IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

TAIHO PHARMACEUTICAL CO., LTD. and TAIHO ONCOLOGY, INC. Plaintiffs, v. EUGIA PHARMA SPECIALITIES LTD., AUROBINDO PHARMA LTD., and AUROBINDO PHARMA U.S.A., INC., Defendants.	Civil Action No. 19-2309-CFC

TAIHO PHARMACEUTICAL CO., LTD. and TAIHO ONCOLOGY, INC. Plaintiffs, v. ACCORD HEALTHCARE INC., Defendant.	Civil Action No. 19-2321-CFC

TAIHO PHARMACEUTICAL CO., LTD. and TAIHO ONCOLOGY, INC. Plaintiffs, v. MSN LABORATORIES PRIVATE LTD. and MSN PHARMACEUTICALS, INC., Defendants.	Civil Action No. 19-2342-CFC-JLH

TAIHO PHARMACEUTICAL CO., LTD. and TAIHO ONCOLOGY, INC. Plaintiffs, v. NATCO PHARMA LTD. and NATCO PHARMA, INC. Defendants.	Civil Action No. 19-2368-JLH

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OPINION

August 15, 2023
Wilmington, Delaware

COLM F. CONNOLLY
CHIEF JUDGE

This patent infringement case arises out of the submissions by Defendants Eugia Pharma Specialties Ltd, Aurobindo Pharma Ltd., and Aurobindo Pharma U.S.A., Inc. (collectively, Eugia); Accord Healthcare Inc. (Accord); MSN Laboratories Private Ltd. and MSN Pharmaceuticals, Inc. (collectively, MSN); and Natco Pharma Ltd. and Natco Pharma, Inc. (collectively, Natco) of Abbreviated New Drug Applications (ANDAs) to the U.S. Food and Drug Administration (FDA) for approval to manufacture, use, or sell a generic version of Lonsurf®.

Lonsurf® is marketed by Plaintiffs Taiho Pharmaceutical Co., Ltd. and Taiho Oncology, Inc. (collectively, Taiho). It is an oral combination therapy used for treating adult patients with metastatic colorectal cancer who have already received certain other prior treatments. This combination therapy is also known as TAS-102. Lonsurf® contains two active ingredients: trifluorothymidine (FTD), which is a two-prime deoxypyrimidine nucleoside; and tipiracil, which is a uracil derivative and thymidine phosphorylase inhibitor.

Taiho alleges that Defendants' ANDA submissions constitute infringement under 35 U.S.C. § 271(e)(2)(A) of claim 13 of U.S. Patent No. RE46,284 (the #284 patent). Claim 13 is directed towards a method of treating patients with colorectal cancer by orally administering a specific dosage and molar ratio of FTD and

tipiracil, in two divided portions per day, for a period of five days of treatment followed by two days off treatment.

Defendants do not dispute that they infringe the #284 patent, but they argue that the #284 patent is invalid for obviousness and for lack of an adequate written description.

With respect to obviousness, Defendants argue that TAS-102 and its oral administration; dosage; molar ratio; and five days on, two days off administration schedule are all explicitly disclosed in the prior art. Defendants point to a 2001 abstract (Dwivedy) that describes a Phase I clinical trial that Taiho conducted. That piece of prior art discloses once-daily oral administration of FTD and a thymidine phosphorylase inhibitor to gastrointestinal cancer patients for five days, followed by two days of rest, in the dosage range taught in claim 13. Defendants also point to a January 2004 article (Emura II) that describes a study in which mice were grafted with human gastric cancer cells and treated with either once-daily or thrice-daily oral administration of TAS-102 in the molar ratio taught by claim 13. Defendants say that it would have been "common sense," based on the relevant prior art, to administer TAS-102 in twice-daily doses, and that Emura II and Dwivedy, in light of the state of the art, would have taught each element of claim 13 to an artisan of ordinary skill in January 2005. Defendants also assert that a

skilled artisan would have been motivated to combine the teachings of Emura II and Dwivedy and would have had a reasonable expectation of success in doing so.

Taiho insists that an artisan of ordinary skill would not have been motivated, based on Emura II, Dwivedy, and the state of the art, to administer TAS-102 in twice-daily doses. Taiho also argues that a skilled artisan would not have been motivated to administer TAS-102 in accordance with Dwivedy's administration schedule. Thus, to Taiho, Defendants' proposed motivation to combine and reasonable expectation of success arguments are nothing more than impermissible hindsight. Taiho also points to four objective indicia of nonobviousness: unexpected results, long-felt need, industry praise, and commercial success.

With respect to the written description requirement, Defendants argue that the #284 patent's specification does not show that the inventors were in possession of all of claim 13's inventive aspects—namely, twice-daily administration of TAS-102 to a patient with colorectal cancer. Although the #284 patent's written description describes a study in which TAS-102 was administered twice-daily to breast cancer patients, Defendants say that breast and colorectal cancer are too distinct to compare helpfully. Taiho responds that breast and colorectal cancer studies can be helpfully compared, and the #284 patent's written description demonstrates that the inventor possessed the claimed subject matter.

I held a two-day bench trial, and, as required by Federal Rule of Civil Procedure 52(a)(1), I have set forth separately below my findings of fact and conclusions of law.

I. THE STATUTORY AND REGULATORY FRAMEWORK

The ANDA procedures out of which this case arises were established by FDA regulations promulgated pursuant to the Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. § 301 *et seq.*, and specifically by the so-called Hatch-Waxman Amendments to the FDCA. Justice Kagan provided, in *Caraco Pharmaceutical Laboratories, Ltd. v. Novo Nordisk A/S*, 566 U.S. 399 (2012), this helpful summary of the provisions of the Amendments and the FDA regulations that bear on this case:

> The FDA regulates the manufacture, sale, and labeling of prescription drugs under a complex statutory scheme. To begin at the beginning: When a brand manufacturer wishes to market a novel drug, it must submit a new drug application (NDA) to the FDA for approval. The NDA must include, among other things, a statement of the drug's components, scientific data showing that the drug is safe and effective, and proposed labeling describing the uses for which the drug may be marketed. The FDA may approve a brand-name drug for multiple methods of use—either to treat different conditions or to treat the same condition in different ways.
>
> Once the FDA has approved a brand manufacturer's drug, another company may seek permission to market a generic version pursuant to legislation known as the Hatch-Waxman Amendments.

Those amendments allow a generic competitor to file an abbreviated new drug application (ANDA) piggy-backing on the brand's NDA. Rather than providing independent evidence of safety and efficacy, the typical ANDA shows that the generic drug has the same active ingredients as, and is biologically equivalent to, the brand-name drug. As we have previously recognized, this process is designed to speed the introduction of low-cost generic drugs to market.

Because the FDA cannot authorize a generic drug that would infringe a patent, the timing of an ANDA's approval depends on the scope and duration of the patents covering the brand-name drug. Those patents come in different varieties. One type protects the drug compound itself. Another kind . . . gives the brand manufacturer exclusive rights over a particular method of using the drug. In some circumstances, a brand manufacturer may hold such a method–of–use patent even after its patent on the drug compound has expired.

To facilitate the approval of generic drugs as soon as patents allow, the Hatch-Waxman Amendments and FDA regulations direct brand manufacturers to file information about their patents. The statute mandates that a brand submit in its NDA the patent number and the expiration date of any patent which claims the drug for which the brand submitted the NDA or which claims a method of using such drug. And the regulations issued under that statute require that, once an NDA is approved, the brand provide a description of any method-of-use patent it holds. That description is known as a use code, and the brand submits it on FDA Form 3542. . . . [T]he FDA does not attempt to verify the accuracy of the use codes that brand manufacturers supply. It simply publishes the codes, along with the corresponding patent numbers and expiration dates, in a fat, brightly hued volume called the Orange Book (less colorfully but more officially denominated Approved Drug Products With Therapeutic Equivalence Evaluations).

