synthesized in a matter of days and others compounds took months to successfully produce. (Tr. (Bouchard) 1027:24-1028:5.)

Once Sanofi had successfully synthesized a novel compound, it was evaluated in a series of *in vitro* and *in vivo* tests to determine the biological properties of the compound. (Tr. (Bouchard) 1019:1-1020:16; Tr. (Vrignaud) 1109:10-24.) First, an *in vitro* tubulin assay was used to confirm that the newly synthesized compound was still acting as a taxane, *i.e.*, binding to the tubulin target. (Tr. (Bouchard) 1019:7-17; Tr. (Vrignaud) 1109:10-1110:14, 1112:9-12; *see also* Tr. (Roush) 1348:4-1349:12.) Second, *in vitro* cellular assays were used to assess a compound's potency in

sensitive and resistant cell lines. (Tr. (Bouchard) 1019:25-1020:11; Tr. (Vrignaud) 1109:10-24, 1115:22-1117:22, 1120:16-1121:1.) These tests compared the novel compounds head-to-head to docetaxel in each cell line. (Tr. (Vrignaud) 1117:17-1118:8, 1121:2-16; *see also* Tr. (Roush) 1280:19-24.) Third, the *in vivo* activity of the new compounds was then assessed in an animal model using mice bearing tumors treated with docetaxel. (Tr. (Bouchard) 1020:12-16; Tr. (Vrignaud) 1125:6-1126:17.)

Sanofi researchers, including the three inventors of the '170 patent, would review the data from the *in vitro* and *in vivo* tests and "decide[] which new compounds should be made afterwards." (Tr. (Bouchard) 1020:17-23.) The *in vitro* and *in vivo* tests each had inherent limitations. (Tr. (Bouchard) 1019:18-24; Tr. (Vrignaud) 1115:8-21, 1119:6-1120:15.) Initial attempts to modify the C-7 and C-10 positions were unsuccessful. (JTX-153 at 186, 188; Tr. (Bouchard) 1043:1-1047:15.) In January 1994, Sanofi scientists discovered that replacement of the C-7 hydroxy with a C-7, 8, 19 cyclopropane structure led to improvements *in vitro* and *in vivo* in docetaxel-resistant tumors. (Tr. (Bouchard) 1040:13-1041:11.) This led to the discovery of larotaxel, which was chosen as the lead candidate for further development. (JTX-133 at SA_JEV_0182637; Tr. (Bouchard) 1040:13-1041:11; Tr. (Vrignaud) 1152:20-1153:8, 1203:6-8.) Dr. Bouchard testified that he made more than 450 compounds as part of the tax analog project and, out of those, only larotaxel and cabazitaxel entered into human studies. (Tr. (Bouchard) 1020:24-1021:1.)

In April 1994, a derivative of docetaxel was synthesized at RPR with a single C-10 methoxy group: RPR 112698. (JTX-133 at SA_JEV_0182655; Tr. (Bouchard) 1036:14-1037:14, 1050:18-1051:2, 1100:2-18.) Dr. Bouchard also added back the acetoxy group removed when modifying paclitaxel to docetaxel onto the C-10 of docetaxel, forming 10-acetoxy docetaxel. (JTX-133 at

SA_JEV_0182586; Tr. (Bouchard) 1035:7-14.) Dr. Bouchard found that this new compound had good *in vitro* and *in vivo* activity. (*Id.*) On November 15, 1994, Dr. Bouchard synthesized cabazitaxel, the C-7, C-10 di-methyoxy derivative, for the first time. (JTX-154 at 96; Tr. (Bouchard) 1054:2-25, 1057:19-1058:8.)

**B. Infringement**

Defendants concede that their products infringe Claims 1 and 2 of the '170 patent. (Infringement Stipulation, ECF No. 242.) Accordingly, the Court will consider whether the patent is invalid.

**C. Invalidity**

**1. POSA**

Plaintiffs assert that a POSA "in March 1995 would have been someone with a Ph.D. in organic chemistry, medicinal chemistry, or a closely related discipline and at least two years of experience synthesizing or characterizing drug molecules. Alternatively, a POSA could have had a bachelor's degree or master's degree in organic chemistry, medicinal chemistry, or a closely related discipline with a greater amount of experience synthesizing or characterizing drug molecules." (Tr. (Roush) 1242:21-1244:12.) Defendants assert that a POSA for the '170 patent would have had a high level of education, such as having at least a master's degree, but more likely a Ph.D. in organic chemistry, medicinal chemistry, or a related discipline, and experience in the design and synthesis of drug molecules. (Tr. (Kingston) 106:3-13; Tr. (Heathcock) 822:14-23.) Alternatively, a POSA could have had a lower level of formal education if such a person had a greater amount of experience. (Tr. (Heathcock) 822:23-823:9.) Here, the parties essentially agree on the skills of a POSA. Moreover, the experts all testified that their opinions would be the same even if the Court adopted the opposing party's definition of a POSA. The Court finds the proposed

POSA definitions substantially similar and the differences inconsequential and declines to adopt either definition.

**2. Testimony[6]**

**a. Herve Bouchard, Ph.D.[7]**

Dr. Bouchard is a medicinal chemist at Sanofi and the lead inventor on the '170 patent. (Tr. (Bouchard) 1016:4-8, 1017:14-24.) Dr. Bouchard was responsible for the group of medicinal chemists within the taxane analogue group at RPR, a predecessor to Sanofi, and personally synthesized cabazitaxel for the first time on November 15, 1994. (*Id.* at 1016:18-23, 1021:6-11, 1057:13-1058:17.)

**b. Clayton R. Heathcock, Ph.D.[8]**

Dr. Heathcock testified that "because docetaxel had been superior in all of the kinds of comparisons that had been made, I think a person of skill would certainly consider that the best starting point" for a lead compound. (Tr. (Heathcock) 843:3-6.) According to Dr. Heathcock, the docetaxel side chain gave better results than paclitaxel and "you got a better compound if you didn't have the acetoxy group at C-10." (*Id.* at 843:22-25.)

Dr. Heathcock testified that Claims 1 and 2 of the '170 patent would have been obvious to a POSA in light of the prior art compound docetaxel and the knowledge that was available in the art at the time. (*Id.* at 819:2-6.) Dr. Heathcock's testimony largely centered on P-Glycoprotein

[6] The Court will not set forth testimony in detail in this section. In addition, certain testimony may be reflected in the Prior Art and other sections of this Opinion.

[7] Details with respect to Dr. Bouchard's research are set forth in the Invention Story at III.A, *supra*.

[8] Dr. Heathcock was accepted by the Court as an expert in medicinal chemistry and chemical synthesis. (Tr. 816:7-817:2.)

("Pgp"), including how Pgp works to cause multidrug resistance, the reasons why a POSA would focus on Pgp as the mechanism of resistance, and the strategic modifications a POSA would be motivated to make to docetaxel to address the Pgp issues. (*Id.* at 858:19-897:19.) Dr. Heathcock testified that it was known that Pgp affected both paclitaxel and docetaxel, the prior art suggested the approaches of improving cell permeability or reducing the Pgp affinity to overcome the problem of Pgp, and that a POSA "would be led to the conclusion that changing the hydroxyl groups at [C-]7 and [C-]10 to methoxy groups would be expected to accomplish both of these goals." (*Id.* at 897:16-19.)

**c. David G.I. Kingston, Ph.D.**[9]

Dr. Kingston testified on behalf of Defendants that a POSA would choose docetaxel as a lead compound for further development. Dr. Kingston testified that the data in Ringel, Riou, Bissery and Verweij all lent support for the proposition that a POSA would choose docetaxel. (Tr. (Kingston) 147:23-148:1.)

Dr. Kingston also testified that Claims 1 and 2 of the '170 patent would be obvious to a POSA based on the prior art. (*Id.* at 99:11-13; 187:21-25.) Specifically, Dr. Kingston opined that Claim 1 of the '170 patent is obvious in light of Wong, Golik, and Kant. (*Id.* at 186:12-13.) Dr. Kingston testified that Claim 2 was "gobbledygook," "[f]ull of sound and fury, signifying nothing" because a POSA would have a reasonable expectation of success using taxane formulations for cabazitaxel. (*Id.* at 187:1-15.) According to Dr. Kingston, the hydroxyl groups are chemically the easiest to modify and, of the four OH groups, the hydroxyl groups at the C-7 and C-10 positions could be modified readily by known chemistry. (*Id.* at 153:18-22.) Dr. Kingston testified that the

[9] Dr. Kingston was accepted by the Court as an expert in taxane chemistry, organic chemistry, and taxane synthesis. (Tr. (Kingston) 105:6-9.)

C-2' position on the side chain was not a good candidate compared to the other hydroxyl groups because the body of work by 1995 showed that changes to that hydroxyl group resulted in loss of activity. (*Id.* at 152:18-153:1.) In addition, Dr. Kingston testified that the C-1 position was not a good candidate because it is in a very difficult position to change. (*Id.* at 153:5-16.) Dr. Kingston further testified that a POSA would be interested in maintaining the entire structure of docetaxel with small modifications at the C-7 and C-10 positions. (*Id.* at 155:7-9.)

Dr. Kingston testified that a POSA would combine the teachings and make changes at both C-7 and C-10 based on "the additivity principle," "a well-known principle of medicinal chemistry." (*Id.* at 179:13-19.) Dr. Kingston also testified that a POSA would have a reasonable expectation of success that making the change to C-7 and C-10 would result in an improved compound. (*Id.* at 179:20-24.)

**d. Richard Ludueña, Ph.D.**

Defendants offered the videotaped deposition testimony of Plaintiffs' expert, Dr. Ludueña. Dr. Ludueña testified that he did not have any opinion as to whether docetaxel would have been a good starting point for taxane development by 1995. (DTX-2724 (Ludueña) at Clip 29.) Dr. Ludueña testified that a POSA in 1995 would have viewed docetaxel as a promising compound, but with some issues related to activity in resistant cells. (*Id.* at Clip 30.) Dr. Ludueña also testified that someone working in the field of developing docetaxel analogues in 1995 would be interested in improving the performance of those analogues against drug-resistant cells (*id.* at Clips 34-35).

In addition, Dr. Ludueña testified that he does not consider himself an expert in Pgp. (*Id.* at Clip 72.) Nevertheless, he testified regarding mechanisms of resistance and noted that, as of 1995, Pgp was known and an object of interest. (*Id.* at Clip 69.) Dr. Ludueña, however, disagreed

with the proposition that, as of 1995, Pgp was the most well-known mechanism of drug resistance for chemotherapy agents. (*Id.* at Clip 68.) Dr. Ludueña also acknowledged that abstracts from the American Society of Clinical Oncology's 30th annual meeting in May 1994 provides some evidence that Pgp-mediated resistance was relevant to clinically observed Taxol resistance. (*Id.* at Clips 107-08.)

**e. Professor Iwao Ojima**

Defendants offered the videotaped deposition testimony of Plaintiffs' expert, Dr. Ojima. The excerpts included testimony regarding a number of prior art references, including: Wils; Ojima 1994; Hait; Kant, Klein, Golik, Wong, Ford and Hait.[10]

**f. Dr. Roush[11]**

With respect to the selection of a lead compound, Dr. Roush, Plaintiffs' expert, testified that he did not agree that a POSA would only select docetaxel as the lead compound because a POSA would have looked to the FDA-approved drug, which was paclitaxel. (Tr. (Roush) 1282:8-19.) In addition, Dr. Roush testified that Dr. Kingston and other laboratories were using paclitaxel as a lead compound in March 1995. (*Id.* at 1286:8-1288:10.) Dr. Roush, nevertheless, acknowledged that there were prior art paper publications that showed that docetaxel was more potent in a variety of cell lines. (*Id.* at 1284:15-17.)

With respect to simultaneous changes to multiple sites, Dr. Roush testified that "a [POSA] doesn't go off and start making changes to multiple sites simultaneously." (*Id.* at 1258:9-11.) He noted that Dr. Bouchard, the inventor of the '170 patent, was not "just looking at one place at a

[10] Dr. Ojima's testimony is reflected in the Prior Art section *infra*.

[11] Dr. Roush was accepted by the Court as an expert in medicinal chemistry and organic chemistry. (Tr. 1241:21-25.)

time and then moving to a different place. He's looking at the entire molecule in a contemporaneous manner, but with each series of experiments it's one change at a time." (*Id.* at 1258:23-1259:2.) As to the different positions that could be modified on taxanes, Dr. Roush testified that virtually every position on the paclitaxel molecule was being modified in the relevant time period. (*Id.* at 1290:21-1291:2.) Dr. Roush testified that the prior art was not focused on the C-7 and C-10 positions. (*Id.* at 1295:22-25.) Dr. Roush further testified that modifications were being attempted at the C-1, C-2, C-4, C-5, C-7, C-8, C-9, C-10, C-11, C-12, C-13, C-14, C-2', and C-3' positions. (*Id.* at 1290:22-1294:23.) In addition, Dr. Roush testified that "integrating over all the various prior publications, . . . at least a thousand" taxane compounds were discussed as of March 1995. (*Id.* at 1295:16-21.)

**g. Patricia Vrignaud, Ph.D.**[12]

Dr. Vrignaud, a former Sanofi employee, was involved in the preclinical screening program for cabazitaxel and RPR's other docetaxel analogues. (Tr. (Vrignaud) 1105:5-1108:20.) Dr. Vrignaud helped prepare the cabazitaxel preclinical dossier for submission to the FDA during the cabazitaxel approval process. (*Id.* at 1153:9-14.)

**3. Prior Art**

The prior art to the '170 patent includes:

**a. The '470 Patent**

U.S. Patent No. 4,814,470 ("the '470 patent") was issued on March 21, 1989 and was assigned to RPR, a predecessor to Sanofi. This patent discloses the structure and synthesis of

[12] Details with respect to Dr. Vrignaud's role in the research process are set forth in the Invention Story at III.A, *supra*.

docetaxel from 10-DAB and the anticancer activity of docetaxel. (Tr. (Heathcock) 829:11-831:8; JTX-119, '470 patent (CabRef0001534-44).)

**b. *Taxane Anticancer Agents* (Georg)** (JTX-162)

*Taxane Anticancer Agents*, published in December 1994, contains chapters summarizing some of the key lectures from the March 1994 ACS taxane symposium. The book, co-edited by Dr. Ojima, was referred to as the "taxane bible" because it presented the key work in the taxane field at the time. (Tr. (Heathcock) 833:10-23, 849:21-850:4, 910:10-911:4; Tr. (Bouchard) 1077:3-16, 1078:21-1079:5; Tr. (Roush) 1286:23-1287:11, 1288:18-1289:19; DTX-2725 (Ojima) at Clips 101-02; JTX-162/DTX-2196I Georg, ix (CabRef0000820).)

**c. Bissery** (JTX 32)

The Bissery article ("Bissery") is entitled *Experimental Antitumor Activity of Taxotere, a Taxol Analogue*. (JTX-32.) Dr. Kingston testified that from the Bissery article, a POSA would conclude that docetaxel would be the better compound to start with over paclitaxel because the two doses of Taxotere that were evaluated resulted in longer life extensions for the treated animals. (Tr. (Kingston) 141:18-142:9.)

**d. Commerçon** (JTX-109)

Commerçon is a chapter in *Taxane Anticancer Agents* (Georg) which was authored by RPR scientists and provides a summary of taxane structure activity relationships ("SAR"). Specifically, Commerçon discloses the potency impact of making changes at certain positions on the taxane core. (Tr. (Heathcock) 849:21-852:21; JTX-109 at 235 (CabRef0000200).) Dr. Bouchard testified that the contents of Commerçon reflected the state of RPR's taxane work as of March 1994. (Tr. (Bouchard) 1097:11-1099:5).

**e. EP '910** (JTX-125)

EP '910 is a European patent application assigned to BMS. It was published in 1994 and discloses: (1) the efficacy of paclitaxel and docetaxel to treat cancer; and (2) that increasing the lipophilicity of the C-7 hydroxy position of the taxane core could improve the potency of the compound in treating resistant cancer cells. (Tr. (Heathcock) 893:6-896:19; JTX-125, EP '910 (CabRef0000215-310).)

**f. Golik** (JTX-111)

The Golik patent ("Golik" or "the '577 patent") is entitled "Phosphonooxymethyl or methylbiomethys ethers of taxane derivatives as antitumor agents." (JTX-111.) The Golik researchers were chemists from Bristol-Myers Squibb (JTX-111 at Cover) looking to discover more water-soluble taxanes (JTX-111 at 2:42-51; JTX-125 at 2:36-49). The Golik researchers provided *in vitro* data for four compounds: Examples 1, 3, 4, and 1(a). (JTX-111 at 22:1-17; JTX-125 at 17:16-50.) The 7-O methylthiomethyl derivative of docetaxel is referred to as compound Example 1(a). (Tr. (Kingston) 166:8-16; JTX-111 at 22 (CabRef0000332)). Example 1(a) was more potent than docetaxel and paclitaxel in a single resistant cell line. (Tr. (Heathcock) 895:18-896:1; Tr. (Roush) 1363:20-1364:19; JTX-125 17:49-50.) Page 22 of Golik discloses biological testing data of certain taxane derivatives. (JTX 111 at 22 (CabRef0000332); Tr. (Kingston) 166:5-7). This data compares the effect of paclitaxel, docetaxel, and Example 1(a) on normal and resistant cell lines. (Tr. (Kingston) 166:8-22.)

Golik teaches that both paclitaxel and docetaxel have effective antitumor activity in *in vivo* animal models. Specifically, Golik teaches that "a semi-synthetic analogue of paclitaxel named Taxotere® has also been found to have good antitumor activity in animal models" and "is also currently undergoing clinical trials in Europe and the United States." (JTX-111, Golik at 2

(CabRef0000312).) Dr. Ludueña testified that Golik shows that, prior to 1995, Bristol-Myers Squibb had been studying the effects of modification on a group of cell lines thought to be resistant. (DTX-2724 (Ludueña) at Clips 164-65.) Furthermore, Dr. Ludueña testified that modification of the C-7 position of the taxane increased the cytotoxicity of the compound in Golik. (*Id.* at Clip 175.)

**g. Greene** (JTX-128)

Greene was published in 1991 and is a well-known and widely-used reference in the chemical arts that provides methods for performing many types of chemical reactions. The chemical methods disclosed by Greene are derived from examples in the contemporary scientific literature. (Tr. (Heathcock) 928:16-929:5; Tr. (Bouchard) 1066:22-1067:5.) Greene stated that ethers are the most used protective groups in organic synthesis and noted that ethers "are formed and removed under a wide variety of conditions." (JTX-128 at 14 (CabRef0012735).) Greene discloses eleven different procedures for converting a hydroxy group into a methoxy group. (Tr. (Heathcock) 928:24-931:11; JTX-128 at 15-16 (CabRef0012735-37).) Dr. Heathcock testified that Item 11 ["MeI or $Me_2SO_4$,[13] NaH or KH, THF] represents Greene's "standard method for introducing the methyl ether function on to hindered and unhindered alcohols." (Tr. (Heathcock) 929:14-930:3; JTX-128 at 16 (CabRef00127-37).) Dr. Heathcock further testified that a medicinal chemist would consider the hydroxyl groups at C-7 and C-10 in docetaxel to be unhindered alcohols. (*Id.* at 930:15-21.)

**h. Hait** (JTX-102)

The Hait paper ("Hait"), published in 1992, provides a "hypothetical drug binding site on Pgp based on analogies with the binding of antipsychotic drugs to calmodulin." (JTX-102 at 104 (Fig. 2.)) According to Dr. Heathcock, Hait teaches that good substrates for Pgp would have both

a more hydrophobic region and a more hydrophilic region. (Tr. (Heathcock) 882:20-888:19; JTX-102 at 103-107 (CabRef0001259-63)). Hait's hypothetical binding model relates to inhibitors, also called "chemosensitizers." (JTX-102 at 104 (Fig. 2); Tr. (Roush) 1332:12-1333:8; Tr. (Heathcock) 973:10-25.) Inhibitors are compounds which shut down pumping activity but are not themselves pumped out of cells. (Tr. (Roush) 1332:12-1333:25.) Dr. Ludueña testified that nothing from Hait suggests that the binding interactions between phenothiazine and Pgp reflect or would be similar to the binding interactions between a taxane and Pgp. (DTX-2724 (Ludueña) at Clips 202-03.)

**i. Kant** (JTX-114)

The Kant paper ("Kant"), entitled "A Chemoselective Approach to Functionalize the C-10 Position of 10-Deacetylbaccatin III Synthesis and Biological Properties of Novel C-10 Taxol Analogues," describes work by taxane researchers at Bristol-Myers Squibb. (JTX-114 at 5543.) Kant was published in 1994 and studied the effect of replacing the C-10 group of paclitaxel with other substituents including a methoxy group. (JTX-114 at 5545 (CabRef0001266).) Kant also taught that the preferred way to synthesize high-yielding taxane analogues was to start with 10-DAB. Kant was considered by the U.S. Patent and Trademark Office ("PTO") while the '170 patent was pending. (JTX-1 at Cover; Tr. (Heathcock) 967:22-968:5.)

As shown in Table II, Kant prepared analogues and evaluated them for tubulin binding and for *in vitro* potency. (JTX-114 at Table II.) Six analogues had a paclitaxel side chain (R2 = Ph) and four had a docetaxel side chain (R2 = t-BuO). (*Id.*) In a head-to-head comparison, compounds with the docetaxel side chain were more potent in the tubulin binding as well as in their $IC_{50}$ data. (Tr. (Heathcock) 899:23-906:8; JTX-114 at 5545-46 (CabRef0001266-67).)

**j. Kingston 1994** (JTX-107)

The Kingston paper ("Kingston 1994"), published in 1994, is a chapter in *Taxane Anticancer Agents* (Georg), which discusses both general taxane SAR and synthesis. Kingston 1994 provides a diagram of the taxane core detailing what chemical modifications (if any) are tolerated at each position. (Tr. (Roush) 1449:2-1450:1; JTX-107 at 214 (CabRef0001038).)

**k. Klein** (JTX-110)

The Klein paper ("Klein"), published in 1994, is a chapter in *Taxane Anticancer Agents* (Georg), and discloses 9(R)-dihydrotaxanes and the activities of numerous analogs having the 9(R)-dihydro structure. (Tr. (Heathcock) 906:14-909:10; JTX-110, Klein at 281 (CabRef0001294).) Klein prepared and evaluated analogs in which the C-7 hydroxy groups are alkylated. (Tr. (Heathcock) 906:20-906:25.)

**l. Lampidis** (DTX-2241)

The Lampidis paper ("Lampidis") was published in 1989 and teaches that a strategy for overcoming Pgp-mediated resistance in cancer cells was to increase the lipophilicity and, therefore, cell permeability of a drug, which would then, in effect, overwhelm the Pgp efflux mechanism. (DTX-2241 at 4271.) This results in increased concentration of the drug in the cell which could eventually kill the cell. (Tr. (Heathcock) 878:11-21; DTX-2241 at 4271 (CabRef0005374).) Dr. Ludueña acknowledged that the Lampidis reference indicates that an increase in lipophilicity likely increases the ability of the compounds to accumulate in and then kill multidrug-resistant cells. (DTX-2724 (Ludueña) at Clips 200-01.)

**m. Ojima 1994** (JTX-104)

The Ojima paper ("Ojima 1994"), published in 1994, is a chapter in *Taxane Anticancer Agents* (Georg), authored by Dr. Ojima and scientists from RPR. Some of the co-authors of the

paper were researchers at RPR. (Tr. (Heathcock) 888:22-889:4). The Ojima 1994 reference teaches that using small lipophilic groups at C-10 improved performance against resistant cancer cells. (*Id.* at 888:22-889:11, 890:14-892:2; JTX-104 at 272-73 (CabRef0001097-98).) Dr. Ludueña testified that Ojima 1994 shows that taxanes can be modified chemically to improve their performance in certain multidrug-resistant cell lines. Dr. Ludueña also acknowledged that CabRef1098 teaches that modification at the C-10 position could improve performance in a multidrug-resistant cell line. (DTX-2724 (Ludueña) at Clips 172-73.)

**n. Riou** (JTX-98)

The Riou paper ("Riou"), published in 1992, discloses the use of a specialized cancer cell line, P388/DOX, selected to over-express Pgp. (Tr. (Heathcock) 838:3-840:12, 867:4-870:19; JTX-98 at 164-170 (CabRef0001443-49).) By comparing the activities of taxanes against resistant P388/DOX and normal P388 cancer cells, it showed that docetaxel was more potent than paclitaxel in resistant cells. This taught that docetaxel is less recognized than paclitaxel by Pgp and was less likely to be ejected from the cell by Pgp. (Tr. (Heathcock) 867:4-868:4, 870:3-19; JTX-98 at 67-168 (CabRef0001446-47).) Riou also confirmed that overexpression of Pgp was a cause of resistance to taxane compounds in cell lines. (Tr. (Heathcock) 868:5-869:1; JTX-98 at 167-68 Table IV (CabRef0001446-47).) Dr. Kingston testified that a POSA would conclude that docetaxel is better than Taxol against normal cell lines and docetaxel is "way better" than Taxol at the P388/DOX drug-resistant cell line. (Tr. (Kingston) 137:20-138:18.) Dr. Ludueña testified that it was "certainly possible" based on Riou that reduced affinity for Pgp could lead to improved performance of a drug like Taxotere in drug-resistance cell lines. (DTX-2724 (Ludueña) at Clips 130-31.)

**o. Verweij** (JTX-29)

The Verweij paper ("Verweij"), published in 1994, describes the mechanism of action of taxanes. (Tr. (Heathcock) 830:23-833:9, 836:22-838:2; JTX-29 at 495-505 (CabRef0001719-29).) Verweij explains that binding of taxanes enhances polymerization of the tubulin into stable microtubules. (Tr. (Heathcock) 831:17-23.) Verweij reported that docetaxel was more potent than paclitaxel in about six different kinds of cancer cells, including two mouse cell lines and five human tumor cell lines. (Tr. (Heathcock) 836:22-838:2; JTX-29 at 496 (CabRef0001720).) Docetaxel was also more potent than paclitaxel in *in vivo* animal studies. (Tr. (Kingston) 138:19-147:11; Tr. (Heathcock) 837:16-838:2; JTX-29 at CabRef0001721-25.)

**p. Wils** (JTX-31)

The Wils paper ("Wils") is entitled "Polarized transport of docetaxel and vinblastine medicated by Pglycoprotein in human intestinal epithelial cell monolayers." (JTX-31.) Wils was published in 1994 by RPR and confirmed that the mechanism of action for multidrug resistance in docetaxel is mediated by Pgp. (Tr. (Heathcock) 865:6-866:15; JTX-31, Wils at 1528-30 (CabRef0001782-84); DTX-2725 (Ojima) 64:22-23, 65:1-2, 65:3-7, 65:10-11; DTX-2724 ( Ludueña) at Clips 136-37).)

**q. Wong** (JTX-115)

The Wong patent ("Wong"), entitled "7-0-Ethers of Taxane Derivatives," was invented by chemists at Bristol-Myers Squibb. (JTX-115; Tr. (Kingston) 220:1-4.) Wong generally discloses 7-ethers of taxane derivatives, including multiple taxane derivatives having a methyl ether group at the C-7 position. (JTX-115 at 1:44-64 (CabRef0001702).)

#### 4. Obviousness

Defendants did not demonstrate obviousness by clear and convincing evidence. The Court finds that a POSA would have selected either docetaxel or paclitaxel as a lead compound, which does not foreclose Defendants' case. Defendants, however, failed to demonstrate that a POSA would have been motivated to simultaneously modify docetaxel with a methyl ether at the C-7 and C-10 positions to arrive at cabazitaxel. This is fatal to Defendants' position on obviousness. In addition, the Court finds that the secondary considerations weigh in favor of Plaintiffs. The Court will discuss each in turn.

##### a. Selection of Lead Compound

The Court finds that a POSA would have selected either docetaxel or paclitaxel as a lead compound. Dr. Kingston testified that: docetaxel was better than paclitaxel at the equivalent doses for patients in ovarian cancer studies; docetaxel was better than paclitaxel with respect to Phase II breast cancer studies; with one exception, docetaxel was better than paclitaxel with respect to several other types of cancer; docetaxel was better than paclitaxel with respect to a doxorubicin-resistant breast cancer; and a POSA would conclude that docetaxel is better than paclitaxel in almost every situation. (Tr. (Kingston) 145:1-147:11.) Dr. Heathcock similarly testified that a POSA would chose docetaxel as a lead compound. (Tr. (Heathcock) 843:3-8.) The Court found the testimony of Drs. Kingston and Heathcock credible with respect to the fact that a POSA may have selected docetaxel as the lead compound. In addition, Dr. Roush acknowledged that certain prior art publications showed that docetaxel was more potent in a variety of cell lines. (Tr. (Roush) 1284:15-17.)

Nevertheless, Dr. Kingston acknowledged that he selected paclitaxel as the lead compound for one of his patents during the relevant time period. (Tr. (Kingston) 196:21-197:4.) In addition,

Dr. Ojima testified that there was interest in modifying both paclitaxel and docetaxel during the relevant time period and that he used docetaxel as a lead compound. (DTX-2725 at Clips 4-5, 31-32.) Based on the testimony and the prior art references, which reflect selection of both paclitaxel and docetaxel as a lead compound, the Court finds that a POSA would have selected either docetaxel or paclitaxel as a lead compound.

**b. Simultaneous Modifications with Methyl Ether at C-7 and C-10 Positions**

The Court has considered the testimony and evidence and finds that Defendants have failed to demonstrate that a POSA would have been motivated to make simultaneous modifications of docetaxel with a methyl ether at the C-7 and C-10 positions. Neither Dr. Kingston's nor Dr. Heathcock's theories persuaded the Court. Rather, the Court finds that both theories are based on impermissible hindsight analysis.

Dr. Kingston testified regarding a number of prior art references, including Golik, Wong, and Kant. Four compounds disclosed in the '577 patent, Examples 1, 3, 14(b), and 15, were tested in animals. (Tr. (Kingston) 22:19-24:8.) Of the four compounds that were tested *in vivo*, Examples 14(b) and 15 are structurally similar to Example 1(a), except they have either the docetaxel side chain or the docetaxel side chain with a "prodrug" modification on the C-2' location. (Tr. (Kingston) 218:2-219:16; Tr. (Roush) 1365:21-1367:8.) The four compounds that were tested *in vivo*, however, were not tested in animals with resistant tumors. (*Id.*) In addition, although *in vivo* data is provided for other compounds, no *in vivo* data is provided for Example 1(a). (Tr. (Kingston) 215:1-5; Tr. (Heathcock) 972:23-25; Tr. (Roush) 1365:6-20.)

Golik disclosed that Example 1(a) was more active than docetaxel and paclitaxel in a single resistant cell line. (Tr. (Heathcock) 895:18-896:1; Tr. (Roush) 1363:20-1364:19.) Example 1(a), however, contained a MTM group, a unique chemical group that is three atoms long and contains

a sulfur atom. Cabazitaxel contains a methoxy group that is one atom long and contains no sulfur atom. (Tr. (Heathcock) 969:23-970:10; Tr. (Roush) 1363:20-1364:9.) In addition, there is no evidence in Golik that the methoxy group in cabazitaxel would confer a similar benefit as the MTM in Example 1(a). (Tr. (Roush) 1368:2-25.) Furthermore, Dr. Kingston acknowledged that Golik did not test the methyl ether substitution at C-7. (Tr. (Kingston) 171:16-18.)

Wong discloses and claims derivatives of docetaxel and paclitaxel and provides *in vivo* testing for several compounds, all of which have an acetyl group at the C-10 position. (Tr. (Kingston) 224:1-5.) Wong Example 2 is not the most active compound tested in Wong; Wong Example 8 is more potent. (JTX-115 at 9:15-28 (Table I); Tr. (Kingston) 221:5-21; Tr. (Roush) 1371:7-20.) Wong Example 8 has a modification to the C-2' of the side chain and a methoxymethyl group on C-7. (Tr. (Roush) 1369:12-1370:13.) Wong does not disclose any compound with the C-10 hydroxyl found in docetaxel or the C-10 methoxy found in cabazitaxel. (Tr. (Kingston) 224:6-11.) Wong also does not provide data on resistant cell lines. (Tr. (Roush) 1371:2-6.)

With respect to the Golik and Wong patents, Dr. Kingston testified that a POSA would notice that the patents together pointed towards improved activity if the OH group at C-7 is converted to an O-methyl group. (Tr. (Kingston) 179:1-9.)

Kant discloses a series of paclitaxel and docetaxel analogs modified at the C-10 position, along with tubulin binding data and $IC_{50}$ data in one sensitive cancer cell line. (JTX-114 at 5545; Tr. (Kingston) 224:19-225:8; Tr. (Roush) 1347:14-23.) Kant does not disclose or discuss: (1) data in any sensitive cell line other than HCT 116 (Tr. (Kingston) 205:17-206:3, 245:5-12; Tr. (Roush) 1349:13-1351:8); (2) data in resistant cell lines (JTX 114 at 5545; Tr. (Roush) 1351:5-8; Tr. (Kingston) 225:6-14); or (3) drug metabolism, toxicity, or solubility, which are properties that could be modified when structural changes are made (Tr. (Heathcock) 847:25- 848:12). Additionally,

Kant does not provide any data for docetaxel and, therefore, does not establish whether any of its compounds perform better or worse than docetaxel. (Tr. (Kingston) 159:13-14; Tr. (Roush) 1352:17-1353:4.)

Dr. Kingston's testimony with respect to Kant included a discussion of Table 2, for which Dr. Kingston testified that Compound 20 was the outstanding compound. (JTX 117; Tr. (Kingston) 156:4-158:23.) Kant Compound 18, however, which provides more information to the POSA than the tubulin test, could be considered the best compound in the cellular assay. (JTX-114 at 5545 (Table II comparing Kant Compound 18 with Compound 20); Tr. (Kingston) 236:13-16; Tr. (Roush) 1351:14-1352:5, 1356:3-22.) Kant also discloses that Compound 22 is more active than paclitaxel, but Compound 22 does not include one of the changes necessary to reach cabazitaxel. (JTX-114 at 5546.)

Dr. Kingston testified that because Kant did not report results on docetaxel, he gathered data about docetaxel to include as a comparator to Compound 20. (Tr. (Kingston) 159:13-23.) Dr. Kingston imported docetaxel data from experiments in other publications. (*Id.* at 159:15-23; Tr. (Roush) 1353:5-1354:3.) Dr. Kingston found that Kant Compound 20 was better than docetaxel in tubulin ratio and HCT 116 cytotoxicity. (Tr. (Kingston) at 164:6-9.) The change that made Kant Compound 20 better was "the simple conversion of the OH group of docetaxel to the O methyl group of Compound 20." (*Id.* at 164:12-13.) According to Dr. Kingston, a POSA would "conclude that making a methyl ether at the C-10 position was a very positive step to take." (*Id.* at 164:17-10.)

Kant does not disclose or discuss compounds modified at the C-7 position, including the C-7 methoxy found in cabazitaxel. In addition, all of the compounds in Kant have a C-7 hydroxyl group. (JTX-114 at 5545; Tr. (Kingston) 225:23-25; Tr. (Roush) 1347:24-1348:3.)

Dr. Kingston concluded that a POSA would combine the teachings and make changes at both C-7 and C-10 because:

> it's a well-known principle of medicinal chemistry that if you make a change at position A and it improves activity, you make a change at position B and it improves activity. If you make that change at both positions, A and B, you'd expect an additive effect to get even better activity. This is known as the additivity principle of medicinal chemistry.

(Tr. (Kingston) 179:13-19.) Dr. Kingston also testified that a POSA would have a reasonable expectation of success that making the changes to C-7 and C-10 would result in an improved compound. (*Id.* at 179:20-24.)

Dr. Heathcock's testimony focused on Pgp as a mechanism of resistance and the modifications a POSA would be motivated to make to docetaxel in order to address the Pgp resistance issues. (Tr. (Heathcock) 858:19-897:19.) Dr. Heathcock discussed a number of prior art references, including Klein, Hait, Lampidis, and Ojima.

Klein discloses a series of C-9 modified hydroxyl compounds. (JTX-110; Tr. (Roush) 1357:4-11.) All Klein compounds have the C-10 hydroxyl or aceteyl group found in paclitaxel and docetaxel, respectively. (JTX-110 at 280-81; Tr. (Roush) 1357:4-19, 1360:10-18.) Klein teaches that its "9(R)-dihydrotaxanes show great promise as a second generation class of agents in that they have greater solubility and stability and also show excellent *in vivo* activity in several solid tumor models." (JTX-110 at 276.) A POSA would have considered this teaching. (Tr. (Roush) 1359:16-1360:1, *see also id.* at 1357:20-1359:15.) Klein does not disclose or discuss compounds modified at the C-10 position, including the C-10 methoxy found in cabazitaxel, or data for compounds modified at that position. (JTX-110 at 280-81; Tr. (Heathcock) 933:8-17.) In addition, Klein does not disclose or discuss data in resistant cell lines. (Tr. (Heathcock) 968:14-19;

Tr. (Roush) 1361:13-15.) Klein also does not disclose or discuss Pgp or how to avoid Pgp. (Tr. (Heathcock) 968:17-19.)

Hait discusses compounds called phenothiazines, which are antipsychotic compounds and differ from taxanes in size and chemical structure. (Tr. (Roush) 1334:1-1337:20; DTX-2725 at 267:18-269:16; DTX-2724 at 208:4-14.) Hait was not cited in any prior art taxane references, including the references discussed by Defendants' experts. (Tr. (Kingston) 227:16-228:19.) In addition, Hait provides only a hypothetical binding model for a protein called calmodulin, which is different from and unrelated to Pgp. (JTX-102 at 104 (Fig. 2); Tr. (Roush) 1334:1-25; DTX-2725 at 104:10-15.) Furthermore, Defendants apply Hait's hypothetical model to substrates rather than inhibitors, as taught by Hait. (Tr. (Roush) 1332:12-1333:25; Tr. (Heathcock) 887:14-888:1.)

Lampidis discusses a series of charged rhodamine dye compounds in certain MDR cells. (DTX-2241 at 4267.) Lampidis concludes that "positively-charged" dye compounds being made more lipophilic accumulate at higher levels in MDR cells. (DTX-2241 at 4271; Tr. (Heathcock) 953:20-955:8.) Lampidis, however, does not discuss taxane compounds. (DTX-2241; Tr. (Heathcock) 879:5-7.) Taxane compounds do not have a positive charge like the Lampidis compounds. (Tr. (Heathcock) 954:12-955:5.)

Ojima 1994 discloses a series of taxane compounds with modifications in the C-13 side chain, which includes the C-3' position. (JTX-104 at 272-73; Tr. (Heathcock) 966:2-19.) Dr. Ojima tested several of his modified taxane compounds in a resistant breast cancer cell line (*i.e.*, MCF7-R). (JTX-104 at 273, Table IV; Tr. (Heathcock) 863:19-864:6, 955:13-16.) As of 1994, changes to the C-3' position, and, particularly, using C-3' alkyl and alkenyl groups, were a new development for modifying taxane compounds in an attempt to address resistance. (JTX-104 at 273.) Ojima 1994 does not teach that making the "Northern Hemisphere" of docetaxel more

lipophilic increases activity in resistant cancer cells. (JTX-104; Tr. (Heathcock) 889:5-11, 891:5-892:2.) As evidenced by Ojima 1994, changes to the side chain can modulate activity in resistant cell lines. (Tr. (Heathcock) 959:18-21; JTX-104 at 273, Table IV.)

Dr. Heathcock focused on only two of Dr. Ojima's compounds: SB-T-1101 and SB-T-1102. (Tr. (Heathcock) 890:22-892:21.) Dr. Ojima's SB-T-1101 compound differs structurally from docetaxel only in the side chain. (Tr. (Heathcock) 956:6-17.) The "core" of the molecule is the same as docetaxel. (*Id.* at 955:17-21.) Dr. Ojima's SB-T-1102 compound, which was identified as "noteworthy," had improved activity in resistant cancer cells and differs structurally from paclitaxel only in the side chain. (JTX-104 at 273; Tr. (Heathcock) 956:14-20.) The "core" of the molecule is the same as paclitaxel. (*Id.* at 955:22-956:20.) In his direct testimony, Dr. Heathcock did not discuss Dr. Ojima's SB-T-1212, which was also identified as "noteworthy."[13] (JTX-104 at 273.) Dr. Heathcock acknowledged that SB-T-1212 only differs from paclitaxel at the side chain. (Tr. (Heathcock) 959:2-5.)

Dr. Heathcock concluded that a POSA would be led to the conclusion that changing the hydroxyl groups at C-7 and C-10 to methoxy groups would be expected to accomplish the goals of improving cell permeability or reducing Pgp affinity. (Tr. (Heathcock) 897:16-19.)

The Court did not find credible the lines of reasoning employed by Dr. Kingston and Dr. Heathcock in order to reach simultaneous methoxy adjustments at the C-7 and C-10 positions. Dr. Kingston and Dr. Heathcock were both knowledgeable with respect to the subject areas. In particular, they provided strong testimony with respect to the underlying science and had a good

[13] The reference states, in relevant part, "*It is noteworthy that SB-T-1102 and SB-T-1212 show one order of magnitude better activity than paclitaxel and docetaxel against MCF7-R. This finding may provide significant information for the development of newer antitumor agents effective against drug-resistant tumors.*" (emphasis in original). (JTX-104 at 273.)

understanding of the prior art references. Nevertheless, the Court finds that based on their selection of prior art references and the specific portions of those references upon which they relied, Dr. Kingston and Dr. Heathcock each "cherry-picked" his way to cabazitaxel. Here, the Court finds that their testimony fell short in their respective leaps from their selected prior art references to their ultimate obviousness conclusions. While Dr. Kingston and Dr. Heathcock took different paths to their obviousness conclusions, it was clear to the Court from their testimony that "all paths led to cabazitaxel." In effect, Dr. Kingston and Dr. Heathcock both engaged in impermissible hindsight analysis.