> After consulting the Orange Book, a company filing an ANDA must assure the FDA that its proposed generic drug will not infringe the brand's patents. When no patents are listed in the Orange Book or all listed patents have expired (or will expire prior to the ANDA's approval), the generic manufacturer simply certifies to that effect. Otherwise, the applicant has two possible ways to obtain approval.
>
> * * * *[One of those ways] is to file a so-called paragraph IV certification, which states that a listed patent "is invalid or will not be infringed by the manufacture, use, or sale of the generic drug." 21 U.S.C. § 355(j)(2)(A)(vii)(IV). A generic manufacturer will typically take this path in either of two situations: if it wants to market the drug for all uses, rather than carving out those still allegedly under patent; or if it discovers, as described above, that any carve-out label it is willing to adopt cannot avoid the brand's use code. Filing a paragraph IV certification means provoking litigation. The patent statute treats such a filing as itself an act of infringement, which gives the brand an immediate right to sue [under 35 U.S.C. § 271(e)(2)(A)]. Assuming the brand does so, the FDA generally may not approve the ANDA until 30 months pass or the court finds the patent invalid or not infringed. Accordingly, the paragraph IV process is likely to keep the generic drug off the market for a lengthy period, but may eventually enable the generic company to market its drug for all approved uses.

566 U.S. at 404–08 (cleaned up).

II. FINDINGS OF FACT

A. The Parties

1) Taiho Pharmaceutical Co., Ltd. is a Japanese corporation with its principal place of business in Japan. No. 19-2309[1], D.I. 146-1 ¶ 1.

2) Taiho Oncology, Inc. is a Delaware corporation with its principal place of business in New Jersey. D.I. 146-1 ¶ 2.

3) Eugia Pharma Specialties Ltd. and Aurobindo Pharma Ltd. are Indian corporations with principal places of business in India. D.I. 146-1 ¶¶ 3–4.

4) Aurobindo Pharma U.S.A., Inc. is a Delaware corporation with its principal place of business in New Jersey. D.I. 146-1 ¶ 5.

5) Accord Healthcare Inc. is a North Carolina corporation with its principal place of business in North Carolina. D.I. 146-1 ¶ 6.

6) MSN Laboratories Private Ltd. is an Indian corporation with its principal place of business in India. D.I. 146-1 ¶ 7.

7) MSN Pharmaceuticals Inc. is a Delaware corporation with its principal place of business in New Jersey. D.I. 146-1 ¶ 8.

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[1] Although the four cases have not been consolidated, they were tried together. Because identical briefs were filed in all four cases, I cite only to one docket—19-2368—the same docket that the parties cited to in their briefs. Thus, all D.I. citations refer to the No. 19-2368 docket.

8) Natco Pharma Ltd. is an Indian corporation with its principal place of business in India. D.I. 146-1 ¶ 9.

9) Natco Pharma, Inc. is a Delaware corporation with its principal place of business in Pennsylvania. D.I. 146-1 ¶ 10.

B. The Parties' Witnesses

1. Fact Witnesses

10) Dr. Martin Birkhofer is the Senior Vice President and Chief Medical Officer of Taiho Oncology, Inc. He ran the group "responsible for the clinical development of Taiho's pipeline assets outside of Japan." Tr. of March 29–30, 2023 bench trial at 247:4–8. Dr. Birkhofer did not testify live during trial. Instead, portions of his deposition were read aloud. Tr. 239:9–12.

11) Akira Mita is a named inventor on the #284 patent. D.I. 146-1 ¶ 33. Mita has worked at Taiho for "about 35 years." Tr. 257:23–24. He has contributed to Taiho's TAS-102 research. *See, e.g.*, Tr. 261:4–10.

12) Timothy Whitten is the President and Chief Executive Officer of Taiho Oncology, Inc. Tr. 309:6–8. He testified about Taiho's pre- and post-approval activities relating to Lonsurf®. *See, e.g.*, Tr. 314:17–24.

2. Defendants' Expert Witnesses

13) Dr. Mark Ratain has worked in the area of drug development in the oncology field since he received his medical degree from Yale University in 1980. Tr. 86:21–87:6. He testified as an expert in the fields of oncology and clinical

pharmacology, with particular expertise in clinical trials and clinical trial design. Tr. 90:11–17.

14) Ivan Hofmann is an economist with a focus on pharmaceutical economics and intellectual property economics. Tr. 497:7–22. He received a Bachelor of Business Administration from the University of Notre Dame. D.I. 146-10 at 64. He testified as an expert on pharmaceutical economics. Tr. 498:3–6.

3. Taiho's Expert Witnesses

15) Dr. Richard Goldberg received a medical degree from SUNY Upstate Medical University. He received specialty training in medical oncology at Georgetown University. Tr. 340:1–5. Dr. Goldberg testified as an expert in cancer treatment of digestive cancers and in Phase I clinical trial studies. Tr. 341:25–42:5.

16) Mohan Rao is an economist and the chief executive officer of Epsilon Economics and Expression Therapeutics. Tr. 455:9–11. He received a Bachelor of Science in engineering from the University of Michigan, was a pre-doctoral fellow at Harvard University, and holds a MA and PhD in economics from the University of Colorado. Tr. 455:11–13; D.I. 146-9 at 76. Dr. Rao testified "as an economics expert with expertise in evaluating commercial success." Tr. 457:10–14.

C. Taiho's NDA

17) Taiho Oncology, Inc. is the holder of NDA No. 207981 for Lonsurf®. D.I. 146-1 ¶ 11.

18) "Lonsurf® is indicated for the treatment of metastatic colorectal cancer in patients [who] have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and, if RAS wild-type, an anti-EGFR therapy as well as the treatment of metastatic gastric or gastroesophageal junction adenocarcinoma previously treated with at least two prior lines of chemotherapy that included a fluoropyrimidine, a platinum, either a taxane or irinotecan, and if appropriate, a HER2/neu-targeted therapy." D.I. 146-1 ¶ 16.

19) Lonsurf® is a combination therapy that involves the oral administration of two active ingredients: (1) trifluorothymidine (FTD), and (2) tipiracil. D.I. 146-1 ¶ 12.

20) FTD is a nucleoside metabolic inhibitor, and tipiracil is a uracil derivative and thymidine phosphorylase inhibitor (TPI). D.I. 146-1 ¶ 12.[2]

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[2] A brief note on acronyms. As noted below, claim 1 of the #284 patent, from which claim 13 depends, teaches orally administering a composition comprising α,α,α-trifluorothymidine (FTD) and 5-chloro-6-(l-(2-iminopyrrolidinyl)methyl)uracil hydrochloride." *See* ¶ 47. The first component of that composition is trifluorothymidine, which is abbreviated as "FTD." The second component of TAS-102 is 5-chloro-6-(l-(2-iminopyrrolidinyl)methyl)uracil hydrochloride, which is also known as "tipiracil." Tipiracil is a type of thymidine

21) This combination therapy of FTD and tipiracil is also known as TAS-102. D.I. 146-1 ¶ 18.

22) Lonsurf® is sold as a tablet with FTD and tipiracil present in a molar ratio of 1:0.5. D.I. 146-1 ¶ 17.

23) Lonsurf®'s current label recommends an administration schedule of "35 mg/m^2/dose orally twice daily with food on Days 1 through 5 and Days 8 through 12 of each 28-day cycle." JTX 0151 at 1; *see also* Tr. 310:16–19 (Whitten).

24) The FDA approved Lonsurf® on September 22, 2015. D.I. 146-1 ¶ 15.

D. Defendants' ANDAS

25) Eugia has submitted ANDA No. 213893, seeking approval to engage in the commercial manufacture, use, sale, and/or importation of a generic version of Lonsurf®. Eugia's ANDA No. 213893 contains a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) that the #284 patent is invalid or would not be infringed. D.I. 146-1 ¶ 22.

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phosphorylase inhibitor. *See* D.I. 146-1 ¶ 12. The parties, however, at many points during the trial and in their briefs, referred to tipiracil as "TPI." But because tipiracil is only one type of thymidine phosphorylase inhibitor, I refer to a thymidine phosphorylase inhibitor as "TPI," and I refer to "tipiracil" as "tipiracil."

26) Eugia concedes that its ANDA product will, upon FDA approval, infringe claim 13 of the #284 patent, "assuming that patent is not deemed invalid." D.I. 146-1 ¶ 23.

27) Accord has submitted ANDA No. 214036, seeking approval to engage in the commercial manufacture, use, sale, and/or importation of a generic version of Lonsurf®. Accord's ANDA No. 214036 contains a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) that the #284 patent is invalid or would not be infringed. D.I. 146-1 ¶ 24.

28) Accord concedes that its ANDA product will, upon FDA approval, infringe claim 13 of the #284 patent, "assuming that patent is not deemed invalid." D.I. 146-1 ¶ 25.