The Court, on the other hand, found credible Dr. Roush's testimony regarding the experimentation process and the modifications that were being made at multiple positions on the taxane molecule. (Tr. (Roush) 1258:1-1259:2.) In addition, the Court affords weight to Dr. Roush's interpretation of Hait's hypothetical model. (*Id.* at 1332:12-1333:25.) The Court also found Dr. Ludueña's testimony credible. During his video-taped deposition, Dr. Ludueña recognized and acknowledged the findings of several prior art references. (*See generally* DTX-2724.) For example, Dr. Ludueña acknowledged that the combined teachings of Riou and Wils suggest that to overcome docetaxel's resistance, one strategy might be to reduce the recognition or affinity of docetaxel for Pgp. (*Id.* at Clips 143-44.) In addition, Dr. Ludueña readily conceded that as of 1995, there was some evidence that Pgp was overexpressed in cancer cells as compared to healthy cells. (*Id.* at Clip 184.) Dr. Ludueña also testified that a POSA "would do a survey and say, 'There [are] several [known] mechanisms [of resistance]. Pgp sounds real[ly] interesting. I'll work on that. But I may also want to work on some other things.'" (*Id.* at Clip 122.)

Here, Defendants demonstrated that the issue of Pgp overexpression presented an area of interest for research during the relevant time period. The testimony regarding the prior art references Defendants relied upon, however, does not demonstrate obviousness. As discussed above, the testimony presented on behalf of Defendants reflects improper hindsight analysis. Here, in light of the fact that modifications were being made at multiple positions, including the C-2, C-4, C-5, C-7, C-8, C-9, C-10, C-11, C-12, C-13, C-14, C-2', and C-3' positions, the Court finds that a POSA would have been motivated to make modifications on the C-7 or C-10 position. Defendants, however, failed to demonstrate that a POSA would have been motivated to make the simultaneous methoxy substitutions at the C-7 and C-10 positions required to form cabazitaxel.

**c. Secondary Considerations**

The Court will next examine the secondary considerations. The Court commences its analysis with a presumption of a nexus between the '170 patent and the following secondary considerations: unexpected properties, failure of others, and commercial success. *See WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1329 (Fed. Cir. 2016) ("[T]here is a presumption of nexus for objective considerations when the patentee shows that the asserted objective evidence is tied to a specific product and that product 'is the invention disclosed and claimed in the patent.'") (citations omitted).

**(1) Nexus with the claimed invention**

The Court finds Plaintiffs' argument that "Jevtana is both an embodiment of, and coextensive with, Claims 1 and 2 of the '170 patent," valid. (Pls.' Post-Trial Br. 34, ECF No. 280.) Defendants do not contest this argument. (Defs.' Post-Trial Br. 52-57, ECF No. 264-1.)

The burden, therefore, shifts to Defendants to rebut the presumption of a nexus. *See Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1130 (Fed. Cir. 2000) ("[I]f

the marketed product embodies the claimed features, and is coextensive with them, then a nexus is presumed and the burden shifts to the party asserting obviousness to present evidence to rebut the presumed nexus."). "The presumed nexus cannot be rebutted with mere argument; evidence must be put forth." *Id.*

**(2) Unexpected Properties**

"To qualify as unexpected, the claimed properties or results must be different in 'kind and not merely in degree' from the results of the prior art." *Daiichi Sankyo Co. v. Mylan Pharm. Inc.*, 670 F. Supp. 2d 359, 382 (D.N.J. 2009), *aff'd sub nom. Daiichi Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346 (Fed. Cir. 2010), *cert. denied*, 526 U.S. 1286 (2011) (quoting *In re Huang*, 100 F.3d 135, 139 (Fed. Cir. 1996)). "While a marked superiority in an expected property may be enough in some circumstances to render a compound patentable, a mere difference in degree is insufficient." *Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014) (internal quotations omitted) (quoting *In re Papesch*, 315 F.2d 381, 392 (CCPA 1963)). "When assessing unexpected properties, . . . [the Court] must evaluate the significance and 'kind' of expected results along with the unexpected results." *Bristol-Myers Squibb Co.*, 752 F.3d 967 at 977.

Plaintiffs proffer two arguments for unexpected properties: (1) the addition of methoxy groups at C-7 and C-10 positions to docetaxel results in a compound with significant improvements in its properties as compared to docetaxel; and (2) cabazitaxel's superior activity over docetaxel, with activity of five to ten times better than docetaxel, given that it is a Pgp substrate, is not merely a difference in the level of potency as compared to docetaxel but is also a difference with respect to type of body interaction. (Pls.' Post-Trial Br. 34-35.)

Defendants assert that Dr. Roush's argument that the "FDA approval [of cabazitaxel] is evidence of unexpected results" is undercut by "[t]he inventors' ability to predict clinical success for cabazitaxel, without clinical data." (Defs.' Post-Trial Br. 55.) Defendants further assert that Dr. Roush's argument that "cabazitaxel's performance against resistant cancer cells was somehow unexpected" is also unavailing because it "conflicts with prior art, which disclosed numerous examples of taxane compounds with similar structures to cabazitaxel that showed improved potency against MDR cells." (*Id.*) Defendants also argue that cabazitaxel's "better performance" in comparison to "its peers in the prior art . . . is a 'mere difference in degree'[,] insufficient to establish unexpected results." (*Id.*) Defendants argue that cabazitaxel's improved performance against resistant cells, despite being "less of a Pgp substrate" is not unexpected "given that docetaxel (a known Pgp substrate) performed better than paclitaxel against MDR cells lines." (*Id.* at 55-56.)

The Court is persuaded by Plaintiffs' argument that it was unexpected that adding methoxy groups at the C-7 and C-10 positions to docetaxel could have resulted in a compound with significant improvements in its properties as compared to docetaxel. Researchers modified thousands of taxane analogs at almost all locations around the taxane core and side chain. (Tr. (Roush) 1295:16-21, 1381:18-1382:21.) The Court finds, however, that cabazitaxel's superior activity over docetaxel, even activity that is five to ten times better, is not entirely unexpected. The prior art disclosed that certain taxanes showed improved potency against MDR cells. Those taxanes included docetaxel, which the prior art disclosed was more potent in a variety of cell lines. (Tr. (Roush) 1284:15-17.) A POSA would therefore expect that cabazitaxel would show improved potency over docetaxel but would not expect the particular degree of superiority that cabazitaxel

showed. Cabazitaxel's superior performance, therefore, cannot be said to be entirely unexpected because it differs not in kind but only in degree, from docetaxel's performance.

The case cited by Plaintiffs in support of their argument that cabazitaxel's superiority over docetaxel is an unexpected property is distinguishable from the case at bar. In *Daiichi Sankyo Co. v. Mylan Pharm. Inc.*, the court found that the drug exhibited unexpected results due to increased drug potency, in addition to insurmountable antagonism (an activity totally lacking in the other compound), drug-drug interactions, inverse antagonism, and other rehabilitative properties. *Daiichi Sankyo Co.*, 670 F. Supp. 2d at 382. Cabazitaxel's increased potency is not a new property for a taxane. Further, cabazitaxel's superior performance over docetaxel, given that it is a Pgp substrate, is also not novel because docetaxel, also a Pgp substrate, performed better than paclitaxel against MDR cell lines. The Court, therefore, declines to adopt the reasoning in *Daiichi Sankyo Co.*, and provides minimal weight to Plaintiffs' arguments regarding unexpected results.

**(3) Failure of Others**

"Evidence that others within the field have tried and failed to make the claimed invention can demonstrate that the invention was nonobvious." *AstraZeneca LP v. Breath Ltd.*, 88 F. Supp. 3d 326, 390-92 (D.N.J. 2015), *aff'd*, 603 F. App'x 999 (Fed. Cir. 2015). "The purpose of evidence of failure of others is to show indirectly the presence of a significant defect in the prior art, while serving as a simulated laboratory test of the obviousness of the solution to a skilled artisan." *Warner Chilcott Co., LLC v. Teva Pharm. USA, Inc.*, 89 F. Supp. 3d 641, 672 (D.N.J. 2015), *aff'd*, 642 F. App'x 996 (Fed. Cir. 2016) (citing *In re Cyclobenzaprine Hydrochloride Extended–Release Capsule Patent Litig.*, 676 F.3d 1063, 1081-83 (Fed. Cir. 2012)).

Plaintiffs argue that cabazitaxel is one of only three taxane compounds ever to receive FDA approval and remains the last such compound to be approved despite attempts by multiple groups

around the world to develop taxanes into new anticancer treatments. (Pls.' Post-Trial Br. 35.) Plaintiffs assert that the taxanes which were brought to clinical trials failed either due to toxicities or lack of activity and that these worldwide failures support a finding that cabazitaxel would not have been obvious. (*Id.* at 35-36.) Defendants, on the other hand, argue that the proper standard for evaluating whether a drug is successful is whether it shows some anticancer activity, not whether it is approved by the FDA. (Defs.' Post-Trial Br. 54.)

The Court is not persuaded by Defendants' argument. Failure to obtain FDA approval is evidence of failure of others. *See Pfizer Inc. v. Teva Pharm. USA, Inc.*, 460 F. Supp. 2d 659, 662 (D.N.J. 2006) (relying on the Federal Circuit's indirect endorsement, in *Knoll Pharm. Co. v. Teva Pharms. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004), of the use of "'failure to obtain FDA approval' as a benchmark for an analysis under 'failure of others'").

"In deciding how to approach the issue of failure of others to solve the problem which the patented invention solved, it is appropriate methodology to first state the problem[.]" *Pfizer Inc.*, 460 F. Supp. 2d at 662. Multiple groups around the world tried unsuccessfully to develop taxanes into effective therapies (Tr, (Sartor) 1490:8-10) and only Plaintiffs succeeded in developing a compound that showed superior activity over docetaxel, namely cabazitaxel, and obtained FDA approval. (*Id.* at 1528:1-9.)

The Court finds that Plaintiffs' success, where others had failed, in consideration of the state of the prior art during relevant time frame, points to a finding of non-obviousness and, thus, gives considerable weight to Plaintiffs' argument on this point.

**(4) Commercial Success**

"When a patentee can demonstrate commercial success, usually shown by significant sales in a relevant market, and that the successful product is the invention disclosed and claimed in the

patent, it is presumed that the commercial success is due to the patented invention." *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 740 (Fed. Cir. 2013) (quoting *J.T. Eaton & Co. v. Atl. Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997)). However, "if the feature that creates the commercial success was known in the prior art, the success is not pertinent." *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1312 (Fed. Cir. 2006).

The Court finds that Jevtana has achieved commercial success. Dr. Tate testified that Jevtana's sales from 2010 to the end of 2016 totaled approximately $975 million in the United States and $2.1 billion worldwide. (Tr. (Tate) 666:20, 668:15-17.) Dr. Tate also testified that, based on the estimated sales for 2017, the total sales figure is expected to reach $[redacted] in the United States and approximately $[redacted] worldwide, respectively. (*Id.* at 666:20-667:3, 668:19-21.) This success was also in the relevant market. Plaintiffs defined Jevtana's relevant market as "post-docetaxel mCRPC" because Jevtana can only be given to patients who have previously taken docetaxel. In addition, even with the inception of two key competitors in this market in 2013, Jevtana's market share [redacted] (*Id.* at 676:21-677:2.) It is not necessary for Jevtana to command the greatest market share. *See Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 923 F. Supp. 2d 602, 679 (D. Del. 2013), *aff'd*, 752 F.3d 967 (Fed. Cir. 2014) (quoting *Takeda Chem. Indus., Ltd. v. Mylan Labs. Inc.*, 417 F. Supp. 2d 341, 386 (S.D.N.Y. 2006)) ("There is no requirement that the invention be the only successful product in its market niche or the most successful.").

The Court finds that Defendants' argument fails because although there are multiple patents that cover Jevtana in the FDA's Orange Book, Plaintiffs successfully demonstrated, with evidence of Jevtana's performance in the "post-docetaxel mCRPC market" that Jevtana's

commercial success is due to Claims 1 and 2. The Court, therefore, affords considerable weight to Plaintiffs' argument with respect to commercial success.

Based on the foregoing, the Court finds that Defendants have failed to demonstrate obviousness by clear and convincing evidence.

**5. Obviousness-Type Double Patenting**

Obviousness-type double patenting is a judicially created doctrine that precludes one person from obtaining more than one valid patent for an obvious modification of the same invention. *Otsuka Pharma. Co. v. Sandoz, Inc.*, 678 F.3d 1297-98 (Fed. Cir. 2012). The Court finds that Claim 2 of the '470 patent covers docetaxel and Claim 6 of the '470 patent covers a pharmaceutical composition of docetaxel. (JTX-119 at col. 10., ll. 30-33, 42-45.) The Court further finds that because cabazitaxel is not an obvious modification of docetaxel, Defendants have failed to demonstrate obviousness-type double patenting by clear and convincing evidence.

## IV. '592 PATENT

### A. Post-Trial Filings

**1. Summary**

Subsequent to the conclusion of the bench trial on November 8, 2017, the parties filed several items of correspondence. Plaintiffs' November 17, 2017 correspondence indicated that: (1) Plaintiffs were not appealing the Board's determination of the unpatentability of Claims 1-5, 7-20, and 22-29; (2) the USPTO would issue and publish a certificate canceling those claims after the time for appeal expired on November 24, 2017; and (3) as of November 24, 2017, any remaining arguments by Defendants as to the validity or non-infringement of those claims would become moot. (Pls.' 11/17/17 Ltr., ECF No. 285.)

Defendants' December 4, 2017 response to Plaintiffs' correspondence asserted that the invalidity and non-infringement of the asserted claims remained ripe for decision. (Defs.' 12/4/17 Ltr., ECF No. 298.) According to Defendants, they presented evidence of invalidity and non-infringement on the '592 patent claims that Plaintiffs originally asserted at trial and, therefore, are entitled to receive a decision on their counterclaims. (*Id.*) Defendants also argued that there continues to be a substantial controversy between the parties sufficient to support Article III jurisdiction over Defendants' Declaratory Judgment counterclaims because Plaintiffs seek to amend claims as part of their appeal of the IPR decision. (*Id.*) Defendants argue that if Plaintiffs receive narrower, amended claims through the IPR process, a judgment of invalidity or non-infringement from this Court as to the originally asserted claims would preclude Plaintiffs from asserting those narrower claims against Defendants as a matter of law. (*Id.*)

On December 11, 2017, Plaintiffs filed correspondence indicating that they filed a statutory disclaimer with the USPTO pursuant to 35 U.S.C. § 253 and 37 C.F.R. § 1.321(a). Plaintiffs asserted that the statutory disclaimer becomes part of the original patent, and Claims 7, 11, 14-16, and 26 are now viewed as though they "never existed." (Pls.' 12/11/17 Ltr., ECF No. 300.) Defendants' December 11, 2017 responsive correspondence argued that there continues to be a substantial controversy between the parties sufficient to support Article III jurisdiction over Defendants' Declaratory Judgment counterclaims with respect to Claims 7, 11, 14-16, and 26 of the '592 patent. (Defs.' 12/4/17 Ltr., ECF No. 298.)

Because the parties' correspondence contained minimal case law citations and legal analysis, the Court required the parties to brief the issues raised in the correspondence. (12/12/17 Letter Order, ECF No. 302.) The parties filed legal briefs on December 13, 2017. (Pls.' Br., ECF No. 303; Defs.' Br., ECF No. 304.) The Court has reviewed and carefully considered the parties'

positions and finds good cause to issue a decision with respect to Claims 7, 11, 14-16, and 26, as set forth below.

**2. Discussion**

**a. The Court's Jurisdiction**

The Court has carefully considered the parties' submissions and is unpersuaded by Plaintiffs' arguments. The Supreme Court has stated that the standard for determining whether a declaratory judgment action satisfies the case or controversy requirement of Article III is "whether the facts alleged,[14] under all the circumstances, show that there is a substantial controversy, between parties having adverse legal interests, of sufficient immediacy and reality to warrant the issuance of a declaratory judgment." *MedImmune, Inc. v. Genetech, Inc.*, 549 U.S. 118, 127 (2007) (quoting *Md. Cas. Co. v. Pac. Coal & Oil Co.*, 312 U.S. 270, 273 (1941)). There is no bright-line rule that dictates which cases satisfy the requirement and which do not. *MedImmune, Inc.*, 549 U.S. at 127. The issues raised in the case "must be 'definite and concrete, touching the legal relations of parties having adverse legal interests'; and . . . be 'real and substantial' and 'admi[t] of specific relief through a decree of a conclusive character, as distinguished from an opinion advising what the law would be upon a hypothetical state of facts.'" *Id.* (quoting *Aetna Life Ins. Co. v. Haworth*, 300 U.S. 227, 240-41 (1937)) (alteration in original).

Here, the parties conducted an entire trial of this case. On September 21, 2017, after the trial was underway, the PTAB issued its decision with respect to the '592 patent. (Defs.' 9/21/17 Letter, ECF No. 21.) On the final day of the trial, Plaintiffs simply indicated that they "were going to focus Dr. Sartor's examination . . . on Claims 21 and 30." (Tr. 1480:9-13.) Defendants

[14] The district court in the *MedImmune* case disposed of the declaratory judgment claims on its grant of a motion to dismiss. *MedImmune, Inc. v. Genetech, Inc.*, 549 U.S. 118, 120 (2007).

responded that they "continue[d] to ask for a judgment of invalidity on all of the claims that have been a part of the case." (*Id.* at 1480:16-22.) Plaintiffs did not object. In addition, Plaintiffs did not move at any time prior to the conclusion of the trial to voluntarily dismiss their assertion of Claims 7, 11, 14-16, and 26. The current procedural posture of the case also reflects that the claims at issue have not been cancelled. The Court, therefore, finds that it has subject matter jurisdiction over Claims 7, 11, 14-16, and 26.

**b. Additional Legal Standards**

**(1) Infringement**

The patentee bears the burden of proving infringement. *Medtronic, Inc. v. Mirowski Family Ventures, LLC*, 134 S. Ct. 843, 846 (2014). In the event that the patentee fails to offer evidence to rebut a counterclaim of non-infringement, the patent infringer may be entitled to a declaratory judgment or summary judgment. In *Medtronic*, the Supreme Court held that when a licensee seeks a declaratory judgment against a patentee to establish that there is no infringement, the burden of proving infringement remains with the patentee—the burden never shifts to the patent infringer. *Id.* Several practical considerations support the patentee's burden requirement: (1) shifting the burden based on the form of action could create post-litigation uncertainty about a patent's scope; (2) compelling a licensee to prove a negative may create unnecessary complexity; and (3) burden shifting is difficult to reconcile with the Declaratory Judgment Act's purpose of ameliorating the "dilemma" posed by requiring one challenging a patent's scope to choose between abandoning rights or risking suit. *MedImmune*, 549 U.S. at 129.

In *Apple, Inc. v. Samsung Electronics Co.*, the court granted the alleged patent infringer's motion for judgment as a matter of law that the products at issue did not infringe the patent because the patentee had the burden to demonstrate infringement but presented no evidence. 67 F. Supp.

3d 1100, 1125-27 (N.D. Cal. 2014), *aff'd*, 816 F.3d 788 (Fed. Cir. 2016), *vacated in part on reh'g en banc*, 839 F.3d 1034 (Fed. Cir. 2016). The court held that although Samsung presented no evidence at trial on the issue of infringement as to the products, it was clear that both Apple and Samsung expected to try the issue of infringement as to those products and that these claims were not akin to claims merely "referenced in the complaint." *Id.* Relevant to the court's consideration was the fact that Apple was forced to prepare its defense in advance of trial and had to try the case for three weeks. *Id.* Finally, the court found that Samsung's dismissal of its claim of infringement did not moot Apple's counterclaim. *Id.* The court, therefore, found that the issue of non-infringement was "fairly placed in issue" such that Apple was entitled to a determination on its counterclaim. *Id.*

In *Radware, Ltd. v. A10 Networks, Inc.*, the court granted the alleged patent infringer's motion for summary judgment of non-infringement on all claims that the patentee no longer asserted because: (i) the patentee's original infringement contentions asserted every claim; and (ii) the alleged patent infringer's declaratory judgment counterclaims were directed to all of the same claims. Case Nos. C-13-02021; C-13-02024, 2014 WL 2738538, at *9 (N.D. Cal. June 11, 2014). The Court noted that the patentee bore the burden of proving infringement under *Medtronic, Inc.*, and did not meet this burden; thus, the alleged patent infringer was entitled to summary judgment of non-infringement as to the claims that the patentee no longer asserted. *Id.*; *but see Alcon Research Ltd. v. Barr Labs., Inc.*, 745 F.3d 1180 (Fed. Cir. 2014) (holding that judgment was not warranted because the patents were not litigated or fairly placed in issue during the trial). Here, the Court finds that Claims 7, 11, 14-16, and 26 were fairly placed in issue during the trial and the Court may issue a judgment with respect to such claims.

**(2) Invalidity**

"Where a declaratory judgment action asserts invalidity of patents, the Supreme Court of the United States has admonished that the issue of validity should be considered and not avoided by dispositions based on non-infringement grounds." *Windmoller v. Laguerre*, 284 F. Supp. 563, 565 (D.D.C 1968). "When an alleged infringer attacks the validity of an issued patent, well-established law places the burden of persuasion on the attacker to prove invalidity by clear and convincing evidence." *Tech. Licensing Corp. v. Videotek, Inc.*, 545 F.3d 1316, 1327 (Fed. Cir. 2008).

"A patent is presumed valid, and the burden of persuasion to the contrary is and remains on the party asserting invalidity." *PowerOasis, Inc. v. T-Mobile USA, Inc.*, 522 F.3d 1299, 1303 (Fed. Cir. 2008) (quoting *Ralston Purina Co. v. Far-Mar-Co, Inc.*, 772 F.2d 1570, 1573 (Fed. Cir. 1985)); *see also Research Corp. Techs. v. Microsoft Corp.*, 627 F.3d 859, 870 (Fed. Cir. 2010) (same). "[T]he party asserting invalidity also bears the initial procedural burden of going forward to establish a legally sufficient *prima facie* case of invalidity. If this burden is met, the party relying on validity is then obligated to come forward with evidence to the contrary." *Ralston Purina Co.*, 772 F.2d at 1573 (alteration in original). "Rebuttal is merely 'a showing of facts supporting the opposite conclusion,' and may relate to any of the *Graham* factors including the so-called secondary considerations." *ABB Air Preheater, Inc. v. Regenerative Envt'l Equip. Co.*, 167 F.R.D. 668, 673 (D.N.J. 1996).

The trial court has the responsibility to determine whether the challenger has met its burden by clear and convincing evidence. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1360 (Fed. Cir. 2007) (citing *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1534 (Fed. Cir. 1983)). The trial court considers the totality of the evidence, including any rebuttal evidence presented by the

patentee. *Id.* Clear and convincing evidence exists when the movant "place[s] in the mind of the ultimate fact finder an abiding conviction that the truth of its factual contentions [is] 'highly probable.'" *Medinol Ltd. v. Guidant Corp.*, 412 F. Supp. 2d 301, 312 (S.D.N.Y. 2005) (alteration in original); *see also Buildex Inc. v. Kason Indus., Inc.*, 849 F.2d 1461, 1463 (Fed. Cir. 1988) ("The 'clear and convincing' standard of proof of facts is an intermediate standard which lies somewhere between 'beyond a reasonable doubt' and a 'preponderance of the evidence.'" (citing *Addington v. Texas*, 441 U.S. 418, 425 (1979)).

**B. Testimony**

**1. Sunil Gupta**

Dr. Gupta, an Associate Vice-President of Global Regulatory Affairs and Head of Sanofi LLC's North American Region for Regulatory Affairs, is the sole inventor of the '592 patent and testified by means of video deposition excerpts. (Gupta Video Day 1 Clip 1-2; DTX-2723 Clip 11.) Dr. Gupta testified regarding the '592 patent and the clinical trials using cabazitaxel. (*See generally* DTX-2722.) He stated that he had no involvement in the Phase I or Phase II clinical trials conducted on cabazitaxel and first became involved with cabazitaxel in 2005. (*Id.* at Clips 6, 9.) Dr. Gupta also testified that he led the multinational team through the preparation and filing of the NDA related to cabazitaxel. (*Id.* at Clip 8.) Dr. Gupta testified that several decisions were made in parallel with respect to the '592 patent: (1) the 25 $mg/m^2$ dose; (2) the three per week schedule as opposed to a weekly schedule; and (3) combining the cabazitaxel with prednisone. (*Id.* at Clips 43, 54.) Dr. Gupta testified that he did not recall any journal articles or publications that praised the work performed in developing the inventions claimed in the '592 patent or reading any articles or publications describing a need for a drug like the one he invented. (*Id.* at Clips 78-79.)

### 2. Rachel A. Hansard[15]

Rachel Hansard, the director of solid tumor marketing at Sanofi, testified by means of video deposition excerpts regarding a number of marketing-related issues. (*See generally* DTX-2721.) Ms. Hansard testified that Jevtana and its competitors, [redacted] (JTX-2721 Clip 4.) In addition, Ms. Hansard testified that she considered Jevtana to be [redacted] (*Id.* at Clip 8.) Ms. Hansard also testified that the jump in Jevtana's sales figures from 2010 to 2011 represented long-felt need. (*Id.* at Clips 17-18.) According to Ms. Hansard, "there [were] a significant number of patients at that time that had progressed on or after docetaxel that were waiting for Jevtana to be approved by the FDA. And that is representative of the long[-]felt need." (*Id.* at Clip 18.) Ms. Hansard testified that Jevtana arguably has [redacted] (*Id.* at Clip 28.) Ms. Hansard testified that Jevtana [redacted] (*Id.* at Clips 33, 85.) In addition, Ms. Hansard testified about Jevtana's commercial rebate program. (*Id.* at Clips 36-39.) When asked whether there have been any losses on Jevtana and whether Jevtana is profitable for Sanofi, Ms. Hansard testified "I don't know." (*Id.* at Clips 41-44.)

### 3. DeForest McDuff, Ph.D.[16]

Dr. McDuff testified on behalf of Defendants with respect to commercial success. Dr. McDuff testified regarding the basis for his opinions that: (1) Jevtana sales have not been

[15] Ms. Hansard was designated by Sanofi as a Rule 30(b)(6) witness on topics relating to Sanofi's sales and marketing of the cabazitaxel product. (FPT Order Sec. 6, Pls.' Witnesses § A.1.)

[16] Dr. McDuff, a partner at Insight Economics, has more than ten years of experience in consulting, finance, and economic research, including in more than forty litigations involving

commercially successful; and (2) there is a lack of nexus between the commercial performance of Jevtana and the '592 patent. (Tr. (McDuff) 716:13-22.)

Dr. McDuff testified that Jevtana's sales are somewhat unimpressive and relatively low compared to benchmarks, including competitors as well as the industry generally. (Tr. (McDuff) 719:22-25.) Dr. McDuff also testified that: (1) two competitive products that came on the market after Jevtana, Xtandi and Zytiga, significantly outperformed Jevtana with sales in excess of $2 billion a year (*id.* at 726:18-23, 737:10-11); (2) Jevtana's sales show that it is not a top selling or impressive drug in the industry and its sales are even below average for new drug products (*id.* at 730:5-8); (3) Jevtana is not a top selling oncology drug and not capturing much of that market (*id.* at 732:25-733:4); and (4) Jevtana is [redacted] (*id.* at 761:6). Upon cross-examination, Dr. McDuff acknowledged that there are two separate patient populations, pre-docetaxel and post-docetaxel. (*Id.* at 770:8-19.) In addition, Dr. McDuff testified that he was not offering an opinion as to nexus with respect to the '170 patent. (*Id.* at 771:2-4.)

**4. Daniel P. Petrylak, M.D.**[17]

Dr. Petrylak testified on behalf of Plaintiffs that he reviewed the '592 patent for two issues: (1) to determine whether Jevtana or cabazitaxel is covered by the particular patent; and (2) whether Defendants' proposed use of cabazitaxel encourages and causes the practice of methods related to the '592 patent. (Tr. (Petrylak) 515:18-23.) Dr. Petrylak testified that there are no differences

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pharmaceuticals. Dr. McDuff has Bachelor's degrees in economics and mathematics from University of Maryland, a Master's degree in economics from Princeton University, and a Ph.D. in economics from Princeton University. (Tr. (McDuff) 713:9-715:2.)

[17] Dr. Petrylak was accepted as an expert with respect to the treatment of prostate cancer and the evaluation of prostate cancer treatments. (Tr. (Petrylak) 514:25-515:6.)

between Defendants' labels and Jevtana's label and that it is only necessary to look at one product label as representative of all Defendants' labels.[18] (*Id.* at 525:1-4, 525:13-16.)

Dr. Petrylak testified that there is more than one corticoid that is used with Defendants' product: dexamethasone and prednisone are both used, and both are prescribed by an attending physician. (*Id.* at 535:16-20, 537:4-6, 537:19-21.) Both corticoids are part of a pre-medication regimen that is used half an hour before cabazitaxel is administered. (*Id.* at 535:25-536:2.) The pre-medication regimen consists of three different components: an antihistamine, dexamethasone, and an H2 blocker. (*Id.* at 536:3-5.)

Dr. Petrylak testified that giving dexamethasone prior to cabazitaxel is considered "in combination with cabazitaxel" because "even though [dexamethasone is] given a half an hour before[, it] is still in the system, it's still affecting the cells that may cause the anaphylaxis, it's affecting a variety of different areas, so it is still present." (*Id.* at 536:21-537:3.) With respect to prednisone, Dr. Petrylak testified that Defendants' label instructs the physician to prescribe to the patient 10 mg of prednisone in combination with cabazitaxel, and it is either administered in one dose or two different dosages. (*Id.* at 537:19-538:10.) The doctor writes the prescription, but the patients take the prednisone themselves (*id.* at 358:13-16), unlike the dexamethasone that is administered by an infusion nurse at the infusion center (*id.* at 533:24-534:7). Dr. Petrylak testified that Section 17 of Defendants' label, entitled "Patient Counselling and Information," explains the importance of prednisone to the patient and provides that if they do not take the prednisone, they are to report it to their physician. (*Id.* at 539:7-14.) Furthermore, Dr. Petrylak testified that prednisone has anti-inflammatory effects that can help control patients' pain and help them feel

[18] For the purpose of his testimony, Dr. Petrylak choose Fresenius's label (PTX-1023). (*Id.* at 525:17-20.)

better. (*Id.* at 539:25-540:2.) He noted that studies have demonstrated prednisone's activity against prostate cancer, but there has not been a study testing cabazitaxel without prednisone and he does not know the effect of cabazitaxel absent the prednisone. (*Id.* at 540:5-10.)

Dr. Petrylak testified that the 1989 Tannock paper (JTX-38) explains the importance of prednisone. (*Id.* at 540:11-19.) Dr. Petrylak also testified that Tannock found that 38% of patients with castration-resistant prostate cancer taking prednisone had some improvement in various quality of life parameters (*e.g.*, pain, energy, appetite, and fatigue), lasting between three and thirty months with a median duration of four months, and 19% of these patients maintained this improvement. (*Id.* at 540:22-541:4, 541:24-542:3.) Next, Dr. Petrylak testified that Defendants' label (PTX-1363) indicates that prednisone has significant anti-inflammatory effects. (*Id.* at 541:8-16.) Dr. Petrylak concluded that the Fresenius label: (1) instructs the physician to tell patients to report when they do not take prednisone; and (2) advises patients to report to the physician when they do not take prednisone. (*Id.* at 544:19-24.)

Dr. Petrylak acknowledged on cross examination that Tannock was not a randomized trial establishing that prednisone was an effective anticancer agent and that the aim of the study was palliation. (*Id.* at 556:5-12.) Furthermore, Dr. Petrylak acknowledged that the study: (1) provided little evidence of a consistent anticancer response from prednisone (*id.* at 556:16-21); (2) provided no convincing evidence that systemic therapy with prednisone improves the survival of patients with metastatic prostate cancer and that further measures of symptom control should be used to assess palliation (*id.* at 557:2-9); and (3) is clearly insufficient for FDA-approved prednisone to be considered as an anticancer therapy (*id.* at 557:10-13). Dr. Petrylak also acknowledged that prednisone has not been approved by the FDA to treat cancer as a single agent and that, as a single agent in a control trial, prednisone is likely palliative. (*Id.* at 557:14-560:25). Dr. Petrylak testified

that out of the hundreds of times he prescribed cabazitaxel, only once did he decline to prescribe prednisone to a patient. (*Id.* at 569:15-17.) Dr. Petrylak stated that cabazitaxel is not lethal with respect to safety and efficacy if administered to a patient who is not taking prednisone. (*Id.* at 563:3-10.)

Dr. Petrylak additionally testified that he understands the Jevtana data is applicable to Defendants' products through Defendants' bioequivalence waivers PTX-1014, PTX-1025, PTX-1060, PTX-1076, PTX-1143, PTX-1208 and PTX-1244. (*Id.* at 547:9-15.)

Dr. Petrylak testified that element D of Claim 21, which states "wherein the prostate cancer is a castration-resistant or hormone-refractory metastatic prostate cancer," instructs the physician to give cabazitaxel to these types of patients and it does so within the "indications and usage section" of the Defendants' label. (*Id.* at 552:4-11.)

Dr. Petrylak concluded that Defendants' label will cause a physician to infringe the '592 asserted claims because the label:

> is a guideline for physicians to direct and control the administration of cabazitaxel, and that's seen in the label for both the physician who directs the infusion nurse, as well as the patient who is going to receive the drug and then administer the prednisone to themselves. The nurses are absolutely required to follow what the physician says and the directions of the physician in the situation. And, again, to control side effects and to control the outcome, the patients must follow what the physician says as far as the prednisone or potentially suffer adverse events that are related to lack of prednisone. [D]efendants' labels direct and encourage the use of methods claimed in the '592 patent, and the physician, in fact, uses all of these methods to treat the patients, and these are very desperately ill patients that must follow these protocols exactly.

(*Id.* at 553:21-554:12.)

### 5. Mark J. Ratain, M.D.[19]

Dr. Ratain testified on behalf of Defendants that, to a POSA, all of the asserted claims in the '592 patent would have been obvious over the prior art because there is no significant difference between the asserted claims and the prior art. (Tr. (Ratain) 305:21-4, 386:16-25). Dr. Ratain also testified that any required combinations are obvious combinations that a POSA would have been motivated to combine and that a POSA would have had a reasonable expectation of success in arriving at the asserted claims. (*Id.* at 386:19-25.) Furthermore, Dr. Ratain testified that a number of prior art references provided knowledge about cabazitaxel during the relevant time period, prior to 2009 when the compound was disclosed in the patent. (*Id.* at 334:7-16.)

With respect to the Mita study ("Mita"), a Phase I study published on January 15, 2009 (JTX-45), Dr. Ratain testified that a POSA would understand from reading Mita that cabazitaxel was developed as a solution to the multidrug resistance problem. (Tr. (Ratain) 338:2-13; 338:21-340:5.) Mita teaches a POSA that some patients will have more toxicity than others and concludes that cabazitaxel has a favorable safety profile for hematologic toxicity. (*Id.* at 443:9-14, 479:9-16.) Dr. Ratain further testified that "Mita teaches you that you could start somebody at 25 [mg/m$^2$] and monitor them closely, or you could start somebody at 20 [mg/m$^2$] and potentially escalate them." (*Id.* at 443:9-14.) Dr. Ratain acknowledged that measuring anticancer activity of cabazitaxel in prostate cancer was not the primary objective of the Mita study. (*Id.* at 408:16-25.)

[19] Dr. Ratain was accepted by the Court as an expert in treating cancer and oncology, including pharmacokinetics in clinical trials and drug development for advanced solid tumors, with experience in studying and treating prostate cancer. (Tr. (Ratain) 298:22-299:4.)

Dr. Ratain testified that the Attard[20] paper ("Attard"), published online on May 3, 2005, interpreted Mita the same way he interpreted Mita, which is the way a POSA would have interpreted Attard. (*Id.* at 348:12-350:23.) "Attard reports that cabazitaxel is not a Pgp substrate, that it's given intravenously over a one-hour infusion every three weeks, that the maximally tolerated dose is 20 [mg/m$^2$], that it's active in taxane refractory prostate cancer, and that it's dose from the toxicity is neutropenia." (*Id.* at 350:12-18.)

Dr. Ratain testified that the Pivot study ("Pivot"), which studied cabazitaxel in taxane resistant metastatic breast cancer patients (*id.* at 351:6-9), concludes that: (1) "cabazitaxel appears to be active in docetaxel or paclitaxel resistant breast cancer"; and (2) "the safety profile of cabazitaxel was very favorable when compared with the known safety profile of the market of taxanes or other compounds under development." (*id.* at 353:15-354:1). Dr. Ratain further testified that a POSA would understand Pivot to demonstrate the activity of cabazitaxel in a notoriously difficult population and to treat patients with diseases that are initially responsive to taxanes but then become resistant—a concept relevant to treating both breast cancer and prostate cancer. (*Id.* at 354:15-21.)

Dr. Ratain testified that he did not use hindsight analysis because even prior art such as the Beardsley paper ("Beardsley") relied on Pivot and related it to prostate cancer. (*Id.* at 354:24-355:4.) Dr. Ratain noted that the Beardsley paper relates the breast cancer in Pivot to prostate cancer and states that:

> a Phase II trial with cabazitaxel has not been performed in patients with prostate cancer; however, given its activity in the docetaxel refractory setting described above, referring to [Pivot], this agent is currently being investigated in a Phase III multi-center randomized

[20] John De Bono was the author of Attard, investigator on Mita, and co-principal investigator in the TROPIC study. (Tr. (Ratain) 428:1-9.)

> superior trial comparing three weekly cabazitaxel with prednisone to mitoxantrone with prednisone in patients with castrate-resistant metastatic prostate cancer previously treated with docetaxel-containing treatment.

(*Id.* at 356:19-357:4.) According to Dr. Ratain, a POSA, therefore, would understand that a Phase III trial has been initiated and that the rationale for the Phase III trial was the "exciting results observed for cabazitaxel in [Pivot]." (*Id.* at 357:7-11.) Dr. Ratain also testified that Beardsley described the next study, the Phase III study, to include 720 patients and was performed in May 2010. (*Id.* at 357:12-18.)

Dr. Ratain further testified that multiple publications, specifically the Rodrigues, Winquist and MacKenzie publications, published in the Canadian Journal of Urology, reported this Phase III clinical trial prior to the filing of the '592 patent application in 2009. (*Id.* at 357:19-358:15.) Dr. Ratain also testified that archived listings from clinicaltrials.gov publications (DDTX-2135 and 2136) contained details about the TROPIC trial and the annual report of GCRI, a cancer center in India, contained a description of the Phase III TROPIC trial. (*Id.* at 358:19-359:11, 365:23-366:1; DDTX-2209.)

Dr. Ratain testified that from Rodrigues, Winquist, MacKenzie, clinicaltrials.gov, and the GCRI report, a POSA would understand that cabazitaxel was being studied at a dosage of 25 $mg/m^2$ in combination with prednisone every three weeks for treatment of hormone-refractory prostate cancer. (Tr. (Ratain) 360:21-361:2.) Dr. Ratain also testified that even though the Rodrigues, Winquist, and MacKenzie publications do not explicitly reference anything about measuring neutrophil levels or stopping treatment if neutrophil levels fall below a certain level, a POSA would understand that "to practice as a medical oncologist[, it is implied that] one would need to monitor the neutrophils and to not administer the toxic chemotherapy drug if the neutrophil count was below [] 1,500 [cells/$mm^3$]." (*Id.* at 361:18-362:6.) Furthermore, a POSA "would

understand that to be eligible for the study[,] the patients would have had to previously been treated with docetaxel and demonstrate a progression of disease." (*Id.* at 367:22-25)

Dr. Ratain then provided specific testimony with respect to the various claims of the '592 patent in relationship to the prior art. He testified that Claim 1 is a method for the administration of cabazitaxel to a patient with prostate cancer and it is not limiting. He testified that the TROPIC protocol disclosures, Rodrigues, Winquist, the GCRI Report, and clinicaltrials.gov disclose: (1) that the limitation is prostate cancer that has progressed during or after treatment with docetaxel; (2) the dose of 20 to 25 mg/m$^2$ of cabazitaxel or a hydrate or solvate; (3) that cabazitaxel needs to be given in combination with a corticoid; and (4) the particular corticoid to be used is prednisone. (*Id.* at 369:9-370:8). Therefore, according to Dr. Ratain, "all the limitations of Claim 1 are anticipated because they are all disclosed in each of the Phase III Disclosures and these five individual references." (*Id.* at 370:11-14.) Dr. Ratain testified that because Claim 27 has the same substantive limitations as Claim 1, all the references of TROPIC protocol, the TROPIC listings have limitations in Claim 27. (*Id.* at 370:20-24.)

Dr. Ratain also testified that Claims 15, 21, 26, and 30 all add the same element to Claim 1 or Claim 27, which is the specific dosage limitation of 20 mg/m$^2$. (*Id.* at 379:4-7.) Furthermore, Dr. Ratain noted that there is no difference between Claims 15, 21, 26, and 30 and the prior art because: (1) 20 mg/m$^2$ is explicitly disclosed in both Mita and Pivot (*id.* at 379:8-14); (2) a POSA would understand that if a patient started at 25 mg/m$^2$ and developed unacceptable toxicity, one would need to lower the dose to 20 mg/m$^2$ which is an obvious reduction of 20% (*id.* at 379:14-19); and (3) the Taxotere label disclosed that the dosage shall be reduced for patients with an unacceptable toxicity from 75 mg/m$^2$ to 60 mg/m$^2$, which is a 20% reduction (*id.* at 379:20-380:2).

Dr. Ratain testified that Mita teaches that not everyone can tolerate a dose of 25 mg/m$^2$. (*Id.* at 380:21-22.)

Dr. Ratain testified that all of the asserted claims are obvious because there is no significant difference between the "asserted claims and the prior art; any combinations required are obvious combinations; and a POSA would be motivated to combine them and have a reasonable expectation of success in arriving at the asserted claims." (*Id.* at 386:19-25.) Dr. Ratain additionally testified that in 2006, as the basis of the Phase III study in mCRPC, Sanofi provided the FDA with the following disclosure: "based on the fact that with cabazitaxel, three responses were observed in prostate cancer patients in earlier Phase I study [Mita] and in patients whose metastatic breast cancer was resistant to prior taxanes promising activity with low incidence of adverse events [Pivot], except neutropenia, cabazitaxel is well suited for development in the second line setting in patients with hormone-refractory prostate cancer that progress after Taxotere based treatment." (*Id.* at 392:23-393:7.) According to Dr. Ratain, Sanofi informed the FDA that the Mita and Pivot studies supported the TROPIC study, which studied the hormone-refractory, docetaxel resistant prostate cancer. (*Id.* at 393:16-21.)

Dr. Ratain testified that: (1) after Mita was published, a POSA would have been focused on prostate cancer with cabazitaxel because there were two responses observed in prostate cancer; (2) by 2006, a POSA would have known that Sanofi was focused on cabazitaxel in mCRPC patients whose treatment failed on docetaxel because of the clinicaltrials.gov archive; and (3) by the time the '592 patent was filed, a POSA would have known that the "Phase III trial had been ongoing for almost three years and was scheduled to be completed in the next seven months." (*Id.* at 481:10-482:8.)

### 6. Alton Oliver Sartor, M.D.[21]

Dr. Sartor was an investigator on the TROPIC study that led to the FDA approval of Jevtana. Dr. Sartor testified that Claims 21 and 27 specify the corticoids, prednisone or prednisolone, which can be used in combination with 20 mg/m$^2$ of cabazitaxel and given to a castration-resistant or hormone-refractory metastatic prostate cancer patient that has progressed during or after treatment with docetaxel. (Tr. (Sartor) 1481:3-11.) Dr. Sartor opined that a POSA in October of 2009 would not have had a reasonable expectation that a dose of 20 mg/m$^2$ of cabazitaxel, in combination with a corticoid, would have anticancer activity in a patient with mCRPC who has progressed during or after docetaxel. (*Id.* at 1481:12-20.) According to Dr. Sartor, "[t]here simply was not adequate data available at this particular dose in that particular patient population." (*Id.* at 1481:21-22.)

Dr. Sartor testified that prior to 2009, "we didn't have any method that was known to prolong survival" in mCRPC patients who failed on docetaxel therapy. (*Id.* at 1485:21-1486:3, 1486:16-23.) Dr. Sartor further testified that "[t]here was an urgent need for systemic treatment options for patients with castration-resistant prostate cancer who progressed after receiving first-line docetaxel chemotherapy." (*Id.* at 1487:5-8.) Dr. Sartor also testified that prior to 2009, there were a number of compounds that had entered clinical development which were shown to overcome taxane resistance in preclinical studies in cell lines or rodent models. (*Id.* at 1489:14-21.) These included: (1) XRP6258 (cabazitaxel), by Sanofi; (2) the BMS compounds, by Bristol Myers Squibb; (3) the M compounds under development through Wyeth; and (4) the

[21] Dr. Sartor was accepted by the Court as an expert in the treatment of patients with prostate cancer, including the clinical development and evaluation of potential new methods of treating patients with prostate cancer. (Tr. (Sartor) 1474:18-24.)

Daiichi compound. (*Id.* at 1489:22-1490:2.) Dr. Sartor testified that other than cabazitaxel, none of the taxanes under clinical development were "developed into effective therapies." (*Id.* at 1490:8-11.)

Dr. Sartor also testified regarding his interpretation of Mita and Attard. (*Id.* at 1492:9-1578:24.) Dr. Sartor testified that no Phase II study was conducted with cabazitaxel in prostate cancer. (*Id.* at 1506:18-21.) In addition, Dr. Sartor testified that Sanofi's Phase II breast cancer cabazitaxel study (Pivot) concerned a different disease than prostate cancer. (*Id.* at 1506:22-25.) Dr. Sartor testified that it would be difficult for a POSA to conclude from Pivot that cabazitaxel has anticancer activity at a dose of 20 $mg/m^2$ in patients with taxane-resistant metastatic breast cancer. (*Id.* at 1510:5-12.) Dr. Sartor indicated that because there is "no specification of dose, it's very difficult to make a conclusion regarding the dose and the tumor shrinkage that was seen" in Pivot. (*Id.*)

On cross examination, Dr. Sartor testified that he focused his testimony on a dose of 20 $mg/m^2$ and only on Claims 21 and 30 even though he previously provided an expert opinion regarding other doses. (*Id.* at 1529:11-1530:14.) On cross examination, Dr. Sartor acknowledged that: (1) the FDA news release from the TROPIC study was not at 20 $mg/m^2$ (*id.* at 1530:19-25); (2) a dose reduction is standard in a clinical trial with a cancer agent (*id.* at 1531:2-13); (3) by looking at the Kaplain-Meier curve (*i.e.*, the survival curve) in the '592 patent, one cannot tell from the data which patients were treated with 20 $mg/m^2$ and which patients were treated with 25 $mg/m^2$ (*id.* at 1533:4); (4) the only time the '592 patent actually discusses the 20 $mg/m^2$ dose is for dose reductions in Column 17, Example 2 in Table 6 (*id.* at 1540:16-18; 1541:1-18); and (5) Table 5 in Column 17 of the '592 patent, which provides the results of the TROPIC study,

"suggests that the vast majority were treated at the 25 [mg/m$^2$]" dose and the results in the patent do not really speak to 20 mg/m$^2$ dose (*id.* at 1541:20-24, 1542:2-4, 1543:9).

**7. Jonathan D. Schiff, M.D.**[22]

Dr. Schiff testified as an expert on behalf of Defendants with respect to Jevtana's label (JTX-16). (Tr. (Schiff) 589:2-7.) Dr. Schiff testified that many of his patients do not comply with the prescribed regimen of 10 mg/day of prednisone and miss anywhere from five to six doses over a thirty-day period. (*Id.* at 596:16-597:7.) Additionally, Dr. Schiff testified that even if his patients advise him that they are not taking their prednisone as prescribed, he does not discontinue or delay their Jevtana treatment. (*Id.* at 597:8-14; 597:21-25.)

Dr. Schiff testified that if Defendants' products are approved, they will: (1) induce infringement of Claims 7, 11, 14, 15, 16, 21, 26, and 30 (*id.* at 602:1-5); and (2) contributorily infringe Claim 14 (*id.* at 602:6-10). In order to prove induced or contributory infringement, Dr. Schiff stated that Plaintiffs must first demonstrate direct infringement by showing "that either a single actor carries out all of the method steps or that a single actor directs or controls others to collectively carry out all the method steps." (*Id.* at 602:11-25.) Dr. Schiff testified that in this case there is no single actor that carries out all the method steps because the "Jevtana infusion is done in an infusion center that's typically been administered by an infusion nurse, and the prednisone is administered by the patient himself, by taking the pill orally every day." (*Id.* at 603:5-9.)

[22] Dr. Schiff was accepted by the Court as an expert in the treatment of prostate cancer, including the interactions between prostate cancer patients who have been prescribed prednisone to be taken along with docetaxel or cabazitaxel and the physicians who are treating those patients and the premedication that is given to the patients before they receive an infusion of Jevtana. (Tr. (Schiff) 587:23-588:8.)

Dr. Schiff further testified that the administration of the premedication, which includes dexamethasone, followed by the administration of cabazitaxel thirty minutes later, does not satisfy the requirements in Claims 7, 11, 21, and 26 that the cabazitaxel be administrated in combination with a corticoid because "to be given in combination as is stipulated in the [C]laims, the medication would have to be present in the patient's bloodstream throughout the duration of time of effect of the Jevtana." (*Id.* at 610:4-7.) Dr. Schiff stated that 10 mg of prednisone is given by mouth every day and "will be present and active in the patient's bloodstream if it's used in that fashion." (*Id.* at 610:7-10.)

Dr. Schiff testified that Claims 14, 15, 16, and 30 of the '592 patent do not use the term "corticoid." (*Id.* at 616:12-17.) Dr. Schiff also testified that Plaintiffs' arguments with respect to dexamethasone do not apply to Claims 14, 15, 16, and 30 of the '592 patent. (*Id.* at 616:18-21.) According to Dr. Schiff, there is no direct infringement because: (1) the doctor does not direct or control the administration of prednisone; (2) the doctor does not condition administration of Jevtana on the patient taking prednisone as prescribed; and (3) the doctor does not condition receiving the benefit of Jevtana treatments on the patient taking pre-prednisone as prescribed. (*Id.* at 616:24-617:6.) Furthermore, Dr. Schiff opined that "there is no direct infringement from the administration of dexamethasone as a premedication because administering dexamethasone once every three weeks is not in combination with cabazitaxel." (*Id.* at 617:7-10.) Finally, Dr. Schiff testified that "without an act of direct infringement, there cannot be any induced or contributory infringement." (*Id.* at 617:11-12.)

### 8. Michael E. Tate[23]

Michael Tate, a vice president within the intellectual property practice at the consulting firm Charles River Associates, testified on behalf of Plaintiffs with respect to commercial success. (Tr. (Tate) 654:22-25, 657:17-19.) Mr. Tate testified that he understood the analysis of commercial success to constitute a two-step process: (1) evaluate the performance of the particular product; and (2) determine whether the success can be attributed to the claimed invention. (*Id.* at 658:22-25.) Mr. Tate acknowledged that he did not analyze whether Jevtana's success can be attributed to the claimed invention. (*Id.* at 659:7-11.) Rather, his work in this matter related to the first step only. (*Id.*) Mr. Tate then testified to the basis of his opinion that Jevtana was a commercial success. (*Id.* at 659:12-677:6.) Mr. Tate found JEVTANA® to be a commercial success based upon his analysis of the products in the relevant market and considering the sales and market share of Jevtana. (*Id.* at 661:4-677:6.) In reaching his decision, Mr. Tate also considered the promotional efforts for Jevtana. (*Id.* at 675:21-676:8.)

## C. Infringement

Plaintiffs demonstrated by a preponderance of the evidence that Defendants' proposed cabazitaxel products will induce infringement of Claims 21 and 30 of the '592 patent.[24]

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[23] Mr. Tate was accepted by the Court as an expert in the field of economic analysis as it pertains to commercial success. (Tr. (Tate) 657:17-22.)

[24] Because invalidity is an affirmative defense, the Court will first address the issue of infringement. The Court, however, will only address infringement of Claims 21 and 30 of the '592 patent because Plaintiffs appeared to abandon their infringement arguments as to Claims 7, 14, 15, 16, and 26 in conjunction with their decision to not rebut the evidence Defendants proffered in support of their invalidity defenses as to Plaintiffs' previously-asserted claims. Indeed, Plaintiffs' Proposed Findings of Fact and Conclusions of Law only address Claims 21 and 30 of the '592 patent. As set forth in Section IV.D, *infra*, the Court finds Claims 21 and 30 to be invalid. Nevertheless, the Court will make its Findings of Facts and Conclusion of law on infringement for purposes of a complete record.

The methods of Claims 21 and 30 have three elements: (1) administering cabazitaxel in combination with a corticoid (specifically prednisone or prednisolone for Claim 30); (2) to a patient having castration-resistant or hormone-refractory, metastatic prostate cancer that has progressed during or after treatment with docetaxel; and (3) wherein the dose of cabazitaxel is 20 mg/m$^2$.

Each of Defendants' proposed cabazitaxel products, if approved, will be sold with a product label (collectively, "Defendants' labels"). (PTX-1013; PTX-1023; PTX-1057; PTX-1140; JTX-20A; JTX-25; DTX-2467; Tr. (Petrylak) 523:6-15.) The purpose of a product label is to instruct physicians on the proper patients for treatment, how to treat the patients, potential side effects, and how to manage side effects. (Tr. (Petrylak) 523:16-25.) Physicians will read Defendants' labels before administering Defendants' proposed cabazitaxel products. (*Id.* at 524:1-5; Tr. (Schiff) 635:13-24.) There are no substantive differences between any of Defendants' proposed labels and the Jevtana label. (Tr. (Petrylak) 524:22-525:16; Tr. (Schiff) 600:3-10.)[25] Defendants' proposed cabazitaxel products, if approved, will be used the same way that Jevtana is used because the instructions in Defendants' labels are the same as the instructions in the Jevtana label. (Tr. (Schiff) 621:10-17.)

Defendants' labels instruct physicians to administer Defendants' proposed cabazitaxel products in combination with a corticoid as described in Claim 21. (Tr. (Petrylak) 535:21-537:6, 551:24-552:20, 553:17-554:12.) Defendants' labels instruct physicians to administer Defendants' proposed cabazitaxel products as a "one-hour intravenous infusion every three weeks in combination with oral prednisone 10 mg administered daily throughout" cabazitaxel

[25] *See also* Section I.F, *supra*, which summarizes the Stipulated Facts with respect to the product labels.

treatment. (PTX-1013 at FCAB00011922; PTX-1023 at FCAB00345171; PTX-1057 at ACCORD_CABA0064412; PTX-1140 at AAPO-CAB00013928; JTX-20A at ACCORD_CABA0066572; JTX-25 at MYL_CAB0000150; DTX-2467 at DTX-2467.3; Tr. (Petrylak) 537:15-538:12, 545:22-24, 553:17-554:12; Tr. (Schiff) 590:19-591:13.) Defendants' labels also instruct physicians to advise patients to read the Patient Information section of the label and to explain the importance of prednisone: "Explain that it is important to take the oral prednisone as prescribed. Instruct patients to report if they were not compliant with oral corticosteroid regimen." (PTX-1013 at FCAB00011937; PTX-1023 at FCAB00345187-88; PTX-1057 at ACCORD_CABA0064430; PTX-1140 at AAPO-CAB00013944-45; JTX-20A at ACCORD_CABA0066591; JTX-25 at MYL_CAB0000168-69; DTX-2467 at DTX-2467.19; Tr. (Petrylak) 539:2-17; Tr. (Schiff) 591:14-592.)

Product labels have a section directed to patients, the Patient Information section, which informs patients of the product's potential side effects and benefits. (Tr. (Petrylak) 524:6-21.) The Patient Information section of Defendants' labels informs patients that the physician will tell the patient how and when to take the prednisone, that it is "important" for the patient to take the prednisone "exactly as prescribed by your doctor," and to "make sure to tell [the] doctor or nurse" if the patient forgets to take the prednisone or does not take it on schedule. (PTX 1013 at FCAB00011940; PTX-1023 at FCAB00345191; PTX-1057 at ACCORD_CABA0064434; PTX-1140 at AAPO-CAB00013948; JTX-20A at ACCORD_CABA0066595; JTX-25 at MYL_CAB0000171; DTX-2467 at DTX-2467.21; Tr. (Petrylak) 544:3-18; Tr. (Schiff) 593:22-595:3.)

Defendants' proposed cabazitaxel products will be administered in combination with two corticoids, dexamethasone and prednisone. (Tr. (Petrylak) 535:14-20.) The terms "corticoid" and

"corticosteroid" are interchangeable. (*Id.* at 537:9-14.) Dexamethasone is a corticoid. (Tr. (Schiff) 608:14-16.) Defendants' labels instruct physicians to administer dexamethasone intravenously as part of a premedication regimen thirty minutes prior to the administration of each dose of Defendants' proposed cabazitaxel products. (PTX-1013 at FCAB00011923; PTX-1023 at FCAB00345171; PTX-1057 at ACCORD_CABA0064414; PTX-1140 at AAPO-CAB00013928; JTX-20A at ACCORD_CABA0066572; JTX-25 at MYL_CAB0000151; DTX-2467 at DTX-2467.4; Tr. (Petrylak) 535:21-536:9; Tr. (Schiff) 606:25-608:4.)

The dexamethasone premedication is given "in combination" with cabazitaxel because both drugs are present in the body at the same time. (Tr. (Petrylak) 536:21-537:3; *see also* JTX-6 at col. 6, ll. 35-60, 56-61.) The dexamethasone and cabazitaxel will be in a patient's body at the same time for a few days. (Tr. (Petrylak) 563:21-564:2.) Some physicians who prescribe cabazitaxel will infuse the drug and any premedications into the patients themselves. (Tr. (Schiff) 632:3-9.) If the prescribing physician does not infuse the cabazitaxel products, the healthcare provider who will be infusing Defendants' proposed cabazitaxel products and the dexamethasone premedication is under the direction and control of the prescribing physician. (Tr. (Petrylak) 536:18-20; Tr. (Schiff) 632:10-16.) If the infusion of cabazitaxel is performed by a nurse (or other healthcare professional), typically that same nurse will infuse the dexamethasone-containing premedication to the patient. (Tr. (Petrylak) 536:13-20, 553:17-554:12; Tr. (Schiff) 631:19-632:2.)

The patient administers the prednisone orally to himself under the direction and control of the physician. (Tr. (Petrylak) 538:3-16, 553:17-554:12.) The physician directs and controls how a patient takes prednisone (orally), how much to take (10 mg), and how often to take it (daily). (*Id.* at 537:19-539:1, 553:17-554:12; Tr. (Schiff) 634:4-24.) The prescribing physician

establishes the manner and timing of administration of prednisone based on Defendants' labels. (Tr. (Petrylak) 537:19-539:1; Tr. (Schiff) 634:4-24.)

Administration of prednisone is important for the safe and effective use of Defendants' proposed cabazitaxel products. (Tr. (Petrylak) 539:18-540:4; 553:17-554:12.) Because the Phase III TROPIC study investigated only cabazitaxel in combination with prednisone, it is not known whether patients will receive the clinical benefits reported in TROPIC from administration of cabazitaxel alone. (*Id.* at 539:18-540:10; Tr. (Schiff) 641:22-642:3.) Although it does not prolong survival as a single agent, prednisone has been reported to reduce inflammation and pain. (PTX-1363 at SA_JEV_0183327; JTX-38 at 590; (Tr. (Petrylak) 539:18-540:4, 540:11-541:20, 557:18-558:2, 558:24-559:10; Tr. (Schiff) 583:9-17, 636:15-23.) Prednisone also improves energy and increases appetite thereby counteracting the side effects of cabazitaxel, such as fatigue, nausea and vomiting. (JTX-38 at 590; Tr. (Ratain) 324:12-15; Tr. (Petrylak) 540:11-541:4, 541:21-542:3; Tr. (Schiff) 583:9-17, 636:6-637:23.)

When a patient who is scheduled to receive a cycle of cabazitaxel has not been taking his prednisone as directed and is, therefore, suffering from fatigue, physicians will often delay administration of chemotherapy until the patient is back on prednisone and feels strong enough for more chemotherapy. (Tr. (Ratain) 412:18-413:13; Tr. (Petrylak) 542:17-544:2; Tr. (Schiff) 628:21-629:4.) Dr. Petrylak had one patient out of approximately 100 that could not take prednisone. (Tr. (Petrylak) 545:2-4, 561:1-16, 562:3-24, 569:3-19.) Dr. Schiff's patients on cabazitaxel have been prescribed prednisone, and none have refused to take it. (Tr. (Schiff) 583:9-11, 604:24-605:2, 633:22-25.) If a patient has not been taking prednisone and does not advise the physician, physicians will likely know anyway due to changes in the patient's physical appearance. (Tr. (Petrylak) 545:2-21; Tr. (Schiff) 639:1-10.)

Defendants' labels instruct physicians to administer Defendants' proposed cabazitaxel products in combination with prednisone as described in Claims 21 and 30 and to condition the benefit of Defendants' proposed cabazitaxel products for at least some patients on the patient taking prednisone. (Tr. (Petrylak) 542:4-544:2, 551:24-552:20, 552:25-553:3, 553:17-554:12.)

In addition, Defendants' labels instruct physicians to administer Defendants' proposed cabazitaxel products to patients having hormone-refractory metastatic prostate cancer who have progressed during or after a docetaxel-containing treatment regimen. (PTX-1013 at FCAB00011922, FCAB00011935; PTX-1023 at FCAB00345171, FCAB00345185; PTX-1057 at ACCORD_CABA0064412, ACCORD_CABA0064427-28; PTX-1140 at AAPO-CAB00013928, AAPO-CAB00013942-43; JTX-20A at ACCORD_CABA0066572, ACCORD_CABA0066589; JTX-25 at MYL_CAB0000150, MYL_CAB0000166; DTX-2467 at DTX-2467.3, DTX-2467.16-17; Tr. (Petrylak) 526:21-527:16, 528:2-22, 551:25-552:20, 552:25-553:3; Tr. (Schiff) 581:7-13, 589:19-590:8.) There are no other approved uses for cabazitaxel. (Tr. (Schiff) 621:6-9.)

Defendants' proposed cabazitaxel products, if approved and marketed, will be administered at a dose of 20 mg/m$^2$ to at least some patients. (Tr. (Petrylak) 531:23-532:2, 532:7-13; Tr. (Schiff) 629:11-630:1.) Defendants' labels instruct and will inevitably lead to the administration of cabazitaxel in combination with a corticoid (including prednisone) to patients having castration-resistant or hormone-refractory, metastatic prostate cancer that has progressed during or after treatment with docetaxel at a cabazitaxel dose of 20 mg/m$^2$, in accordance with the methods of Claims 21 and 30. Defendants' labels instruct physicians that the patient should receive a dose of 20 mg/m$^2$ of cabazitaxel if he experiences certain side effects on the recommended dose of 25 mg/m$^2$. (PTX-1013 at FCAB00011922-23; PTX-1023

at FCAB00345171-72; PTX-1057 at ACCORD_CABA0064412-13; PTX-1140 at AAPO-CAB00013928-29; JTX-20A at ACCORD_CABA0066573; JTX-25 at MYL_CAB0000150-51; DTX-2467 at DTX-2467.3-4; Tr. (Petrylak) 529:21-532:2; Tr. (Schiff) 627:19-628:13.)

Dr. Schiff acknowledged on cross examination that he is not a medical oncologist, does not have training in medical oncology, has never been involved in any research involving chemotherapy in the treatment of prostate cancer, has never published on the use of chemotherapy in the treatment of prostate cancer, has never taught classes specifically relating to oncology, has never written a prescription for cabazitaxel because if one of his patients develops mCRPC he refers them to a medical oncologist, and does not have intimate knowledge of what happens at an infusion center other than his experience with his father, what his patients tell him and his discussion with his colleagues. (Tr. (Schiff) 618:2-619:20.) Dr. Schiff also conceded that if Defendants' cabazitaxel products are approved, they will be used in the same way that Jevtana is used because the instructions in Defendants' product labels are the same as the instructions in the Jevtana label. (*Id.* at 621:9-17.) Also, Dr. Schiff acknowledged that the person doing the premedication infusion, which includes the corticoid dexamethasone, is under the control of the physician. (*Id.* at 632:10-20.) In addition, Dr. Schiff acknowledged that patients taking cabazitaxel had all previously been on docetaxel and that docetaxel is only given in combination with prednisone. (*Id.* at 637:8-14.) Dr. Schiff also testified that he recommends that his patients with mCRPC that have progressed on docetaxel receive cabazitaxel with prednisone. (*Id.* at 639:15-20.) During certain portions of his testimony, it also appeared that Dr. Schiff attempted to revisit the Court's previous claim construction analysis.[26] (*Id.* at 608:17-609:3, 610:4-7.)

[26] Defendants did not raise the "in combination with the corticoid" element for claim construction. Furthermore, in its decision on one of Defendants' *in limine* motions, the Court denied Defendants' alternative request to reopen claim construction at this late stage of the proceeding.

The Court, on the other hand, found Dr. Petrylak's testimony both credible and persuasive and credits significant weight to his testimony. Here, the Court finds that Plaintiffs demonstrated by a preponderance of the evidence that Defendants' proposed cabazitaxel products will induce infringement of Claims 21 and 30 of the '592 patent.

**D. Invalidity**

**1. POSA**

Plaintiffs assert that a POSA for the '592 patent would possess the following qualifications: (a) a medical degree; (b) board-certification in medical oncology; (c) experience treating prostate cancer patients including patients with metastatic disease; and (d) experience evaluating prostate cancer therapies. (Tr. (Petrylak) 516:11-517:6; Tr. (Sartor) 1481:23-1482:7.) Defendants acknowledge that the parties generally agree that the POSA would be an individual (or team) with a working knowledge of clinical oncology and training in medical oncology, and would have experience with cancer patients. (Tr. (Ratain) at 301:3-302:3.) According to Defendants, while there are subtle differences between the parties' definitions, the analysis is the same regardless of which definition is used. The Court finds the proposed POSA definitions substantially similar and the differences inconsequential and declines to adopt either definition.

**2. Prior Art**

The prior art to the '592 patent includes:

**a. Attard** (JTX-42)

Attard, entitled "Update on tubulin-binding agents," is a review article on tubulin binding agents, which is the class of anticancer agents that encompasses taxanes and other antimitotic drugs. (JTX-42). Attard interpreted the positive results in Mita to mean that cabazitaxel "may overcome some forms of . . . tumor resistance." (Tr. (Ratain) 349:15-25; JTX-42 at 75.) Table 3

of Attard noted that cabazitaxel is not a Pgp substrate, and is active in taxane-refractory CRPC tumors. (JTX-42 at 75).

**b. Beardsley** (DTX-2090)

Beardsley, entitled "Systemic therapy after first-line docetaxel in metastatic castration-resistant prostate cancer," was published in 2008. (Tr. (Ratain) 354:24-355:12; DTX-2090.) The paper discloses treatment options after failure of docetaxel in patients with castration-resistant prostate cancer, and specifically references Pivot, noting that cabazitaxel is being investigated in Phase III trials for docetaxel-resistant metastatic castration-resistant prostate cancer. (Tr. (Ratain) 355:13-357:4.)

**c. Mita** (JTX-45)

Mita, entitled "Phase I and Pharmacokinetic Study of XRP6258 (RPR116258A), a Novel Taxane Administered as a 1-Hour Infusion Every 3 Weeks in Patients with Advanced Solid Tumors," was published on January 15, 2009. (Tr. (Ratain) 334:17-335:2; JTX- 45). The Mita paper discloses the use of cabazitaxel in clinical trials based on encouraging cytotoxic antitumor activity in cancer cell lines expressing a multidrug-resistant phenotype. (Tr. (Ratain) 338:25-339:14).

**d. Mitoxantrone Label** (JTX-37)

The mitoxantrone label was published in the 2006 Edition of the Physician's Desk Reference, which is a compendium of all FDA-approved drug labels for the convenience of the physician. (Tr. (Ratain) 325:22-25.) The mitoxantrone label reported that grade 4 neutropenia occurred in 54% of hormone-refractory prostate cancer patients receiving mitoxantrone. (JTX- 37 at 3162; Tr. (Sartor) 1573:14-1574:3.) The mitoxantrone label also reported that mitoxantrone was administered together with 10 mg/day of prednisone. (JTX-37 at 3159; Tr. (Ratain) 326:15-19.)

**e. The Phase III Disclosures— Winquist (DTX-2391), Rodrigues (DTX-2316), and the GCRI Report** (DTX-2209)

Several details of the TROPIC study were published prior to October 2009, including in Winquist (DTX-2391), Rodrigues (DTX-2316), and the GCRI Report (DTX-2209) (collectively "Phase III Disclosures").

The Winquist article, entitled "Open clinical uro-oncology trials in Canada," was published in February 2008 and disclosed the ongoing Phase III TROPIC study using cabazitaxel. (Tr. (Ratain) 358:6-18, 363:2-22; DTX-2391 at 3948.) The Rodrigues article, entitled "Open Clinical Uro-oncology Trials in Canada," was published in 2007 and disclosed Sanofi's multi-center study for the administration of 25 mg/m$^2$ of XRP-6258 in combination with prednisone every three weeks compared to mitoxantrone in combination with prednisone for the treatment of hormone refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen. (Tr. (Ratain) 360:3-361:2; DTX-2316, Rodrigues at 3784 (CabRef0002996).)

The GCRI Report was published in August 2008 and describes the ongoing clinical trial as "[a] randomized, open label multi-center study of [cabazitaxel] at 25 mg/m$^2$ in combination with prednisone every three weeks compared to Mitoxantrone in combination with prednisone for the treatment of hormone refractory metastatic prostate cancer previously treated with a Taxotere-containing regimen." (Tr. (Ratain) 365:11-366:1; DTX-2209 at 78 (CabRef0002789).) The GCRI Report also disclosed that the TROPIC study included monitoring of neutrophil counts in all patients. (Tr. (Ratain) 366:26-17; DTX-2209 at 79 (CabRef0002790).)

Each of the Phase III Disclosures disclosed that the TROPIC study involved administration of cabazitaxel with prednisone. (Tr. (Ratain) 363:10-13.) In addition, each of the Phase III Disclosures discloses a method for treating patients with hormone-refractory metastatic prostate

cancer previously treated with docetaxel to increase overall survival by providing 25 mg/m$^2$ cabazitaxel with prednisone. (*Id.* at 361:2-17; 363:2-6, 367:19-25.)

**f. Pivot** (JTX-47)

Pivot, entitled "A multicenter phase II study of XRP6258 administered as a 1-h i.v. infusion every 3 weeks in taxane-resistant metastatic breast cancer patients," was published in 2008. (Tr. (Ratain) 350:24-351:9; JTX-47.) Pivot reports activity of cabazitaxel in taxane-resistant metastatic breast cancer patients, using a starting dose of 20 mg/m$^2$. (Tr. (Ratain) 350:24-351:9, 353:13-18, 354:6-21.)

**g. Taxol® Label** (DTX-2361)

The Taxol® label was last revised in February of 2000, and instructs physicians on how to prescribe paclitaxel. (DTX-2361 at 6.) The Taxol® label reported that neutropenia occurred in 90% of patients, and grade 4 neutropenia occurred in 52% of patients receiving paclitaxel. (DTX-2361 at 3.) The Taxol® label also instructed physicians to reduce the dose of paclitaxel by 20% in case of severe neutropenia. (DTX-2361 at 5.)

**h. Taxotere® Label** (JTX-56)

The Taxotere® Label (JTX-56) was last revised in September of 2007, and instructs physicians how to prescribe docetaxel. (JTX-56 at 1.) The Taxotere® Label indicated that the recommended dose of docetaxel to treat prostate cancer was 75 mg/m$^2$, and instructed to reduce the dose of docetaxel by 20% from 75 mg/m$^2$ to 60 mg/m$^2$ in the case of unacceptable toxicity. (JTX-56 at 6; Tr. (Ratain) 312:7-10, 329:2-18.) Such dose reductions would often be used in patients with febrile (accompanied by fever) or prolonged grade 4 neutropenia (neutrophil levels less than 500 cells/mm$^3$). (Tr. (Ratain) 329:2-22; JTX-56 at 6.) Grade 4 neutropenia occurs in 85% of patients given 100 mg/m$^2$ and 75% of patients given 60 mg/ m$^2$ of docetaxel. (JTX-56 at

11; Tr. (Ratain) 312:1-10.) Because the standard dose of docetaxel for prostate cancer is 75 mg/m$^2$, grade 4 neutropenia is an expected side effect of docetaxel treatment. (Tr. (Ratain) 312:11-19.) The Taxotere® label reported that docetaxel was administered together with 10 mg/day of prednisone. (JTX-56 at 4; Tr. (Ratain) 328:18-329:1.)

**3. The Asserted Claims Are Invalid**

**a. Claims 21 and 30**

The '592 patent is directed to the use of a 20-25 mg/m$^2$ dose of cabazitaxel to treat mCRPC. (JTX-6.) Claim 21 states, "The method according to claim 20, where the cabazitaxel, or hydrate or solvate thereof, is administered at a dose of 20 mg/m$^2$." (JTX-006, column 20, lines 22-24.) Claim 21 depends from Claim 20, which depends from Claim 1. Claim 20 requires that the prostate cancer is a castration-resistant or hormone-refractory, metastatic prostate cancer. Claim 21 adds the additional limitation requiring the dose of cabazitaxel to be 20 mg/m$^2$. Claim 30 states, "The method according to claim 27, where the cabazitaxel, or hydrate or solvate thereof, is administered at a dose of 20 mg/m$^2$." (JTX-006, column 20, lines 37-39.) Claim 30 depends from Claim 27, and requires the dose of cabazitaxel to be 20 mg/m$^2$. Based on the Court's previous claim construction, the claim preamble is not limiting. Accordingly, efficacy is not a requirement of the claims as construed. Claims 1 and 27, therefore, are anticipated by the Phase III Disclosures. (Tr. (Ratain) 369:17-370:24.)

The TROPIC trial was a trial done at a dose of 25 mg/m$^2$ of cabazitaxel. (Tr. (Sartor) 1532:20-1533:2.) The 20 mg/m$^2$ dose was not studied in the TROPIC trial except as a dose reduction in a small percentage of patients. (*Id.*) Accordingly, the results of the TROPIC trial do not tell a POSA specific and detailed information about a 20 mg/m$^2$ dose. (*Id.* at 1533:14-24; 1534:14-18.) Nevertheless, a POSA would expect the TROPIC trial to include a dose reduction,

like the standard 20% dose reductions instructed in the docetaxel and paclitaxel labels. (DTX-2361, Taxol label at 5 (CabRef0003458); JTX-56, Taxotere label at 7 (CabRef0003466).) Twenty percent is a typical dose reduction because physicians still want the dose administered to have some efficacy. (Tr. (Ratain) 330:3-13.) Dr. Sartor acknowledged that dose reductions are relatively standard events within chemotherapy trials. (Tr. (Sartor) 1531:10-13.) Furthermore, Dr. Sartor acknowledged that a POSA would know about the 20% dose reduction that was used with other taxanes, and would "conjecture" that the same dose reduction was used in the TROPIC trial. (*Id.* at 1546:25-1547:10.)

A POSA would have been motivated to start patients at risk for complications at a 20 $mg/m^2$ dose, rather than at the higher 25 $mg/m^2$ dose. (Tr. (Ratain) 379:8-19.) Mita recommended a 20 $mg/m^2$ dose for further development because of the toxicities associated with a 25 $mg/m^2$ dose. (JTX-45 at 727 (CabRef0002902).) Mita also disclosed activity in the form of a partial response for both a 15 $mg/m^2$ dose and a 25 $mg/m^2$ dose. (JTX-45 at Table 3 (CabRef0002901).) In addition, Pivot noted that cabazitaxel was "active and well-tolerated" at a dose of 20 $mg/m^2$. (JTX-47 at 1547 (CabRef0002984).)

The Court found Dr. Ratain's testimony both credible and persuasive. Dr. Ratain provided a clear summary of the prior art. Moreover, Dr. Ratain's expert testimony was strongly supported by the evidence of record and the Court found Dr. Ratain's opinions to be well-reasoned, logical, and internally consistent. The Court, therefore, affords great weight to Dr. Ratain's testimony.

The Court, on the other hand, found that Dr. Sartor lacked credibility with respect to the key aspect of his testimony, the 20 $mg/m^2$ dose. Rather, the Court found Dr. Sartor's testimony to be litigation-inspired. For example, Dr. Sartor attempted to explain why the PTAB misunderstood his position in the PTAB proceeding. (Tr. (Sartor) 1475:16-1476:14.) Dr. Sartor also responded

numerous times during cross examination that he could not remember or was trying to remember. (*See, e.g., id.* at 1544:9-10, 1549:21, 1550:3-5, 1550:17-20, 1553:3-4, 1553:7-9, 1553:12, 1559:2-6, 1565:19-21, 1593:9-10.) In addition, Dr. Sartor's testimony regarding the 20 mg/m$^2$ dose in relationship to the prior art references was not persuasive. (Tr. (Sartor) 1509:21-1510:12, 1532:15-19). Dr. Sartor testified that the TROPIC trial was started at 25 mg/m$^2$ and that there was a built-in dose reduction to 20 mg. (*Id.* at 1531:2-6.) Dr. Sartor acknowledged that "there were prescribed dose reductions built in depending on certain toxicities or events that occurred during the [clinical] trial." (*Id.*) Dr. Sartor also conceded that a dose reduction is a relatively standard event within a chemotherapy trial.[27] (*Id.* at 1531:21-22.) The Court, accordingly, affords minimal weight to Dr. Sartor's testimony.

With respect to secondary considerations, Plaintiffs do not argue that there is a presumption of nexus between the '592 patent and secondary considerations. (*But see* Pls.' Post-Trial Br. 33-34 (arguing that there is a presumed nexus between the '170 patent and secondary considerations because the Jevtana patent is both an embodiment of, and coextensive with, Claims 1 and 2 of the '170 patent).) Plaintiffs argue only that unexpected results support the nonobviousness of Claims 21 and 30. (Pls.' Post-Trial Br. 52.)

Plaintiffs assert that while Dr. Sartor's involvement in the Tropic trial was met with initial skepticism by his colleagues, experts' responses to the results of the Trial were "[h]ugely positive." (Tr. (Sartor) 1522:9-14, 1527:4-14.) Plaintiffs also assert that the results of the Tropic trial were unexpected because "[the Tropic trial] was more likely to fail than succeed given the unpredictability in the art and given that [the Tropic trial] patients received another taxane despite

[27] The Court recognizes that even Dr. Petrylak acknowledged on cross examination that he has "dose reduced patients to 20 [mg/m$^2$]." (Tr. (Petrylak) at 567:16-17.)

being docetaxel-resistant." (Pl.'s Post-Trial Br. 53.) Plaintiffs further argue that while "the FDA expedited cabazitaxel availability based primarily on [the results of the] TROPIC [trial], cabazitaxel is used today at a dose of 20 mg/m$^2$ to prolong patient lives," and that "[t]he unexpected survival benefit at that dose is further evidence that the methods of Claims 21 and 30 were nonobvious as of October 2009." (*Id.* at 54.)

Defendants argue that there is no nexus between any alleged secondary consideration and the '592 patent because "Dr. Sartor never testified about the nexus and Mr. Tate 'specifically testified that he did not consider the question of nexus.'" (Defs.' Post-Trial Br. 52.) Defendants also argue that "even if [Plaintiffs] were to argue that Jevtana is an embodiment of the claims and thus nexus is presumed," there is no nexus to Claims 21 and 30 of the '592 patent because "[t]he data presented in the patent that Sanofi relies on is directed to the 25 mg/m$^2$ dose, . . . [and] that there is no independent data on the 20 mg/m$^2$ dose", which "appears in the '592 patent only as a dose reduction from 25 mg/m$^2$." (*Id.*)

The Court is not persuaded by Plaintiffs' arguments. "[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art." *Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 970 (Fed. Cir. 2006) (quoting *In Re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991)). Plaintiffs rely on the TROPIC trial, which involved the administration of cabazitaxel to some patients and mitoxantrone to others, to support their argument of unexpected results. (Pls.' Post-Trial Br. 52-54.)

As Defendants correctly point out, however, the Phase III Disclosures, and not the Tropic trial, were the closest prior art. (Defs.' Post-Trial Br. 56; Tr. (Ratain) 398:5-8.) Even if the Court considers the TROPIC trial as the closest prior art, Plaintiffs' argument is still unavailing because it was not unexpected that cabazitaxel would outperform mitoxantrone, which did not have a

history of improving survival. (Tr. (Ratain) 399:10-12.) Plaintiffs' argument that "[t]he unexpected survival benefit at [the 20 mg/m$^2$] dose is further evidence that the methods of Claims 21 and 30 were nonobvious as of October 2009" (Pls.' Post-Trial Br. 54) does not prevail because the TROPIC trial expressly included a dose reduction from 25 mg/m$^2$ to 20 mg/m$^2$ (Tr. (Sartor) 1532:20-1533:2), which is a typical dose reduction that considers the retention of efficacy. (Tr. (Ratain) 330:3-13; Tr. (Sartor) 1546:25-1547:10.) In addition, the Court found Dr. McDuff's testimony persuasive with respect to the "lack of nexus between the commercial performance of Jevtana and the '592 patent." (Tr. (McDuff) 716:18-20.) Here, the Court finds that Plaintiffs failed to demonstrate nexus.

The Court, thus, gives little weight to Plaintiffs' argument, having found an absence of nexus between the '592 patent and unexpected results. (Tr. (Tate) 698:11-16; *See Muniauction, Inc. v. Thomson Corp.*, 532 F.3d 1318, 1327 (Fed. Cir. 2008) ("[A] nexus between the merits of the claimed invention and evidence of secondary considerations is required in order for the evidence to be given substantial weight in an obviousness decision.").

Based on the factual findings set forth above, the Court finds that Defendants have demonstrated by clear and convincing evidence that Claims 21 and 30 of the '592 patent are obvious in view of the prior art. 35 U.S.C. § 103.

**b. Claims 7, 11, 14, 15, 16, and 26**

The Court will examine each of the claims that Plaintiffs asserted going into the trial, despite that immediately prior to the last day of trial, Plaintiffs elected not to present testimony regarding such claims.

**(1) Claim 7**

Claim 7 states, "The method according to claim 1, wherein said cabazitaxel, or hydrate or solvate thereof, is administered in an amount to provide an AUC of about 991 ng•h/mL (CV

34%)." (JTX-006, column 19, lines 3-5.) Claim 7 depends from Claim 1 and recites the additional limitation that the cabazitaxel "is administered in an amount to provide an AUC of about 991 ng•h/mL (CV 34%)." AUC is a pharmacokinetic parameter that measures the area under the concentration-time curve for a drug. (Tr. (Ratain) at 313:12-25.)

Defendants met the procedural burden of establishing a legally sufficient *prima facie* case of invalidity with respect to Claim 7. As Dr. Ratain testified, the claimed AUC value is the natural result of administering 25 mg/m$^2$ of cabazitaxel and, therefore, is anticipated by the Phase III Disclosures. (*Id.* at 371:13-372:13.) In addition, Claim 7 is rendered obvious by the AUC disclosure in Mita of 1,038 +/- 299 µg•h/L for the 25 mg/m$^2$ dose of cabazitaxel (JTX-45 at 729), which is approximately the same as the claimed value of 991 µg•h/L (CV 34%). (Tr. (Ratain) at 372:21-373:9.) Accordingly, Plaintiffs were obligated to come forward with evidence to the contrary. *See Ralston Purina Co.*, 772 F.2d at 1573 (alteration in original). Plaintiffs, however, failed to present evidence to the contrary.

Based on the factual findings set forth above, Defendants have shown by clear and convincing evidence that Claim 7 of the '592 patent is invalid as obvious in view of the prior art. 35 U.S.C. § 103.

**(2) Claim 11**

Claim 11 states, "The method according to claim 10, further comprising discontinuing cabazitaxel treatment in a patient with a neutrophil count of ≤1,500 cells/mm$^3$." (JTX-006, column 19, lines 15-17.) Claim 11 depends from Claim 10, which depends from Claim 1, and adds the limitation that blood counts be monitored and neutrophil levels be measured in the patient.