29) MSN has submitted ANDA No. 214024, seeking approval to engage in the commercial manufacture, use, sale, and/or importation of a generic version of Lonsurf®. MSN's ANDA No. 214024 contains a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) that the #284 patent is invalid or would not be infringed. D.I. 146-1 ¶ 26.

30) MSN concedes that its ANDA product will, upon FDA approval, infringe claim 13 of the #284 patent, "assuming that patent is not deemed invalid." D.I. 146-1 ¶ 27.

31) Natco has submitted ANDA No. 214008, seeking approval to engage in the commercial manufacture, use, sale, and/or importation of a generic version of Lonsurf®. MSN's ANDA No. 214008 contains a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) that the #284 patent is invalid or would not be infringed. D.I. 146-1 ¶ 28.

32) Natco concedes that its ANDA product will, upon FDA approval, infringe claim 13 of the #284 patent, "assuming that patent is not deemed invalid." D.I. 146-1 ¶ 29.

E. The #284 Patent

33) The #284 patent is titled: "Method of Administering an Anticancer Drug Containing α,α,α-Trifluorothymidine [(FTD)] and Thymidine Phosphorylase Inhibitor [(TPI)]." D.I. 146-1 ¶ 33.

34) Taiho is the owner of all right, title, and interest in the #284 patent. D.I. 146-1 ¶ 30.

35) The #284 patent's named inventors are Tomohiro Emura and Akira Mita. D.I. 146-1 ¶ 33.

36) The parties agree that January 26, 2005 is the priority date for claim 13 of the #284 patent. D.I. 146-1 ¶ 32.

1. The Reissue Proceedings

37) The #284 patent is a reissue of U.S. Patent No. 7,799,783 (the #783 Patent). The #783 patent was filed on January 26, 2005 and issued on September 21, 2010. D.I. 146-1 ¶ 30.

38) Originally, the #783 patent was filed as U.S. Patent Application No. 11/042,059 (the #059 Application) on January 26, 2005. D.I. 146-1 ¶ 30.

39) As noted above, the parties agree that the #059 Application's filing date—January 26, 2005—is the priority date for claim 13 of the #284 patent. D.I. 146-1 ¶ 32.

40) Taiho filed U.S. Patent Application No. 14/985,148 on December 30, 2015, seeking reissuance of the #783 patent. D.I. 146-1 ¶ 31.

41) Taiho filed the reissue application because it discovered that an article (Emura II, *see* ¶¶ 134–47) authored by named inventor Tomohiro Emura was prior art to the #783 patent. Taiho had believed that Emura II was not prior art, but Taiho later learned that Emura II was published in a British library one week before the January 26, 2004 critical date. JTX 0012 at 194, 206.

42) Taiho's counsel conceded that during the reissue proceedings, Taiho surrendered the original #783 patent. Tr. 61:15–16.

43) Taiho surrendered the #783 patent because Taiho "claimed less than it had the right to claim in the patent." JTX 0012 at 207.

44) During the reissue proceedings, claims 1 and 10 were narrowed, and claim 13 was added. Paragraphs 47–49 of this opinion, which recite claims 1, 10, and 13 of the #284 patent, detail the changes. The text in italics in those paragraphs is claim language that was not in the #783 patent but was added to the #284 patent. The text in brackets is claim language that was in the #783 patent but was not included in the #284 patent. #284 patent at claims 1, 10, 13; D.I. 146-1 ¶¶ 34–35.

2. The Relevant Claims

45) Taiho asserts infringement of claim 13 of the #284 patent, which depends from claims 1 and 10. D.I. 146 ¶ 22.

46) Defendants have stipulated to infringement of claim 13 of the #284 patent. D.I. 146 ¶ 24.

47) Independent claim 1 of the #284 patent reads:

> A method for treating at least one of a digestive cancer and a breast cancer, comprising
>
> orally administering a composition comprising α,α,α-trifluorothymidine (FTD) and 5-chloro-6-(1-(2-iminopyrrolidinyl)methyl)uracil hydrochloride in a molar ratio of 1:0.5 at a dose of 50 to 70 mg/m^2/day in terms of FTD in 2 [or 3] divided portions per day to a human patient in need of treatment of at least one of a digestive cancer and a breast cancer,
>
> wherein the administration of a daily dose of said composition is in 2 [or 3] portions per day for 5 days followed by 2 days off treatment in the week

> on a one-week dosing schedule *wherein* m^2 *is the human patient's body surface area.*

48) Claim 10 depends from claim 1 and reads:

> The method [according to] *of* claim **1**, wherein the [cancer] *method* is *for treating* digestive cancer *which is selected from the group consisting of esophageal, gastric, liver, gallbladder-bile duct, pancreatic, and colorectal cancers.*

D.I. 1-1 at 30 (alterations and emphasis in the original); D.I. 146-1 ¶ 34. (Again, the text in italics is claim language that was not in the #783 patent but was added to the #284 patent. The text in brackets is claim language that was in the #783 patent but was not included in the #284 patent.)

49) Claim 13 depends from claim 10 and reads, "*The method of claim 10, wherein the digestive cancer is colorectal cancer.*" D.I. 1-1 at 30 (emphasis in the original).

F. The Artisan of Ordinary Skill[3]

50) Before trial, the parties agreed that an artisan of ordinary skill in the field of the #284 patent, as of January 26, 2005, "would be a physician with a medical degree and at least five years of practical experience in the clinical treatment of patients suffering from cancer. The [artisan of ordinary skill] would

[3] Determination of the level of ordinary skill in the pertinent art is a factual inquiry. *Daiichi Sankyo Co. v. Matrix Lab'ys, Ltd.*, 619 F.3d 1346, 1352 (Fed. Cir. 2010).

have at least 2–3 years of residency or fellowship training in oncology and would be an oncologist in the everyday practice of treating cancer patients. Because the drug development process is multidisciplinary, the person (or team) would have at least practical training in one or more areas of pharmacy, pharmaceutical sciences, preclinical and clinical drug development, medicine, pharmacokinetics and/or pharmacology." D.I. 146-1 ¶¶ 36–37.

51) Defendants referred to the artisan of ordinary skill as a "hypothetical investigator" during the trial. *See, e.g.*, Tr. 21:8–12 ("Our person of ordinary skill in the art, Your Honor, our hypothetical person of ordinary skill in the art -- we'll call him a hypothetical investigator because I get tired of saying those four words over and over again.").

52) During Dr. Ratain's testimony, Defendants asked Dr. Ratain if he was aware of the parties' agreed-upon definition of an artisan of ordinary skill. Tr. 93:20–94:15.

53) Dr. Ratain testified that he was aware of the parties' agreed-upon definition of an artisan of ordinary skill and that he applied that definition in his analysis. Tr. 93:20–94:15.

54) After Dr. Ratain testified about the artisan of ordinary skill, he acknowledged that if counsel referred to a "hypothetical investigator," he was referring to the parties' agreed-upon definition of an artisan of ordinary skill. *See*

Tr. 94:20–23 ("Q: And if I say "hypothetical investigator," will you understand we are talking about the person with the skill set that we've just described? Would that be all right? A. Yes.").

55) During trial, Taiho never objected to Defendants' use of the phrase "hypothetical investigator" or suggested that Defendants were referring to anyone other than the parties' agreed-upon definition of an artisan of ordinary skill.

56) I therefore find that when Defendants referred to a "hypothetical investigator," they were referring to the parties' agreed-upon definition of an artisan of ordinary skill.

57) Defendants' expert, Dr. Ratain, meets the parties' agreed-upon definition of an artisan of ordinary skill. Dr. Ratain received a medical degree in 1980, and the "focus of [his] career" has been the "area of drug development in the oncology field." Tr. 87:3–6. His listed experience includes, for example, working as a Fellow at the University of Chicago's Hematology/Oncology section from 1983–86 and as an instructor, then assistant professor, in the University of Chicago's Hematology/Oncology section from 1986–91. Since 2002, Dr. Ratain has worked as the Leon O. Jacobson Professor in the University of Chicago's Hematology/Oncology section. D.I. 146-10 at 10–11. He also testified that he has experience in early clinical trials involving oral chemotherapy drugs, Tr. 87:7–18, and in treating patients with colorectal or breast cancer, Tr. 90:8–10.