Defendants met the procedural burden of establishing a legally sufficient *prima facie* case of invalidity with respect to Claim 11. Defendants asserted that Claim 11 was obvious in view of Mita, Pivot, the Phase III Disclosures, the docetaxel label and based on the standard of care, as

found in the docetaxel and taxol labels. Dr. Ratain testified that monitoring blood counts and measuring neutrophil levels are part of the standard of care inherent in providing chemotherapy. (Tr. (Ratain) 327:22-25.) Dr. Ratain also testified that a POSA would have expected that threshold to be used in the TROPIC trial. (*Id.* at 374:12-376:5.) The GCRI Report also disclosed that blood counts be monitored and neutrophil levels be measured in the patient in the TROPIC trial. (DTX-2209 at 79 (CabRef0002790); Tr. (Ratain) 366:2-17.) In addition, many chemotherapy drugs, including docetaxel, mitoxantrone, and paclitaxel, had labels that instructed physicians to cease treatment if neutrophils dropped below 1,500 cells/$mm^3$. (JTX-37 at 3158 (CabRef0002978); JTX-56 at 11 (CabRef0003470); DTX-2361 at 1 (CabRef0003454); Tr. (Ratain) 327:1-12, 375:5-19.) Accordingly, Plaintiffs were obligated to come forward with evidence to the contrary. *See Ralston Purina Co.*, 772 F.2d at 1573. Plaintiffs did not, however, present evidence to the contrary.

Based on the factual findings set forth above, Defendants have shown by clear and convincing evidence that Claim 11 of the '592 patent is invalid as obvious in view of the prior art. 35 U.S.C. § 103.

**(3) Claims 14 and 16**

Claim 14 states, "The method according to claim 13, where the prednisone or prednisolone is administered at a dose of 10 mg/day." (JTX-006, column 19, lines 24-25.) Claim 14 depends from Claim 13, which depends from Claim 1, and specifies that the corticoid be prednisone or prednisolone.

Defendants met the procedural burden of establishing a legally sufficient *prima facie* case of invalidity with respect to Claim 14. Defendants asserted that Claim 14 is obvious in view of the Phase III Disclosures, and the docetaxel and taxol labels. The exact dosage of prednisone in the TROPIC trial is not disclosed in the Phase III Disclosures. A POSA, however, would expect the standard prednisone regimen (10 mg/day), as was used with mitoxantrone and with docetaxel, to

be continued in the TROPIC trial. (Tr. (Ratain) 377:6-378:7; JTX-30; JTX-37; JTX-56.) Accordingly, Plaintiffs were obligated to come forward with evidence to the contrary. *See Ralston Purina Co.*, 772 F.2d at 1573. Plaintiffs, however, did not present evidence to the contrary.

Defendants also met the procedural burden of establishing a legally sufficient *prima facie* case of invalidity with respect to Claim 16. Claim 16 states, "The method according to claim 14, where the cabazitaxel, or hydrate or solvate thereof, is administered at a dose of 25 mg/m$^2$." (JTX-006, column 19, lines 29-31.) Claim 16 depends from Claim 14, and specifies that the cabazitaxel is administered at a dose of 25 mg/m$^2$. According to Defendants, Claim 16 is obvious in light of the Phase III Disclosures, and the docetaxel and taxol labels. The 25 mg/m$^2$ dose is explicitly disclosed in the Phase III Disclosures. (Tr. (Ratain) 377:6-16.) Accordingly, Plaintiffs were obligated to come forward with evidence to the contrary. *Ralston Purina Co.*, 772 F.2d at 1573. Plaintiffs, however, did not present evidence to the contrary.

Based on the factual findings set forth above, Defendants have shown by clear and convincing evidence that Claims 14 and 16 of the '592 patent are invalid as obvious in view of the prior art. 35 U.S.C. § 103.

**(4) Claims 15 and 26**

Claim 15 states, "The method according to claim 14, where the cabazitaxel, or hydrate or solvate thereof, is administered at a dose of 20 mg/m$^2$." (JTX-006, column 19, lines 26-28.) Claim 15 depends from Claim 14, which depends from Claim 13, which depends from Claim 1. Claim 15 requires the dose of cabazitaxel to be 20 mg/m$^2$. Claim 26 states, "The method according to Claim 1, where the cabazitaxel, or hydrate or solvate thereof, is administered at a dose of 20 mg/m$^2$." (JTX-006, column 20, lines 4-6.) Claim 26 depends from Claim 1, and requires the dose of cabazitaxel to be 20 mg/m$^2$.

Defendants met the procedural burden of establishing a legally sufficient *prima facie* case of invalidity with respect to Claims 15 and 26. According to Defendants, Claims 15 and 26 are obvious in view of Mita, Pivot, and the Taxotere and Taxol labels. Specifically, both Claims 15 and 26 add the same 20 mg/m$^2$ dose limitation and are obvious for the same reasons as Claims 21 and 30. Accordingly, Plaintiffs were obligated to come forward with evidence to the contrary. *See Ralston Purina Co.*, 772 F.2d at 1573. Plaintiffs, however, did not present evidence to the contrary.

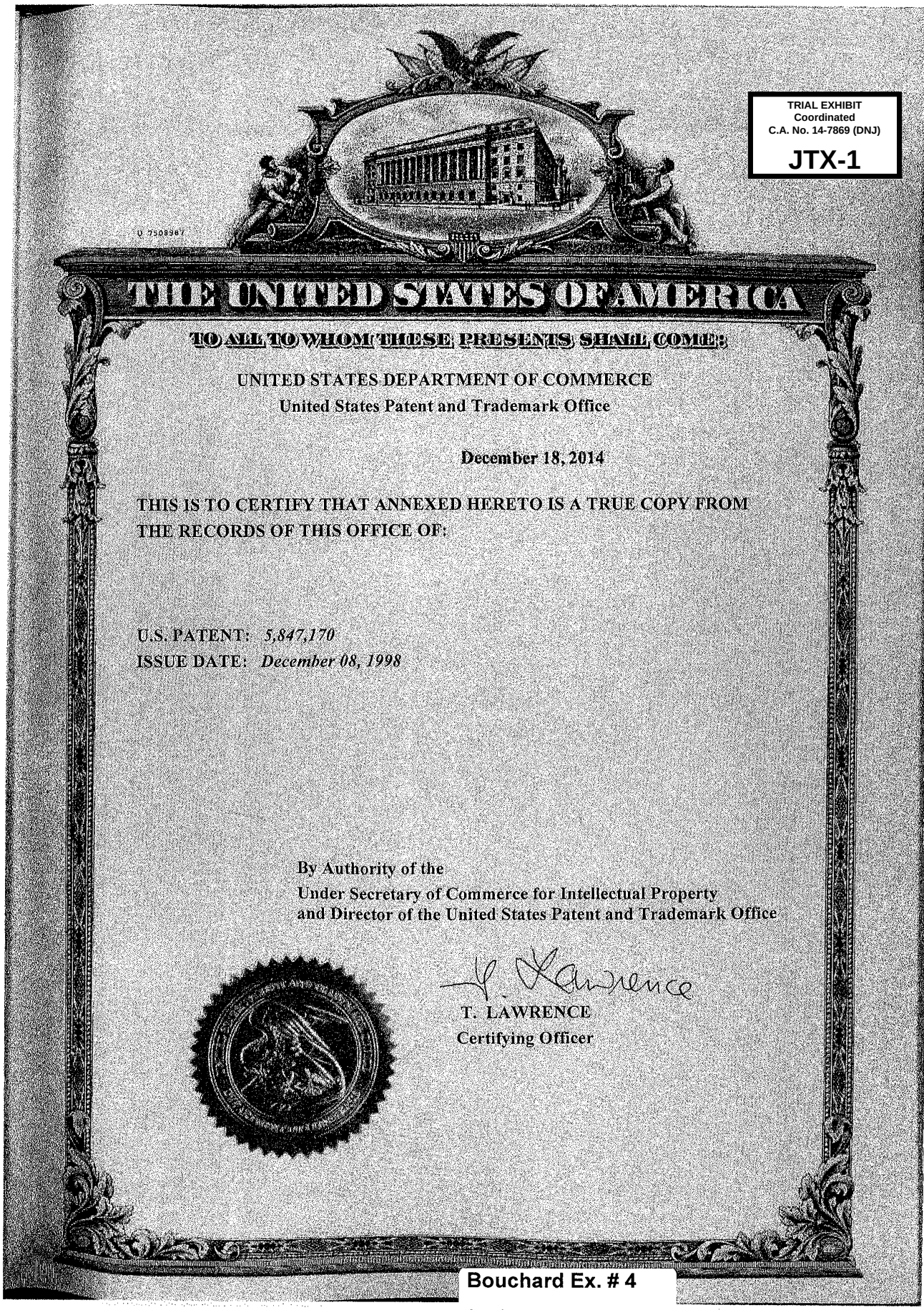
Based on the factual findings set forth above, Defendants have shown by clear and convincing evidence that Claims 15 and 26 of the '592 patent are invalid as obvious in view of the prior art. 35 U.S.C. § 103.

## V. CONCLUSION

For the reasons set forth above, the Court finds that: (i) Defendants infringed the '170 patent; (ii) Defendants failed to demonstrate invalidity of the '170 patent by clear and convincing evidence; (iii) Plaintiffs demonstrated by a preponderance of the evidence that Defendants will induce infringement of the '592 patent; and (iv) Defendants demonstrated invalidity of the asserted claims of the '592 patent by clear and convincing evidence. An order consistent with this Opinion will be entered.

s/ Michael A. Shipp
**MICHAEL A. SHIPP**
**UNITED STATES DISTRICT JUDGE**

Dated: December 19, 2017



TRIAL EXHIBIT
Coordinated
C.A. No. 14-7869 (DNJ)
JTX-1

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# THE UNITED STATES OF AMERICA

## TO ALL TO WHOM THESE PRESENTS SHALL COME:

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December 18, 2014

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF:

U.S. PATENT: *5,847,170*
ISSUE DATE: *December 08, 1998*

By Authority of the
Under Secretary of Commerce for Intellectual Property
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T. LAWRENCE
Certifying Officer

Bouchard Ex. # 4
Sanofi v. Fresenius, 14-cv-7869

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# United States Patent [19]

**Bouchard et al.**

[11] **Patent Number: 5,847,170**

[45] **Date of Patent: Dec. 8, 1998**

[54] **TAXOIDS, THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM**

[75] Inventors: **Hervé Bouchard**, Ivry-sur-Seine; **Jean-Dominique Bourzat**, Vincennes; **Alain Commerçon**, Vitry-sur-Seine, all of France

[73] Assignee: **Rhône-Poulenc Rorer, S.A.**, Antony Cedex, France

[21] Appl. No.: **622,011**

[22] Filed: **Mar. 26, 1996**

**Related U.S. Application Data**

[60] Provisional application No. 60/010,144, Jan. 17, 1996.

[30] **Foreign Application Priority Data**

Mar. 27, 1995 [FR] France ..... 95 03545
Dec. 22, 1995 [FR] France ..... 95 15381

[51] **Int. Cl.**[6] ..... **C07D 305/14**

[52] **U.S. Cl.** ..... **549/510**; 549/511

[58] **Field of Search** ..... 549/510, 511

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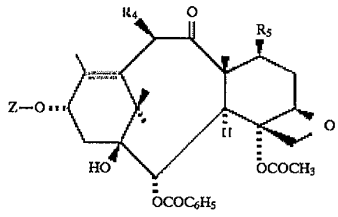
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*Primary Examiner*—Ba K. Trinh

*Attorney, Agent, or Firm*—Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P.

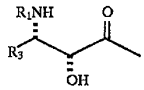
[57] **ABSTRACT**

New taxoids of general formula (I):




(I)

their preparation and pharmaceutical compositions containing them, and the new products of general formula (I) in which Z represents a radical of general formula (II):




(II)

display noteworthy antitumour and antileukaemic properties.

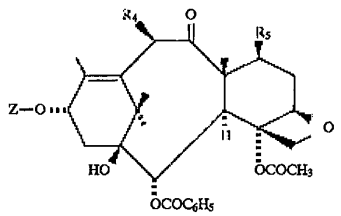
**22 Claims, No Drawings**

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# TAXOIDS, THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

This application claims the priority of U.S. provisional application 60/010,144 filed Jan. 17, 1996.

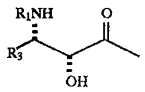
The present invention relates to new taxoids of general formula (I)




(I)

in which:

Z represents a hydrogen atom or a radical of general formula (II):




(II)

in which:

$R_1$ represents

a benzoyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms, alkoxy radicals containing 1 to 4 carbon atoms and trifluoromethyl radicals,

a thenoyl or furoyl radical or

a radical $R_2$—O—CO— in which $R_2$ represents:

an alkyl radical containing 1 to 8 carbon atoms,

an alkenyl radical containing 2 to 8 carbon atoms,

an alkynyl radical containing 3 to 8 carbon atoms,

a cycloalkyl radical containing 3 to 6 carbon atoms,

a cycloalkenyl radical containing 4 to 6 carbon atoms or

a bicycloalkyl radical containing 7 to 10 carbon atoms,

these radicals being optionally substituted with one or more substituents selected from halogen atoms, hydroxyl radicals, alkoxy radicals containing 1 to 4 carbon atoms, dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms, piperidino radicals, morpholino radicals, 1-piperazinyl radicals, said piperazinyl radicals being optionally substituted at position 4 with an alkyl radical containing 1 to 4 carbon atoms or with a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms, cycloalkyl radicals containing 3 to 6 carbon atoms, cycloalkenyl radicals containing 4 to 6 carbon atoms, phenyl radicals, said phenyl radicals being optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms, and alkoxy radicals containing 1 to 4 carbon atoms, cyano radicals, carboxyl radicals and alkoxycarbonyl radicals in which the alkyl portion contains 1 to 4 carbon atoms,

a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms, and alkoxy radicals containing 1 to 4 carbon atoms,

a 5-membered aromatic heterocyclic radical preferably selected from furyl and thienyl radicals,

or a saturated heterocyclic radical containing 4 to 6 carbon atoms, optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms,

$R_3$ represents

an unbranched or branched alkyl radical containing 1 to 8 carbon atoms,

an unbranched or branched alkenyl radical containing 2 to 8 carbon atoms,

an unbranched or branched alkynyl radical containing 2 to 8 carbon atoms,

a cycloalkyl radical containing 3 to 6 carbon atoms,

a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl, alkenyl, alkynyl, aryl, aralkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, formyl, acyl, acylamino, aroylamino, alkoxycarbonylamino, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, cyano, nitro and trifluoromethyl radicals,

or a 5-membered aromatic heterocycle containing one or more identical or different hetero atoms selected from nitrogen, oxygen and sulphur atoms and optionally substituted with one or more identical or different substituents selected from halogen atoms, alkyl, aryl, amino, alkylamino, dialkylamino, alkoxycarbonylamino, acyl, arylcarbonyl, cyano, carboxyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl and alkoxycarbonyl radicals,

with the understanding that, in the substituents of the phenyl, α- or β-naphthyl and aromatic heterocyclic radicals, the alkyl radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms, the alkenyl and alkynyl radicals contain 2 to 8 carbon atoms, and the aryl radicals are phenyl or α- or β-naphthyl radicals,

$R_4$ represents

an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain,

an alkenyloxy radical containing 3 to 6 carbon atoms in an unbranched or branched chain,

an alkynyloxy radical containing 3 to 6 carbon atoms in an unbranched or branched chain,

a cycloalkyloxy radical containing 3 to 6 carbon atoms or a cycloalkenyloxy radical containing 4 to 6 carbon atoms,

these radicals being optionally substituted with one or more substituents selected from halogen atoms, an alkoxy radical containing 1 to 4 carbon atoms, an alkylthio radical containing 1 to 4 carbon atoms, a carboxyl radical, an alkyloxycarbonyl radical in which the alkyl portion contains 1 to 4 carbon atoms, a cyano radical, a carbamoyl radical, an N-alkylcarbamoyl radical and a N,N-dialkylcarbamoyl radical in which each alkyl portion contains 1 to 4 carbon atoms, or both alkyl portions, together with the nitrogen atom to which they are linked, form a saturated 5- or 6-membered heterocyclic radical optionally containing a second hetero atom selected from oxygen, sulphur and nitrogen atoms, said saturated 5- or 6-membered heterocyclic radical optionally being substituted with a substituent selected from an alkyl radical containing 1 to 4 carbon atoms, a phenyl radical, and a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms,



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$R_5$ represents

an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain,

an alkenyloxy radical containing 3 to 6 carbon atoms,

an alkynyloxy radical containing 3 to 6 carbon atoms,

a cycloalkyloxy radical containing 3 to 6 carbon atoms or

a cycloalkenyloxy radical containing 3 to 6 carbon atoms,

these radicals being optionally substituted with at least one substituent selected from halogen atoms, an alkoxy radical containing 1 to 4 carbon atoms, an alkylthio radical containing 2 to 4 carbon atoms, a carboxyl radical, an alkyloxycarbonyl radical in which the alkyl portion contains 1 to 4 carbon atoms, a cyano radical, a carbamoyl radical, an N-alkylcarbamoyl radical, and a N,N-dialkylcarbamoyl radical in which each alkyl portion contains 1 to 4 carbon atoms or, with the nitrogen atom to which it is linked, forms a saturated 5- or 6-membered heterocyclic radical optionally containing a second hetero atom selected from oxygen, sulphur and nitrogen atoms, optionally substituted with a substituent selected from an alkyl radical containing 1 to 4 carbon atoms, a phenyl radical and a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms.

Preferably, the aryl radicals which can be represented by $R_3$ are phenyl or α- or β-naphthyl radicals optionally substituted with one or more atoms or radicals selected from halogen atoms (fluorine, chlorine, bromine, iodine) alkyl, alkenyl, alkynyl, aryl, arylalkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, formyl, acyl, acylamino, aroylamino, alkoxycarbonylamino, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, carbamoyl, dialkylcarbamoyl, cyano, nitro and trifluoromethyl radicals, on the understanding that the alkyl radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms, that the alkenyl and alkynyl radicals contain 2 to 8 carbon atoms and that the aryl radicals are phenyl or α- or β-naphthyl radicals.

Preferably, the heterocyclic radicals which can be represented by $R_3$ are 5-membered aromatic heterocyclic radicals containing one or more identical or different atoms selected from nitrogen, oxygen and sulphur atoms, optionally substituted with one or more identical or different substituents selected from halogen atoms (fluorine, chlorine, bromine, iodine), alkyl radicals containing 1 to 4 carbon atoms, aryl radicals containing 6 or 10 carbon atoms, alkoxy radicals containing 1 to 4 carbon atoms, aryloxy radicals containing 6 or 10 carbon atoms, amino radicals, alkylamino radicals containing 1 to 4 carbon atoms, dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms, acylamino radicals in which the acyl portion contains 1 to 4 carbon atoms, alkoxycarbonylamino radicals containing 1 to 4 carbon atoms, acyl radicals containing 1 to 4 carbon atoms, arylcarbonyl radicals in which the aryl portion contains 6 or 10 carbon atoms, cyano radicals, carboxyl radicals, carbamoyl radicals, alkylcarbamoyl radicals in which the alkyl portion contains 1 to 4 carbon atoms, dialkylcarbamoyl radicals in which each alkyl portion contains 1 to 4 carbon atoms, and alkoxycarbonyl radicals in which the alkoxy portion contains 1 to 4 carbon atoms.

Preferably, the radicals $R_4$ and $R_5$, which may be identical or different, represent unbranched or branched alkoxy radicals containing 1 to 6 carbon atoms, optionally substituted with a methoxy, ethoxy, ethylthio, carboxyl, methoxycarbonyl, ethoxycarbonyl, cyano, carbamoyl, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-pyrrolidinocarbonyl or N-piperidinocarbonyl radical.

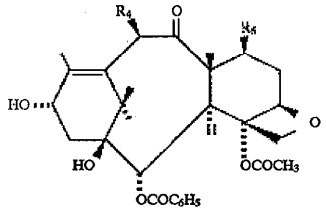


More particularly, the present invention relates to the products of general formula (I) in which Z represents a hydrogen atom or a radical of general formula (II) in which $R_1$ represents a benzoyl radical or a radical $R_2$—O—CO— in which $R_2$ represents a tert-butyl radical and $R_3$ represents an alkyl radical containing 1 to 6 carbon atoms, an alkenyl radical containing 2 to 6 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a phenyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms (fluorine, chlorine), alkyl (methyl), alkoxy (methoxy), dialkylamino (dimethylamino), acylamino (acetylamino), alkoxycarbonylamino (tert-butoxycarbonylamino), trifluoromethyl, a 2-furyl radical, a 3-furyl radical, a 2-thienyl radical, a 3-thienyl radical, a 2-thiazolyl radical, a 4-thiazolyl radical, and a 5-thiazolyl radical, and $R_4$ and $R_5$, which may be identical or different, each represent an unbranched or branched alkoxy radical containing 1 to 6 carbon atoms.

Still more particularly, the present invention relates to the products of general formula (I) in which Z represents a hydrogen atom or a radical of general formula (II) in which $R_1$ represents a benzoyl radical or a radical $R_2$—O—CO— in which $R_2$ represents a tert-butyl radical and $R_3$ represents an isobutyl, isobutenyl, butenyl, cyclohexyl, phenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl or 5-thiazolyl radical, and $R_4$ and $R_5$, which may be identical or different, each represent a methoxy, ethoxy or propoxy radical.

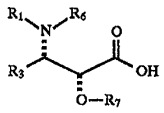
The products of general formula (I) in which Z represents a radical of general formula (II) display noteworthy antitumour and antileukaemic properties.

According to the present invention, the new products of general formula (I) in which Z represents a radical of general formula (II) may be obtained by esterification of a product of general formula (III):




(III)

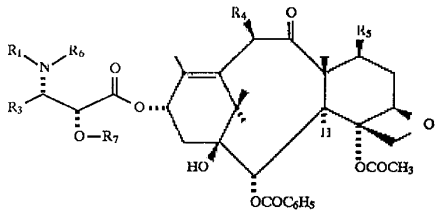
in which $R_4$ and $R_5$ are defined as above, by means of an acid of general formula (IV):




(IV)

in which $R_1$ and $R_3$ are defined as above, and either $R_6$ represents a hydrogen atom and $R_7$ represents a group protecting the hydroxyl function, or $R_6$ and $R_7$ together form a saturated 5- or 6-membered heterocycle, or by means of a derivative of this acid, to obtain an ester of general formula (V):

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(V)

in which $R_1$, $R_3$, $R_4$, $R_5$, $R_6$ and $R_7$ are defined as above, followed by replacement of the protective groups represented by $R_7$ and/or $R_6$ and $R_7$ by hydrogen atoms.

The esterification by means of an acid of general formula (IV) may be performed in the presence of a condensing agent (carbodiimide, reactive carbonate) and an activating agent (aminopyridines) in an organic solvent (ether, ester, ketones, nitriles, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons, aromatic hydrocarbons) at a temperature from −10° to 90° C.

The esterification may also be carried out using the acid of general formula (IV) in the form of the symmetrical anhydride, working in the presence of an activating agent (aminopyridines) in an organic solvent (ethers, esters, ketones, nitrites, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons, aromatic hydrocarbons) at a temperature of from 0° to 90° C.

The esterification may also be carried out using the acid of general formula (IV) in halide form or in the form of a mixed anhydride with an aliphatic or aromatic acid, optionally prepared in situ, in the presence of a base (tertiary aliphatic amine), working in an organic solvent (ethers, esters, ketones, nitriles, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons, aromatic hydrocarbons) at a temperature of from 0° to 80° C.

Preferably, $R_6$ represents a hydrogen atom and $R_7$ represents a group protecting the hydroxyl function, or alternatively $R_6$ and $R_7$ together form a saturated 5- or 6-membered heterocycle.

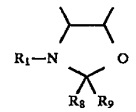
When $R_6$ represents a hydrogen atom, $R_7$ preferably represents a methoxymethyl, 1-ethoxyethyl, benzyloxymethyl, trimethylsilyl, triethylsilyl, β-trimethylsilylethoxymethyl, benzyloxycarbonyl or tetrahydropyranyl radical.

When $R_6$ and $R_7$ together form a heterocycle, the latter is preferably an oxazolidine ring optionally monosubstituted or gem-disubstituted at position 2.

Replacement of the protective groups $R_7$ and/or $R_6$ and $R_7$ by hydrogen atoms may be performed, depending on their nature, in the following manner:

1) when $R_8$ represents a hydrogen atom and $R_7$ represents a group protecting the hydroxyl function, replacement of the protective groups by hydrogen atoms is performed by means of an inorganic acid (hydrochloric acid, sulphuric acid, hydrofluoric acid) or organic acid (acetic acid, methanesulphonic acid, trifluoromethanesulphonic acid, p-toluenesulphonic acid) used alone or mixed, working in an organic solvent chosen from alcohols, ethers, esters, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons, aromatic hydrocarbons or nitriles at a temperature of from −10° to 60° C., or by means of a source of fluoride ions such as a hydrofluorine acid/triethylamine complex, or by catalytic hydrogenation,

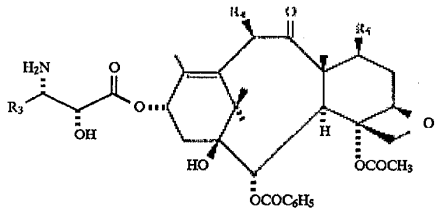
2) when $R_6$ and $R_7$ together form a saturated 5- or 6-membered heterocycle, and more especially an oxazolidine ring of general formula (VI):



(VI)

in which $R_1$ is defined as above and $R_6$ and $R_9$, which may be identical or different, represent a hydrogen atom or an alkyl radical containing 1 to 4 carbon atoms, or an aralkyl radical in which the alkyl portion contains 1 to 4 carbon atoms and the aryl portion preferably represents a phenyl radical optionally substituted with one or more alkoxy radicals containing 1 to 4 carbon atoms, or an aryl radical preferably representing a phenyl radical optionally substituted with one or more alkoxy radicals containing 1 to 4 carbon atoms, or alternatively $R_8$ represents an alkoxy radical containing 1 to 4 carbon atoms or a trihalomethyl radical such as trichloromethyl or a phenyl radical substituted with a trihalomethyl radical such as trichloromethyl and $R_9$ represents a hydrogen atom, or alternatively $R_8$ and $R_9$, together with the carbon atom to which they are linked, form a 4- to 7-membered ring, replacement of the protective group formed by $R_6$ and $R_7$ by hydrogen atoms may be performed, depending on the meanings of $R_1$, $R_8$ and $R_9$, in the following manner:

a) when $R_1$ represents a tert-butoxycarbonyl radical and $R_8$ and $R_9$, which may be identical or different, represent an alkyl radical or an aralkyl (benzyl) or aryl (phenyl) radical, or alternatively $R_8$ represents a trihalomethyl radical or a phenyl radical substituted with a trihalomethyl radical and $R_9$ represents a hydrogen atom, or alternatively $R_8$ and $R_9$ together form a 4- to 7-membered ring, treatment of the ester of general formula (V) with an inorganic or organic acid, where appropriate in an organic solvent such as an alcohol, yields the product of general formula (VII):



(VII)

in which $R_3$, $R_4$ and $R_5$ are defined as above, which is acylated by means of benzoyl chloride in which the phenyl ring is optionally substituted or by means of thenoyl chloride, of furoyl chloride or of a product of general formula:

$$R_2—O—CO—X \qquad \text{(VIII)}$$

in which $R_2$ is defined as above and X represents a halogen atom (fluorine, chlorine) or a residue —O—$R_2$ or —O—CO—O—$R_2$, to obtain a product of general formula (I) in which Z represents a radical of general formula (II).

Preferably, the product of general formula (V) is treated with formic acid at a temperature in the region of 20° C. to yield the product of general formula (VII).

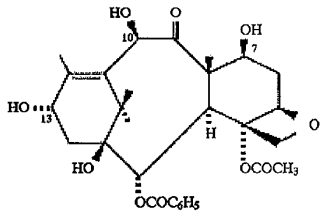
Preferably, the acylation of the product of general formula (VII) by means of a benzoyl chloride in which the phenyl radical is optionally substituted or by means of thenoyl chloride, of furoyl chloride or of a product of general formula (VIII) is performed in an inert organic solvent

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chosen from esters such as ethyl acetate, isopropyl acetate or n-butyl acetate and halogenated aliphatic hydrocarbons such as dichloromethane or 1,2-dichloroethane, in the presence of an inorganic base such as sodium bicarbonate or an organic base such as triethylamine. The reaction is performed at a temperature of from 0° to 50° C., and preferably at about 20° C.

b) when $R_1$ represents an optionally substituted benzoyl radical, a thenoyl or furoyl radical or a radical $R_2O—CO—$ in which $R_2$ is defined as above, $R_8$ represents a hydrogen atom or an alkoxy radical containing 1 to 4 carbon atoms or a phenyl radical substituted with one or more alkoxy radicals containing 1 to 4 carbon atoms and $R_9$ represents a hydrogen atom, replacement of the protective group formed by $R_6$ and $R_7$ by hydrogen atoms is performed in the presence of an inorganic acid (hydrochloric acid, sulphuric acid) or organic acid (acetic acid, methanesulphonic acid, trifluoromethanesulphonic acid, p-toluenesulphonic acid) used alone or mixed in a stoichiometric or catalytic amount, working in an organic solvent chosen from alcohols, ethers, esters, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons and aromatic hydrocarbons at a temperature of from −10° to 60° C., and preferably from 15° to 30° C.

According to the invention, the products of general formula (III), that is to say the products of general formula (I) in which Z represents a hydrogen atom and $R_4$ and $R_5$ are defined as above, may be obtained from 10-deacetylbaccatin III of formula (IX):

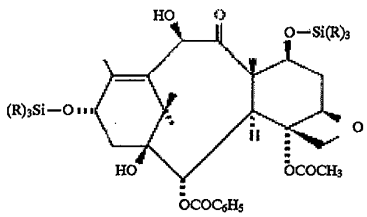



(IX)

It can be especially advantageous to protect the hydroxyl functions at the positions 7 and 13 selectively, for example in the form of a silyl diether which may be obtained by the action of a silyl halide of general formula:

$$(R)_3—Si—Hal \quad (X)$$

in which the symbols R, which may be identical or different, represent an alkyl radical containing 1 to 6 carbon atoms, optionally substituted with a phenyl radical, or a cycloalkyl radical containing 3 to 6 carbon atoms or a phenyl radical, on 10-deacetylbaccatin III, to obtain a product of general formula (XI):

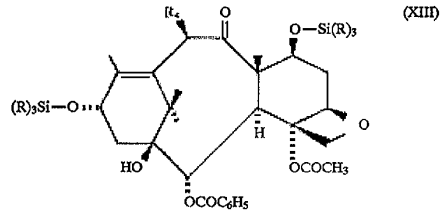



(XI)

in which R is defined as above, followed by the action of a product of general formula:

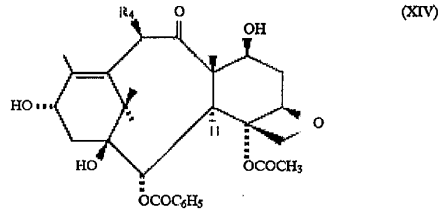
$$R'_4—X_1 \quad (XII)$$

in which $R'_4$ represents a radical such that $R'_4—O$ is identical to $R_4$ defined as above and $X_1$ represents a reactive ester residue such as a sulphuric or sulphonic ester residue or a halogen atom, to obtain a product of general formula (XIII):




(XIII)

in which R and $R_4$ are defined as above, the silyl protective groups of which are replaced by hydrogen atoms to obtain a product of general formula (XIV):




(XIV)

in which $R_4$ is defined as above, which is etherified selectively at position 7 by the action of a product of general formula:

$$R'_5—X_2 \quad (XV)$$

in which $R'_5$ represents a radical such that $R'_5—O$ is identical to $R_5$ defined as above and $X_2$ represents a halogen atom or a reactive ester residue such as a sulphuric or sulphonic ester residue, to give the product of general formula (III).

Generally, the action of a silyl derivative of general formula (X) on 10-deacetylbaccatin III is performed in pyridine or triethylamine, where appropriate in the presence of an organic solvent such as an aromatic hydrocarbon, for instance benzene, toluene or xylenes, at a temperature between 0° C. and the refluxing temperature of the reaction mixture.

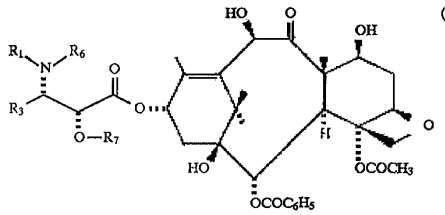
Generally, the action of a product of general formula (XII) on a product of general formula (XI) is performed, after metalation of the hydroxyl function at position 10 by means of an alkali metal hydride, such as sodium hydride, an alkali metal amide, such as lithium amide, or an alkali metal alkylide, such as butyllithium, working in an organic solvent, such as dimethylformamide or tetrahydrofuran, at a temperature of from 0° to 50° C.

Generally, the replacement of the silyl protective groups of the product of general formula (XIII) by hydrogen atoms is performed by means of an acid such as hydrofluoric acid or trifluoroacetic acid in the presence of a base such as triethylamine or pyridine optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms, the base optionally being combined with an inert organic solvent such as a nitrile, for instance acetonitrile, or a halogenated aliphatic hydrocarbon, such as dichloromethane, at a temperature of from 0° to 80° C.

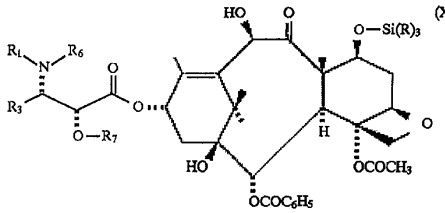
Generally, the action of a product of general formula (XV) on a product of general formula (XIV) is performed under the conditions described above for the action of a product of general formula (XII) on a product of general formula (XI).

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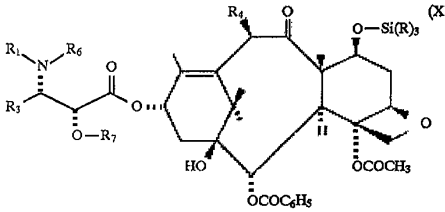
According to the invention, the products of general formula (I) in which Z represents a radical of general formula (II), $R_4$ is defined as above and $R_5$ is defined as above may be obtained from a product of general formula (XVI):


(XVI)

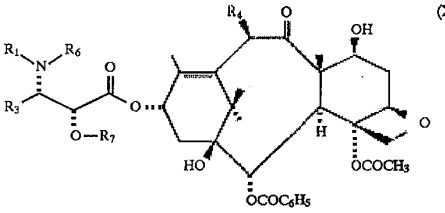
in which $R_1$, $R_3$, $R_6$ and $R_7$ are defined as above, by silylation at position 7 by means of a product of general formula (X), to obtain a product of general formula (XVII):


(XVII)

in which R, $R_1$, $R_3$, $R_6$ and $R_7$ are defined as above, which is functionalized at position 10 by means of a product of general formula (XII) to give a product of general formula (XVIII):


(XVIII)

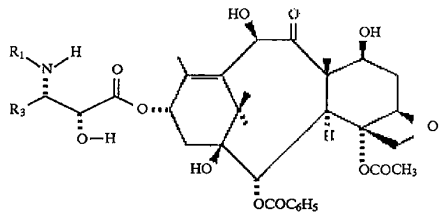
in which R, $R_1$, $R_3$, $R_4$, $R_6$ and $R_7$ are defined as above, the silyl protective group of which is replaced by a hydrogen atom to give a product of general formula (XIX):


(XIX)

which, by the action of a product of general formula (XV), yields the product of general formula (V), the protective groups of which are replaced by hydrogen atoms to give a product of general formula (I) in which Z represents a radical of general formula (II).

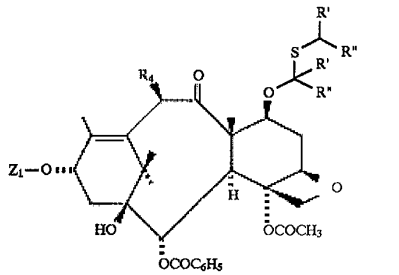
The reactions used for silylation, functionalization and replacement of the protective groups by hydrogen atoms are performed under conditions similar to those described above.

The products of general formula (XVI) may be obtained under the conditions described in European Patent EP 0,336,841 and international Applications PCT WO 92/09589 and WO 94/07878, the disclosures of which are hereby incorporated by reference in their entirety, or from the products of general formula (XX):

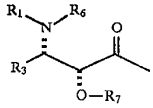

(XX)

in which $R_1$ and $R_3$ are defined as above, according to known methods for protecting the hydroxyl function of the side chain without affecting the remainder of the molecule.

According to the invention, the products of general formula (I) in which Z represents a hydrogen atom or a radical of general formula (II) may be obtained by the action of activated Raney nickel, in the presence of an aliphatic alcohol containing 1 to 3 carbon atoms or an ether such as tetrahydrofuran or dioxane, on a product of general formula (XXI):

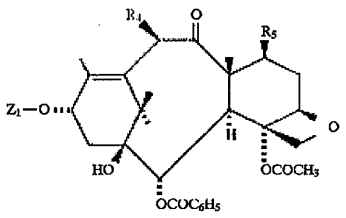

(XXI)

in which $R_4$ is defined as above and R' and R", which may be identical or different, represent a hydrogen atom or an alkyl radical containing 1 to 6 carbon atoms, an alkenyl radical containing 2 to 6 carbon atoms, an alkynyl radical containing 2 to 6 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms or a cycloalkenyl radical containing 3 to 6 carbon atoms, optionally substituted, or alternatively R' and R", together with the carbon atom to which they are linked, form a cycloalkyl radical containing 3 to 6 carbon atoms or a cycloalkenyl radical containing 4 to 6 carbon atoms, and $Z_1$ represents a hydrogen atom or a radical of general formula (XXII):


(XXII)

in which $R_1$, $R_3$, $R_6$ and $R_7$ are defined as above, and, to obtain a product of general formula (XXIII):

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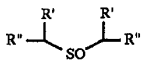



(XXIII)

followed, when $Z_1$ represents a radical of general formula (XXII), that is to say when the product of general formula (XXIII) is identical to the product of general formula (V), by replacement of the protective groups represented by $R_6$ and/or $R_6$ and $R_7$ by hydrogen atoms under the conditions described above.

Generally, the action of activated Raney nickel in the presence of an aliphatic alcohol or an ether is performed at a temperature of from −10° to 60° C.

According to the invention, the product of general formula (XXI) in which $Z_1$ and $R_4$ are defined as above may be obtained by the action of a sulphoxide of general formula (XXIV):




(XXIV)

in which R' and R" are defined as above, on a product of general formula (XIX).

Generally, the reaction of the sulphoxide of general formula (XXIV), preferably dimethyl sulphoxide, with the product of general formula (XIX) is performed in the presence of a mixture of acetic acid and acetic anhydride or a derivative of acetic acid such as a haloacetic acid at a temperature of from 0° to 50° C., and preferably at about 25° C.

The new products of general formula (I) obtained by carrying out the processes according to the invention may be purified according to known methods such as crystallization or chromatography.

The products of general formula (I) in which Z represents a radical of general formula (II) display noteworthy biological properties.

In vitro, measurement of the biological activity is performed on tubulin extracted from pig's brain by the method of M. L. Shelanski et al., Proc. Natl. Acad. Sci. USA, 70, 765–768 (1973). Study of the depolymerization of microtubules to tubulin is performed according to the method of G. Chauvière et al., C.R. Acad. Sci., 293, series II, 501–503 (1981). In this study, the products of general formula (I) in which Z represents a radical of general formula (II) were shown to be at least as active as taxol and Taxotere.

In vivo, the products of general formula (I) in which Z represents a radical of general formula (II) were shown to be active in mice grafted with B16 melanoma at doses of from 1 to 30 mg/kg administered intraperitoneally, as well as on other liquid or solid tumours.

The new products have antitumour properties, and more especially activity against tumours which are resistant to Taxol® or to Taxotere®. Such tumours comprise colon tumours which have a high expression of the mdr 1 gene (multiple drug resistance gene). Multiple drug resistance is a customary term relating to the resistance of a tumour to different products having different structures and mechanisms of action. Taxoids are generally known to be strongly recognized by experimental tumours such as P388/DOX, a cell line selected for its resistance to doxorubicin (DOX) which expresses mdr 1.

The examples which follow illustrate the present invention.

## EXAMPLE 1

126 mg of dicyclohexylcarbodiimide and then 14 mg of 4-(N,N-dimethylamino)pyridine were added successively at a temperature in the region of 20° C. to a suspension containing 217.8 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,13α-dihydroxy-7β,10β-dimethoxy-9-oxo-11-taxene, 200 mg of (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylic acid and 50 mg of powdered 4 Å molecular sieve in 2 $cm^3$ of ethyl acetate. The suspension obtained was stirred at a temperature in the region of 20° C. under an argon atmosphere for 16 hours, and then concentrated to dryness under reduced pressure (0.27 kPa) at a temperature in the region of 40° C. The residue obtained was purified by chromatography at atmospheric pressure on 50 g of silica (0.063–0.2 mm) contained in a column 2 cm in diameter (elution gradient: ethyl acetateldichloromethane from 10:90 to 40:60 by volume), collecting 10-$cm^3$ fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40° C. for 2 hours. 271.8 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy- 1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate were thereby obtained in the form of a white solid, the characteristics of which were as follows:

$^1H$ NMR spectrum (400 MHz; $CDCl_3$ with a few drops of $CD_3OD$-$d_4$; chemical shifts δ in ppm; coupling constants J in Hz): 1.02 (s, 9H: $C(CH_3)_3$); 1.10 (s, 3H: $CH_3$); 1.17 (s, 3H: $CH_3$); 1.63 (s, 3H: $CH_3$); from 1.65 to 1.85 and 2.60 (2 mts, 1H each; $CH_2$ at position 6); 1.78 (unres. comp., 3H: $CH_3$); 2.02 and 2.15 (2 dd, J=14 and 9, 1H each: $CH_2$ at position 14); 2.14 (s, 3H: $CH_3$); 3.22 and 3.35 (2 s, 3H each: $OCH_3$); 3.64 (d, J=7, 1H: H at position 3); 3.73 (mt, 1H: H at position 7); 3.76 (s, 3H: $ArOCH_3$); 4.06 and 4.16 (2 d, J=8.5, 1H each; $CH_2$ at position 20); 4.53 (d, J=5, 1H: H at position 2'); 4.67 (s, 1H: H at position 10); 4.85 (broad d, J=10, 1H: H at position 5); 5.36 (mt, 1H: H at position 3'); 5.52 (d, J=7, 1H: H at position 2); 6.07 (mt, 1H: H at position 13); 6.33 (unres. comp., 1H: H at position 5'); 6.88 (d, J=8, 2H: aromatic H at the ortho position with respect to $OCH_3$); from 7.25 to 7.40 (mt, 7H: aromatic H at position 3' and aromatic H at the meta position with respect to $OCH_3$); 7.43 (t, J=7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.58 (t, J=7.5, 1H: $OCOC_6H_5$ H at the para position); 7.96 (d, J=7.5, 2H: $OCOC_6H_5$ H at the ortho position).