58) Taiho's expert, Dr. Goldberg, also meets the parties' agreed-upon definition of an artisan of ordinary skill. Dr. Goldberg received his medical degree in 1979. D.I. 146-9 at 13. After his residency, Dr. Goldberg spent two years as a research fellow in Georgetown University's oncology department. D.I. 146-9 at 13. Dr. Goldberg testified that he has "been both a patient care giver and a researcher, including mainly a focus on gastrointestinal cancers, and within that specialty mainly on colorectal cancer. And [he has] conducted Phase I, II, III studies . . . , as well as supervised research programs for National Cancer Institute-funded cooperative oncology research groups." Tr. 340:25–41:6. His work experience also includes working from 2003–11 as the Chief of the University of North Carlina, Chapel Hill's Hematology/Oncology Division. D.I. 146-1 at 14.

G. An Ordinarily Skilled Artisan's Knowledge as of January 26, 2005

1. Companies Were Developing Oral Chemotherapy Treatments

59) By January 26, 2005, the use of oral chemotherapy treatments was well known in the art. Tr. 105:23–25 (Ratain).

60) Oral chemotherapy treatment expanded in part because in 1996, changes in Medicare policy "began reimbursing for oral equivalents of intravenous chemotherapy drugs." That change "created the motivation for companies to suddenly be interested in developing oral chemotherapy drugs." Tr. 106:4–9 (Ratain).

61) Oral chemotherapy treatment also expanded because oral chemotherapies can "be administered and delivered to patients without the costs of the infusion unit," thus reducing treatment costs. Tr. 106:16–21 (Ratain); *see also* DTX 0253 (a 1998 article co-authored by Dr. Ratain that describes the trend towards increased use of oral chemotherapy drugs).

62) Furthermore, oral chemotherapy treatments were seen as more convenient for patients because the drugs could be taken in the patients' homes. Tr. 106:25–07:6, 108:10–14 (Ratain); Tr. 393:9–13 (Goldberg).

63) By January 26, 2005, some oral chemotherapies had been approved for twice-daily dosing schedules. *See* Tr. 113:23–14:8 (Ratain); Tr. 396:16–97:3 (Goldberg).

2. Administering FTD Could Produce Strong Anticancer Effects

64) It is undisputed that in 1971, artisans of ordinary skill knew that scientists had studied the use of FTD as an anticancer drug.

65) A 1971 article, "Phase I and II Studies of 2'-Deoxy-5-(trifluoromethyl)-uridine (NSC-75520)" (Ansfield), reports the results of Phase I and II trials in which FTD was administered to cancer patients. *See* DTX 0333, Tr. 142:1–6 (Ratain); Tr. 369:12–20 (Goldberg). Because Ansfield was published in 1971, it is prior art to the #284 patent.

66) Most of the patients in Ansfield had breast or colorectal cancer. DTX 0333 at 1.

67) Some patients received once-daily doses of FTD; other patients received eight doses per day, every three hours apart. DTX 0333 at 2.

68) Ansfield did not report any studies in which TAS-102 was administered twice-daily. DTX 0333.

69) Ansfield also involved intravenous, not oral, administration of FTD. DTX 0333 at 2.

70) The Ansfield authors concluded that FTD itself can produce strong antitumor effects, but FTD must be administered "more than once within 24 hours" to be effective. Tr. 144:9–15 (Ratain); DTX 0333.

71) Ansfield reports that administering FTD can produce promising anticancer effects. *See* Tr. 143:15–18 ("[T]he study clearly demonstrated that FTD was a highly active drug. I mean, I wish I could have done, sometime in my career, a Phase I trial that gave this magnitude of anticancer activity.") (Ratain); Tr. 369:14–16 ("[A]s Dr. Ratain remarked, the Ansfield study, which gave the drug eight times a day, showed pretty remarkable antitumor activity for a Phase I study.") (Goldberg).

3. FTD Works by Binding to a Cancer Cell's DNA and Preventing That Cancer Cell from Replicating

72) During opening statements, Defendant's counsel stated that FTD works by "attach[ing] to the DNA of the cancer cell to keep [the cell] from replicating very easily." Tr. 14:20–22.

73) Dr. Goldberg agreed, during cross examination, that FTD works by attaching to the cancer cells' DNA. Tr. 387:20–22; *see also* DTX 0011 at 1 ("[T]he incorporation of FTD into DNA is expected to be an important factor, discriminating it from 5-FU showing TS inhibitory activity as their main mechanism of action."); Tr. 129:15–19 (Ratain).

4. FTD is a Toxic Chemotherapy Drug

74) "[B]ecause chemotherapy is toxic and, therefore, the body requires a break periodically," most oral chemotherapy compounds cannot be administered continuously. Tr. 107:7–13 (Ratain).

75) Despite FTD's documented anticancer activity, FTD's "toxicity precluded further clinical development." Tr. 369:17–20 (Goldberg).

5. FTD's Short Half-Life Hindered Clinical Development

76) It was also well-known in the art that despite Ansfield's documentation of FTD's anticancer effects, FTD was considered infeasible to administer because it has a short half-life. Tr. 143:20–44:8 (Ratain); Tr. 369:17–20 (Goldberg).

77) FTD has a short half-life because once administered, it is metabolized by the enzyme thymidine phosphorylase. Tr. 146:7–19 (Ratain); Tr. 370:6–9 (Goldberg).

78) Because of FTD's short half-life, after Ansfield was published, "there was very little clinical work done [on FTD] until Taiho scientists decided to try to solve the problem of the short half-life of the drug." Tr. 369:21–23 (Goldberg).

6. Administering FTD with a Thymidine Phosphorylase Inhibitor Could Increase FTD's Half-Life

79) As of January 26, 2005, skilled artisans knew that Taiho scientists had tried unsuccessfully to solve FTD's half-life problem by (1) making a "prodrug" and (2) using a "depot formulation." Tr. 369:25–70:5 (Goldberg).

80) Eventually, "Taiho scientists came to a third strategy for clinical development, which was to try and slow the breakdown of the drug by inhibiting thymidine phosphorylase" through administration of FTD with a thymidine phosphorylase inhibitor (TPI). Tr. 370:6–9 (Goldberg); *see also* Tr. 146:10–25 (Dr. Ratain discussing Taiho's efforts to use TPIs to inhibit FTD breakdown).

81) Taiho discovered that administering FTD with a TPI could help solve FTD's half-life problem. Tr. 146:10–22 (Ratain).

82) The strategy of "combining a drug with another drug that inhibits its metabolism had been well-described in the past, but never applied to FTD" until Taiho began researching TPIs. Tr. 146:10–16 (Ratain).

7. Tipiracil Could be Used as a TPI to Administer With FTD

83) As of January 26, 2005, ordinarily skilled artisans knew that Taiho had received two patents relating to its TAS-102 research.

84) First, U.S. Patent No. 5,744,475 (the #475 patent) was issued on April 28, 1998. PTX 0543. It therefore is prior art to the #284 patent.

85) The #475 patent was listed in the Orange Book from October 20, 2014 until it expired on March 28, 2016. D.I. 146-1 ¶ 20.

86) Taiho listed the #475 patent in the "Orange Book as covering the Lonsurf® product and one or more methods of use for which Lonsurf® was approved." D.I. 146-1 ¶ 20.

87) Second, U.S. Patent No. 6,294,535 (the #535 patent) was issued on September 25, 2001. DTX 0362. It therefore is also prior art to the #284 patent.

88) The #475 and #535 patents are related and share the same written description. Tr. 145:7–9 (Ratain); Tr. 350:11–22 (Goldberg); PTX 0543; DTX 0362.

89) Dr. Goldberg called the #535 patent an "umbrella patent[]" that includes a "huge range of possible dosing for the two components of the drug" and "d[oes] not specify [a] molar ratio." Tr. 350:12–22.

90) Dr. Ratain described the #535 patent as "disclos[ing] novel compounds -- they happen to be uracil derivatives -- that are inhibitors of thymidine phosphorylase." Tr. 146:2–4.

91) Claim 11 of the #535 patent reads in pertinent part: "a therapeutic method for treating cancer, which comprises administering to a patient in need of treatment an effective amount of a uracil derivative . . . and a 2'-deoxypyrimidine nucleoside." DTX 0362 at claim 11.

92) Tipiracil is a type of uracil derivative. *See* Tr. 149:22–23 (Ratain); Tr. 385:3–10 (Goldberg).

93) Tipiracil is disclosed in the #535 patent. *See* DTX 0362 at 26:1–2; Tr. 350:16–19 (Goldberg).

94) FTD is a type of two-prime deoxypyrimidine nucleoside. *See* Tr. 149:24 (Ratain).

95) FTD is disclosed in the #535 patent. *See* Tr. 350:16–19 (Goldberg).

96) Claim 11 of the #535 patent therefore teaches "a therapeutic method for treating cancer which comprises administering to a patient a uracil derivative, such as tipiracil, in combination with a two-prime deoxypyrimidine nucleoside, such as FTD." Tr. 149:21–24 (Ratain).

97) The #535 patent also teaches one-daily dosing or dosing two-to-four times per day. Tr. 150:4–6 (Ratain); Tr. 350:15–16 (Goldberg).

98) I agree with both experts' characterizations of the #535 patent. The #535 patent describes many uracil derivatives, including tipiracil; many two-prime deoxypyrimidine nucleosides, including FTD; many molar ratios, including 1:0.5; and many cancers, including colorectal cancer. *See* DTX 0362.

99) Therefore, I find as a matter of fact that the #535 patent would have taught an artisan of ordinary skill the twice-daily oral administration of tipiracil, in combination with FTD, at a molar ratio of 1:0.5, to treat colorectal cancer. But an artisan of ordinary skill also would have recognized that many other potential combinations of uracil derivatives and two-prime deoxypyrimidine nucleosides could be used, at many different administration schedules, to treat many different cancer types.

100) In addition to the #475 and #535 patents, Taiho disclosed in Emura II that Taiho had developed the specific TAS-102 treatment of FTD and tipiracil in a molar ratio of 1:0.5. As discussed below, Emura II disclosed TAS-102 as "a combination drug consisting of [FTD] and thymidine phosphorylase inhibitor (TPI)." DTX 0011 at 1. And in describing the reagents used in the studies, Emura II states that "FTD . . . and TPI, which is [tipiracil], were mixed at a molar ratio of 1:0.5." DTX 0011 at 2; *see also* Tr. 156:4–57:6 (Ratain).

H. The Relevant Prior Art

1. The Phase I Trials

a. Hoff

101) The abstract, "Phase I safety and pharmacokinetic study of oral TAS-102 once daily for fourteen days in patients with solid tumors" (Hoff), was published in 2000. PTX 0534. It is undisputed that Hoff is prior art to the #284 patent.

102) Hoff is a Phase I study conducted by Taiho at the University of Texas M.D. Anderson Cancer Center. PTX 0534.

103) Hoff describes a Phase I trial to determine the "maximum tolerated dose, dose limiting toxicity (DLT), and pharmacokinetics (PK) of TAS-102" when "given orally once-daily for 14 days every 21 days." PTX 0534; Tr. 398:5–24 (Goldberg).

104) Hoff does not disclose whether tipiracil was the specific TPI used in the TAS-102 treatment. Instead, TAS-102 is described in Hoff as "an oral combination of [FTD] with a thymidine phosphorylase inhibitor." PTX 0534.

105) Hoff describes 14 patients with gastrointestinal cancer who were entered into the study. Each of these 14 patients had received second-line treatment for gastrointestinal cancer. PTX 0534.

106) The patients received TAS-102 doses of 50, 60, or 100 mg/m^2/day. PTX 0534.

107) At the initial 100 mg/m^2/d dose, "1/2 [patients] experienced [dose-limiting toxicity (DLT)] (granulocytopenia). The dose was reduced to 50 mg/m^2 in the next 3 [patients] with no DLTs observed." PTX 0534.

108) "At 60 mg/m^2, DLT again occurred with 3/6 [patients] developing grade 3–4 granulocytopenia." PTX 0534.

109) "An additional three [patients] were then entered at 50 mg/m^2; no DLTs were observed in these [patients]." PTX 0534.

110) Other reported side effects included "mild or moderate nausea, vomiting, diarrhea, fatigue, and altered taste." PTX 0534.

111) Five patients "demonstrated stable disease." PTX 0534.

112) Hoff concludes that "[t]he recommended dose of TAS-102 on this schedule is 50 mg/m^2/day." PTX 0534.

113) During cross examination, Dr. Goldberg agreed that Hoff reflects "[a] standard approach to drug development." Tr. 399:17.

b. Dwivedy

114) The abstract, "Safety and Pharmacokinetics (PK) of an Antitumor/Antiangiogenic Agent, TAS-102: a Phase I Study for Patients (PTS) with Solid Tumors" (Dwivedy), was published in 2001. PTX 0533. It is undisputed that Dwivedy is prior art to the #284 patent.

115) Like Hoff, Dwivedy is a Phase I study conducted by Taiho at the University of Texas M.D. Anderson Cancer Center. PTX 0533.

116) Dwivedy refers to Hoff and the dosage schedule disclosed in Hoff. PTX 0533; Tr. 412:13–17 (Goldberg).

117) Dwivedy also describes a then-ongoing Phase I trial "to determine the Phase II dose . . . of once-daily dosing of TAS-102 administered for 5 days a week for 2 weeks repeated every 4 weeks." PTX 0533; *see also* Tr. 151:25–52:4 (Ratain).

118) Like Hoff, Dwivedy does not disclose whether tipiracil was the specific TPI used in the TAS-102 treatment. Instead, TAS-102 is described as "an oral combination of [FTD] and a thymidine phosphorylase (TP) inhibitor." PTX 0533; *see also* Tr. 151:10–13 ("From this document alone, the [artisan of ordinary skill] wouldn't know . . . which thymidine phosphorylase inhibitor it was.") (Ratain).

119) The scientists in Dwivedy "hypothesized that the 2-day treatment rest may allow us to administer higher doses of TAS-102 compared to the continuous daily schedule, as . . . previously demonstrated with another oral fluoropyrimidine." PTX 0533.

120) The patients in Dwivedy had received second-line treatment for gastrointestinal cancer. PTX 0533.

121) The first dosage tested in Dwivedy was 50 mg/m^2/d. PTX 0533; Tr. 409:16–25 (Goldberg).

122) "At dose level 1 of TAS-102 50 mg/m^2/d, no DLTs were observed in 3 [patients]." PTX 0533.

123) Dr. Goldberg testified that because "no dose limiting toxicity was seen" at 50 mg/m^2/d, the Dwivedy scientists "followed the protocol and escalated the dose." Tr. 410:7–9.

124) "At the second level of 70 mg/m^2/d, 1 of 6 [patients] developed grade 4 neutropenia." Other observed side effects included mild to moderate nausea, vomiting, diarrhea, and taste alterations. PTX 0533; Tr. 410:13–11:10 (Goldberg).

125) At dose level three of 80 mg/m^2/d, "[n]o objective responses had[d] been observed but 1 [patient] demonstrated stable disease for more than 3 months." PTX 0533; *see also* Tr. 411:21–12:1 ("Q: Ok. So they started with some patients at 50; they moved up to 70. They have another patient population that's up to 80 milligrams per meter squared per day, right? A: Right. And that was as far as the study had gone at the time that this abstract was generated.") (Goldberg).

c. Thomas

126) The abstract, "A dose-finding, safety and pharmacokinetics study of TAS-102, an antitumor/antiangiogenic agent given orally on a once-daily schedule for five days every three weeks in patients with solid tumors" (Thomas), was

published in 2002. PTX 0538. It is undisputed that Thomas is prior art to the #284 patent.

127) Like Hoff and Dwivedy, Thomas is a Phase I study that was conducted by Taiho at the University of Texas M.D. Anderson Cancer Center. PTX 0538.

128) Like Hoff and Dwivedy, Thomas does not disclose whether tipiracil was the specific TPI used in the TAS-102 treatment. Instead, TAS-102 is described as "an oral combination of [FTD] and a thymidine phosphorylase inhibitor (TPI)." PTX 0538.

129) Thomas refers to the Hoff and Dwivedy studies and the dosage schedules in those studies. PTX 0538.

130) In Thomas, TAS-102 was administered orally, once-daily, for five days every three weeks, to 21 patients with solid tumors. PTX 0538.

131) As of the date of publication, "21 [patients] . . . ha[d] been treated at doses ranging from 100–140 mg/m^2/d." PTX 0538.