A solution of 446.3 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate in 11.6 $cm^3$ of a 0.1N solution of hydrogen chloride in ethanol was stirred constantly at a temperature in the region of 0° C. for 16 hours under an argon atmosphere. The reaction mixture was then diluted with 40 $cm^3$ of dichloromethane and 5 $cm^3$ of distilled water. After settling had taken place, the aqueous phase was separated and extracted with 5 $cm^3$ of dichloromethane. The organic phases were combined, dried over magnesium sulphate, filtered through sintered glass and then concentrated to dryness under reduced pressure (0.27 kPa) at a temperature in the region of 40° C. 424.2 mg of a pale yellow solid were obtained, which product was purified by preparative thin-layer chromatog-

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raphy [12 Merck preparative silica gel $60F_{254}$ plates, thickness 1 mm, application in solution in a methanol/dichloromethane (5:95 by volume) mixture, eluting with a methanol/dichloromethane (5:95 by volume) mixture]. After elution of the zone corresponding to the main product with a methanol/dichloromethane (15:85 by volume) mixture, filtration through sintered glass and evaporation of the solvents under reduced pressure (0.27 kPa) at a temperature in the region of 40° C., 126 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate were obtained in the form of an ivory-coloured foam, the characteristics of which were as follows:

optical rotation $[\alpha]_{20}^{D}$=-32.9 (c=0.5; methanol)

$^1$H NMR spectrum (400 MHz; $CDCl_3$; chemical shifts δ in ppm; coupling constants J in Hz): 1.23 (s, 3H: $CH_3$); 1.25 (s, 3H: $CH_3$); 1.39 (s, 9H: $C(CH_3)_3$); 1.70 (s, 1H: OH at position 1); 1.75 (s, 3H: $CH_3$); 1.82 and 2.72 (2 mts, 1H each: $CH_2$ at position 6); 1.91 (s, 3H: $CH_3$); 2.31 (limiting AB, 2H: $CH_2$ at position 14); 2.39 (s, 3H: $COCH_3$); 3.33 and 3.48 (2 s, 3H each: $OCH_3$); 3.48 (mt, 1H: OH at position 2'); 3.85 (d, J=7, 1H: H 3); 3.88 (dd, J=11 and 7, 1H: H 7); 4.20 and 4.33 (2 d, J=8.5, 1H each: $CH_2$ at position 20); 4.65 (mt, 1H: H at position 2'); 4.83 (s, 1H: H at position 10); 5.00 (broad d, J=10, 1H: H at position 5); 5.30 (broad d, J=10, 11H: H at position 3'); 5.47 (d, J=10, 1H: CONH); 5.66 (d, J=7, 1H: H at position 2); 6.24 (broad t, J=9, 1H: H at position 13); from 7.30 to 7.50 (mt, 5H: aromatic H at position 3'); 7.52 (t, J=7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.63 (t, J=7.5, 1H: $OCOC_6H_5$ H at the para position); 8.12 (d, J=7.5, 2H: $OCOC_6H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,13α-dihydroxy-7β,10β-dimethoxy-9-oxo-11-taxene (or 7β,10β-dimethoxy-10-deacetoxybaccatin III) was prepared in the following manner:

86 mg of sodium hydride at a concentration of 50% by weight in liquid paraffin were added portionwise to a solution, maintained under an argon atmosphere, at a temperature in the region of 0° C., of 500 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,13α-trihydroxy-10β-methoxy-9-oxo-11-taxene in 5 $cm^3$ of iodomethane and 0.5 $cm^3$ of dimethylformamide. After 45 minutes at a temperature in the region of 0° C., the reaction mixture was diluted with 50 $cm^3$ of ethyl acetate and 8 $cm^3$ of distilled water. After settling had taken place, the organic phase was separated and washed with twice 8 $cm^3$ of distilled water and then 8 $cm^3$ of saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered through sintered glass and concentrated to dryness under reduced pressure (0.27 kPa) at a temperature in the region of 40° C. 570 mg of a pale yellow solid were thereby obtained, which product was purified by chromatography at atmospheric pressure on 50 g of silica (0.063–0.2 mm) contained in a column 2.5 cm in diameter, eluting with a methanol/dichloromethane (2:98 by volume) mixture and collecting 10-$cm^3$ fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40° C. for 2 hours. 380 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,13α-dihydroxy-7β,10β-dimethoxy-9-oxo-11-taxene were thereby obtained in the form of a pale yellow solid, the characteristics of which were as follows:

$^1$H NMR spectrum (400 MHz; $CDCl_3$; with a few drops of $CD_3OD$-$d_4$, chemical shifts δ in ppm; coupling constants J in Hz): 1.03 (s, 3H: $CH_3$); 1.11 (s, 3H: $CH_3$); 1.65 (s, 3H: $CH_3$); 1.72 and 2.67 (2 mts, 1H each: $CH_2$ at position 6); 2.05 (s, 3H: $CH_3$): 2.21 (limiting AB, J=14 and 9, 2H: $CH_2$ at position 14); 2.25 (s, 3H: $COCH_3$); 3.26 and 3.40 (2 s, 3H each: $OCH_3$); 3.85 (d, J=7, 1H: H at position 3); 3.89 (dd, J=11 and 6.5, 1H: H at position 7); 4.12 and 4.25 (2 d, J=8.5, 1H each: $CH_2$ at position 20); 4.78 (broad t, J=9, 1H: H at position 13); 4.83 (s, 1H: H at position 10); 4.98 (broad d, J=10, 1H: H at position 5); 5.53 (d, J=7, 1H: H at position 2); 7.43 (t, J=7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.56 (t, J=7.5, 1H: $OCOC_6H_5$ H at the para position); 8.05 (d, J=7.5, 2H: $OCOC_6H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,13α-trihydroxy-10β-methoxy-9-oxo-11-taxene (or 10β-methoxy-10-deacetoxybaccatin III) was prepared in the following manner:

50 $cm^3$ of hydrogen fluoride/triethylamine complex ($3HF.Et_3N$) were added slowly to a solution, maintained under an argon atmosphere, at a temperature in the region of 0° C., of 3.62 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-methoxy-9-oxo-7β,13α-bis(triethylsilyoxy)-11-taxene in 30 $cm^3$ of dichloromethane. After 48 hours at a temperature in the region of 20° C., the reaction mixture was poured into a suspension of 100 $cm^3$ of supersaturated aqueous sodium hydrogen carbonate solution maintained at a temperature in the region of 0° C. After settling had taken place, the aqueous phase was separated and re-extracted with three times 80 $cm^3$ of dichloromethane and then twice 80 $cm^3$ of ethyl acetate. The organic phases were combined, dried over magnesium sulphate, filtered through magnesium sulphate and concentrated to dryness under reduced pressure (0.27 kPa) at a temperature in the region of 40° C. 3.45 g of a yellow foam were thereby obtained, which product was purified by chromatography at atmospheric pressure on 150 g of silica (0.063–0.2 mm) contained in a column 3.5 cm in diameter, eluting with a methanol/dichloromethane (5:95 by volume) mixture and collecting 35-$cm^3$ fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40° C. for 2 hours. 1.97 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,13α-trihydroxy-10β-methoxy-9oxo-11-taxene were thereby obtained in the form of a white solid, the characteristics of which were as follows:

$^1$H NMR spectrum (400 MHz; $CDCl_3$; chemical shifts δ in ppm: coupling constants J in Hz): 1.10 (s, 3H: $CH_3$); 1.19 (s, 3H: $CH_3$); 1.48 (d, J=8.5, 1H: OH at position 13); 1.70 (s, 3H: $CH_3$); 1.81 and 2.61 (2 mts, 1H each: $CH_2$ at position 6); 2.09 (d, J=5, 1H: OH at position 7); 2.11 (s, 3H: $CH_3$); 2.30 (s, 3H: $COCH_3$); 2.32 (d, J=9, 2H: $CH_2$ at position 14); 3.48 (s, 3H: $OCH_3$); 3.97 (d, J=7, 1H: H at position 3); 4.18 and 4.33 (2 d, J=8.5, 1H each: $CH_2$ at position 20); 4.31 (mt, 1H: H at position 7); 4.93 (mt, 1H: H at position 13); 4.99 (s, 1H: H at position 10); 5.01 (broad d, J=10, 1H: H at position 5); 5.66 (d, J=7, 1H: H at position 2); 7.49 (t, J=7.5, 2H: $OCOC_8H_5$ H at the meta position); 7.63 (t, J=7.5, 1H: $OCOC_8H_5$ H at the para position); 8.12 (d, J=7.5, 2H: $OCOC_8H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-methoxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene (or 10β-methoxy-10-deacetoxy-7,13-bis(triethylsilyl) baccatin III) was prepared in the following manner:

375 mg of sodium hydride at a concentration of 50% by weight in liquid paraffin were added portionwise to a solution, maintained under an argon atmosphere, at a temperature in the region of 0° C., of 5 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-9-oxo-7β,13α-

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bis(triethylsilyloxy)-11-taxene in 25 $cm^3$ of iodomethane. The solution was stirred constantly for 45 minutes at a temperature in the region of 0° C., and then for 5 hours 30 minutes at a temperature in the region of 20° C. The reaction mixture was cooled again to a temperature in the region of 0° C., and 125 mg of sodium hydride at a concentration of 50% by weight in liquid paraffin were added portionwise. After 1 hour at 20° C. and then 18 hours at 5° C., the reaction mixture was diluted by adding 50 $cm^3$ of dichloromethane and poured into 50 $cm^3$ of saturated aqueous ammonium chloride solution, and settling was allowed to take place. The aqueous phase was separated and extracted with twice 30 $cm^3$ of dichloroemethane, and the organic phases were then combined, washed with 10 $cm^3$ of distilled water, dried over magnesium sulphate, filtered through sintered glass and concentrated to dryness under reduced pressure (0.27 kPa) at a temperature in the region of 40° C. 5.15 g of a yellow foam were thereby obtained, which product was purified by chromatography at atmospheric pressure on 300 g of silica (0.063–0.2 mm) contained in a column 5 cm in diameter (elution gradient: ethyl acetate/dichloromethane from 0:100 to 10:90 by volume), collecting 30-$cm^3$ fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40° C. for 2 hours. 3.62 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-methoxy-9-oxo-7β,13α-bis (triethylsilyloxy)-11-taxene were thereby obtained in the form of a pale yellow foam, the characteristics of which were as follows:

$^1H$ NMR spectrum (600 MHz; $CDCl_3$; chemical shifts δ in ppm; coupling constants J in Hz): 0.58 and 0.69 (2 mts, 6H each: ethyl $CH_2$); 0.97 and 1.04 (2 t, J=7.5, 9H each: ethyl $CH_3$); 1.15 (s, 3H: $CH_3$); 1.18 (s, 3H: $CH_3$); 1.58 (s, 1H: OH at position 1); 1.68 (s, 3H: $CH_3$); 1.89 and 2.48 (2 mts, 1H each: $CH_2$ at position 6); 2.04 (s, 3H: $CH_3$); 2.15 and 2.23 (2 dd, J=16 and 9, 1H each: $CH_2$ at position 14); 2.29 (s, 3H: $COCH_3$); 3.40 (s, 3H: $OCH_3$); 3.83 (d, J=7, 1H: H: H at position 13); 4.15 and 4.30 (2 d, J=8.5, 1H each: $CH_2$ at position 20); 4.43 (dd, J=11 and 7, 1H: H at position 7); 4.91 (s 1H: H at position 10); 4.96 (broad d, J=10, 1H at position 5); 5.01 (broad t, J=9, 1H: H at position 13); 5.62 (d, J=7, 1H: H at position 2); 7.46 (t, J=7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.60 (t, J=7.5, 1H: $OCOC_6H_5$ H at the para position); 8.09 (d, J=7.5, 2H: $OCOC_8H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene (or 10-deacetyl-7,13-bis(triethylsilyl)baccatin III) was prepared in the following manner:

10.8 $cm^3$ of triethylsilyl chloride were added to a solution, maintained under an argon atmosphere, at a temperature in the region of 20° C., of 14 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,10β,13α-tetrahydroxy-9-oxo-11-taxene (10-deacetylbaccatin III) in 50 $cm^3$ of anhydrous pyridine. After 17 hours at a temperature in the region of 20° C., the reaction mixture was brought to a temperature in the region of 115° C. and 10.8 $cm^3$ of triethylsilyl chloride were then added. After 3 hours 15 minutes at a temperature in the region of 115° C., the reaction mixture was brought back to a temperature in the region of 20° C. and diluted with 30 $cm^3$ of ethyl acetate and 100 $cm^3$ of distilled water. After settling took place, the aqueous phase was separated and extracted with twice 50 $cm^3$ of ethyl acetate. The organic phases were combined, washed with 50 $cm^3$ of saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered through sintered glass and then concentrated to dryness under reduced pressure (0.27 kPa) at a temperature in the region of 40° C. 63.1 g of a brown oil were thereby obtained, which product was purified by chromatography at atmospheric pressure on 800 g of silica (0.063–0.2 mm) contained in a column 7 cm in diameter (elution gradient: ethyl acetate/dichloromethane from 0:100 to 5:95 by volume), collecting 60-$cm^3$ fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40° C. for 2 hours. 9.77 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene were thereby obtained in the form of a cream-coloured foam, the characteristics of which were as follows:

$^1H$ NMR spectrum (400 MHz; $CDCl_3$; chemical shifts δ in ppm; coupling constants J in Hz): 0.55 and 0.68 (2 mts, 6H each: ethyl $CH_2$); 0.94 and 1.03 (2 t, J=7.5, 9H each: ethyl $CH_3$); 1.08 (s, 3H: $CH_3$); 1.17 (s, 3H: $CH_3$); 1.58 (s, 1H: OH at position 1); 1.73 (s, 3H: $CH_3$); 1.91 and 2.57 (2 mts, 1H each: $CH_2$ at position 2); 2.04 (s, 3H: $CH_3$); 2.12 and 2.23 (2 dd, J=16 and 9, 1H each: $CH_2$ at position 14); 2.30 (s, 3H: $COCH_3$); 3.88 (d, J=7, 1H: H at position 3); 4.16 and 4.32 (2 d, J=8.5, 1H each: $CH_2$ at position 20); 4.27 (d, J=1, 1H: OH at position 10); 4.40 (dd, J=11 and 7, 1H: H at position 7); 4.95 (broad d, J=10, 1H: H at position 5); 4.95 (mt, 1H: H at position 13): 5.16 (d, J=1, 1H: H at position 10); 5.60 (d, J=7, 1H: H at position 2); 7.46 (t, J=7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.60 (t, J=7.5, 1H: $OCOC_6H_5$ H at the para position); 8.09 (d, J=7.5, 2H: $OCOC_6H_5$ H at the ortho position).

## EXAMPLE 2

340 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate were dissolved in 8 $cm^3$ of a 0.1N ethanolic solution of hydrochloric acid containing 1% of water. The solution thereby obtained was stirred for 13 hours at a temperature in the region of 20° C. and then for 80 hours at 4° C., and 20 $cm^3$ of dichloromethane were added. The organic phase was separated after settling had taken place and washed successively with 3 times 5 $cm^3$ of saturated aqueous sodium hydrogen carbonate solution, dried over magnesium sulphate, filtered and concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. 300 mg of a white foam were obtained, which product was purified by chromatography on silica gel deposited on plates [gel 1 mm thick, plates is 20×20 cm, eluent: dichloromethane/methanol (95:5 by volume)] in 80-mg fractions (4 plates). After localization with UV rays of the zone corresponding to the adsorbed desired product, this zone was scraped off, and the silica collected was washed on sintered glass with 10 times 5 $cm^3$ of ethyl acetate. The filtrates were combined and concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. A white foam was obtained, which was repurified according to the same technique [3 plates; 20×20×1 mm; eluent: dichloromethane/ethyl acetate (90:10 by volume)]. 205 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate were thereby obtained in the form of a white foam, the characteristics of which were as follows:

optical rotation: $[\alpha]_{20}^{D}$=−33 (c=0.5; methanol).

$^1H$ NMR spectrum (400 MHz; $CDCl_3$; chemical shifts δ in ppm; coupling constants J in Hz): 1.23 (s, 3H: —$CH_3$); 1.25 (s, 3H: —$CH_3$); 1.39 [s, 9H: —$C(CH_3)_3$]; 1.70 (s, 1H: —OH at position 1); 1.75 (s, 3H: —$CH_3$); 1.82 and 2.72 (2 mts, 1H each: —$CH_2$ at position 6); 1.91 (s, 3H: —$CH_3$);

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2.31 (limiting AB, 2H: —$CH_2$ at position 14); 2.39 (s, 3H: —$COCH_3$); 3.33 and 3.48 (2 s, 3H each: —$OCH_3$); 3.48 (mt, 1H: OH at position 2'); 3.85 (d, J=7, 1H: —H at position 3); 3.88 (dd, J=11 and 7, 1H: —H at position 7); 4.20 and 4.33 (2d, J=8.5, 1H each: —$CH_2$ at position 20); 4.65 (mt, 1H: —H at position 2'); 4.83 (s, 1H: —H at position 10); 5.00 (broad d, J=10, 1H: —H at position 5); 5.30 (broad d, J=10, 1H: —H at position 3'); 5.47 (d, J=10, 1H: —CONH—); 5.66 (d, J=7, 1H: —H at position 2); 6.24 (broad t, J=9, 1H: —H at position 13); from 7.30 to 7.50 (mt, 5H: —$C_6H_5$ at position 3'); 7.52 [t, J=7.5, 2H: —$OCOC_8H_5$ (—H at position 3 and H at position 5)]; 7.63 [t, J=7.5, 1H: —$OCOC_6H_5$ (—H at position 4)]; 8.12 [d, J=7.5, 2H: —$OCOC_8H_5$ (—H at position 2 and H at position 6)].

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate was prepared in the following manner:

100 $cm^3$ of an ethanolic suspension of activated nickel according to Raney (obtained from 80 $cm^3$ of the approximately 50% commercial aqueous suspension by successive washing, to a pH in the region of 7, with 15 times 100 $cm^3$ of distilled water and with 5 times 100 $cm^3$ of ethanol) were added at a temperature in the region of 20° C. to a solution, maintained under an argon atmosphere and kept stirring, of 1 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-bis(methylthiomethoxy)-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate in 100 $cm^3$ of anhydrous ethanol. The reaction medium was kept stirring for 24 hours at a temperature in the region of 20° C. and then filtered through sintered glass. The sintered glass was washed with 4 times 80 $cm^3$ of ethanol, and the filtrates were combined and concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. 710 mg of a yellow foam were obtained, which product was purified by chromatography on 60 g of silica (0.063–0.2 mm) contained in a column 2.5 cm in diameter [eluent: dichloromethane/ethyl acetate (90:10 by volume)], collecting 6-$cm^3$ fractions. Fractions containing only the desired product are pooled and concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. 350 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate were thereby obtained in the form of a white foam.

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-bis(methylthiomethoxy)-9-oxo-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxy-phenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate was prepared in the following manner:

2.3 $cm^3$ of acetic acid and 7.55 $cm^3$ of acetic anhydride were added at a temperature in the region of 20° C. to a solution, maintained under an argon atmosphere and kept stirring, of 3.1 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,10β-trihydroxy-9oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate dissolved in 102 $cm^3$ of dimethyl sulphoxide. The reaction mixture was kept stirring for 7 days at a temperature in the region of 20° C., and then poured into a mixture of 500 $cm^3$ of distilled water and 250 $cm^3$ of dichloromethane. 30 $cm^3$ of saturated aqueous potassium carbonate solution were then added with efficient stirring to a pH in the region of 7. After 10 minutes of stirring, the organic phase was separated after settling had taken place and the aqueous phase was re-extracted with twice 250 $cm^3$ of dichloromethane. The organic phases were combined, washed with 250 $cm^3$ of distilled water, dried over magnesium sulphate, filtered and concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. 5.2 g of a pale yellow oil were obtained, which product was purified by chromatography on 200 g of silica (0.063–0.4 mm) contained in a column 3 cm in diameter [eluent: dichloromethane/methanol (99:1 by volume)], collecting 50-$cm^3$ fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. 1.25 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-bis (methylthiomethoxy)-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate were thereby obtained in the form of a white foam.

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,10β-trihydroxy-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate was prepared in the following manner:

A solution of 5.1 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-9-oxo-7β,10β-bis(2,2,2-trichloroethoxycarbonyloxy)-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate in a mixture of 100 $cm^3$ of methanol and 100 $cm^3$ of acetic acid was heated, with stirring and under an argon atmosphere, to a temperature in the region of 60° C., and 10 g of powdered zinc were then added. The reaction mixture was then stirred for 15 minutes at 60° C., thereafter cooled to a temperature in the region of 20° C. and filtered through sintered glass lined with Celite. The sintered glass was washed with twice 15 $cm^3$ of methanol. The filtrate was concentrated to dryness under reduced pressure (2.7 kPa) at a temperature in the region of 40° C. 50 $cm^3$ of ethyl acetate and 25 $cm^3$ of saturated aqueous sodium hydrogen carbonate solution were added to the residue. The organic phase was separated after settling had taken place and washed successively with 25 $cm^3$ of saturated aqueous sodium hydrogen carbonate solution and with 25 $cm^3$ of distilled water, then dried over magnesium sulphate, filtered through sintered glass and concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. 3.1 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,10β-trihydroxy-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate were thereby obtained in the form of a white foam.

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-9-oxo-7β,10β-bis(2,2,2-trichloroethoxy-carbonyloxy)-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxy-carbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate was prepared under the conditions described in Patent WO 94/07878, the disclosure of which is specifically incorporated by reference herein.

## EXAMPLE 3

76 mg of dicyclohexylcarbodiimide and then 8.5 mg of 4-N,N-dimethylamino)pyridine were added successively at a temperature in the region of 20° C. to a suspension containing 135 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-ethoxy-1β,13α-dihydroxy-7β-methoxy-9-oxo-11-taxene, 120 mg of (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylic acid and 50 mg of powdered 4 Å molecular sieve in 1 $cm^3$ of anhydrous toluene. The suspension obtained was stirred at

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a temperature in the region of 20° C. under an argon atmosphere for 1 hour, and then purified by direct application to a column for chromatography at atmospheric pressure on 30 g of silica (0.063–0.2 mm) contained in a column 2.5 cm in diameter (elution gradient: ethyl acetate/dichloromethane from 2:98 to 10:90 by volume), collecting 10-$cm^3$ fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. for 2 hours. 320.6 mg of a white solid were thereby obtained, which product was purified by preparative thin-layer chromatography: 10 Merck preparative silica gel $60F_{254}$ plates, thickness 0.5 mm, application in solution in dichloromethane, eluting with a methanol/dichloromethane (3:97 by volume) mixture. After elution of the zones corresponding to the main products with a methanol/dichloromethane (15:85 by volume) mixture, filtration through cotton wool and then evaporation of the solvents under reduced pressure (2.7 kPa) at a temperature in the region of 40° C., 47.7 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-ethoxy-1β,13α-dihydroxy-7β-methoxy-9-oxo-11-taxene were obtained in the form of a cream-coloured solid and 37 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-ethoxy-1β-hydroxy-7β-methoxy-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate were obtained in the form of a white foam, the characteristics of which 5-carboxylate product were as follows:

$^1H$ NMR spectrum (600 MHz; $CDCl_3$; at a temperature of 333 K; chemical shifts δ in ppm; coupling constants J in Hz): 1.09 (s, 9H: $C(CH_3)_3$; 1.19 (s, 3H: $CH_3$); 1.21 (s, 3H: $CH_3$); 1.27 (t, J=7, 3H: ethyl $CH_3$); 1.43 (s, 1H: OH at position 1); 1.62 (s, 3H: $CH_3$); 1.68 (s, 3H: $CH_3$); 1.77 and 2.63 (2 mts, 1H each: $CH_2$ at position 6); 1.86 (s, 3H: $COCH_3$); 2.13 and 2.22 (2 dd, J=16 and 9, 1H each: $CH_2$ at position 14); 3.27 (s, 3H: $OCH_3$); 3.45 and 3.68 (2 mts, 1H each: ethyl $CH_2$); 3.76 (d, J=7, 1H: H3); 3.81 (s, 3H: $ArOCH_3$); 3.85 (dd, J=11 and 7, 1H: H at position 7); 4.13 and 4.23 (2 d, J=8.5, 1H each: $CH_2$ at position 20); 4.58 (d, J=4.5, 1H: H at position 2'); 4.83 (s, 1H: H at position 10); 4.90 (broad d, J=10, 1H: H at position 5); 5.46 (d, J=4.5, 1H: H at position 3'); 5.60 (d, J=7 Hz, 1H: H2); 6.13 (broad t, J=9 Hz, 1H: H13); 6.38 (s, 1H: H5'); 6.92 (d, J=8.5, 2H: aromatic H at the ortho position with respect to $OCH_3$); from 7.30 to 7.50 (mt, 9H: aromatic H at position 3'-aromatic H at the meta position with respect to $OCH_3$ and $OCOC_6H_5$ H at the meta position); 7.59 (t, J=7.5, 1H: $OCOC_6H_5$ H at the para position); 8.03 (d, J=7.5, 2H: $OCOC_6H_5$ H at the ortho position).

A solution of 48 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-ethoxy-1β-hydroxy-7β-methoxy-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate in 0.5 $cm^3$ of ethyl acetate and 0.004 $cm^3$ of concentrated 37% hydrochloric acid was kept stirring at a temperature in the region of 20° C. for 1.5 hours under an argon atmosphere. The reaction mixture was then purified by preparative thin-layer chromatography: application of the crude reaction mixture to 5 Merck preparative silica gel $60F_{254}$ plates, thickness 0.5 mm, eluting with a methanol/dichloromethane (4:96 by volume) mixture. After elution of the zone corresponding to the main product with a methanol/dichloromethane (15:85 by volume) mixture, filtration through cotton wool and then evaporation of the solvents under reduced pressure (2.7 kPa) at a temperature in the region of 40° C., 28.5 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-ethoxy-1β-hydroxy-7β-methoxy-9-oxo-11-taxen-13α-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate were obtained in the form of an ivory-coloured foam, the characteristics of which were as follows:

$^1H$ NMR spectrum (400 MHz; $CDCl_3$; chemical shifts δ in ppm; coupling constants J in Hz): 1.22 (s, 3H: $CH_3$); 1.25 (s, 3H: $CH_3$); 1.32 (t, J=7, 3H: ethyl $CH_3$); 1.38 (s, 9H: $C(CH_3)_3$; 1.64 (s, 1H: OH at position 1); 1.73 (s, 3H: $CH_3$); 1.80 and 2.70 (2 mts, 1H each: $CH_2$ at position 6); 1.88 (s, 3H: $CH_3$); 2.30 (mt, 2H; $CH_2$ at position 14); 2.38 (s, 3H: $COCH_3$); 3.31 (s, 3H: $OCH_3$); 3.44 (unres. comp., 1H: OH at position 2'); 3.50 and 3.70 (2 mts, 1H each ethyl $OCH_2$); 3.84 (d, J=7.5, 1H: H at position 3); 3.87 (dd, J=11 and 6.5, 1H: H at position 7); 4.18 and 4.32 (2 d, J=8.5, 1H each: $CH_2$ at position 20); 4.64 (mt, 1H: H at position 2'); 4.90 (s, 1H: H at position 10); 4.98 (broad d, J=10, 1H: H at position 5); 5.28 (broad d, J=10, 1H: H at position 3'); 5.42 (d, J=10, 1H: CONH); 5.64 (d, J=7.5, 1H: H at position 2); 6.22 (broad t, J=9, 1H: H at position 13); from 7.25 to 7.45 (mt, 5H: aromatic H at position 3'); 7.50 (d, J=7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.62 (t, J=7.5, 1H: $OCOC_6H_5$ H at the para position); 8.12 (d, J=7.5, 2H: $OCOC_6H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-ethoxy-1β,13α-dihydroxy-7β-methoxy-9-oxo-11-taxene (or 10β-ethoxy-7β-methoxy-10-deacetoxybaccatin III) may be prepared in the following manner:

43 mg of sodium hydride at a concentration of 50% by weight in liquid paraffin were added portionwise to a solution, maintained under an argon atmosphere, at a temperature in the region of 0° C., of 235 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,13α-trihydroxy-10β-ethoxy-9-oxo-11-taxene in 2.5 $cm^3$ of iodomethane and 1 $cm^3$ of dimethylformamide After 30 minutes at a temperature in the region of 0° C., the reaction mixture was diluted with 40 $cm^3$ of ethyl acetate, 6 $cm^3$ of distilled water and 8 $cm^3$ of saturated aqueous ammonium chloride solution. After settling had taken place, the organic phase was separated and washed with three times 8 $cm^3$ of distilled water and then 8 $cm^3$ of saturated aqueous NaCl solution, dried over magnesium sulphate, filtered through sintered glass and concentrated to dryness under reduced pressure (2.7 kPa) at a temperature in the region of 40° C. 268 mg of a yellow solid were thereby obtained, which product was purified by chromatography at atmospheric pressure on 30 g of silica (0.063–0.2 mm) contained in a column 2.5 cm in diameter (elution gradient: ethyl acetate/dichloromethane from 0:100 to 15:85 by volume), collecting 10-$cm^3$ fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40° C. for 2 hours. 380 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-ethoxy-1β,13α-dihydroxy-7β-methoxy-9-oxo-11-taxene are thereby obtained in the form of a white powder, the characteristics of which were as follows:

$^1H$ NMR spectrum (300 MHz; $CDCl_3$ with the addition of a few drops of $CD_3OD$-$d_4$; chemical shifts δ in ppm, coupling constants J in Hz): 0.99 (s, 3H: $CH_3$); 1.09 (s, 3H: $CH_3$); 1.22 (t, J=7, 3H: ethyl $CH_3$); 1.62 (s, 3H: $CH_3$); 1.68 and 2.66 (2 mts, 1H each: $CH_26$); 2.03 (s, 3H, $CH_3$); 2.13 and 2.22 (2 dd, J=16 and 9, 1H each: $CH_2$ at position 14); 2.23 (s, 3H: $COCH_3$); 3.23 (s, 3H: $OCH_3$); from 3.40 to 3.65 (mt, 2H: ethyl $CH_2$); 3.84 (d, J=7.5, 1H: H at position 3); 3.88 (dd, J=10 and 6.5, 1H: H at position 7); 4.10 and 4.23 (2 d, J=8.5, 1H each: $CH_2$ 20); 4.75 (broad t, J=9, 1H: H at position 13); 4.90 (s, 1H: H at position 10); 4.97 (broad d, J=10, 1H: H at position 5); 5.51 (d, J=7.5, 1H: H at position 2); 7.42 (t, J=7.5, 2H: $OCOC_6H_5$ H at the meta position);

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7.53 (t, J=7.5, 1H: $OCOC_6H_5$ at the para position); 8.03 (d, J=7.5, 2H: $OCOC_6H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,13α-trihydroxy-10β-ethoxy-9-oxo-11-taxene (or 10β-ethoxy-10-deacetoxybaccatin III) was prepared in the following manner:

9 $cm^3$ of hydrogen fluoride/triethylamine complex ($3HF.Et_3N$) were added to a solution, maintained under an argon atmosphere, at a temperature in the region of 20° C., of 591 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,hydroxy-10β-ethoxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene in 6 $cm^3$ of dichloromethane. After 21 hours at a temperature in the region of 20° C., the reaction mixture was diluted with 40 $cm^3$ of dichloromethane and poured into a suspension of 40 $cm^3$ of supersaturated aqueous sodium hydrogen carbonate solution maintained at a temperature in the region of 0° C. After dilution with 10 $cm^3$ of distilled water and when settling had taken place, the aqueous phase was separated and re-extracted with twice 20 $cm^3$ of diethyl ether. The organic phases were combined, washed with 20 $cm^3$ of distilled water and 20 $cm^3$ of saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered through magnesium sulphate and concentrated to dryness under reduced pressure (2.7 kPa) at a temperature in the region of 40° C. 370 mg of a pale yellow foam were thereby obtained, which product is purified by chromatography at atmospheric pressure on 35 g of silica (0.063–0.2 mm) contained in a column 2.5 cm in diameter, eluting with a methanol/dichloromethane (2:98 by volume) mixture and collecting 15-$cm^3$ fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. for 2 hours. 236.2 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,13α-trihydroxy-10β-ethoxy-9-oxo-11-taxene were thereby obtained in the form of a white solid, the characteristics of which were as follows:

$^1H$ NMR spectrum (400 MHz; $CDCl_3$: chemical shifts δ in ppm, coupling constants J in Hz): 1.08 (s, 3H: $CH_3$); 1.19 (s, 3H: $CH_3$); 1.29 (t, J=7.5, 3H: ethyl $CH_3$); 1.38 (d, J=9, 1H: OH at position 7); 1.59 (s, 1H: OH at position 1); 1.69 (s, 3H: $CH_3$); 1.82 and 2.62 (2 mts, 1H each: $CH_2$ at position 6); 2.02 (d, J=5, 1H: OH at position 13); 2.08 (s, 3H: $CH_3$); 2.30 (s, 3H: $COCH_3$),; 2.32 (d, J=9, 2H: $CH_2$ at position 14); 3.56 and 3.67 (2 mts, 1H each: ethyl $OCH_2$); 3.98 (d, J=7, 1H: H at position 3); 4.18 and 4.33 (2 d, J=8.5 Hz, 1H each: $CH_220$); 4.30 (mt, 1H: H7); 4.90 (mt, 1H: H at position 13); 4.99 (dd, J=10 and 1.5, 1H: H at position 5); 5.05 (s, 1H: H at position 10); 5.66 (d, J=7, 1H: H at position 2); 7.49 (t, J=7.5, 2H: $OCOC_8H_5$ H at the meta position); 7.63 (t, J=7.5, 1H: $OCOC_6H_5$ H at the para position); 8.12 (d, J=7.5, 2H: $OCOC_6H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-ethoxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene (or 10β-ethoxy-10-deacetoxy-7,13-bis(triethylsilyl)baccatin III) was prepared in the following manner:

93 mg of sodium hydride at a concentration of 50% by weight of liquid paraffin were added portionwise to a solution, maintained under an argon atmosphere, at a temperature in the region of 20° C., of 1 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene in 3 $cm^3$ of iodoethane and 4 $cm^3$ of dimethylformamide. The solution was kept stirring for 17 hours at a temperature in the region of 20° C., and 93 mg of sodium hydride at a concentration of 50% by weight in liquid paraffin was then added portionwise. After 50 minutes at a temperature in the region of 20° C., the reaction mixture was diluted with 100 $cm^3$ of ethyl acetate and 10 $cm^3$ of saturated aqueous ammonium chloride solution. The organic phase was separated after settling had taken place and washed with six times 10 $cm^3$ of distilled water and then 10 $cm^3$ of saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered through sintered glass and concentrated to dryness under reduced pressure (2.7 kPa) at a temperature in the region of 40° C. 1.2 g of a yellow foam were thereby obtained, which product was purified by chromatography at atmospheric pressure on 150 g of silica (0.063–0.2 mm) contained in a column 3.5 cm in diameter, eluting with an ethyl acetateldichloromethane (2:98, then 5:95 by volume) mixture and collecting 15-$cm^3$ fractions. Fractions containing only the desired products were pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40° C. for 2 hours. 379.2 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene were thereby obtained in the form of a pale yellow foam and 430 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-ethoxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene were thereby obtained in the form of a white foam, the characteristics of which 10-β-ethoxy product were as follows:

$^1H$ NMR spectrum (400 MHz, $CDCl_3$; chemical shifts δ in ppm, coupling constants J in Hz): 0.57 and 0.70 (2 mts, 6H each; ethyl $CH_2$); 0.97 and 1.03 (2 t, J=7.5, 9H each: ethyl $CH_3$); 1.13 (s, 3H: $CH_3$); 1.20 (s, 3H: $CH_3$); 1.29 (t, J=7.5, 3H: $CH_3$ of ethoxy at position 10); 1.58 (s, 1H: OH at position 1); 1.66 (s, 3H: $CH_3$); 1.89 and 2.58 (2 mts, 1H each: $CH_2$ at position 2); 2.03 (s, 3H: $CH_3$); 2.13 and 2.23 (2 dd, J=16 and 9, 1H each $CH_2$ at position 14); 2.30 (s, 3H: $COCH_3$); 3.53 (mt, 2H: $CH_2$ of ethoxy at position 10); 3.84 (d, J=7, 1H: H at position 3); 4.15 and 4.30 (2 d, J=8.5, 1H each: $CH_2$ at position 20); 4.43 (dd, J=11 and 6.5, 1H: H at position 7); from 4.90 to 5.00 (mt, 2H: H at position 13 and H at position 5), 5.01 (s, 1H: H at position 10); 5.61 (d, J=7, 1H: H at position 2); 7.48 (t, J=7.5, 2H: $OCOC_8H_5$ H at the meta position); 7.61 (t, J=7.5, 1H: $OCOC_6H_5$ H at the para position); 8.10 (d, J=7.5, 2H: $OCOC_6H_5$ H at the ortho position).

## EXAMPLE 4

65 mg of dicyclohexylcarbodiimide and then 7 mg of 4-(N,N-dimethylaminopyridine were added successively at a temperature in the region of 20° C. to a suspension containing 115 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-(1-propyl)oxy-1β,13α-dihydroxy-7β-methoxy-9-oxo-11-taxene and 100 mg of (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylic acid in 1 $cm^3$ of anhydrous toluene. The suspension obtained was stirred at a temperature in the region of 20° C. under an argon atmosphere for 1 hour, and then purified by direct application to a column for chromatography at atmospheric pressure on 30 g of silica (0.063–0.2 mm) contained in a column 2.5 cm in diameter (elution gradient: ethyl acetate/dichloromethane from 2:98 to 10:90 by volume), collecting 10-$cm^3$ fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. for 2 hours. 276.2 mg of a white solid were thereby obtained, which product was purified by preparative thin-layer chromatography: 10 Merck preparative silica gel $60F_{254}$ plates, thickness 0.5 mm, application in solution in dichloromethane, eluting with a methanol/dichloromethane (3:97 by volume) mixture. After elution of the zones corresponding to the main products with a methanolldichloromethane (15:85 by volume) mixture, filtration through

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cotton wool and then evaporation of the solvents under reduced pressure (2.7 kPa) at a temperature in the region of 40° C., 84.8 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-(1-propyl)oxy-1β-hydroxy-7β-methoxy-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate were obtained in the form of a white foam, the characteristics of which were as follows:

$^1$H NMR spectrum (300 MHz; $CDCl_3$; chemical shifts δ in ppm; coupling constants J in Hz): 0.97 (t, J=7, 3H: propyl $CH_3$); 1.07 (s, 9H: $C(CH_3)_3$); 1.19 (s, 6H: $CH_3$); from 1.50 to 1.80 (mt, 3H: OH at position 1 and central $CH_2$ of propyl); 1.60 (s, 3H: $CH_3$); 1.70 (s, 3H: $CH_3$); 1.78 and 2.63 (2 mts, 1H each: $CH_2$ at position 6); 1.82 (unres. comp. 3H: $COCH_3$); 2.07 and 2.19 (2 dd, J=16 and 9, 1H each: $CH_2$ at position 14); 3.26 (s, 3H: $OCH_3$); 3.30 and 3.58 (2 mts, 1H each: propyl $OCH_2$); 3.73 (d, J=7.5, 1H: H at position 3); 3.81 (s, 3H: $ArOCH_3$); 3.81 (mt, 1H: H at position 7); 4.09 and 4.23 (2 d, J=8.5, 1H each: $CH_2$ at position 20); 4.57 (d, J=4.5, 1H: H at position 2'); 4.79 (s, 1H: H at position 10); 4.90 (broad d, J=10, 1H: H at position 5); 5.40 (unres. comp. 1H: H at position 3'); 5.58 (d, J=7.5, 1H: H at position 2); 6.13 (broad t, J=9, 1H: H at position 13); 6.40 (spread unres. comp 1H: H at position 5'); 6.92 (d, J=8.5, 2H: aromatic H at the ortho position with respect to $OCH_3$); from 7.30 to 7.60 (mt, 9H: aromatic H at position 3'-aromatic H at the meta position with respect to $OCH_3$ and $OCOC_6H_5$ meta H); 7.63 (t, J=7.5, 1H: $OCOC_6H_5$ H at the para position); 8.03 (d, J=7.5, 2H: $OCOC_6H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-(1-propyl)oxy-1β-hydroxy-7β-methoxy-9-oxo-11-taxen-13α-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate was prepared in the following manner:

A solution of 84 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-(1-propyl)oxy-1β-hydroxy-7β-methoxy-9-oxo-11-taxen-13α-yl(2R,4S,5R)-3-tert-butoxy-carbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate in 0.84 $cm^3$ of ethyl acetate and 0.0071 $cm^3$ of concentrated 37% hydrochloric acid was kept stirring at a temperature in the region of 20° C. for 1 hour under an argon atmosphere. The reaction mixture was then purified by preparative thin-layer chromatography: application of the crude reaction mixture to 6 Merck preparative silica gel $60F_{254}$ plates, thickness 0.5 mm, eluting with a methanol/acetonitrile/dichloromethane (3:7:90 by volume) mixture. After elution of the zone corresponding to the main product with a methanol/dichloromethane (15:85 by volume) mixture, filtration through cotton wool and then evaporation of the solvents under reduced pressure (2.7 kPa) at a temperature in the region of 40° C., 27 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-(1-propyl)oxy-1β-hydroxy-7β-methoxy-9-oxo-11-taxen-13α-yl(2R ,3S)-3tert-butoxycarbonylamino-2-hydroxy-3-phenyl-propionate were obtained in the form of a white foam, the characteristics of which are as follows:

$^1$H NMR spectrum (400 MHz; $CDCl_3$; chemical shifts δ in ppm; coupling constants J in Hz): 0.99 (t, J=7, 3H: propyl $CH_3$); 1.22 (s, 3H: $CH_3$); 1.25 (s, 3H: $CH_3$); 1.38 (s, 9H: $C(CH_3)_3$; 1.64 (s, 1H: OH at position 1); 1.69 (mt, 2H: central $CH_2$ of propyl); 1.73 (s, 3H: $CH_3$); 1.80 and 2.70 (2 mts, 1H each: $CH_2$ at position 6); 1.88 (s, 3H: $CH_3$); 2.30 (mt, 2H: $CH_2$ at position 14): 2.38 (s, 3H: $COCH_3$); 3.31 (s, 3H: $OCH_3$); 3.36 and 3.64 (2 mts, 1H each: propyl $OCH_2$); 3.44 (unres. comp. 1H: OH at position 2'); 3.84 (d, J=7.5, Hz, 1H: H at position 3); 3.87 (dd, J=11 and 6.5, 1H: H at position 7); 4.18 and 4.30 (2 d, J=8.5, 1H each: $CH_2$ at position 20); 4.64 (mt, 1H: H at position 2'); 4.89 (s, 1H: H at position 10); 4.98 (broad d, J=10, 1H: H at position 5); 5.28 (broad d, J=10, 1H: H at position 3'); 5.42 (d, J=10, 1H: CONH); 5.64 (d, J=7.5, 1H: H at position 2); 6.22 (broad t, J=9, 1H: H at position 13); from 7.25 to 7.45 (mt, 5H: aromatic H at position 3'); 7.50 (d, J=7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.61 (t, J=7.5, 1H: $OCOC_6H_5$ H at the para position); 8.12 (d, J=7.5, 2H: $OCOC_8H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-(1-propyl)oxy-1β,13α-dihydroxy-7β-methoxy-9-oxo-11-taxene (or 10β-(1-propyl)oxy-7β-methoxy-10-deacetoxybaccatin III) was prepared in the following manner:

30 mg of sodium hydride at a concentration of 50% by weight in liquid paraffin were added portionwise to a solution, maintained under an argon atmosphere, at a temperature in the region of 0° C., of 165 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,13α-trihydroxy-10β-(1-propyl)oxy-9-oxo-11-taxene in 1.7 $cm^3$ of iodomethane and 1 $cm^3$ of dimethylformamide. After 30 minutes at a temperature in the region of 0° C., the reaction mixture was diluted with 40 $cm^3$ of ethyl acetate, 5 $cm^3$ of distilled water and 7 $cm^3$ of saturated aqueous ammonium chloride solution. After settling had taken place, the organic phase was separated and washed with three times 7 $cm^3$ of distilled water and then 7 $cm^3$ of saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered through sintered glass and concentrated to dryness under reduced pressure (2.7 kPa) at a temperature in the region of 40° C. 224 mg of the yellow solid were thereby obtained, which product was purified by chromatography at atmospheric pressure on 20 g of silica (0.063–0.2 mm) contained in a column 2.5 cm in diameter (elution gradient: ethyl acetate/dichloromethane from 0:100 to 15:85 by volume), collecting 10-$cm^3$ fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40° C. for 2 hours. 117.5 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-10β-(1-propyl) oxy-1β,13α-dihydroxy-7β-methoxy-9-oxo-11-taxene were thereby obtained in the form of a white foam, the characteristics of which were as follows:

$^1$H NMR spectrum (300 MHz; $CDCl_3$; chemical shifts δ in ppm, coupling constants J in Hz): 0.98 (t, J=7, 3H: propyl $CH_3$); 1.05 (s, 3H: $CH_3$), 1.19 (s, 3H: $CH_3$); from 1.60 to 1.80 (mt, 2H: central $CH_2$ of propyl); from 1.65 to 1.85 and 2.66 (2 mts, 1H each: $CH_2$ at position 6); 1.72 (s, 3H: $CH_3$); 2.10 (s, 3H: $CH_3$); from 2.05 to 2.35 (mt, 2H: $CH_2$ at position 14); 2.28 (s, 3H: $COCH_3$); 3.32 (s, 3H: $OCH_3$); 3.45 and 3.65 (2 mts, 1H each: propyl $OCH_2$); 3.92 (d, J=7.5, 1H: H3); 3.93 (dd, J=11 and 6, 1H: H at position 7); 4.16 and 4.32 (2 d, J=8.5, 1H each: $CH_2$ at position 20); 4.90 (mt, 1H: H at position 13); 4.94 (s, 1H: H at position 10); 5.03 (broad d, J=10, 1H: H at position 5); 5.60 (d, J=7.5, 1H: H at position 2); 7.48 (t, J=7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.62 (t, J=7.5, 1H: $OCOC_6H_5$ H at the para position); 8.11 (d, J=7.5, 2H: $OCOC_8H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,13α-trihydroxy-10β-(1-propyl)oxy-9-oxo-11-taxene (or 10β-(1-propyl)oxy-10-deacetoxybaccatin III) was prepared in the following manner:

8.75 $cm^3$ of hydrogen fluoride/triethylamine complex ($3HF.Et_3N$) were added to a solution, maintained under an argon atmosphere, at a temperature in the region of 20° C., of 585 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-(1-propyl)oxy-9-oxo-7β,13α-bis

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(triethylsilyloxy)-11-taxene in 6 $cm^3$ of dichloromethane. After 24 hours at a temperature in the region of 20° C., the reaction mixture was diluted with 30 $cm^3$ of dichloromethane and poured into a suspension of 30 $cm^3$ of supersaturated aqueous sodium hydrogen carbonate solution maintained at a temperature in the region of 0° C. After dilution with 10 $cm^3$ of distilled water and when settling had taken place, the aqueous phase was separated and re-extracted with twice 20 $cm^3$ of diethyl ether. The organic phases were combined, washed with 20 $cm^3$ of distilled water and 20 $cm^3$ of saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered through magnesium sulphate and concentrated to dryness under reduced pressure (2.7 kPa) at a temperature in the region of 40° C. 500 mg of a pale yellow foam were thereby obtained, which product was purified by chromatography at atmospheric pressure on 40 g of silica (0.063–0.2 mm) contained in a column 2.5 cm in diameter, eluting with a methanol/dichloromethane (2:98 by volume) mixture and collecting 15-$cm^3$ fractions. Fractions containing only the desired product were pooled and concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. for 2 hours. 373.8 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,7β,13α-trihydroxy-10β-(1-propyl)oxy-9-oxo-11-taxene were thereby obtained in the form of a white solid, the characteristics of which were as follows:

$^1H$ NMR spectrum (300 MHz; $CDCl_3$; chemical shifts δ in ppm, coupling constants J in Hz): 0.95 (t, J=7, 3H: propyl $CH_3$); 1.06 (s, 3H: $CH_3$); 1.22 (s, 3H: $CH_3$); 1.45 (d, J=7.5, 1H: OH at position 7); from 1.60 to 1.80 (mt, 2H: central $CH_2$ of propyl); 1.67 (s, 3H: $CH_3$); 1.83 and 2.62 (2 mts, 1H each: $CH_2$ at position 6); 2.05 (s, 3H: $CH_3$); 2.05 (mt, 1H: OH at position 13); 2.27 (limiting AB, 2H: $CH_2$ at position 4); 2.28 (s, 3H: $COCH_3$); 3.40 and 3.57 (2 mts, 1H each: propyl $OCH_2$); 3.97 (d, J=7.5, 1H: H at position 3); 4.15 and 4.30 (2 d, J=8.5, 1H each: $CH_2$ at position 20); 4.28 (mt, 1H: H at position 7); 4.90 (mt, 1H: H at position 13); 4.98 (broad d, J=10, 1H: H at position 5); 5.03 (s, 1H: H at position 10); 5.65 (d, J=7.5, 1H: H at position 2); 7.50 (t, J=7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.60 (t, J=7.5, 1H: $OCOC_6H_5$ H at the para position); 8.00 (d, J=7.5, 2H: $OCOC_6H_5$ H at the ortho position).

4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-(1-propyl)oxy-9-oxo-7β,13α-bis(triethyl-silyloxy)-11-taxene (or 10β-(1-propyl)oxy-10-deacetoxy-7,13-bis (triethylsilyl)baccatin III) was prepared in the following manner:

93 mg of sodium hydride at a concentration of 50% by weight in liquid paraffin were added portionwise to a solution, maintained under an argon atmosphere, at a temperature in the region of 20° C., of 1 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene in 3 $cm^3$ of iodoethane and 4 $cm^3$ of dimethylformamide. The solution was kept stirring for 19 hours at a temperature in the region of 20° C., and 93 mg of sodium hydride at a concentration of 50% by weight in liquid paraffin were then added portionwise. After 3 hours at a temperature in the region of 20° C., the reaction mixture was diluted with 100 $cm^3$ of ethyl acetate and 10 $cm^3$ of saturated aqueous ammonium chloride solution. The organic phase was separated after settling had taken place and washed with six times 10 $cm^3$ of distilled water and then 10 $cm^3$ of saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered through sintered glass and concentrated to dryness under reduced pressure (2.7 kPa) at a temperature in the region of 40° C. 1.32 g of a pale yellow foam were thereby obtained, which product was purified by chromatography at atmospheric pressure on 150 g of silica (0.063–0.2 mm) contained in a column 3.5 cm in diameter, eluting with an ethyl acetate/dichloromethane (2:98, then 5:95 by volume) mixture and collecting 15-$cm^3$ fractions. Fractions containing only the desired products were pooled and concentrated to dryness under reduced pressure (0.27 kPa) at 40° C. for 2 hours. 376.3 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β,10β-dihydroxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene were thereby obtained in the form of a pale yellow foam and 395.3 mg of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-10β-(1-propyl) oxy-9-oxo-7β,13α-bis(triethylsilyloxy)-11-taxene were thereby obtained in the form of a pale yellow foam, the characteristics of which were as follows:

$^1H$ NMR spectrum (400 MHz; $CDCl_3$; chemical shifts δ in ppm, coupling constants J in Hz); 0.57 and 0.70 (2 mts, 6H each: ethyl $CH_2$); 0.94 and 1.03 (2 t, J=7.5, 9H each: ethyl $CH_3$); 0.94 (t, J=7.5, 3H: propyl $CH_3$); 1.14 (s, 3H: $CH_3$); 1.21 (s, 3H: $CH_3$); 1.67 (s, 3H: $CH_3$); 1.69 (mt, 2H: central $CH_2$ of propyl); 1.88 and 2.48 (2 mts, 1H each: $CH_2$ at position 6); 2.03 (s, 3H: $CH_3$); 2.13 and 2.23 (2 dd, J=16 and 9, 1H each: $CH_2$ at position 14); 2.30 (s, 3H: $COCH_3$); 3.40 (mt, 2H: propyl $OCH_2$); 3.84 (d, J=7.5, 1H: H at position 3); 4.16 and 4.30 (2 d, J=8.5, 1H each: $CH_2$ at position 20); 4.44 (dd, J=11 and 6.5, 1H: H at position 7); 4.96 (broad d, J=10 Hz, 1H: H5); 4.97 (s, 1H: H 10), 4.99 (broad t, J=9 Hz, 1H: H at position 13); 5.62 (d, J=7.5, 1H: H at position 2); 7.48 (t, J=7.5, 2H: $OCOC_6H_5$ H at the meta position); 7.60 (t, J=7.5, 1H: $OCOC_6H_5$ H at the para position); 8.10 (d, J=7.5, 2H: $OCOC_6H_5$ H at the ortho position).

The new products of general formula (I) in which Z represents a radical of general formula (II) manifest significant inhibitory activity with respect to abnormal cell proliferation, and possess therapeutic properties permitting the treatment of patients having pathological conditions associated with abnormal cell proliferation. The pathological conditions include the abnormal cell proliferation of malignant or non-malignant cells of various tissues and/or organs, comprising, without implied limitation, muscle, bone or connective tissue, the skin, brain, lungs, sex organs, the lymphatic or renal systems, mammary or blood cells, liver, the digestive system, pancreas and thyroid or adrenal glands. These pathological conditions can also include psoriasis, solid tumours, cancers of the ovary, breast, brain, prostate, colon, stomach, kidney or testicles, Kaposi's sarcoma, cholangiocarcinoma, choriocarcinoma, neuroblastoma, Wilms' tumour, Hodgkin's disease, melanoma, multiple myeloma, chronic lymphocytic leukaemia and acute or chronic granulocytic lymphoma.

The new products according to the invention are especially useful for the treatment of cancer of the ovary. The products according to the invention may be used to prevent or delay the appearance or reappearance of the pathological conditions, or to treat these pathological conditions.

The products according to the invention may be administered to a patient according to different dosage forms suited to the chosen administration route, which is preferably the parenteral route. Parenteral administration comprises intravenous, intraperitoneal, intramuscular or subcutaneous administration. Intraperitoneal or intravenous administration is more especially preferred.

The present invention also comprises pharmaceutical compositions containing at least one product of general formula (I), in a sufficient amount suitable for use in human or veterinary therapy. The compositions may be prepared

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according to the customary methods, using one or more pharmaceutically acceptable adjuvants, vehicles or excipients. Suitable vehicles include diluents, sterile aqueous media and various non-toxic solvents. Preferably, the compositions take the form of aqueous solutions or suspensions, injectable solutions which can contain emulsifying agents, colourings, preservatives or stabilizers. However, the compositions can also take the form of tablets, pills, powders or granules which can be administered orally.

The choice of adjuvants or excipients may be determined by the solubility and the chemical properties of the product, the particular mode of administration and good pharmaceutical practice.

For parenteral administration, sterile, aqueous or non-aqueous solutions or suspensions are used. For the preparation of non-aqueous solutions or suspensions, natural vegetable oils such as olive oil, sesame oil or liquid petroleum, or injectable organic esters such as ethyl oleate, may be used. The sterile aqueous solutions can consist of a solution of a pharmaceutically acceptable salt dissolved in water. The aqueous solutions are suitable for intravenous administration provided the pH is appropriately adjusted and the solution is made isotonic, for example with a sufficient amount of sodium chloride or glucose. The sterilization may be carried out by heating or by any other means which does not adversely affect the composition.

It is clearly understood that all the products participating in the compositions according to the invention must be pure and non-toxic in the amounts used.

The compositions can contain at least 0.01% of therapeutically active product. The amount of active product in a composition is such that a suitable dosage can be prescribed. Preferably, the compositions are prepared in such a way that a single dose contains from 0.01 to 1000 mg approximately of active product for parenteral administration.

The therapeutic treatment may be performed concurrently with other therapeutic treatments including antineoplastic drugs, monoclonal antibodies, immunotherapy or radiotherapy or biological response modifiers. The response modifiers include, without implied limitation, lymphokines and cytokines such as interleukins, interferons (α, β or δ) and TNF.

Other chemotherapeutic agents which are useful in the treatment of disorders due to abnormal cell proliferation include, without implied limitation, alkylating agents, for instance nitrogen mustards such as mechlorethamine, cyclophosphamide, melphalan and chlorambucil, alkyl sulphonates such as busulfan, nitrosoureas such as carmustine, lomustine, semustine and streptozocin, triazenes such as dacarbazine, antimetabolites such as folic acid analogues, for instance methotrexate, pyrimidine analogues such as fluorouracil and cytarabine, purine analogues such as mercaptopurine and thioguanine, natural products, for instance vinca alkaloids such as vinblastine, vincristine and vindesine, epipodophyllotoxins such as etoposide and teniposide, antibiotics such as dactinomycin, daunorubicin, doxorubicin, bleomycin, plicamycin and mitomycin, enzymes such as L-asparaginase, various agents such as coordination complexes of platinum, for instance cisplatin, substituted ureas such as hydroxyurea, methylhydrazine derivatives such as procarbazine, adrenocortical suppressants such as mitotane and aminoglutethimide, hormones and antagonists such as adrenocorticosteroids such as prednisone, progestins such as hydroxyprogesterone caproate, methoxyprogesterone acetate and megestrol acetate, oestrogens such as diethylstilboestrol and ethynyloestradiol, antioestrogens such as tamoxifen, and androgens such as testosterone propionate and fluoxymesterone.

The doses used for carrying out the methods according to the invention are those which permit a prophylactic treatment or a maximum therapeutic response. The doses vary according to the administration form, the particular product selected and features distinctive to the subject to be treated. In general, the doses are those which are therapeutically effective for the treatment of disorders due to abnormal cell proliferation.

The products according to the invention may be administered as often as necessary to obtain the desired therapeutic effect. Some patients may respond rapidly to relatively high or low doses, and then require low or zero maintenance doses. Generally, low doses will be used at the beginning of the treatment and, if necessary, increasingly stronger doses will be administered until an optimum effect is obtained.

For other patients, it may be necessary to administer maintenance doses 1 to 8 times a day, and preferably 1 to 4 times, according to the physiological requirements of the patient in question. It is also possible that some patients may require the use of only one to two daily administrations.

In man, the doses generally range from 0.01 to 200 mg/kg. For intraperitoneal administration, the doses will generally range from 0.1 to 100 mg/kg, preferably from 0.5 to 50 mg/kg and still more specifically from 1 to 10 mg/kg. For intravenous administration, the doses generally range from 0.1 to 50 mg/kg, preferably from 0.1 to 5 mg/kg and still more specifically from 1 to 2 mg/kg. It is understood that, in order to choose the most suitable dosage, account should be taken of the administration route, the patient's weight, general state of health and age and all factors which may influence the efficacy of the treatment.

The example which follows illustrates a composition according to the invention.

## EXAMPLE

40 mg of the product obtained in Example 1 are dissolved in 1 $cm^3$ of Emulphor EL 620 and 1 $cm^3$ of ethanol, and the solution is then diluted by adding 18 $cm^3$ of physiological saline. The composition is administered by perfusion over 1 hour by introduction in physiological solution.

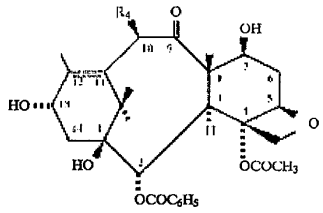
We claim:

1. 4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate.

2. A pharmaceutical composition comprising at least the product according to claim 1 in combination with one or more pharmaceutically acceptable diluents or adjuvants and optionally one or more compatible and pharmacologically active compounds.

3. A method comprising the step of etherifying selectively at position 7 a compound of the formula (XIV):

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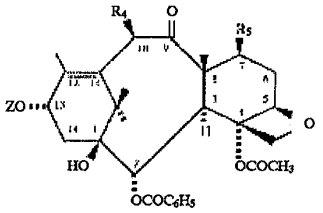
(XIV)

wherein $R_4$ represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain,

with a compound of the formula (XV):

$$R'_5—X_2 \quad \text{(XV)}$$

wherein $R'_5$ represents a radical such that $R'_5$—O represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain and $X_2$ represents a reactive ester residue or a halogen atom, to produce a compound of the formula (I):



(I)

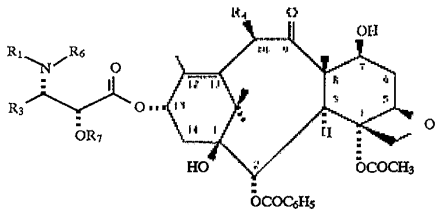
wherein Z is hydrogen, $R_4$ is as defined above, and $R_5$ is identical to $R'_5$ as defined above.

4. A method comprising the step of reacting a product of the formula (XV):

$$R'_5—X_2 \quad \text{(XV)}$$

wherein $R'_5$ represents a radical such that $R'_5$—O represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain, and $X_2$ represents a reactive ester residue or a halogen atom,

with a compound of the formula (XIX):



(XIX)

wherein $R_1$ represents a benzoyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms, alkoxy radicals containing 1 to 4 carbon atoms, and trifluoromethyl radicals,

a thenoyl radical,

a furoyl radical, or

a radical $R_2$—O—CO— in which $R_2$ represents:

an alkyl radical containing 1 to 8 carbon atoms, an alkenyl radical containing 2 to 8 carbon atoms, an alkynyl radical containing 3 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a cycloalkenyl radical containing 4 to 6 carbon atoms or a bicycloalkyl radical containing 7 to 10 carbon atoms, these radicals being optionally substituted with one or more substituents selected from halogen atoms; hydroxyl radicals; alkoxy radicals containing 1 to 4 carbon atoms; dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms; piperidino radicals; morpholino radicals; 1-piperazinyl radicals optionally substituted at position 4 with an alkyl radical containing 1 to 4 carbon atoms or with a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms; cycloalkyl radicals containing 3 to 6 carbon atoms; cycloalkenyl radicals containing 4 to 6 carbon atoms; phenyl radicals optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms and alkoxy radicals containing 1 to 4 carbon atoms; cyano radicals; carboxyl radicals; and alkoxycarbonyl radicals in which the alkyl portion contains 1 to 4 carbon atoms,

a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms; alkyl radicals containing 1 to 4 carbon atoms; and alkoxy radicals containing 1 to 4 carbon atoms,

a 5-membered aromatic heterocyclic radical, or

a saturated heterocyclic radical containing 4 to 6 carbon atoms, optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms,

$R_3$ represents an unbranched or branched alkyl radical containing 1 to 8 carbon atoms, an unbranched or branched alkenyl radical containing 2 to 8 carbon atoms, an unbranched or branched alkynyl radical containing 2 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl, alkenyl, alkynyl, aryl, aralkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, formyl, acyl, acylamino, aroylamino, alkoxycarbonylamino, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, cyano, nitro and trifluoromethyl radicals, or

a 5-membered aromatic heterocycle containing one or more identical or different hetero atoms selected from nitrogen, oxygen and sulphur atoms and optionally substituted with one or more identical or different substituents selected from halogen atoms, alkyl, aryl, amino, alkylamino, dialkylamino, alkoxycarbonylamino, acyl, arylcarbonyl, cyano, carboxyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl and alkoxycarbonyl radicals,

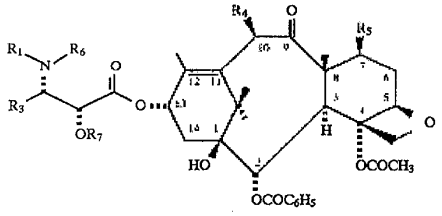
with the proviso that, in the substituents of the phenyl, α- or β-naphthyl and aromatic heterocyclic radicals in the definitions of $R_2$ and $R_3$, the alkyl radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms, and the alkenyl and alkynyl radicals contain 2 to 8 carbon atoms, and the aryl radicals are phenyl or α- or β-naphthyl radicals,

$R_4$ represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain

either $R_6$ represents a hydrogen atom and $R_7$ represents a group protecting the hydroxyl function, or $R_6$ and $R_7$ together form a saturated 5- or 6-membered heterocycle,

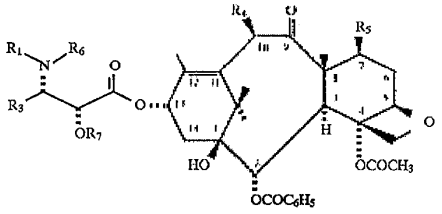
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to form a compound of the formula (V):



wherein $R_5$ represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain and $R_1$, $R_3$, $R_4$, $R_6$, and $R_7$ are as defined above.

5. A method comprising the step of replacing with hydrogen atom(s) group(s) $R_6$ and $R_7$ in a compound of the formula (V):



wherein:

$R_1$ represents a benzoyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms, alkoxy radicals containing 1 to 4 carbon atoms, and trifluoromethyl radicals,

a thenoyl radical,

a furoyl radical, or

a radical $R_2$—O—CO— in which $R_2$ represents:

an alkyl radical containing 1 to 8 carbon atoms, an alkenyl radical containing 2 to 8 carbon atoms, an alkynyl radical containing 3 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a cycloalkenyl radical containing 4 to 6 carbon atoms or a bicycloalkyl radical containing 7 to 10 carbon atoms, these radicals being optionally substituted with one or more substituents selected from halogen atoms; hydroxyl radicals; alkoxy radicals containing 1 to 4 carbon atoms; dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms; piperidino radicals; morpholino radicals; 1-piperazinyl radicals optionally substituted at position 4 with an alkyl radical containing 1 to 4 carbon atoms or with a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms; cycloalkyl radicals containing 3 to 6 carbon atoms; cycloalkenyl radicals containing 4 to 6 carbon atoms; phenyl radicals optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms and alkoxy radicals containing 1 to 4 carbon atoms; cyano radicals; carboxyl radicals; and alkoxycarbonyl radicals in which the alkyl portion contains 1 to 4 carbon atoms,

a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms; alkyl radicals containing 1 to 4 carbon atoms; and alkoxy radicals containing 1 to 4 carbon atoms,

a 5-membered aromatic heterocyclic radical, or

a saturated heterocyclic radical containing 4 to 6 carbon atoms, optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms,

$R_3$ represents an unbranched or branched alkyl radical containing 1 to 8 carbon atoms, an unbranched or branched alkenyl radical containing 2 to 8 carbon atoms, an unbranched or branched alkynyl radical containing 2 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl, alkenyl, alkynyl, aryl, aralkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, formyl, acyl, acylamino, aroylamino, alkoxycarbonylamino, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, cyano, nitro and trifluoromethyl radicals, or

a 5-membered aromatic heterocycle containing one or more identical or different hetero atoms selected from nitrogen, oxygen and sulphur atoms and optionally substituted with one or more identical or different substituents selected from halogen atoms, alkyl, aryl, amino, alkylamino, dialkylamino, alkoxycarbonylamino, acyl, arylcarbonyl, cyano, carboxyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl and alkoxycarbonyl radicals,

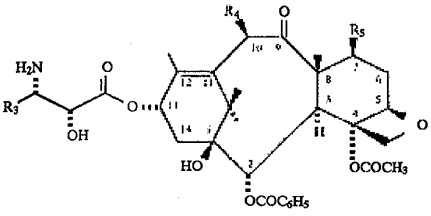
with the proviso that, in the substituents of the phenyl, α- or β-naphthyl and aromatic heterocyclic radicals in the definitions of $R_2$ and $R_3$, the alkyl radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms, and the alkenyl and alkynyl radicals contain 2 to 8 carbon atoms, and the aryl radicals are phenyl or α- or β-naphthyl radicals,

$R_4$ represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain

$R_5$ represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain and

either $R_6$ represents a hydrogen atom and $R_7$ represents a group protecting the hydroxyl function, or $R_6$ and $R_7$ together form a saturated 5- or 6-membered heterocycle,

by treating the compound of formula (V) with an organic or inorganic acid, optionally in an organic solvent to obtain a compound of the formula (VII):



(VII)

wherein $R_3$, $R_4$, and $R_5$ are as defined above.

6. A process for the preparation of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate, said process comprising:

converting 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-bis(methylthiomethoxy)-9-oxo-11-

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taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate to said 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate.

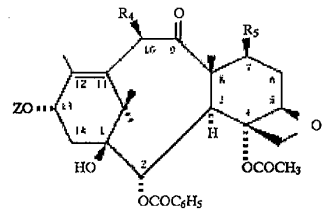
7. A process for the preparation of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate, said process comprising:

(a) reacting 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-7β,10β-trihydroxy-9-oxo-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate with dimethyl sulfoxide in the presence of acetic anhydride and acetic acid to obtain 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-bis(methylthiomethoxy)-9-oxo-11-taxen-13α-yl (2R,4S,5R)-3-tert-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate;

(b) reacting the product obtained in (a) with activated Raney nickel to obtain 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl (2R,4S,5R)-3-tertbutoxy-carbonyl-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate; and

(c) reacting the product obtained in (b) with an acid to obtain 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate.

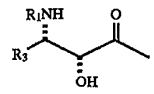
8. A process for preparing a taxoid of the following formula (I):




(I)

in which:

Z represents a radical of formula (II):




(II)

in which:

$R_1$ represents a benzoyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms, alkoxy radicals containing 1 to 4 carbon atoms, and trifluoromethyl radicals,

a thenoyl radical,

a furoyl radical, or

a radical $R_2$—O—CO— in which $R_2$ represents:

an alkyl radical containing 1 to 8 carbon atoms, an alkenyl radical containing 2 to 8 carbon atoms, an alkynyl radical containing 3 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a cycloalkenyl radical containing 4 to 6 carbon atoms or a bicycloalkyl radical containing 7 to 10 carbon atoms, these radicals being optionally substituted with one or more substituents selected from halogen atoms; hydroxyl radicals; alkoxy radicals containing 1 to 4 carbon atoms; dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms; piperidino radicals; morpholino radicals; 1-piperazinyl radicals optionally substituted at position 4 with an alkyl radical containing 1 to 4 carbon atoms or with a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms; cycloalkyl radicals containing 3 to 6 carbon atoms; cycloalkenyl radicals containing 4 to 6 carbon atoms; phenyl radicals optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms and alkoxy radicals containing 1 to 4 carbon atoms; cyano radicals; carboxyl radicals; and alkoxycarbonyl radicals in which the alkyl portion contains 1 to 4 carbon atoms,

a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms; alkyl radicals containing 1 to 4 carbon atoms; and alkoxy radicals containing 1 to 4 carbon atoms,

a 5-membered aromatic heterocyclic radical, or

a saturated heterocyclic radical containing 4 to 6 carbon atoms, optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms,

$R_3$ represents an unbranched or branched alkyl radical containing 1 to 8 carbon atoms, an unbranched or branched alkenyl radical containing 2 to 8 carbon atoms, an unbranched or branched alkynyl radical containing 2 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a phenyl or α- or β-naphthyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl, alkenyl, alkynyl, aryl, aralkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, formyl, acyl, acylamino, aroylamino, alkoxycarbonylamino, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, cyano, nitro and trifluoromethyl radicals, or

a 5-membered aromatic heterocycle containing one or more identical or different hetero atoms selected from nitrogen, oxygen and sulphur atoms and optionally substituted with one or more identical or different substituents selected from halogen atoms, alkyl, aryl, amino, alkylamino, dialkylamino, alkoxycarbonylamino, acyl, arylcarbonyl, cyano, carboxyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl and alkoxycarbonyl radicals,

with the proviso that, in the substituents of the phenyl, α- or β-naphthyl and aromatic heterocyclic radicals in the definitions of $R_2$ and $R_3$, the alkyl radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms, and the alkenyl and alkynyl radicals contain 2 to 8 carbon atoms, and the aryl radicals are phenyl or α- or β-naphthyl radicals,

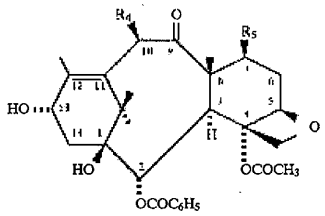
$R_4$ represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain and

$R_5$ represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain,

said process comprising:

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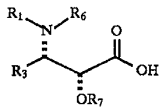
esterifying a product of formula (III):



(III)

in which $R_4$ and $R_5$ are defined as above

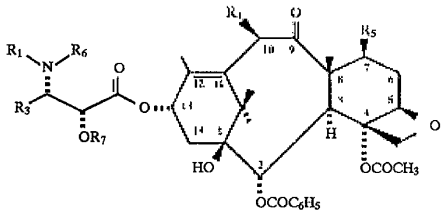
with an acid of formula (IV):



(IV)

in which $R_1$ and $R_3$ are defined as above, and either $R_6$ represents a hydrogen atom and $R_7$ represents a group protecting the hydroxyl function, or $R_6$ and $R_7$ together form a saturated 5- or 6-membered heterocycle, or

with a derivative of said acid, to obtain an ester of formula (V):

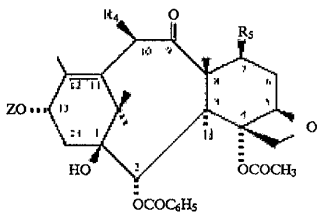


(V)

in which $R_1$, $R_3$, $R_4$, $R_5$, $R_6$ and $R_7$ are defined as above, and

replacing the protective group(s) of said ester of formula (V), represented by $R_7$ or $R_6$ and $R_7$ together, by hydrogen atoms.

9. A process for preparing a new taxoid of the following formula (I):



(I)

in which:

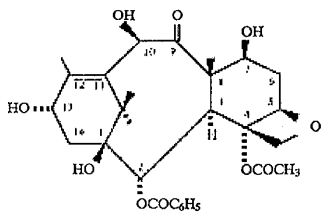
Z represents a hydrogen atom,

$R_4$ represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain and

$R_5$ represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain,

said process comprising:

treating 10-deacetylbaccatin III of formula (IX):

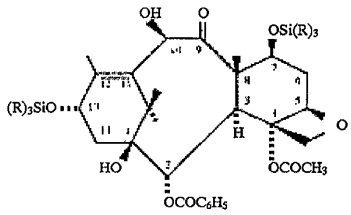


(IX)

with a silyl halide of formula:

$$(R)_3—Si—Hal \qquad (X)$$

in which the symbols R, which may be identical or different, represent an alkyl radical containing 1 to 6 carbon atoms, optionally substituted with a phenyl radical, a cycloalkyl radical containing 3 to 6 carbon atoms or a phenyl radical, to obtain a product of formula (XI):



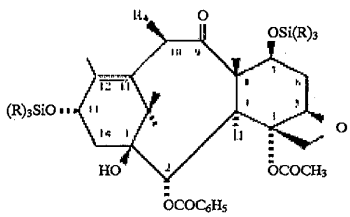
(XI)

in which R is defined as above,

treating said product of formula (XI) with a product of formula:

$$R'_4—X_1 \qquad (XII)$$

in which $R'_4$ represents a radical such that $R'_4$—O is identical to $R_4$ defined above and $X_1$ represents a halogen atom or a reactive ester residue, to obtain a product of formula (XIII):

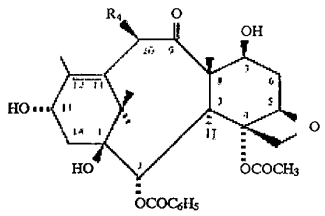


(XIII)

in which R and $R_4$ are defined as above,

replacing the silyl protective groups of said product of formula (XIII) by hydrogen atoms to obtain a product of formula (XIV):

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(XIV)

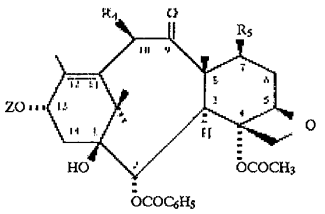
in which $R_4$ is defined as above, and

etherifying said compound of formula (XIV) selectively at position 7 with a product of formula (XV):

$$R'_5—X_2 \quad \text{(XV)}$$

in which $R'_5$ represents a radical such that $R'_5—O$ is identical to $R_5$ defined as above and $X_2$ represents a reactive ester residue or a halogen atom, to give the product of formula (I) in which Z represents a hydrogen atom.

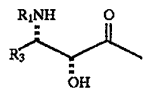
**10**. A process for preparing a taxoid of the following formula (I):



(I)

in which:

Z represents a radical of formula (II):



(II)

in which:

$R_1$ represents a benzoyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms, alkoxy radicals containing 1 to 4 carbon atoms, and trifluoromethyl radicals,

a thenoyl radical,

a furoyl radical, or

a radical $R_2—O—CO—$ in which $R_2$ represents:

an alkyl radical containing 1 to 8 carbon atoms, an alkenyl radical containing 2 to 8 carbon atoms, an alkynyl radical containing 3 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a cycloalkenyl radical containing 4 to 6 carbon atoms or a bicycloalkyl radical containing 7 to 10 carbon atoms, these radicals being optionally substituted with one or more substituents selected from halogen atoms; hydroxyl radicals; alkoxy radicals containing 1 to 4 carbon atoms; dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms; piperidino radicals; morpholino radicals; 1-piperazinyl radicals optionally substituted at position 4 with an alkyl radical containing 1 to 4 carbon atoms or with a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms; cycloalkyl radicals containing 3 to 6 carbon atoms; cycloalkenyl radicals containing 4 to 6 carbon atoms; phenyl radicals optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms and alkoxy radicals containing 1 to 4 carbon atoms; cyano radicals; carboxyl radicals; and alkoxycarbonyl radicals in which the alkyl portion contains 1 to 4 carbon atoms,

a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms; alkyl radicals containing 1 to 4 carbon atoms; and alkoxy radicals containing 1 to 4 carbon atoms,

a 5-membered aromatic heterocyclic radical, or

a saturated heterocyclic radical containing 4 to 6 carbon atoms, optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms,

$R_3$ represents an unbranched or branched alkyl radical containing 1 to 8 carbon atoms, an unbranched or branched alkenyl radical containing 2 to 8 carbon atoms, an unbranched or branched alkynyl radical containing 2 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a phenyl or α- or β-naphthyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl, alkenyl, alkynyl, aryl, aralkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, formyl, acyl, acylamino, aroylamino, alkoxycarbonylamino, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, cyano, nitro and trifluoromethyl radicals, or

a 5-membered aromatic heterocycle containing one or more identical or different hetero atoms selected from nitrogen, oxygen and sulphur atoms and optionally substituted with one or more identical or different substituents selected from halogen atoms, alkyl, aryl, amino, alkylamino, dialkylamino, alkoxycarbonylamino, acyl, arylcarbonyl, cyano, carboxyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl and alkoxycarbonyl radicals,

with the proviso that, in the substituents of the phenyl, α- or β-naphthyl and aromatic heterocyclic radicals in the definitions of $R_2$ and $R_3$, the alkyl radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms, and the alkenyl and alkynyl radicals contain 2 to 8 carbon atoms, and the aryl radicals are phenyl or α- or β-naphthyl radicals,

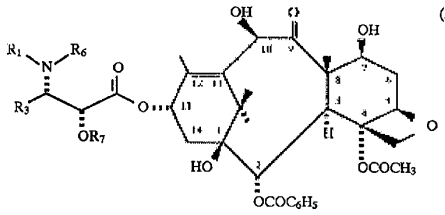
$R_4$ represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain and

$R_5$ represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain,

said process comprising:

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treating a product of formula (XVI):

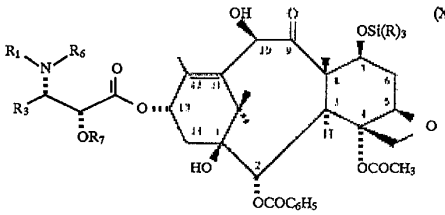


(XVI)

in which $R_1$, $R_3$, $R_6$ and $R_7$ are defined as above, with a product of formula (X):

$$(R)_3Si—Hal \quad (X)$$

in which the symbols R, which may be identical or different, represent an alkyl radical containing 1 to 6 carbon atoms, optionally substituted with a phenyl radical, or a cycloalkyl radical containing 3 to 6 carbon atoms or a phenyl radical, to obtain a product of formula (XVII):



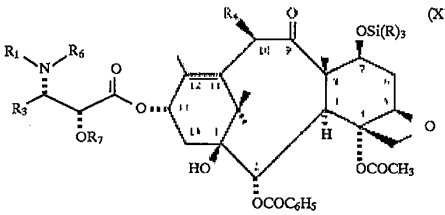
(XVII)

in which R, $R_1$, $R_3$, $R_6$ and $R_7$ are defined as above,

functionalizing said compound of formula (XVII) at position 10 with a product of formula:

$$R'_4—X_1 \quad (XII)$$

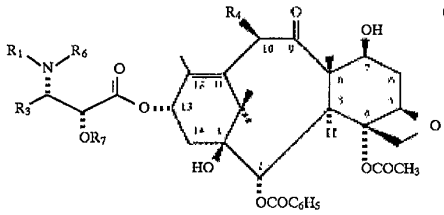
in which $R'_4$ represents a radical such that $R'_4$—O is identical to $R_4$ defined as above and $X_1$ represents a halogen atom or a reactive ester residue, to give a product of formula (XVIII):



(XVIII)

in which R, $R_1$, $R_3$, $R_4$, $R_6$ and $R_7$ are defined as above,

replacing the silyl protective group of said product of formula (XVIII) by a hydrogen atom to give a product of formula (XIX):



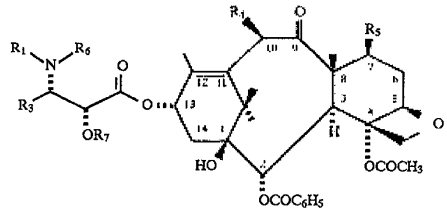
(XIX)

in which $R_1$, $R_3$, $R_4$, $R_6$ and $R_7$ are defined as above which, when reacted with a product of formula (XV):

$$R'_5—X_2 \quad (XV)$$

in which $R'_5$ represents a radical such that $R'_5O$ is identical to $R_5$ defined above and $X_2$ represents a reactive ester residue or a halogen atom,

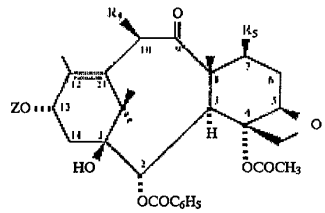
yields the product of formula (V):



(V)

in which $R_1$, $R_3$, $R_4$, $R_5$, $R_6$ and $R_7$ are defined as above and replacing the protective group(s) of formula (V) with one or two hydrogen atoms to give a product of formula (I) in which Z represents a radical of formula (II).