132) Nine patients received doses of 120 mg/m^2/d. One of these nine patients "experienced Grade 3 granulocytopenia." PTX 0538. Other adverse events included anemia and mild or moderate nausea, vomiting, diarrhea, fatigue, and rash. PTX 0538.

133) As of the date of the publication of the Thomas abstract, "no objective responses ha[d] been observed, but two [patients] demonstrated stable disease for more than 4 months and one [patient] for more than 6 months, at the 120–130 mg/m^2/d-dose level." PTX 0538.

2. Emura II

134) Emura II, a paper titled, "An optimal dosing schedule for a novel combination antimetabolite, TAS-102, based on its intracellular metabolism and its incorporation into DNA," was published in 2004. It is undisputed that Emura II is prior art to the #284 patent. DTX 0011.

135) Unlike Hoff, Thomas, or Dwivedy, the studies disclosed in Emura II were not Phase I studies. Rather, the studies were preclinical animal studies. DTX 0011; Tr. 347:13–17 (Goldberg).

136) Emura II describes two studies in which mice were injected with either human pancreatic or gastric cancer cells. Then, the mice were treated with TAS-102. DTX 0011.

137) The enzyme in mice that breaks down FTD is thymidine kinase. This is a different enzyme than thymidine phosphorylase, which is the enzyme that breaks down FTD in humans. Tr. 349:9–15 (Goldberg).

138) The studies disclosed in Emura II are summarized as "Example 1" and "Example 2" in the #284 patent. #284 patent at 6:61–7:50; Tr. 153:23–54:8 (Ratain).

139) Emura II does not refer to Hoff, Dwivedy, or Thomas by name. But it does state that "Phase I studies of TAS-102 for oral administration have been initiated in patients with advanced solid tumors." DTX 0011 at 2; *see also* Tr. 157:13–14 (Ratain). And, as Dr. Ratain credibly testified, it would have been "quite straightforward obviously to find the references of the prior Phase I studies even though they're not cited [explicitly by name] in" Emura II. Tr. 157:13–17.

140) The purpose of Emura II was to "develop an administration schedule preferable to more efficient incorporation of FTD into DNA." DTX 0011 at 2.

141) The mice received FTD and tipiracil in a molar ratio of 1:0.5 in terms of FTD. DTX 0011 at 2; Tr. 156:4–57:6 (Ratain).

142) The mice also received TAS-102 in either once-daily or thrice-daily doses, for either one day or three consecutive days. DTX 0011 at 2; *see also* Tr. 153:25–54:8 (Ratain).

143) None of the mice received TAS-102 in twice-daily doses. DTX 0011; Tr. 348:2–4 (Goldberg).

144) On the once-daily schedule, TAS-102 was administered in doses of either 100 mg/kg/day or 150 mg/kg/day. DTX 0011 at 3.

145) On the thrice-daily schedule, TAS-102 was administered in total daily doses of either 90 mg/kg/day (in 3 doses of 30 mg/kg) or 150 mg/kg/day (in 3 doses of 50/mg/kg. DTX 0011 at 3.

146) Emura II's authors observed higher antitumor effects when TAS-102 was administered thrice-daily rather than once-daily. The authors therefore "concluded that multiple daily dosing may result in better clinical benefits of TAS-102, when compared with single daily dosing[.]" DTX 0011 at 1; *see also* Tr. 154:20–25 (Ratain); Tr. 439:13–17 (Goldberg).

147) Emura II's authors also concluded that "a strategy for obtaining repeated contact of tumor cells with FTD at a several-micro molar level for approximately 10 h[ours] daily may be the best." DTX 0011 at 6; *see also* Tr. 348:19–21 (Goldberg).

148) Administering TAS-102 thrice-daily, every three hours, would have allowed FTD to contact the tumor cells for approximately ten hours. Tr. 348:19–49:3 (Goldberg).

I. An Ordinarily Skilled Artisan's Motivation, as of January 26, 2005, to Administer TAS-102 in Twice-Daily Doses

149) Defendants argue that claim 13 of the #284 patent is invalid as obvious in light of the teachings of (1) Emura II and (2) Dwivedy, as well as the #535 patent and an artisan of ordinary skill's background knowledge of the state of the art. D.I. 160 at 26; D.I. 159 ¶ 139.

150) It is undisputed that that every element of claim 13 except for the twice-daily dosing limitation was disclosed in the prior art. *See* Tr. 546:11–47:5.

151) Defendants concede that twice-daily dosing is not explicitly disclosed in the prior art. Tr. 101:2–3; 160:17–18 (Ratain); Tr. 527:21–24 (Defendants' counsel).

152) But Defendants argue that, after considering the prior art, "common sense" would have motivated an artisan of ordinary skill to administer TAS-102 twice-daily. D.I. 160 at 27–29. According to Defendants, a skilled artisan "would have found it obvious to try combining the[ ] teachings [of Emura II and the state of the art], and then administer TAS-102 in the most convenient schedule between once-a-day dosing and three times a day dosing—*i.e.* twice a day dosing." D.I. 160 at 35.

1. Defendants Have Proven by Clear and Convincing Evidence That the Scope and Content of the Prior Art as of January 26, 2005 Would Have Motivated an Artisan of Ordinary Skill to Administer TAS-102 in Divided Doses

153) The prior art would have motivated an artisan of ordinary skill in January 2005 to administer TAS-102 in divided doses. First, the Ansfield authors concluded that FTD can produce strong antitumor effects, but it must be administered "more than once within 24 hours to be effective." *See* ¶ 70 (citing DTX 0333); *see also* ¶ 71 (citing Tr. 143:15–18 ("[T]he study clearly demonstrated that FTD was a highly active drug. I mean, I wish I could have done, sometime in

my career, a Phase I trial that gave this magnitude of anticancer activity.") (Ratain); Tr. 369:14–16 ("[A]s Dr. Ratain remarked, the Ansfield study, which gave the drug eight times a day, showed pretty remarkable antitumor activity for a Phase I study.") (Goldberg)). Second, after comparing antitumor effects in mice that received TAS-102 in either once- or thrice-daily doses, Emura II's authors "concluded that multiple daily dosing may result in better clinical benefits of TAS-102 when compared with single daily dosing." *See* ¶ 136 (citing DTX 0011 at 6; Tr. 154:20–25 (Ratain); Tr. 439:13–17 (Goldberg)).

2. Defendants Did Not Prove by Clear and Convincing Evidence That the Scope and Content of the Prior Art as of January 26, 2005 Would Have Motivated an Artisan of Ordinary Skill to Administer TAS-102 in Twice-Daily Doses

154) Although Defendants adduced clear and convincing evidence that an artisan of ordinary skill would have been motivated to administer TAS-102 in divided doses, I find that Defendants did not adduce clear and convincing evidence that a skilled artisan as of January 26, 2005 would have been motivated administer TAS-102 in twice-daily doses.

155) Emura II's authors "concluded that *multiple daily dosing* may result in better clinical benefits of TAS-102 when compared with *single daily dosing*." DTX 0011 at 1 (emphasis added).

156) But Emura II compared only the results of thrice-daily and once-daily TAS-102 dosing. Emura II did not report any results about twice-daily TAS-102 dosing. *See* DTX 0011.

157) Emura II's authors also commented that "a strategy for obtaining repeated contact of tumor cells with FTD at a several-micro molar level for approximately 10 h[ours] daily may be the best." DTX 0011 at 6; *see also* Tr. 348:19–21 (Goldberg).

158) Because TAS-102 has a half-life of 1.4 hours, administering it thrice-daily allows FTD to contact the tumor cells for approximately ten hours in one day. Tr. 348:19–49:3 (Goldberg).

159) Dr. Ratain testified at trial that twice-daily dosing is "obvious based on . . . just basic common sense, that if you want to divide the dose, *two is the smallest number of doses per day*, " Tr. 160:18–21 (emphasis added), and that "from a [skilled artisan] and patient perspective, two would be the desirable number of doses, given that one was believed not to be enough doses per day," Tr. 161:22–25.