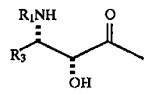
11. A process for preparing a taxoid of the following formula (I):



(I)

in which:

Z represents a hydrogen atom or a radical of formula (II):



(II)

in which:

$R_1$ represents a benzoyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms, alkoxy radicals containing 1 to 4 carbon atoms, and trifluoromethyl radicals,

a thenoyl radical,

a furoyl radical, or

a radical $R_2$—O—CO— in which $R_2$ represents:

an alkyl radical containing 1 to 8 carbon atoms, an alkenyl radical containing 2 to 8 carbon atoms, an

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alkynyl radical containing 3 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a cycloalkenyl radical containing 4 to 6 carbon atoms or a bicycloalkyl radical containing 7 to 10 carbon atoms, these radicals being optionally substituted with one or more substituents selected from halogen atoms; hydroxyl radicals; alkoxy radicals containing 1 to 4 carbon atoms; dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms; piperidino radicals; morpholino radicals; 1-piperazinyl radicals optionally substituted at position 4 with an alkyl radical containing 1 to 4 carbon atoms or with a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms; cycloalkyl radicals containing 3 to 6 carbon atoms; cycloalkenyl radicals containing 4 to 6 carbon atoms; phenyl radicals optionally substituted with one or more atoms or radicals selected from halogen atoms, alkyl radicals containing 1 to 4 carbon atoms and alkoxy radicals containing 1 to 4 carbon atoms; cyano radicals; carboxyl radicals; and alkoxycarbonyl radicals in which the alkyl portion contains 1 to 4 carbon atoms,

a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals selected from halogen atoms; alkyl radicals containing 1 to 4 carbon atoms; and alkoxy radicals containing 1 to 4 carbon atoms,

a 5-membered aromatic heterocyclic radical, or

a saturated heterocyclic radical containing 4 to 6 carbon atoms, optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms,

$R_3$ represents an unbranched or branched alkyl radical containing 1 to 8 carbon atoms, an unbranched or branched alkenyl radical containing 2 to 8 carbon atoms, an unbranched or branched alkynyl radical containing 2 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a phenyl or α- or β-naphthyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms, alkyl, alkenyl, alkynyl, aryl, aralkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, formyl, acyl, acylamino, aroylamino, alkoxycarbonylamino, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, cyano, nitro and trifluoromethyl radicals, or

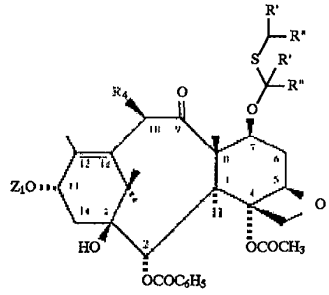
a 5-membered aromatic heterocycle containing one or more identical or different hetero atoms selected from nitrogen, oxygen and sulphur atoms and optionally substituted with one or more identical or different substituents selected from halogen atoms, alkyl, aryl, amino, alkylamino, dialkylamino, alkoxycarbonylamino, acyl, arylcarbonyl, cyano, carboxyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl and alkoxycarbonyl radicals,

with the proviso that, in the substituents of the phenyl, α- or β-naphthyl and aromatic heterocyclic radicals in the definitions of $R_2$ and $R_3$, the alkyl radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms, and the alkenyl and alkynyl radicals contain 2 to 8 carbon atoms, and the aryl radicals are phenyl or α- or β-naphthyl radicals,

$R_4$ represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain and

$R_5$ represents an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain,

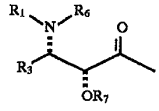
said process comprising reacting activated Raney nickel, in the presence of an aliphatic alcohol containing 1 to 3 carbon atoms or an ether, with a product of formula (XXI):




(XXI)

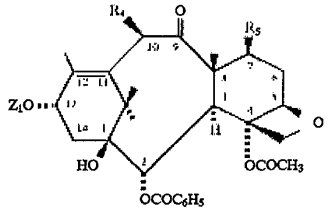
in which $R_4$ is defined as above, and R' and R", which may be identical or different,

represent a hydrogen atom or an alkyl radical containing 1 to 6 carbon atoms, an alkenyl radical containing 2 to 6 carbon atoms, an alkynyl radical containing 3 to 6 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms or a cycloalkenyl radical containing 3 to 6 carbon atoms, optionally substituted, or alternatively R' and R", together with the carbon atom to which they are linked, form a cycloalkyl radical containing 3 to 6 carbon atoms or a cycloalkenyl radical containing 4 to 6 carbon atoms, and $Z_1$ represents a hydrogen atom or a radical of formula (XXII):




(XXII)

in which $R_1$ and $R_3$ are defined as above and either $R_6$ represents a hydrogen atom and $R_7$ represents a group protecting the hydroxyl function, or $R_6$ and $R_7$ together form a saturated 5- or 6-membered heterocycle, to obtain a product of formula (XXIII):




(XXIII)

followed, when $Z_1$ represents a radical of formula (XXII), by replacing the protective group(s) represented by $R_6$ or $R_6$ and $R_7$ together by hydrogen atoms under the following conditions:

1) when $R_6$ represents a hydrogen atom and $R_7$ represents a group protecting the hydroxyl function, said replacing the protective groups by hydrogen atoms is accomplished

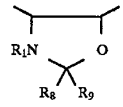
with at least one inorganic or organic acid in an organic solvent selected from alcohols, ethers, esters, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons, aromatic hydrocarbons and nitrites at a temperature from −10° to 60° C., or

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with a source of fluoride ions, or

with catalytic hydrogenation, or

2) when $R_6$ and $R_7$ together form a saturated 5- or 6-membered heterocycle of formula (VI):



(VI)

in which $R_1$ is defined as above and $R_8$ and $R_9$, which may be identical or different,

represent a hydrogen atom or an alkyl radical containing 1 to 4 carbon atoms, or an aralkyl radical in which the alkyl portion contains 1 to 4 carbon atoms, or an aryl radical, or

alternatively $R_8$ represents an alkoxy radical containing 1 to 4 carbon atoms or a trihalomethyl radical or a phenyl radical substituted with a trihalomethyl radical and $R_9$ represents a hydrogen atom, or

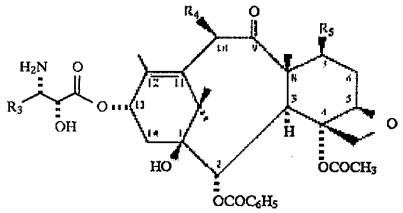
alternatively $R_8$ and $R_9$, together with the carbon atom to which they are linked, form a 4- to 7-membered ring, and further wherein when:

a) $R_1$ represents a tert-butoxycarbonyl radical and $R_8$ and $R_9$, which may be identical or different, represent an alkyl radical or an aralkyl or aryl radical, or

alternatively $R_8$ represents a trihalomethyl radical or a phenyl radical substituted with a trihalomethyl radical and $R_9$ represents a hydrogen atom, or

alternatively $R_8$ and $R_9$ together form a 4- to 7-membered ring, said replacing the protective groups by hydrogen atoms is accomplished

by treating the ester of formula (V) with an inorganic or organic acid, and optionally, with an organic solvent, to obtain the product of formula (VII):



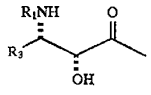
(VII)

in which $R_3$, $R_4$ and $R_5$ are defined as in claim **1**, and acylating said product of formula (VII) with benzoyl chloride in which the phenyl ring is optionally substituted; thenoyl chloride; furoyl chloride; or a product of formula (VIII):

$$R_2—O—CO—X \qquad \text{(VII)}$$

in which $R_2$ is defined as above and X represents a halogen atom or a residue —O—$R_2$ or —O—CO—O—$R_2$,

to obtain a product of formula (I) in which Z represents a radical of formula (II),



(II)

or

b) $R_1$ represents an optionally substituted benzoyl radical, a thenoyl or furoyl radical or a radical $R_2O—CO—$ in which $R_2$ is defined as above, $R_8$ represents a hydrogen atom or an alkoxy radical containing 1 to 4 carbon atoms or a phenyl radical substituted with one or more alkoxy radicals containing 1 to 4 carbon atoms and $R_9$ represents a hydrogen atom,

said replacing of the protective group formed by $R_6$ and $R_7$ together by two hydrogen atoms is accomplished

in the presence of at least one inorganic or organic acid in a stoichiometric or catalytic amount, and in an organic solvent selected from alcohols, ethers, esters, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons and aromatic hydrocarbons

at a temperature of from −10° to 60° C.

**12.** A process according to claim **8**, wherein said esterifying step is performed with an acid of formula (IV) in the presence of a condensing agent and an activating agent in an organic solvent at a temperature of from −10° to 90° C.

**13.** A process according to claim **8**, wherein said esterifying step is performed with an acid of formula (IV) in the form of the symmetrical anhydride thereof, in the presence of an activating agent in an organic solvent at a temperature of from 0° to 90° C.

**14.** A process according to claim **8**, wherein said esterifying step is performed with the acid of formula (IV) in halide form or in the form of a mixed anhydride with an aliphatic or aromatic acid, optionally prepared in situ, in the presence of a base, in an organic solvent at a temperature of from 0° to 80° C.

**15.** A process according to claim **8**, further comprising replacing the protective group(s) $R_7$ or $R_6$ and $R_7$ together by hydrogen atoms, wherein:

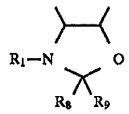
1) when $R_6$ represents a hydrogen atom and $R_7$ represents a group protecting the hydroxyl function, said replacing the protective groups by hydrogen atoms is accomplished

with at least one inorganic or organic acid in an organic solvent selected from alcohols, ethers, esters, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons, aromatic hydrocarbons and nitrites at a temperature from −10° to 60° C., or

with a source of fluoride ions, or

with catalytic hydrogenation,

2) when $R_6$ and $R_7$ together form a saturated 5- or 6-membered heterocycle of formula (VI).



(VI)

in which $R^1$ is defined as in claim **8** and $R_8$ and $R_9$, which may be identical or different,

represent a hydrogen atom or an alkyl radical containing 1 to 4 carbon atoms, or an aralkyl radical in which the alkyl portion contains 1 to 4 carbon atoms, or an aryl radical, or

alternatively $R_8$ represents an alkoxy radical containing 1 to 4 carbon atoms or a trihalomethyl radical or a phenyl radical substituted with a trihalomethyl radical and $R_9$ represents a hydrogen atom, or

alternatively $R_8$ and $R_9$ together with the carbon atom to which they are linked, form a 4- to 7-membered ring, and further wherein when:

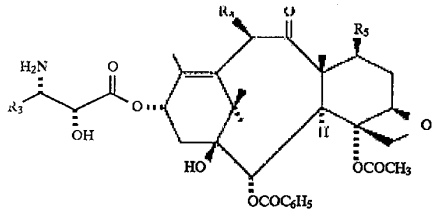
a) $R_1$ represents a tert-butoxycarbonyl radical and $R_8$ and $R_9$ which may be identical or different, represent an alkyl radical or an aralkyl or aryl radical, or

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alternatively $R_6$ represents a trihalomethyl radical or a phenyl radical substituted with a trihalomethyl radical and $R_9$ represents a hydrogen atom, or

alternatively $R_8$ and $R_9$ together form a 4- to 7-membered ring,

the ester of formula (V) is treated with an inorganic or organic acid, and optionally, in an organic solvent, to obtain the product of formula (VII):



(VII)

in which

$R_3$, $R_4$ and $R_5$ are defined in claim **8**, and

said product of formula (VII) is acylated with benzoyl chloride in which the phenyl ring is optionally substituted or thenoyl chloride, or furoyl chloride or a product of formula (VIII):

$$R_2—O—CO—X \quad \text{(VIII)}$$

in which $R_2$ is defined in claim **8** and X represents a halogen atom or a residue —O—$R_2$ or —O—CO—O—$R_2$, to obtain a product of formula (I) in which Z represents a radical of formula (II),

b) when $R_1$ represents an optionally substituted benzoyl radical, a thenoyl or furoyl radical or a radical $R_2O$—CO— in which $R_2$ is defined as above, $R_6$ represents a hydrogen atom or an alkoxy radical containing 1 to 4 carbon atoms or a phenyl radical substituted with one or more alkoxy radicals containing 1 to 4 carbon atoms and $R_9$ represents a hydrogen atom,

the protective group formed by $R_6$ and $R_7$ is replaced by hydrogen atoms in the presence of at least one inorganic or organic acid in a stoichiometric or catalytic amount, and in an organic solvent selected from alcohols, ethers, esters, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons and aromatic hydrocarbons at a temperature of from −10° to 60° C.

**16.** A process according to claim **15**, wherein when $R_6$ and $R_7$ together form a saturated 5- or 6-membered heterocycle of formula (VI), and $R_8$ and $R_9$ which may be identical or different, represent an aralkyl radical in which the alkyl portion contains 1 to 4 carbon atoms, the aryl portion of said aralkyl radical represents a phenyl radical optionally substituted with one or more alkoxy radicals containing 1 to 4 carbon atoms.

**17.** A process according to claim **15**, wherein when $R_6$ and $R_7$ together form a saturated 5- or 6-membered heterocycle of formula (VI), and $R_8$ and $R_9$, which may be identical or different, represent an aryl radical, said aryl radical is a phenyl radical optionally substituted with one or more alkoxy radicals containing 1 to 4 carbon atoms.

**18.** A process according to claim **15**, wherein said temperature ranges from 15° to 30° C.

**19.** A process according to claim **15**, wherein said source of fluoride ions is a hydrofluoric acid/triethylamine complex.

**20.** A process according to claim **15**, wherein said trihalomethyl radical is trichloromethyl.

**21.** A process according to claim **15**, wherein when said ester of formula (V) is treated in an organic solvent, said organic solvent is an alcohol.

**22.** A process according to claim **7**, wherein said activated Raney nickel is present in step (b) in an ethanolic suspension and further wherein said acid in step (c) is an ethanolic solution of hydrochloric acid.

* * * * *

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UNITED STATES PATENT AND TRADEMARK OFFICE

# CERTIFICATE OF CORRECTION

PATENT NO. : 5,847,170 Page 1 of 2

DATED : Dec. 8, 1998

INVENTOR(S) : Herve Bouchard, et al

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Claim 4, Column 29, Line 42, after "chain", delete " , ";

Claim 4, Column 30, Line 63, after "chain", insert --and--;

Claim 4, Column 31, Lines 3-12, to the upper right of the formula, insert --(v)--;

Claim 5, Column 31, Lines 20-29, to the upper right of the formula, insert --(V)--;

Claim 8, Column 33, Line 34, "(1)" should read --(I);

Claim 11, Column 42, Line 66, "nitrites" should read --nitriles--;

Claim 15, Column 44, Line 39, "nitrites" should read --nitriles--;

Claim 15, Column 44, Line 44, "(VI)." should read --(VI):--;

Claim 15, Column 44, Line 66, after "$R_9$", insert --,--;

Claim 15, Column 45, Line 21, after "defined", insert --as--; and

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UNITED STATES PATENT AND TRADEMARK OFFICE

# CERTIFICATE OF CORRECTION

PATENT NO. : 5,847,170 Page 2 of 2
DATED : Dec. 8, 1998
INVENTOR(S) : Herve Bouchard, et al

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Claim 15, Column 45, Line 34, "R6" should read --$R_6$--.

Signed and Sealed this

Seventh Day of September, 1999

*Attest:*

Q. TODD DICKINSON

*Attesting Officer* *Acting Commissioner of Patents and Trademarks*

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**THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF:**

**U.S. PATENT:** *8,927,592*
**ISSUE DATE:** *January 06, 2015*

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**Under Secretary of Commerce for Intellectual Property**
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**JTX-6**




(12) **United States Patent**
**Gupta**

(10) **Patent No.: US 8,927,592 B2**
(45) **Date of Patent: Jan. 6, 2015**

(54) **ANTITUMORAL USE OF CABAZITAXEL**

(75) Inventor: **Sunil Gupta**, Chester Springs, PA (US)

(73) Assignee: **Aventis Pharma SA**, Antony (FR)

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **13/456,720**

(22) Filed: **Apr. 26, 2012**

(65) **Prior Publication Data**

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**Related U.S. Application Data**

(63) Continuation of application No. PCT/IB2010/054866, filed on Oct. 27, 2010.

(60) Provisional application No. 61/389,969, filed on Oct. 5, 2010, provisional application No. 61/383,933, filed on Sep. 17, 2010, provisional application No. 61/369,929, filed on Aug. 2, 2010, provisional application No. 61/355,888, filed on Jun. 17, 2010, provisional application No. 61/355,834, filed on Jun. 17, 2010, provisional application No. 61/293,903, filed on Jan. 11, 2010, provisional application No. 61/256,160, filed on Oct. 29, 2009.

(51) **Int. Cl.**

| | |
|---|---|
| ***A61K 31/337*** | (2006.01) |
| ***A61K 31/573*** | (2006.01) |
| ***A61K 31/164*** | (2006.01) |
| ***A61K 31/56*** | (2006.01) |
| ***A61K 45/06*** | (2006.01) |

(52) **U.S. Cl.**

CPC ..... ***A61K 31/337*** (2013.01); ***A61K 31/164*** (2013.01); ***A61K 31/56*** (2013.01); ***A61K 31/573*** (2013.01); ***A61K 45/06*** (2013.01)

USPC ..... **514/449**

(58) **Field of Classification Search**

CPC ..... A61K 31/337; A61K 31/573

See application file for complete search history.

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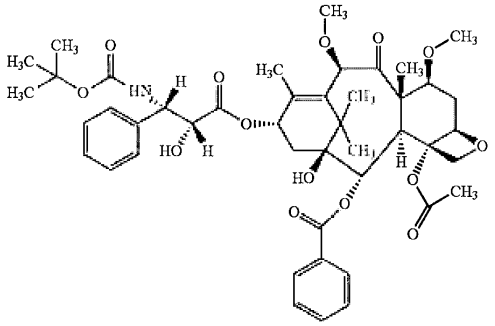
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*Primary Examiner* — James D Anderson
(74) *Attorney, Agent, or Firm* — Kelly L. Bender

(57) **ABSTRACT**

The invention relates to a compound of formula:



which may be in base form or in the form of a hydrate or a solvate, in combination with prednisone or prednisolone, for its use as a medicament in the treatment of prostate cancer, particularly metastatic prostate cancer, especially for patients who are not catered for by a taxane-based treatment.

**30 Claims, 7 Drawing Sheets**

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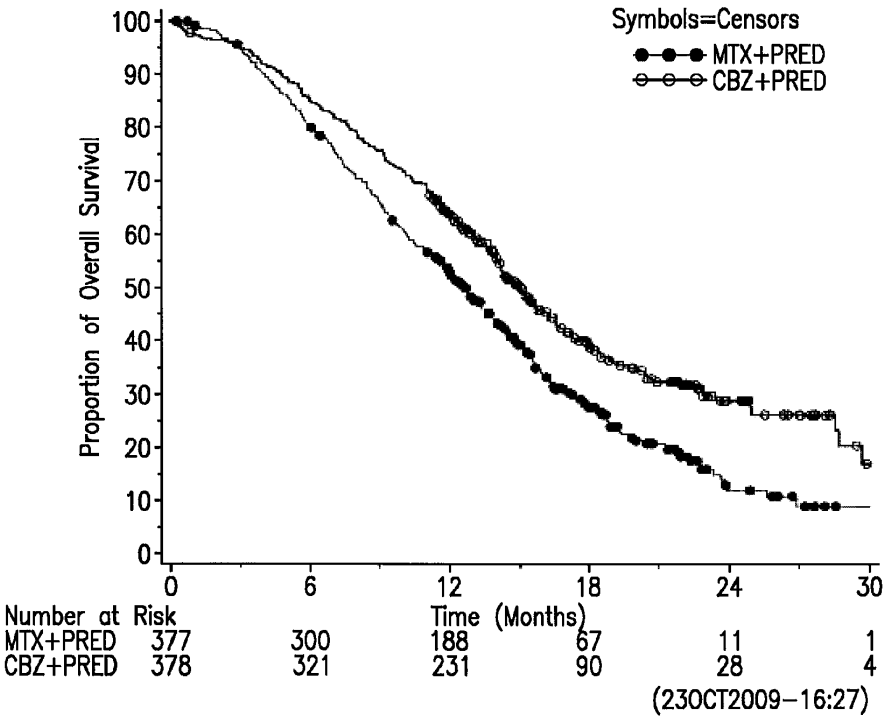



FIG. 1

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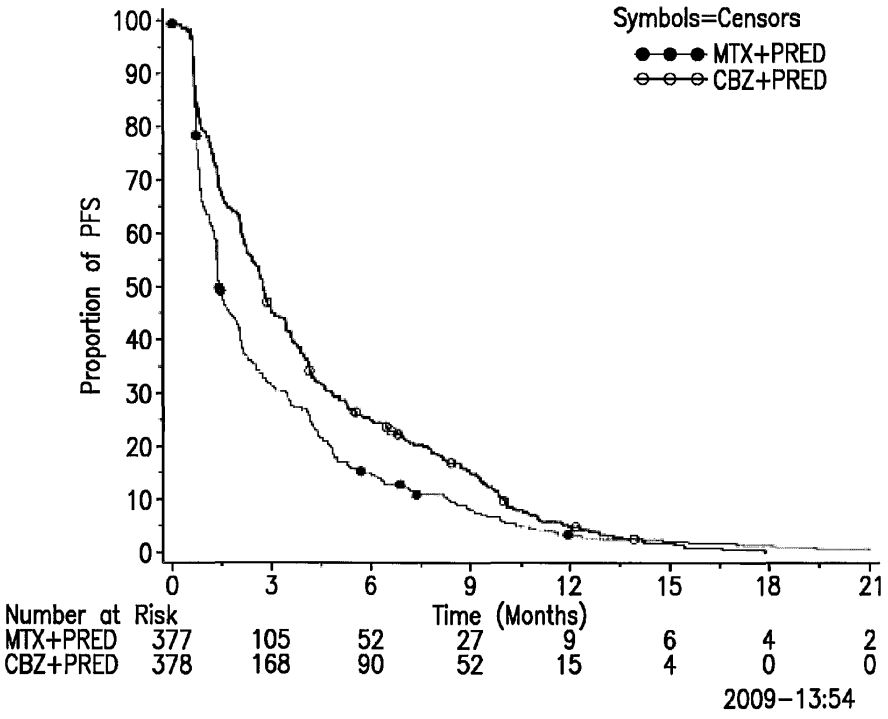



FIG. 2

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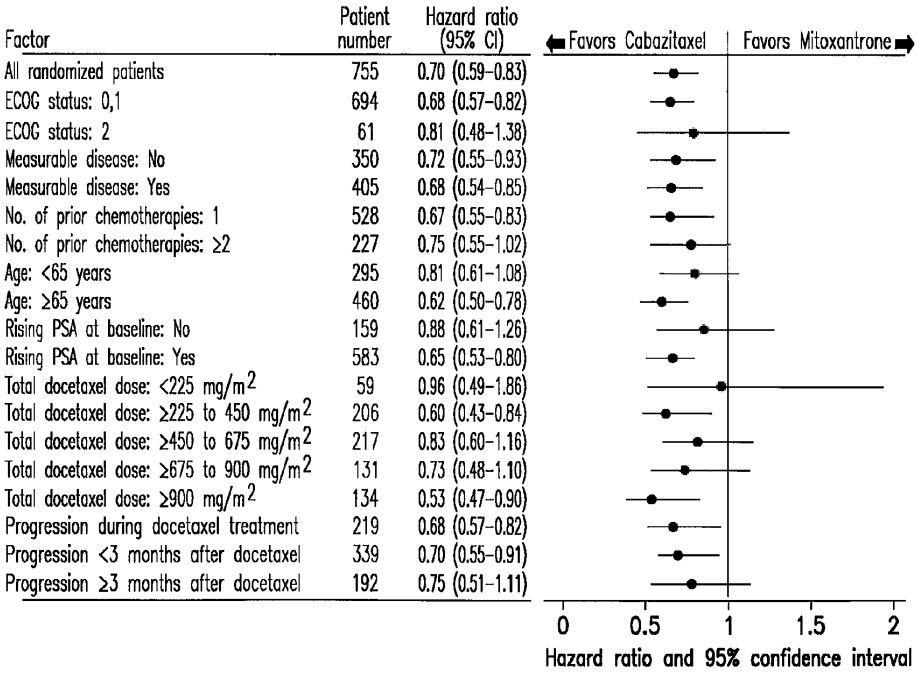



FIG. 3

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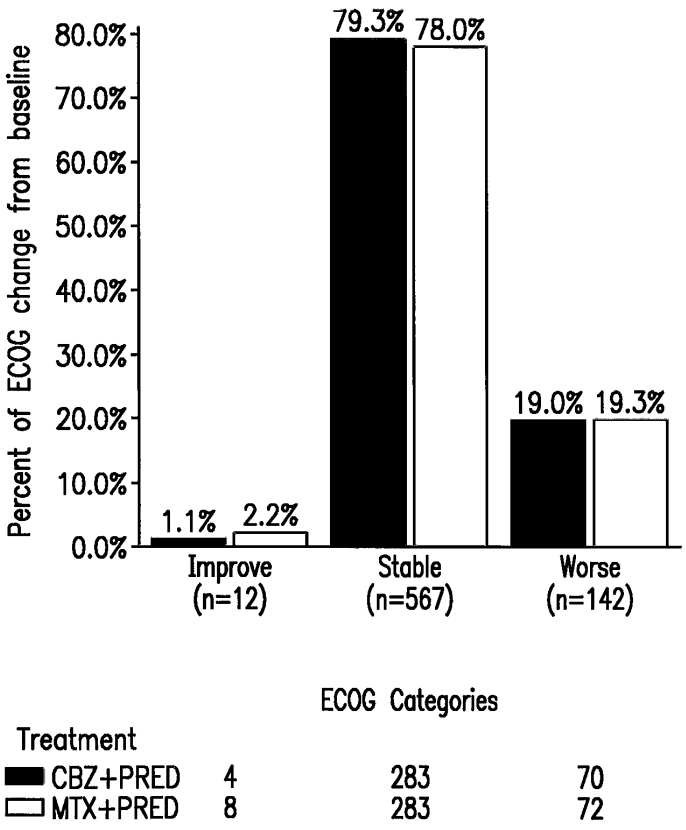



FIG. 4

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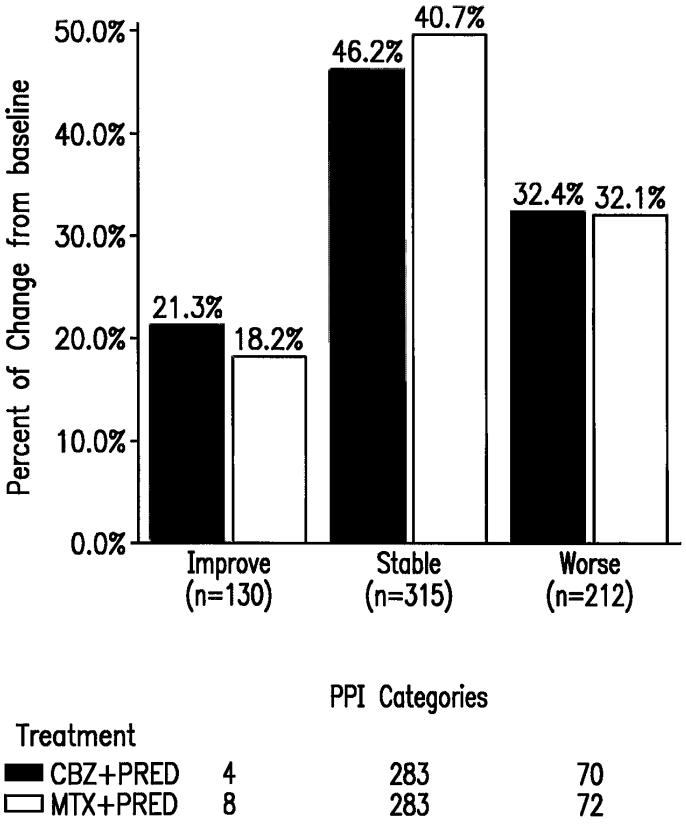



FIG. 5

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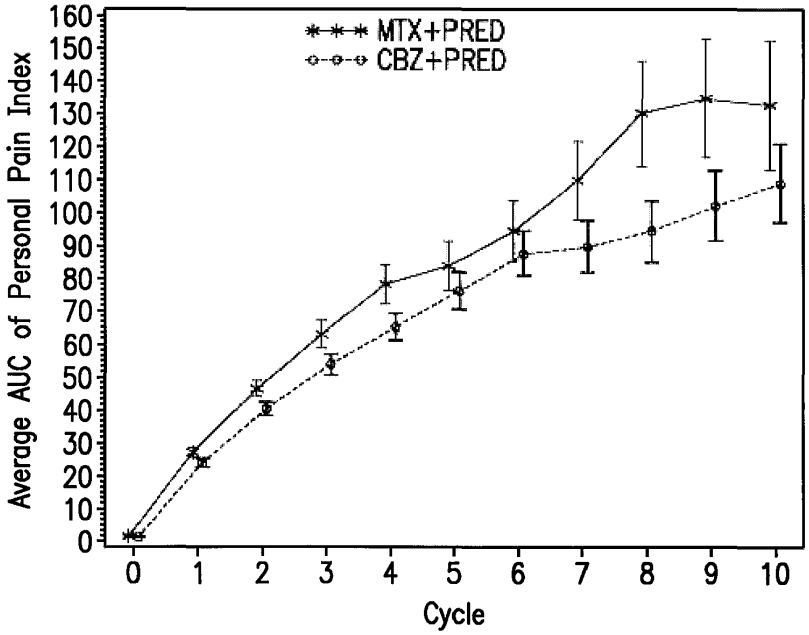



FIG. 6

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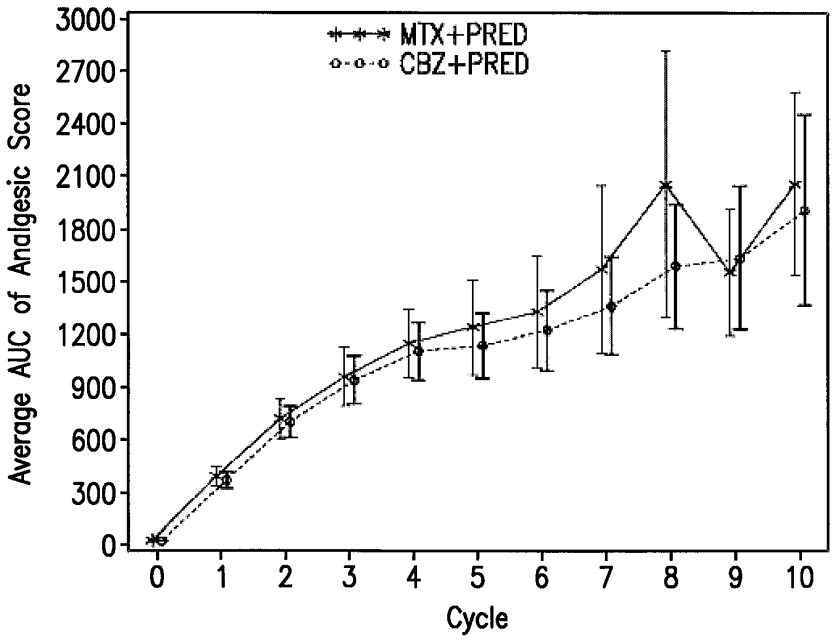



FIG. 7

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# ANTITUMORAL USE OF CABAZITAXEL

## CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of International Application No. PCT/IB2010/054866, filed Oct. 27, 2010, which claims the benefit of priority of U.S. Provisional Application No. 61/256,160, filed Oct. 29, 2009, U.S. Provisional Application No. 61/293,903, filed Jan. 11, 2010, U.S. Provisional Application No. 61/355,834, filed Jun. 17, 2010, U.S. Provisional Application No. 61/355,888, filed Jun. 17, 2010, U.S. Provisional Application No. 61/369,929, filed Aug. 2, 2010, U.S. Provisional Application No. 61/383,933, filed Sep. 17, 2010, and U.S. Provisional Application No. 61/389,969, filed Oct. 5, 2010, all of which are incorporated herein by reference.

The present invention relates to a novel antitumoral use of cabazitaxel in the treatment of prostate cancer, which may be metastatic, especially for patients who are not catered for by a taxane-based treatment. In particular, the present invention relates to the use of cabazitaxel in the treatment of patients with castration resistant metastatic prostate cancer, who have been previously treated with a docetaxel based regimen, an unmet medical need.

## BACKGROUND

Prostate cancer affects a large proportion of the male population worldwide: 680 000 cases worldwide in 2002; it is predicted that there will be 900 000 new cases per year up to 2010 (*CA Cancer J. Clin.*, 2005, 55, 74-108). It is the most frequently occurring cancer in men after lung cancer.

Prostate cancer is generally treated at the start by depriving the androgenic hormones, i.e. by surgical excision of the testicles The Current State of Hormonal Therapy for Prostate Cancer CA Cancer J. Clin., May 2002; 52: 154-179, or by radiotherapy treatment External beam radiation therapy for prostate cancer CA Cancer J. Clin., November 2000; 50: 349-375. Treatments with antiandrogens or hormone manipulations are associated with responses of short duration and without any improvement in the survival time.

The use of cytotoxic chemotherapy is not a routine treatment, whereas its role in alleviating the symptoms and reducing the levels of PSA (prostate-specific antigen) is established. No monotherapy has obtained a degree of response of greater than 30%; combinations with an effect on PSA levels were tested. No effect on the survival time was seen and, what is more, the toxicity of these treatments, particularly on elderly patients, is problematic since, in addition to their tumour, they are generally suffering from related health problems and have a limited reserve of bone marrow.

Until recently, the chemotherapies used were limited to cyclophosphamide, anthracyclines (doxorubicin or mitoxantrone) and estramustine, and the effects of these treatments are relatively mediocre. Palliative effects were observed in patients following the administration of corticoids alone or of mitoxantrone with either prednisone or hydrocortisone. Following Phase II trials, the combination of mitoxantrone with corticoids was recognized as the reference treatment for hormone-resistant prostate cancer. More recently, treatments with docetaxel in combination with estramustine or prednisone have made it possible to treat cancers that are resistant to hormone deprivation Advances in Prostate Cancer Chemotherapy: A New Era Begins CA Cancer J. Clin., September 2005; 55: 300-318, the survival was improved by 2.4 months.



It is generally accepted that the responses in advanced prostate cancers are difficult to evaluate on account of the heterogeneity of the disease and the lack of consensus regarding the treatment response criteria. Many patients with metastatic prostate cancer have no measurable disease, but have symptoms dominated by bone metastases. Measurement of the PSA level has been found to be a means for evaluating novel candidates and also the measurement of the tumour when this is possible, the measurement of bone tumours, the quality of life and the measurement of the pain.

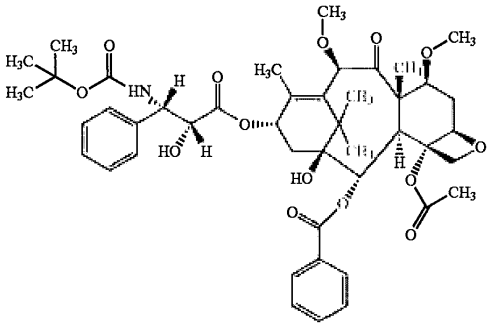
Furthermore, cancer may become resistant to the agents used, in particular to taxanes, which limits the possible treatment options. Several taxane resistance mechanisms have been described (expression of P-glycoprotein P-gp, mdr-1 gene, modified metabolism of taxane, mutation of the tubulin gene, etc.): see *Drug Resistance Updates* 2001, 4(1), 3-8; J. Clin. Onc. 1999, 17(3), 1061-1070.

The technical problem that the invention intends to solve is that of providing a novel therapeutic option for treating prostate cancer, especially for patients who are not catered for by a taxane-based treatment, such as patients with castration resistant metastatic prostate cancer who have been previously treated with docetaxel (sold under the brand name Taxotere®) based regimen, an unmet medical need.

Four clinical trials on cabazitaxel are known since April 2006. Three monotherapy tests have made it possible to determine the maximum tolerated dose and the toxicities at the limit doses: these tests were performed on breast, sarcoma and prostate tumours. Doses of 10-30 mg/m$^2$ every three hours were used. A phase II trial was performed on patients with a breast cancer, who had previously received taxanes and anthracyclines as adjuvant (i.e. after a surgery) or as a first-line treatment. The response levels were 14.6% as adjuvant and 9.5% as second-line treatment.

## SUMMARY

The invention relates to a novel antitumoral pharmaceutical therapeutic use comprising cabazitaxel of formula



The invention also relates to methods of treating patients with prostate cancer comprising administering an effective amount of the antitumoral agent cabazitaxel to said patient.

This antitumoral agent may be in the form of anhydrous base, a hydrate or a solvate, intended for treating prostate cancer, in particular for treating patients who are not catered for by a taxane-based treatment, such as patients who have been previously treated with a docetaxel-based regimen. This compound is preferably administered to a patient with advanced metastatic disease. In particular, the compound is

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administered to a patient with castration resistant prostate cancer. Cabazitaxel is preferably administered in combination with a corticoid chosen especially from prednisone and prednisolone. This corticoid is preferably administered at a daily dose of 10 mg orally.

In some aspects of the invention, cabazitaxel is administered in combination with prednisone for its use as a medicament in the treatment of patients with hormone-refractory prostate cancer who have been previously treated with docetaxel based regimen.

In some aspects of the invention, cabazitaxel is administered at a dose (defined for each administration) of between 20 and 25 mg/m$^2$. Cabazitaxel may be in the form of an acetone solvate. More particularly, the acetone solvate of cabazitaxel contains between 5% and 8% and preferably between 5% and 7% by weight of acetone.

In some aspects of the invention, cabazitaxel may be administered by intravenous infusion at a dose of between 15 and 25 mg/m$^2$, this administration cycle of the antitumour agent being repeated at an interval of 3 weeks between each cabazitaxel administration, which interval may be prolonged by 1 to 2 weeks depending on the tolerance to the preceding cabazitaxel administration.

In some embodiments, the effective amount of cabazitaxel produces at least one therapeutic effect selected from the group consisting of increase in overall survival, partial response, reduction in tumor size, reduction in metastasis, complete remission, partial remission, stable disease, or complete response.

The present invention also relates to a pharmaceutical composition that treats patients with prostate cancer comprising a clinically proven safe and effective amount of cabazitaxel.

Further embodiments of the invention comprise methods or using, treating, promoting, and providing cabazitaxel.

The present invention also relates to packages and articles of manufacture.

## BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** displays the Kaplan-Meier curves of the overall survival in a cabazitaxel study.

FIG. **2** displays the Kaplan-Meier curves of progression-free survival in a cabazitaxel study.

FIG. **3** shows an intention-to-treat analysis of overall survival in subgroups of patients defined by baseline characteristics. Hazard ratios<1 favor the cabazitaxel group, while those >1 favor the mitoxantrone group. CI denotes confidence intervals.

FIG. **4** graphically depicts the proportion of patients with changes in ECOG performance status from baseline during treatment (safety population). The "Improved" column represents PS2 at baseline changed to 0 or 1 during treatment. The "stable" column represents no change, and the "Worse" column represents PS2 at baseline and changed to ≥3, or 0 or 1 at baseline changed to ≥2 during treatment.

FIG. **5** graphically depicts the proportion of patients with changes from baseline in the Present Pain Intensity score during treatment (ITT). The "Improved" column represents patients in which the PPI score during treatment was lower versus baseline. The "Stable" column represents no change, and the "Worse" column represents patients with >1 unit increase in PPI score during treatment versus baseline.

FIG. **6** graphically presents the mean area under the curve for PPI and analgesic scores by treatment cycle.

FIG. **7** graphically presents the mean AUC analgesic score.

## DETAILED DESCRIPTION

### Definitions

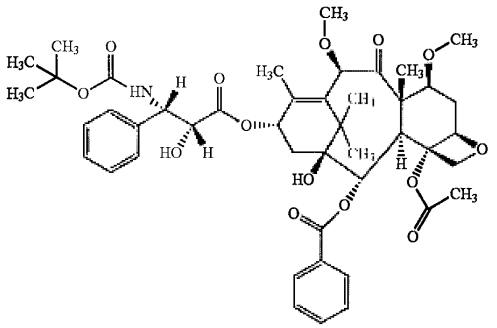
Effective amount, as used herein, means an amount of a pharmaceutical compound, such as cabazitaxel, that produces an effect on the cancer to be treated.

Clinically proven, as used herein, means clinical efficacy results that are sufficient to meet FDA approval standards.

Castration resistant prostate cancer, as used herein, is synonymous with hormone-refractory prostate cancer.

"Patient," as used herein, includes both human and animals. In one embodiment, a patient is a human.

Cabazitaxel belongs to the taxoid family and has the formula:



The chemical name of cabazitaxel is 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonyl-amino-2-hydroxy-3-phenylpropionate. Cabazitaxel is synonymously known as (2α,5β,7β,10β,13α)-4-acetoxy-13-({(2R,3S)-3-[(tertbutoxycarbonyl)amino]-2-hydroxy-3-phenylpropanoyl}oxy)-1-hydroxy-7,10-dimethoxy-9-oxo-5,20-epoxytax-11-en-2-yl benzoate.

This compound and a preparative method thereof is described in WO 96/30355, EP 0 817 779 B1 and U.S. Pat. No. 5,847,170, which are hereby incorporated herein by reference.

Cabazitaxel may be administered in base form (cf. above formula), or in the form of a hydrate. It may also be a solvate, i.e. a molecular complex characterized by the incorporation of the crystallization solvent into the crystal of the molecule of the active principle (see in this respect page 1276 of *J. Pharm. Sci.* 1975, 64(8), 1269-1288). In particular, it may be an acetone solvate, and, more particularly, may be the solvate described in WO 2005/028462. It may be an acetone solvate of cabazitaxel containing between 5% and 8% and preferably between 5% and 7% by weight of acetone (% means content of acetone/content of acetone+cabazitaxel×100). An average value of the acetone content is 7%, which approximately represents the acetone stoichiometry, which is 6.5% for a solvate containing one molecule of acetone. The procedure described below allows the preparation of an acetone solvate of cabazitaxel:

940 ml of purified water are added at 20±5° C. (room temperature) to a solution of 207 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate at about 92% by weight in about 2 liters of acetone, followed by seeding with a suspension of 2 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate isolated from acetone/water in a mixture of 20 ml of water and 20 ml of acetone. The resulting mixture is stirred for about 10 to 22 hours, and 1.5 liters of purified water

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are added over 4 to 5 hours. This mixture is stirred for 60 to 90 minutes, and the suspension is then filtered under reduced pressure. The cake is washed on the filter with a solution prepared from 450 ml of acetone and 550 ml of purified water, and then oven-dried at 55° C. under reduced pressure (0.7 kPa) for 4 hours. 197 g of 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate acetone containing 0.1% water and 7.2% acetone (theoretical amount: 6.5% for a stoichiometric solvate) are obtained.

Cabazitaxel may be administered parenterally, such as via intravenous administration. A galenical form of cabazitaxel suitable for administration by intravenous infusion is that in which the cabazitaxel is dissolved in water in the presence of excipients chosen from surfactants, cosolvents, glucose or sodium chloride, etc. For example, a galenical form of cabazitaxel may be prepared by diluting a premix solution of cabazitaxel contained in a sterile vial (80 mg of cabazitaxel+2 ml of solvent+Polysorbate 80) with a sterile vial containing a solution of 6 ml of water and ethanol (13% by weight of 95% ethanol) in order to obtain 8 ml of a solution ready to be rediluted in a perfusion bag. The concentration of cabazitaxel in this ready-to-redilute solution is about 10 mg/ml. The perfusion is then prepared by injecting the appropriate amount of this ready-to-redilute solution into the perfusion bag containing water and glucose (about 5%) or sodium chloride (about 0.9%).