160) The implicit premise of this testimony is that the fewer number of dosings per day, the better to achieve patient convenience and compliance. (Dr. Ratain never explicitly testified that the fewer the number of dosings is better to achieve patience compliance and convenience.) This premise carries some logical

force, as I acknowledged during trial. *See* Tr. 547:9–20. In general, it makes sense that the fewer number of occasions a patient needs to take a pill, the less inconvenienced the patient is and the better chance the patient will remember to take the pill. A single dosing a day is thus optimal from a patient convenience and compliance perspective. *See Bial-Portela & CA. S.A. v. Alkem Lab'ys Ltd.*, 2022 WL 4244989, at *20 (D. Del. Sept. 15, 2022) (noting that drug formulators consider patient compliance and convenience when formulating pharmaceutical compositions and that a single tablet dosage is the "gold standard").

161) But it also makes sense that a thrice-daily dosing regimen might be more convenient and achieve better patient compliance than a twice-daily dosing regimen, as patients typically have three meals per day and could find it more convenient and easier to remember to take their medicine with their meals.

162) Defendants did not adduce any record evidence, let alone clear and convincing record evidence, to demonstrate that a twice-daily dosing regimen is better than a thrice-daily dosing regimen.

163) Defendants also did not adduce any record evidence, let alone clear and convincing evidence, that explains *why* Emura II, Dwivedy, the #535 patent, and the state of the art would have motivated an artisan of ordinary skill, guided by "common sense," to administer TAS-102 twice-daily dosing as opposed to thrice-daily.

164) Defendants did adduce evidence that "other oral chemotherapy combinations were known to be given two times a day in the relative time frame." D.I. 160 at 28; *see also* ¶ 63. But that evidence does not establish that an artisan of ordinary skill would have been motivated to administered *TAS-102* twice-daily, especially in light of Emura II's conclusion that thrice-daily administration produced more clinical benefits than once-daily dosing.

165) Accordingly, I find that Defendants did not present clear and convincing evidence that "common sense," in light of the state of the art as of January 26, 2005, would have motivated an artisan of ordinary skill to administer TAS-102 twice-daily.

J. Alleged Objective Indicia of Nonobviousness

166) Taiho argues that the nonobviousness of the asserted claims is demonstrated by four objective indicia—unexpected results, long-felt need, industry praise, and commercial success. D.I. 168 at 28.

1. Alleged Unexpected Results of the #284 Patent

167) Taiho argues that "[n]othing in the prior art at the time suggested to" an artisan of ordinary skill "that a twice-daily divided dosing regimen would produce superior results" as compared to thrice-daily divided dosing. D.I. 168 at 30.

168) During the reexamination of the #284 patent, inventor Akira Mita submitted a declaration to the U.S. Patent and Trademark Office (PTO). *See* JTX 0012 at 859–64; Tr. 274:18–22 (Mita).

169) In that declaration, Mita stated that Emura II had "found that dividing the daily dose of TAS-102 into three parts dosed separately in mice was much more effective than the daily dose administered as a single dose." JTX 0012 at 860; Tr. 267:14–17 (Mita).

170) Mita's declaration also states that Taiho decided to conduct a Phase I clinical study in which TAS-102 was administered three times per day. JTX 0012 at 860.

171) Mita further stated in his declaration that "[a]s there w[ere] no data for a twice per day dosing schedule, [Mita] suggested that Taiho have a phase I study conducted administering the daily dose in twice per day with the dosing at least 6 hours apart." JTX 0012 at 860.

172) Mita offered the following testimony about why he suggested a Phase I study with twice-daily dosing:

> Q. [W]hat made you think of two times?
>
> A. From my experience in clinical studies in the past, or thus far, I found that human functions are unpredictable and mysterious beyond one's imagination. So, therefore, I believed that there is a possibility for twice daily dosing and I wanted to try that out.

> Q. What was your impression on how your colleagues reacted to your two times daily dosing idea?
>
> A. They couldn't believe it -- believe the possibility.
>
> Q. Why did you think that they could not believe the possibility?
>
> A. They thought that based on the research papers and their experience up to that point in time, that three times daily or four times daily or even more frequently daily would be more effective; and therefore, they did not believe that there's any possibility for twice daily being effective.

Tr. 268:12–69:4.

173) As I noted during trial, Mita's explanation "sounded mystical," and "I had a really hard time accepting that that was a scientific approach to picking two." Tr. 545:5–7.

174) I find here, based on his demeanor and the manner in which he answered questions, that Mita's testimony that his colleagues "did not believe that there's any possibility for twice daily being effective" was exaggerated and not credible.

175) I do, however, based on the prior art discussed above, find credible Mita's testimony that his colleagues "thought that . . . three times daily or four times daily or even more frequently daily would be more effective" than twice-daily dosing.

176) Taiho then conducted two Phase I studies at the M.D. Anderson Cancer Center in Houston, Texas. These two studies were called IND study 9805 (the 9805 study) and IND study 9804 (the 9804 study). JTX 0012 at 860; Tr. 267:17–19.

177) The 9805 study is described in Example 3 of the #284 patent. #284 patent at 7:54–8:39; D.I. 146-1 ¶ 43.

178) The 9805 study consisted of two trials. In one trial, patients with digestive cancer received TAS-102 by oral administration once-daily at a daily dose of 100 mg/m^2/d in terms of FTD. In the other trial, patients with digestive cancer received TAS-102 by oral administration in three divided portions at a daily dose of 70 mg/m^2/d in terms of FTD. #284 patent at 7:54–57; D.I. 146-1 ¶¶ 42, 45–46.

179) The 9804 study is described in Example 4 of the #284 patent. #284 patent at 8:43–9:2; D.I. 146-1 ¶ 43.

180) The 9804 study also consisted of two clinical trials. In one trial, patients with breast cancer received TAS-102 by oral administration twice-daily at a daily dose of 60 mg/m^2/d in terms of FTD. In the other trial, patients with breast cancer received TAS-102 by oral administration twice-daily at a daily dose of 50 mg/m^2/d in terms of FTD. #284 patent at 8:43–49; D.I. 146-1 ¶¶ 42, 47–48.

181) Mita declared to the PTO, and testified during trial, that the initial results of the 9804 and 9805 studies were surprising to Taiho because "with respect to adverse events, there was no significant difference between the two studies"; and "the twice a day dosing was more effective in reducing tumor growth than the three times per day dosing." JTX 0012 at 0861; *see also* PTX 1704; PTX 1709; Tr. 270:24–71:7, 273:7–9 (Mita).

182) Based on the initial 9804 and 9805 study results, Taiho decided to use twice-daily administration in future TAS-102 studies. Tr. 273:22–25 (Mita).

183) After the initial 9804 and 9805 study results, Taiho did not conduct any further clinical studies using thrice-daily dosing. Tr. 274:1–3 (Mita).

184) The PTO's notice of allowance for the #284 patent includes the following statement: "It was unexpectedly found that more tumors shrunk when treated with the twice-daily dosing schedule than with the three-dose daily dosing schedule." PTX 0012 at 1333.

185) Taiho argues that the 9804 and 9805 study results suggest that twice-daily dosing outperformed thrice-daily dosing when tested at a daily dosage range of 50–70 mg/m^2/d. *See* JTX 0012 at 1259–63, 1280–83, 1309–40.

186) The 9804 and 9805 studies involved patients being treated with different cancers. The patients in the 9804 study were breast cancer patients, *see* #284 patent at 7:54–57; D.I. 146-1 ¶¶ 42, 45–46; and the patients in the 9805 study

were digestive cancer patients, *see* #284 patent at 8:43–49; D.I. 146-1 ¶¶ 42, 47–48.

187) I find that comparing the 9804 and 9805 studies offers little weight with respect to the alleged unexpected result that twice-daily dosing of TAS-102 was more effective than thrice-daily dosing. I do so for four reasons.

188) First, although I find credible Dr. Goldberg's testimony that "Phase I studies are often" conducted with a "collection of patients with many types of primary, including breast and GI cancers," Tr. 357:15–22; and breast and colorectal cancer are both "solid tumors" that "commonly respond to cytotoxic agents," Tr. 376:2–24; I also find credible Dr. Ratain's testimony that the probative value of comparing these studies is diminished by the fact that the patients in the 9804 and 9805 studies had different cancers, *see* Tr. 125:8–12, 126:5–8.

189) Second, I give very little weight to Mita's testimony that the 9804 and 9805 study results were unexpected. I have already noted that Mita's explanation for conducting a twice-daily clinical trial "sounded mystical," and "I had a really hard time accepting that that was a scientific approach to picking two." Tr. 545:5–7. Moreover, Mita is a named inventor with an interest in protecting the validity of the #284 patent, and he has worked on Taiho's TAS-102 project for decades.