Cabazitaxel may be administered in combination with a corticoid, such as prednisone or prednisolone, as two distinct pharmaceutical preparations.

Accordingly, one aspect of the invention is a method of treating prostate cancer comprising administering to a patient in need thereof an effective amount of cabazitaxel in combination with a corticoid, such as prednisone or prednisolone.

The combination is administered repeatedly according to a protocol that depends on the patient to be treated (age, weight, treatment history, etc.), which can be determined by a skilled physician. In one aspect of the invention, cabazitaxel is administered by perfusion to the patient according to an intermittent program with an interval between each administration of 3 weeks, which may be prolonged by 1 to 2 weeks depending on the tolerance to the preceding administration. The median number of cycles is 6. The prednisone or prednisolone may be administered daily, for example in the form of one dosage intake per day, throughout the duration of the treatment. Examples of doses for the two antitumoral agents are given in the "Example" section. The currently recommended dose is 25 mg/m$^2$ of cabazitaxel administered as a on-hour infusion and 10 mg per day of prednisone or prednisolone administered orally.

In some aspects of the invention, the patient to be treated has prostate cancer that is resistant to hormone therapy (i.e., hormone refractory) and has previously been treated with docetaxel. In some aspects, the patient has prostate cancer that progressed during or after treatment with docetaxel. In some aspects, the patient was previously treated with at least 225 mg/m$^2$ cumulative dose of docetaxel. In a particular aspect, the patient showed progression of their disease in the six months following hormone therapy or during docetaxel treatment or after docetaxel treatment. In another particular aspect, the patient showed progression of their disease in the three months following hormone therapy or after docetaxel treatment.

In some aspects of the invention, the patient to be treated has a measurable tumour and may show progression of the disease via a metastatic lesion of the viscera or of a soft tissue of at least 1 cm determined by MRI or by an axial tomographic scan (CT scan).

In some aspects of the invention, the patient to be treated has an unmeasurable tumour and may show an increase in the PSA level with three measurements at a 1-week interval or the appearance of new lesions.

In some aspects of the invention, the patient to be treated has undergone castration by orchidectomy or with LHRH agonists, elimination of the androgens or monotherapy with estramustine.

In a preferred aspect, the life expectancy of the patient to be treated should be at least 2 months.

In some aspects, the treatment does not include patients who have previously received mitoxantrone, or who have received less than 225 mg/m$^2$ of docetaxel, or who have undergone a radiotherapy that has eliminated more than 40% of the marrow, who have received a treatment within the 4 weeks preceding the test, who have a neuropathy or a stomatitis, involving the brain or the meninges, who have shown severe hypersensitivity to polysorbate or to prednisone, whose blood analysis shows an appreciable decrease in neutrophils, haemoglobin or platelets, an increase in bilirubin and/or liver enzymes and creatinine, or who have heart problems or an infection requiring antibiotics.

An aspect of the invention comprises increasing the survival of a patient with hormone refractory metastatic prostate cancer, comprising administering a clinically proven effective amount of cabazitaxel to the patient in combination with prednisone or prednisolone. In a particular aspect, the patient has previously been treated with a docetaxel-containing regimen.

Cabazitaxel may be administered in combination with a medication to prevent or control nausea and vomiting or to prevent or control hypersensitivity to the cabazitaxel treatment. Preferably, a patient is pre-medicated with the medication, for example, at least 30 minutes prior to administering each dose of cabazitaxel.

One aspect of the invention comprises a method of reducing the risk of a severe hypersensitivity reaction in a patient with prostate cancer being treated with cabazitaxel, comprising administering to the patient a medication to prevent hypersensitivity prior to the administration of cabazitaxel.

Severe hypersensitivity reactions to cabazitaxel can occur and may include generalized rash/erythema, hypotension and bronchospasm. Patients should be observed closely for hypersensitivity reactions, especially during the first and second infusions. Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of cabazitaxel, thus facilities and equipment for the treatment of hypotension and bronchospasm should be available. If severe hypersensitivity reaction occurs, cabazitaxel infusion should be immediately discontinued and appropriate therapy should be administered. Examples of medications which may be used to prevent hypersensitivity to the cabazitaxel treatment include antihistamines, such as dexchlorpheniramine (for example 5 mg), and diphenhydramine (for example 25 mg) or equivalent antihistamines; and corticosteroids, such as dexamethasone (for example 8 mg) or an equivalent steroid.

Nevertheless, cabazitaxel should not be given to and may be contraindicated in patients who have a history of severe hypersensitivity reactions to cabazitaxel. Depending on the formulation administered, cabazitaxel may also be contraindicated in patients who have a history of hypersensitivity reactions to other drugs formulated with polysorbate 80.

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One aspect of the invention comprises an article of manufacture comprising:

a) a packaging material;

b) cabazitaxel, and

c) a label or package insert contained within the packaging material indicating that severe hypersensitivity reactions can occur.

Gastrointestinal symptoms, such as, for example nausea, vomiting, and diarrhea, may occur with the treatment of cabazitaxel. Mortality related to diarrhea and electrolyte imbalance has been reported. Therefore, patients may also be rehydrated and treated with anti-diarrheal or anti-emetic medications as needed. Treatment delay or dosage reduction may be necessary if patients experience Grade≥3 diarrhea.

Accordingly, the methods of the invention include administering a medication to prevent hypersensitivity or a medication to prevent or control nausea and vomiting in combination with cabazitaxel.

Examples of medications which may be used to prevent or control nausea and vomiting include histamine $H_2$ antagonists and antiemetics, such as ondansetron, granisetron and dolesetron.

A possible side effect of the treatment with cabazitaxel is neutropenia, which is characterized by a reduced number of neutrophils. Unfortunately, a number of neutropenia deaths have been reported. Therefore, frequent blood counts should be obtained or performed to monitor for neutropenia. If neutropenia occurs, cabazitaxel treatment may be discontinued, and restarted when neutrophil counts recover to a level of >1,500/mm$^3$. Cabazitaxel should not be given to a patient with a neutrophil count≤1,500 cells/mm$^3$.

The present invention therefore also relates to a method of treating prostate cancer with cabazitaxel comprising administering cabazitaxel to the patient, monitoring blood counts in the patient, and measuring neutrophil levels. In one aspect, the method further comprises discontinuing cabazitaxel treatment if neutropenia occurs, and optionally restarting cabazitaxel treatment when neutrophil counts recover to a level of >1,500/mm$^3$. In one aspect, the monitoring comprises taking a blood sample from the patient.

Determining neutrophil counts can be performed according to procedures well know to those skilled in the art.

One aspect of the invention is a method of reducing the risk of neutropenia complications comprising administering cabazitaxel in combination with an agent useful for treating neutropenia. Such a neutropenia treatment agent is, for example, a hematopoietic growth factor which regulates the production and function of neutrophils such as a human granulocyte colony stimulating factor, (G-CSF). In a particular aspect of the invention, the neutropenia is complicated neutropenia. Complicated neutropenia includes febrile neutropenia, prolonged neutropenia, or neutropenic infection. In a preferred embodiment, the neutropenia treatment agent is administered prior to the administration of cabazitaxel.

A particular aspect of the invention comprises a method of reducing the risk of neutropenia complications in a patient with prostate cancer being treated with cabazitaxel, comprising monitoring blood counts in the patient at regular intervals during treatment of the patient with cabazitaxel; reducing the dose of cabazitaxel if the patient experiences febrile neutropenia or prolonged neutropenia; discontinuing cabazitaxel treatment if the patient's neutrophil count is ≤1,500 cells/mm$^3$; and optionally restarting cabazitaxel treatment when the patient's neutrophil counts recover to a level≥1,500 cells/mm$^3$.

In a particular aspect, primary prophylaxis with G-CSF should be considered in patients with high-risk clinical features (age>65 years, poor performance status, previous episodes of febrile neutropenia, extensive prior radiation ports, poor nutritional status, or other serious co-morbidities) that predispose them to increased complications from prolonged neutropenia. Therapeutic use of G-CSF and secondary prophylaxis should be considered in all patients considered to be at increased risk for neutropenia complications.

In another aspect, the monitoring of complete blood counts is performed on a weekly basis during cycle 1 and before each treatment cycle thereafter so that the dose can be adjusted, if needed. Therefore, another aspect for reducing the risk of neutropenia complications comprises, monitoring blood counts in the patient and adjusting the dose of cabazitaxel. An example of a dose modification is described in Example 2.

One aspect of the invention comprises an article of manufacture comprising:

a) a packaging material;

b) cabazitaxel, and

c) a label or package insert contained within the packaging material indicating that cabazitaxel should not be given to patients with neutrophil counts of ≤1,500 cells/mm$^3$.

Cases of renal failure should be identified and managed aggressively, accordingly to procedures known to those skilled in the art. Renal failure may be associated with sepsis, dehydration, or obstructive uropathy. Furthermore, impaired hepatic function (e.g., total bilirubin≥ULN, or AST and/or ALT≥1.5×ULN) may increase cabazitaxel concentrations, and cabazitaxel should not be given to patients with hepatic impairment.

Cabazitaxel may cause fetal harm when administered to a pregnant woman.

Prednisone or prednisolone administered at 10 mg daily does not affect the pharmacokinetics of cabazitaxel.

Cabazitaxel is primarily metabolized through CYP3A. Concomitant administration of strong CYP3A inhibitors (for example, ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) may increase cabazitaxel concentrations. Therefore co-administration of cabazitaxel with strong CYP3A inhibitors should be avoided. Caution should be exercised with concomitant use of moderate CYP3A inhibitors. One aspect of the invention is a method of treating a patient for prostate cancer comprising determining whether the patient is undergoing treatment with a CYP3A inhibitor, discontinuing treatment with a CYP3A inhibitor, and then administering cabazitaxel to the patient.

Concomitant administration of strong CYP3A inducer (e.g., phenyloin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital) may decrease cabazitaxel concentrations. Therefore co-administration of cabazitaxel with strong CYP3A inducers should be avoided. Therefore, one aspect of the invention is a method of treating a patient for prostate cancer comprising determining whether the patient is undergoing treatment with a CYP3A inducer, discontinuing treatment with a CYP3A inducer, and administering cabazitaxel to the patient.

In addition, patients should also refrain from taking St. John's Wort.

In some aspects of the invention, the cabazitaxel is administered in an amount to provide an AUC of about 991 ng·h/mL (CV 34%).

In some aspects of the invention, the cabazitaxel is administered in an amount to provide an $C_{max}$ of about 226 ng·h/mL (CV 107%).

In some aspects of the invention, the cabazitaxel is administered in an amount to provide a plasma clearance of 48.5 L/h (CV 39%).

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One aspect of the invention is a package comprising cabazitaxel and a label, in a position which is visible to prospective purchasers, comprising a printed statement which informs prospective purchasers that the mean $C_{max}$ of cabazitaxel in patients with metastatic prostate cancer was 226 ng/mL (CV 107%).

Another aspect of the invention is a package comprising cabazitaxel and a label, in a position which is visible to prospective purchasers, comprising a printed statement which informs prospective purchasers that the mean AUC of cabazitaxel in patients with metastatic prostate cancer was 991 ng·h/mL (CV 34%).

Another aspect of the invention is a package comprising cabazitaxel and a label, in a position which is visible to prospective purchasers, comprising a printed statement which informs prospective purchasers that cabazitaxel has a plasma clearance of 48.5 L/h (CV 39%).

A variety of educational materials may be employed to ensure proper prescribing, dispensing, and patient compliance according to the methods described herein. For example, a variety of literature and other materials, such as, for example, prescribing information, package inserts, medications guides, physician information sheets, healthcare professional information sheets, medical journal advertisements, and product websites may describe the risks and benefits of taking cabazitaxel.

The invention also concerns a package comprising cabazitaxel and a label, said label comprising one or more messages that:

a) the efficacy and safety of cabazitaxel in combination with prednisone were evaluated in patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel containing regimen; or

b) a total of 755 patients were randomized to receive either cabazitaxel 25 mg/m$^3$ every 3 weeks for a maximum of 10 cycles with prednisone mg orally daily, or to receive mitoxantrone 12 mg/m$^2$ intravenously every 3 weeks for a maximum of 10 cycles with prednisone 10 mg orally daily; or

c) the median number of cycles was 6 in the cabazitaxel group and 4 in the mitoxantrone group.

The invention also concerns a package comprising cabazitaxel and a label, said label comprising one or more messages that:

a) neutropenic deaths have been reported; or

b) frequent blood counts should be obtained to monitor for neutropenia; or

c) cabazitaxel should not be given if neutrophil counts are ≤1,500 cells/mm$^3$.

The invention also concerns a method of promoting the use of cabazitaxel the method comprising the step of conveying to a recipient at least one message selected from:

a) neutropenic deaths have been reported; or

b) frequent blood counts should be obtained to monitor for neutropenia; or

c) cabazitaxel should not be given if neutrophil counts are ≤1,500 cells/mm$^3$;

d) severe hypersensitivity can occur; or

e) severe hypersensitivity can occur and may include generalized rash/erythema, hypotension and brochospasm; or

f) discontinue cabazitaxel immediately if severe reactions occur; or

g) discontinue cabazitaxel immediately if severe reactions occur and administer appropriate therapy; or

h) cabazitaxel is contraindicated in patients with a history of severe hypersensitivity reactions to cabazitaxel or drugs formulated with polysorbate 80.

The invention also concerns a method of providing cabazitaxel, wherein said cabazitaxel is provided along with information indicating that:

a) neutropenic deaths have been reported; or

b) frequent blood counts should be obtained to monitor for neutropenia; or

c) cabazitaxel should not be given if neutrophil counts are ≤1,500 cells/mm$^3$;

d) severe hypersensitivity can occur; or

e) severe hypersensitivity can occur and may include generalized rash/erythema, hypotension and brochospasm; or

f) discontinue cabazitaxel immediately if severe reactions occur; or

g) discontinue cabazitaxel immediately if severe reactions occur and administer appropriate therapy; or

h) cabazitaxel is contraindicated in patients with a history of severe hypersensitivity reactions to cabazitaxel or drugs formulated with polysorbate 80.

Example 1

A clinical study was performed wherein patients received either treatment with cabazitaxel or the reference treatment based on mitoxantrone each combined with prednisone or prednisolone.

More specifically, patients over 18 years of age with metastatic castration resistant metastatic prostate cancer either measurable by RECIST criteria or non-measurable disease with rising PSA levels or appearance of new lesions, ECOG (Eastern Cooperative Oncology Group) performance stage 0-2, and adequate organ function (patients had to have neutrophils>1,500 cells/mm$^3$, platelets>100,000 cells/mm$^3$, hemoglobin>10 g/dL, creatinine<1.5× upper limit of normal (ULN), total bilirubin<1×ULN, AST<1.5×ULN, and ALT<1.5×ULN) who had had prior hormone therapy, chemotherapy, and radiotherapy, but had progressive during or after docetaxel treatment (cumulative dose≥225 mg/m$^2$) were randomized to 10 mg/day of prednisone with either mitoxantrone 12 mg/m$^2$ or cabazitaxel 25 mg/m$^2$, both administered every 3 weeks.

Patients with a history of congestive heart failure, or myocardial infarction within the last 6 months, or patients with uncontrolled cardiac arrhythmias, angina pectoris, and/or hypertension were not included in the study.

720 patients were planned to be included in the clinical study: 360 in each cabazitaxel+prednisone and mitoxantrone+prednisone group. Seven hundred and fifty-five patients (755) (median age 68; 84% white) were actually enrolled, 378 in the cabazitaxel and prednisone/prednisolone group and 377 in the mitoxantrone and prednisone/prednisolone group. The maximal number of treatment cycles was 10 for cabazitaxel and 10 for mitoxantrone. The median number of treatment cycles was 6 for cabazitaxel and 4 for mitoxantrone. The median prior dose of docetaxel treatment was 576 mg/m$^2$ for the cabazitaxel group and 529 mg/m$^2$ for the mitoxantrone group. Median follow-up was 12.8 months.

The measurements of the results are performed via the same tests as at inclusion. MRI and spiral computed tomographic (CT) scans are preferably used.

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The results are evaluated according to the following criteria (cf RECIST guideline):

- overall survival (OS): the time from inclusion to the study to the date of death
- complete response (CR): disappearance of the lesions
- partial response (PR): at least 30% reduction of the largest diameter of the lesion
- progression (PD): at least 20% increase in the sum of the largest diameter of the lesion or appearance of one or more new lesions
- stable disease (SD): reduction of the tumour insufficient to be included in PR and increase of the tumour insufficient to be included in PD.

The confirmations of the measurements are made at least 4 weeks after the response criterion has been established for the first time.

The progression-free survival (PFS) is the time from inclusion in the study and the date of progression or death when the progression is either an increase of the PSA, or of the tumour, or of the pain.

It was found that the combination of cabazitaxel and prednisone is a well-tolerated combination with the safety profile of taxanes. At the dose investigated in this trial (LD2: 25 mg/m$^2$ cabazitaxel+10 mg/m$^2$/day prednisone), patients receiving cabazitaxel demonstrated statistically significant longer overall survival (OS) compared to mitoxantrone ($p<0.0001$). The hazard ratio was 0.70 (95% CI. 0.59, 0.83) in favor of cabazitaxel corresponding to a 30% reduction in risk of death. The median survival for patients in the cabazitaxel group was 15.1 months in comparison to 12.7 months in the mitoxantrone group. Notably, the extension of survival was observed irrespective of ECOG performance status, number of prior chemotherapy regimens and age. Benefit was also seen in the third of patients who were docetaxel-refractory and had progressed during docetaxel therapy.

The data related to the treated patients are given in Table 1:

TABLE 1

| Efficacy analysis (intention-to-treat) | | | |
|---|---|---|---|
| | | CbzP N = 378 Median (months) | MP N = 377 Median (months) |
| Overall survival | Median (months) | 15.1 | 12.7 |
| | Hazard ratio (95% CI) | 0.70 (0.59; 0.83) | |
| | p-value[1] | 0.0001 | |
| PFS | Median (months) | 2.8 | 1.4 |
| | Hazard ratio (95% CI) | 0.74 (0.64-0.86) | |
| | p-value[1] | 0.0001 | |
| Tumor response rate | | 14.4% | 4.4% |
| p-value[2] | | 0.0005 | |
| Time to Tumor (months) | Progression Median | 8.8 | 5.4 |
| | p-value | <0.001 | |
| PSA Response rate | | 39.2% | 17.8% |
| p-value[2] | | 0.0002 | |
| PSA PFS | Median (months) | 6.4 | 3.1 |
| | Hazard ratio (95% CI) | 0.75 (0.63-0.90) | |
| | p-value[1] | 0.0010 | |
| Pain Response rate | | 9.2% | 7.8% |
| p-value[2] | | 0.6526 | |



TABLE 1-continued

| Efficacy analysis (intention-to-treat) | | | |
|---|---|---|---|
| | | CbzP N = 378 Median (months) | MP N = 377 Median (months) |
| Pain PFS | Median (months) | Not reached | 11.1 |
| | Hazard ratio (95% CI) | 0.91 (0.69-1.19) | |
| | p-value[1] | 0.5192 | |

[1]Log-rank test,
[2]Chi-square test
CbzP: cabazitaxel with prednisone
MP: mitoxantrone with prednisone

Progression free survival (PFS) defined as the earliest progression in tumor, PSA or pain was also statistically significantly longer in the cabazitaxel group compared to the mitoxantrone group ($p<0.0001$, hazard ratio=0.74 (95% CI, 0.64, 0.86), and the median progression-free survival was 2.8 months versus 1.4 months. Response rates and PFS for PSA and tumor assessments were statistically significant in favor of cabazitaxel, while response rate and PFS for pain did not show a statistically significant difference.

The most frequent Grade 3/4 toxicities were neutropenia observed with a higher frequency in the cabazitaxel group with 81.7% compared to the mitoxantrone group with 58.0%. Rates of febrile neutropenia were 7.5% in the cabazitaxel group and 1.3% in the mitoxantrone group.

The most common (≥20%) grade 1-4 adverse reactions were anemia, leukopenia, neutropenia, thrombocytopenia, diarrhea, fatigue, nausea, vomiting, asthenia, and constipation.

The most common (≥5%) grade 3-4 adverse reactions in patients who received cabazitaxel were neutropenia, leukopenia, anemia, febrile neutropenia, diarrhea, fatigue, and asthenia.

Subgroup analyses by risk factors and a multivariate analysis showed that OS outcomes were consistent and robust in favor of cabazitaxel as shown in the herebelow table:

TABLE 2

| | MP | | CbzP | | |
|---|---|---|---|---|---|
| | N (%) | Median OS (mos) | N (%) | Median OS (mos) | CbzP vs MP HR (95% CI) |
| ITT | 377 (100) | 12.7 | 378 (100) | 15.1 | 0.70 (0.59-0.83) |
| PD while on D | 103 (27) | 12.0 | 113 (30) | 14.2 | 0.65 (0.47-0.90) |
| PD after last D dose, ≤3 mos | 180 (48) | 10.3 | 158 (42) | 13.9 | 0.70 (0.54-0.90) |
| PD after last D dose, >3 mos | 91 (24) | 17.7 | 103 (27) | 17.5 | 0.78 (0.53-1.14) |

mos = months
D = Docetaxel

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TABLE 3

Incidence of Reported Adverse Reactions[1] and Hematologic Abnormalities in ≥5% of Patients Receiving cabazitaxel in Combination with Prednisone or Mitoxantrone in Combination with Prednisone

| | Cabazitaxel 25 mg/m$^2$ every 3 weeks with prednisone 10 mg daily n = 371 | | Mitoxantrone 12 mg/m$^2$ every 3 weeks with prednisone 10 mg daily n = 371 | |
|---|---|---|---|---|
| | Grade 1-4 n (%) | Grade 3-4 n (%) | Grade 1-4 n (%) | Grade 3-4 n (%) |
| **Any Adverse Reaction** | | | | |
| **Blood and Lymphatic System Disorders** | | | | |
| Neutropenia[2] | 347 (94%) | 303 (82%) | 325 (87%) | 215 (58%) |
| Febrile Neutropenia | 27 (7%) | 27 (7%) | 5 (1%) | 5 (1%) |
| Anemia[2] | 361 (98%) | 39 (11%) | 302 (82%) | 18 (5%) |
| Leukopenia[2] | 355 (96%) | 253 (69%) | 343 (93%) | 157 (42%) |
| Thrombocytopenia[2] | 176 (48%) | 15 (4%) | 160 (43%) | 6 (2%) |
| **Cardiac Disorders** | | | | |
| Arrhythmia[3] | 18 (5%) | 4 (1%) | 6 (2%) | 1 (<1%) |
| **Gastrointestinal Disorders** | | | | |
| Diarrhea | 173 (47%) | 23 (6%) | 39 (11%) | 1 (<1%) |
| Nausea | 127 (34%) | 7 (2%) | 85 (23%) | 1 (<1%) |
| Vomiting | 83 (22%) | 6 (2%) | 38 (10%) | 0 |
| Constipation | 76 (20%) | 4 (1%) | 57 (15%) | 2 (<1%) |
| Abdominal Pain[4] | 64 (17%) | 7 (2%) | 23 (6%) | 0 |
| Dyspepsia[5] | 36 (10%) | 0 | 9 (2%) | 0 |
| **General Disorders and Administration Site Conditions** | | | | |
| Fatigue | 136 (37%) | 18 (5%) | 102 (27%) | 11 (3%) |
| Asthenia | 76 (20%) | 17 (5%) | 46 (12%) | 9 (2%) |
| Pyrexia | 45 (12%) | 4 (1%) | 23 (6%) | 1 (<1%) |
| Peripheral Edema | 34 (9%) | 2 (<1%) | 34 (9%) | 2 (<1%) |
| Mucosal Inflammation | 22 (6%) | 1 (<1%) | 10 (3%) | 1 (<1%) |
| Pain | 20 (5%) | 4 (1%) | 18 (5%) | 7 (2%) |
| **Infections and Infestations** | | | | |
| Urinary Tract Infection[6] | 29 (8%) | 6 (2%) | 12 (3%) | 4 (1%) |
| Pneumonia[7] | 12 (3%) | 9 (2%) | 4 (1%) | 3 (<1%) |
| **Investigations** | | | | |
| Weight Decreased | 32 (9%) | 0 | 28 (8%) | 1 (<1%) |
| **Metabolism and Nutrition Disorders** | | | | |
| Anorexia | 59 (16%) | 3 (<1%) | 39 (11%) | 3 (<1%) |
| Dehydration | 18 (5%) | 8 (2%) | 10 (3%) | 3 (<1%) |
| **Musculoskeletal and Connective Tissue Disorders** | | | | |
| Back Pain | 60 (16%) | 14 (4%) | 45 (12%) | 11 (3%) |
| Arthralgia | 39 (11%) | 4 (1%) | 31 (8%) | 4 (1%) |
| Pain in Extremity | 30 (8%) | 6 (2%) | 27 (7%) | 4 (1%) |
| Muscle Spasms | 27 (7%) | 0 | 10 (3%) | 0 |
| Bone Pain | 19 (5%) | 3 (<1%) | 19 (5%) | 9 (2%) |
| Musculoskeletal Pain | 18 (5%) | 2 (<1%) | 20 (5%) | 3 (<1%) |
| **Nervous System Disorders** | | | | |
| Peripheral Neuropathy[8] | 50 (13%) | 3 (<1%) | 12 (3.2%) | 3 (<1%) |
| Dysgeusia | 41 (11%) | 0 | 15 (4%) | 0 |
| Dizziness | 30 (8%) | 0 | 21 (6%) | 2 (<1%) |
| Headache | 28 (8%) | 0 | 19 (5%) | 0 |
| **Renal and Urinary Tract Disorders** | | | | |
| Hematuria | 62 (17%) | 7 (2%) | 13 (4%) | 1 (<1%) |
| Dysuria | 25 (7%) | 0 | 5 (1%) | 0 |
| **Respiratory, Thoracic and Mediastinal Disorders** | | | | |
| Dyspnea | 43 (12%) | 4 (1%) | 16 (4%) | 2 (<1%) |
| Cough | 40 (11%) | 0 | 22 (6%) | 0 |
| **Skin and Subcutaneous Tissue Disorders** | | | | |
| Alopecia | 37 (10%) | 0 | 18 (5%) | 0 |

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TABLE 3-continued

Incidence of Reported Adverse Reactions[1] and Hematologic Abnormalities in ≥5% of Patients Receiving cabazitaxel in Combination with Prednisone or Mitoxantrone in Combination with Prednisone

| | Cabazitaxel 25 mg/m$^2$ every 3 weeks with prednisone 10 mg daily n = 371 | | Mitoxantrone 12 mg/m$^2$ every 3 weeks with prednisone 10 mg daily n = 371 | |
|---|---|---|---|---|
| | Grade 1-4 n (%) | Grade 3-4 n (%) | Grade 1-4 n (%) | Grade 3-4 n (%) |
| **Vascular Disorders** | | | | |
| Hypotension | 20 (5%) | 2 (<1%) | 9 (2%) | 1 (<1%) |
| Median Duration of Treatment | 6 cycles | | 4 cycles | |

[1]Graded using NCI CTCAE version 3

[2]Based on laboratory values, cabazitaxel: n = 369, mitoxantrone: n = 370.

[3]Includes atrial fibrillation, atrial flutter, atrial tachycardia, atrioventricular block complete, bradycardia, palpitations, supraventricular tachycardia, tachyarrhythmia, and tachycardia.

[4]Includes abdominal discomfort, abdominal pain lower, abdominal pain upper, abdominal tenderness, and GI pain.

[5]Includes gastroesophageal reflux disease and reflux gastritis.

[6]Includes urinary tract infection enterococcal and urinary tract infection fungal.

[7]Includes bronchopneumonia, lobar pneumonia, and pneumonia *klebsiella*.

[8]Includes peripheral motor neuropathy and peripheral sensory neuropathy.

TABLE 4

Patient Characteristics

| | MP (n = 377) | CBZP (n = 378) |
|---|---|---|
| Age (years) | | |
| Median [range] | 67 [47-89] | 68 [46-92] |
| ≥65 (%) | 57.0 | 64.9 |
| ECOG PS (%) | | |
| 0, 1 | 91.2 | 92.6 |
| 2 | 8.8 | 7.4 |
| PSA* (ng/mL) | | |
| Median [range] | 127.5 [2-11220] | 143.9 [2-7842] |
| Measurability of disease (%) | | |
| Measurable | 54.1 | 53.2 |
| Non-measurable | 45.9 | 46.8 |
| Disease site (%) | | |
| Bone | 87.0 | 80.2 |
| Lymph node | 44.8 | 45.0 |
| Visceral | 24.9 | 24.9 |
| Pain at Baseline, no. (%) | 168 (44.6) | 174 (46.0) |
| Previous Therapy, no. (%) | | |
| Hormonal | 375 (99.5) | 375 (99.2) |
| No. of Chemotherapy Regimens | | |
| 1 | 268 (71.1) | 260 (68.8) |
| 2 | 79 (21.0) | 94 (24.9) |
| >2 | 30 (8.0) | 24 (6.3) |
| Radiation | 222 (58.9) | 232 (61.4) |
| Surgery | 205 (54.4) | 198 (52.4) |
| Biologic Agent | 36 (9.5) | 26 (6.9) |
| Previous docetaxel regimens, n (%) | | |
| 1 | 327 (86.7) | 316 (83.6) |
| 2 | 43 (11.4) | 53 (14.0) |
| >2 | 7 (1.9) | 9 (2.4) |
| Median total previous docetaxel dose (mg/m$^2$) | 529.2 | 576.6 |

TABLE 4-continued

Patient Characteristics

| | MP (n = 377) | CBZP (n = 378) |
|---|---|---|
| Disease progression relative to docetaxel administration, n (%) | | |
| During treatment | 104 (27.6) | 115 (30.4) |
| <3 months from last dose | 181 (48.0) | 158 (41.8) |
| ≥3 months from last dose | 90 (23.9) | 102 (27.0) |
| Unknown | 2 (0.5) | 3 (0.8) |
| Median time from last docetaxel dose to disease progression (months) | 0.7 | 0.8 |

The primary reason for treatment discontinuation in both groups was disease progression (Table 5). The median delivered relative dose intensity was 96.1% in the cabazitaxel group and 97.3% in the mitoxantrone group. In the cabazitaxel group, >75% of patients received >90% of the planned dose intensity. Overall, 5.1% of mitoxantrone treatment courses were dose reduced compared with 9.8% of cabazitaxel treatment courses; 6.3 and 7% of all treatment courses were delayed by 9 days or less, and 1.6 and 2.3% of courses were delayed by more than 9 days for mitoxantrone and cabazitaxel respectively (See Table 5).

TABLE 5

Treatment Received and Reasons for Discontinuation in the Intention-to-Treat Population.*

| | Mitoxantrone (N = 377) | Cabazitaxel (N = 378) |
|---|---|---|
| Patients receiving study treatment, no. (%) | 371 (98.4) | 371 (98.1) |
| Patients completing planned ten cycles of study treatment, no. (%) | 46 (12.2) | 105 (27.8) |

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TABLE 5-continued

Treatment Received and Reasons for Discontinuation in the Intention-to-Treat Population.*

| | Mitoxantrone (N = 377) | Cabazitaxel (N = 378) |
|---|---|---|
| Discontinuation of study treatment, no. (%) | 325 (86.2) | 266 (70.4) |
| Reasons for discontinuation of study treatment, no. (%) | | |
| Disease progression | 267 (70.8) | 180 (47.6) |
| Adverse event | 32 (8.5) | 67 (17.7) |
| Non-compliance with protocol | 0 | 1 (0.3) |
| Lost to follow-up | 2 (0.5) | 0 |
| Patient's request | 17 (4.5) | 8 (2.1) |
| Other | 7 (1.9) | 10 (2.7) |
| No. of treatment cycles, median (range)† | 4 (1-10) | 6 (1-10) |
| Relative dose intensity, median % (range)† | 97.3 (42.5-106.0) | 96.1 (49.0-108.2) |
| Treatment delays, no. of cycles (%)‡ | | |
| ≤9 days | 110 (6.3) | 157 (7.0) |
| >9 days | 28 (1.6) | 51 (2.3) |
| Dose reductions, no. of cycles (%)‡ | 88 (5.1) | 221 (9.8) |

The results of this study are further illustrated to FIGS. **1**, **2**, and **3**.

Example 2

Table 6 illustrates an example of a dosage modification for adverse reactions in patients treated with cabazitaxel

TABLE 6

| Toxicity | Dosage Modification |
|---|---|
| Prolonged grade ≥3 neutropenia (greater than 1 week) despite appropriate medication including G-CSF | Delay treatment until neutrophil count is >1,500 cells/mm$^3$, then reduce dosage of cabazitaxel to 20 mg/m$^2$. Use G-CSF for secondary prophylaxis. |
| Febrile neutropenia | Delay treatment until improvement or resolution, and until neutrophil count is >1,500 cells/mm$^3$, then reduce dosage of cabazitaxel to 20 mg/m$^2$. Use G-CSF for secondary prophylaxis. |
| Grade ≥3 diarrhea or persisting diarrhea despite appropriate medication, fluid and electrolytes replacement | Delay treatment until improvement or resolution, then reduce dosage of cabazitaxel to 20 mg/m$^2$. |

Discontinue cabazitaxel treatment if a patient continues to experience any of these reactions at 20 mg/m$^2$.

Example 3

Performance Status and Pain Scores During Treatment

Methods

ECOG PS, pain measures, and analgesic consumption were assessed prior to every treatment cycle and at the end of study treatment.

Pain assessments: Present Pain Intensity (PPI) scale from the McGill-Melzack questionnaire (Melzack R. Pain 1975; 1:277-99). Mean Analgesic Score (AS) derived from analgesic consumption (in morphine equivalents) was calculated for the one-week period prior to each evaluation. Area under the curve (AUC) of PPI and AS was calculated by the trapezoid formula. Cumulative AUC of PPI and AS was calculated up to the last cycle of data available for each patient. Average AUC of the treatment groups was compared from Cycle 1 to Cycle 10.

Results

Performance status remained stable in most patients during the treatment period and was similar between groups. See FIG. **4**.

Overall, PPI scores were comparable; improving from baseline in 21.3% of men in the CbzP group and 18.2% in the MP group. See FIG. **5**.

The CbzP group had a lower mean area under the curve (AUC) of PPI, suggesting less severe pain especially during cycles 7-10. See FIG. **6**.

Analgesic use was comparable between the groups (lower mean AUC of AS means lower pain medication use). See FIG. **7**.

Conclusion

Despite longer treatment with CbzP no worsening in ECOG PS was seen.

Present Pain Intensity score improved in 21% of men in CbzP vs. 18% in MP arm. Assessment of pain scores suggested less severe pain in the CbzP group during treatment.

Pain medication use was similar between groups.

Example 4

A population pharmacokinetic analysis was conducted in 170 patients with solid tumors at doses ranging from 10 to 30 mg/m$^2$ weekly or every 3 weeks.

Based on the population pharmacokinetic analysis, after an intravenous dose of cabazitaxel 25 mg/m$^2$ every 3 weeks, the mean $C_{max}$ in patients with metastatic prostate cancer was 226 ng/mL (CV 107%) and was reached at the end of the 1-hour infusion ($T_{max}$). The mean AUC in patients with metastatic prostate cancer was 991 ng·h/mL (CV 34%). No major deviation from the dose proportionality was observed from 10 to 30 mg/m$^2$ in patients with advanced solid tumors. The volume of distribution (Vss) was 4,864 L (2,643 L/m$^2$ for a patient with a median BSA of 1.84 m$^2$) at steady state.

Based on the population pharmacokinetic analysis, cabazitaxel has a plasma clearance of 48.5 L/h (CV 39%; 26.4 Uh/m$^2$ for a patient with a median BSA of 1.84 m$^2$) in patients with metastatic prostate cancer. Following a 1-hour intravenous infusion, plasma concentrations of cabazitaxel can be described by a 3-compartment PK model with α-, β-, and γ-half-lives of 4 minutes, 2 hours, and 95 hours, respectively.

What is claimed is:

**1**. A method for treating a patient with prostate cancer that has progressed during or after treatment with docetaxel, comprising administering to said patient a dose of 20 to 25 mg/m$^2$ of cabazitaxel, or a hydrate or solvate thereof, in combination with a corticoid.

**2**. The method according to claim **1**, where the prostate cancer is an advanced metastatic disease.

**3**. The method according to claim **1**, where the cabazitaxel is in the form of an acetone solvate.

**4**. The method according to claim **3**, in which the acetone solvate contains between 5% and 8% by weight of acetone.

**5**. The method according to claim **1**, comprising repeating the administration of cabazitaxel, or hydrate or solvate thereof, as a new cycle every 3 weeks.

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6. The method according to claim 1, wherein the cabazitaxel is in base form.

7. The method according to claim 1, wherein said cabazitaxel, or hydrate or solvate thereof, is administered in an amount to provide an AUC of about 991 ng·h/mL (CV 34%).

8. The method according to claim 1, wherein said cabazitaxel, or hydrate or solvate thereof, is administered in an amount to provide an $C_{max}$ of about 226 ng·h/mL (CV 107%).

9. The method according to claim 1 wherein said cabazitaxel, or hydrate or solvate thereof, is administered in an amount to provide a plasma clearance of 48.5 L/h (CV 39%).

10. The method according to claim 1, further comprising monitoring blood counts and measuring neutrophil levels in the patient.

11. The method according to claim 10, further comprising discontinuing cabazitaxel treatment in a patient with a neutrophil count of ≤1,500 cells/mm$^3$.

12. The method according to claim 1, where the cabazitaxel, or hydrate or solvate thereof, is administered at a dose of 25 mg/m$^2$.

13. The method according to claim 1, wherein the corticoid is selected from the group consisting of prednisone and prednisolone.

14. The method according to claim 13, where the prednisone or prednisolone is administered at a dose of 10 mg/day.

15. The method according to claim 14, where the cabazitaxel, or hydrate or solvate thereof, is administered at a dose of 20 mg/m$^2$.

16. The method according to claim 14, where the cabazitaxel, or hydrate or solvate thereof, is administered at a dose of 25 mg/m$^2$.

17. The method according to claim 1, where the prostate cancer is a castration resistant or hormone-refractory prostate cancer.

18. The method according to claim 17, where the cabazitaxel, or hydrate or solvate thereof, is administered at a dose of 25 mg/m$^2$.

19. The method according to claim 17, comprising repeating the administration of said cabazitaxel, or hydrate or solvate thereof, as a new cycle every 3 weeks.

20. The method according to claim 1, wherein the prostate cancer is a castration resistant or hormone-refractory, metastatic prostate cancer.

21. The method according to claim 20, where the cabazitaxel, or hydrate or solvate thereof, is administered at a dose of 20 mg/m$^2$.

22. The method according to claim 20, where cabazitaxel, or hydrate or solvate thereof, is administered at a dose of 25 mg/m$^2$.

23. The method according to claim 20, comprising repeating the administration of said cabazitaxel, or hydrate or solvate thereof, as a new cycle every 3 weeks.

24. The method according to claim 1, wherein the prostate cancer is a castration resistant or hormone-refractory, metastatic prostate cancer, and wherein the corticoid is selected from the group consisting of prednisone and prednisolone, and wherein the cabazitaxel, or hydrate or solvate thereof, is administered at a dose of 25 mg/m$^2$.

25. The method according to claim 24, comprising repeating the administration of said cabazitaxel, or hydrate or solvate thereof, as a new cycle every 3 weeks.

26. The method according to claim 1, where the cabazitaxel, or hydrate or solvate thereof, is administered at a dose of 20 mg/m$^2$.

27. A method of increasing the survival of a patient with a castration resistant or hormone refractory, metastatic prostate cancer that has progressed during or after treatment with docetaxel, comprising administering a dose of 20 to 25 mg/m$^2$ of cabazitaxel, or hydrate or solvate thereof, to the patient in combination with prednisone or prednisolone.

28. The method according to claim 27, where the cabazitaxel, or hydrate or solvate thereof, is administered at a dose of 25 mg/m$^2$.

29. The method according to claim 27, comprising repeating the administration of said cabazitaxel, or hydrate or solvate thereof, as a new cycle every 3 weeks.

30. The method according to claim 27, where the cabazitaxel, or hydrate or solvate thereof, is administered at a dose of 20 mg/m$^2$.

* * * * *

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**PROOF OF SERVICE**

The undersigned counsel for Plaintiffs-Appellants certifies that, on June 25, 2018, the **BRIEF FOR PLAINTIFFS-APPELLANTS** (confidential and non-confidential) was caused to be filed via CM/ECF with:

Clerk of the Court
United States Court of Appeals for the Federal Circuit
717 Madison Place, NW
Washington, DC 20439

The undersigned also certifies that, on June 25, 2018, a true and correct copy of the **BRIEF FOR PLAINTIFFS-APPELLANTS** (confidential and non-confidential) was caused to be served on counsel of record via CM/ECF and electronic mail.

Dated: June 25, 2018

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**CERTIFICATE OF COMPLIANCE WITH TYPE-VOLUME, TYPE-FACE, AND TYPE-STYLE REQUIREMENTS**

The undersigned counsel for Plaintiffs-Appellants hereby certifies that this brief by Plaintiffs-Appellants complies with the type-volume limitation of Federal Circuit Rule 28.1. This brief contains 11,651 words, excluding portions exempted by Federal Rule of Appellate Procedure 32(f). The undersigned counsel also certifies that this brief complies with the type-face requirements of Federal Rule of Appellate Procedure 32(a)(5) or Federal Circuit Rule 28.1 and the type-style requirements of Federal Rule of Appellate Procedure 32(a)(6). The brief was prepared in Microsoft Word 2010 using a proportional 14-point Times New Roman type-face.

Dated: June 25, 2018

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**CERTIFICATE OF COMPLIANCE FOR BRIEFS CONTAINING MATERIAL SUBJECT TO A PROTECTIVE ORDER**

The undersigned counsel for Plaintiffs-Appellants hereby certifies that this brief by Plaintiffs-Appellants complies with the limitations set forth in Federal Circuit Rule 28(d) and contains zero words marked as confidential.

Dated: June 25, 2018

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