190) Third, both sides' experts disagreed about whether the 9804 and 9805 Phase I study results would have shown an artisan of ordinary skill that twice-daily

dosing is more effective than thrice-daily dosing. For example, Taiho points out that the mean duration of stable disease for patients with stable disease was 229.5 days in the 9804 study and 132.9 days in the 9805 study, JTX 0012 at 1309–10; and Dr. Goldberg testified that "a POSA would have looked at this and said that extra hundred days suggests that this approach is worth further investigation," Tr. 354:11–16; *see also* Tr. 452:6–15 (Goldberg). But as Dr. Ratain credibly testified: "[I]t's hard to interpret what 'stable disease' means in a Phase I clinical trial. . . . To me it's uninterpretable. I have seen so much stable disease in Phase I trials of completely ineffective agents that it doesn't mean anything to me when I see it." Tr. 123:5–11. Dr. Ratain further testified that there was "no difference in results between the 9804 and 9805 study." Tr. 181:5–6.

191) Fourth, as noted above, the 9804 and 9805 studies were Phase I clinical studies. JTX 0012 at 860; Tr. 263:6–8 (Mita). In the pretrial order, the parties agreed that "[a] phase 1 study is conducted to understand the relationship of dose and toxicity, historically focusing on identifying the maximum tolerable dose of the compound under study. Antitumor activity and the effect of those doses on the patient's tumor size is typically monitored and evaluated as well, although tumor shrinkage or the extension of time it takes for the tumor to progress are not the primary endpoints of Phase 1 trials." D.I. 146-1 ¶ 58. Although I made a finding of fact, and I reaffirm here, that "Phase I can tell you something about

efficacy," Tr. 532:13–15; I also made a finding of fact, and I reaffirm here, that "getting an efficacious drug [cannot] be determined by a Phase I study" because "[o]ur FDA requires Phase III" trials for efficacy, Tr. 532:7–10.

2. Alleged Long-Felt Need for the Method of Treatment in Claim 13 of the #284 Patent

192) Taiho argues that "LONSURF® satisfied a long-felt unmet need in the treatment of advanced colorectal cancer, including the need for better treatment options that would allow patients to live longer and maintain quality of life." D.I. 168 at 43.

193) I agree with Taiho that as of January 26, 2005, a long-felt need existed for treatment options that would extend the length and quality of life of patients with advanced colorectal cancer that had progressed through first and second lines of therapy.

194) I base this finding on the fact that prior to Lonsurf®'s approval, there was only one other FDA-approved oral treatment for post-second line treatment of colorectal cancer. That treatment was marketed under the brand name Stivarga®. Tr. 361:18–21; 363:15–25 (Goldberg); 321:11–22:17 (Whitten).

195) Dr. Goldberg credibly testified that he prescribed Stivarga® as soon as it entered the market, and he also prescribed Lonsurf® as soon as it entered the market. He preferred to prescribe Lonsurf® over Stivarga® because he and his

patients "felt that Lonsurf was much better tolerated than Stivarga." Tr. 365:10–14.

196) Patients with advanced colorectal cancer who had already received first and second line treatment are focused on quality of life. *See* Tr. 365:5–9 ("[P]atients in this setting are remarkably focused on quality of life. They don't have a lot of life left. They want their life left to be good.") (Goldberg).

197) I also agree with Taiho that Lonsurf® as a product satisfied the long-felt need for treatment options that would extend the length and quality of life of patients with advanced colorectal cancer that had progressed through first and second lines of therapy. The record evidence shows that Lonsurf® was better tolerated by patients than Stivarga®, *see* Tr. 323:24–24:1 ("Lonsurf is preferred by 70 percent of oncologists over Stivarga based on the superior tolerability profile.") (Whitten) (citing JTX 0131 at 10); Tr. 365:10–14 (Goldberg); and that Lonsurf® prolonged patients' lives, *see* Tr. 199:20–23, 218:24–19:4 (Ratain); Tr. 311:25–14:16 (Whitten); JTX 0023 at 1, 9.

198) I give this evidence, however, little weight. First, Dr. Goldberg agreed with Defendants that claim 1 of the #284 patent, which claim 13 depends from, is not directed towards efficacy; it is directed towards administering TAS-102 in accordance with a certain dosage and administration schedule. *See* Tr. 441:8–12, 442:15–17; *see also* Tr. 338:6–9 (THE COURT: . . . . "Is it your

understanding that Lonsurf's covered by the [#]284 patent? [WHITTEN]: Yes. The dose administration schedule as shown in the [Lonsurf®] label."); *see also* Tr. 98:1–13 (Ratain). Second, Whitten admitted that he knew of no data that showed a long-felt need in 2005 for a TAS-102 dose of 50–70 mg/m^2/d in terms of FTD:

> THE COURT: Can you point to anything that would show that there was a long-felt need as of 2005 for dosing between 50 and 70 milligrams per meter squared a day in FTD?
>
> THE WITNESS: In 2005?
>
> THE COURT: Yeah.
>
> THE WITNESS: I think there was not in -- I'm not aware of the data on the dosing schedule in 2005. There's nothing there. And so, no, I can't point to anything that says that there was a need for that particular dosage.
>
> THE COURT: Is it fair to say that to the extent you're here to testify about a long-felt need, it's a long-felt need for effective treatment of digestive cancer, it's not for a particular type of treatment; is that fair?
>
> THE WITNESS: Yes. It's the unmet need. I mean, these patients die.
>
> THE COURT: That's what I'm getting at. But it's an unmet need not for a particular dosage, it's just for an effective treatment of cancer; is that right?
>
> THE WITNESS: That is correct.

Tr. 337:2–23. Third, the record does not suggest that there was a long-felt need in January 2005 for a TAS-102 administration schedule of "5 days followed by 2

days off treatment in the week on a one-week dosing schedule." #284 patent at claim 1. On the contrary, the record suggests that the administration schedule on Lonsurf®'s label was viewed as inconvenient. The dosage on Lonsurf®'s label reads: "35 mg/m^2/dose orally twice daily with food on Days 1 through 5 and Days 8 through 12 of each 28-day cycle." JTX 0151 at 1. And Dr. Goldberg testified that when he prescribed Lonsurf® according to this label, he "had to sit down and write out a calendar for patients to be sure that they took five days in a row, two days off; five more days in a row, and then 16 days off. So it was a more complicated regimen and not one that U.S. patients had commonly been prescribed in the past." Tr. 345:20–25.

3. Alleged Industry Praise of the Method of Treatment in Claim 13 of the #284 Patent

199) Taiho also argues that the #284 patent's "claimed dosing regimen led to industry praise for LONSURF®." D.I. 168 at 45.

200) The results of a Phase III TAS-102 study that Taiho conducted (the RECOURSE study) were published in the *New England Journal of Medicine*. JTX 0023; Tr. 316:2–10 (Whitten); Tr. 362:10–13 (Goldberg).

201) The *New England Journal of Medicine* is a highly prestigious journal. Tr. 362:16–24 (Goldberg).

202) The methodology in the RECOURSE study, as reported by the *New England Journal of Medicine* article, states: "TAS-102 (with each dose consisting

of 35 mg per square meter) or placebo was administered twice daily, after morning and evening meals, 5 days a week, with 2 days of rest, for 2 weeks, followed by a 14-day rest period, thus completing one treatment cycle. The regimen was repeated every 4 weeks." JTX 0023 at 3.

203) The *New England Journal of Medicine* article's abstract states that "TAS-102, as compared with placebo, was associated with a significant improvement in overall survival." JTX 0023 at 1.

204) But, the article does not specifically praise the administration schedule used in the RECOURSE study. *See* JTX 0023.

205) The RECOURSE study results were also featured at the European Society of Medical Oncology annual meeting, a meeting that thousands of people attended. Tr. 313:10–20 (Whitten). But no record evidence states that the TAS-102 administration schedule was praised at the meeting.

206) Dr. Whitten and Dr. Goldberg testified that patient advocacy groups, upon the approval of Lonsurf®, sent out press releases to their patients and their constituents. Tr. 313:21–24 (Whitten); Tr. 372:5–73:11 (Goldberg); PTX 0473; PTX 0516. Again, however, there is no record evidence that these groups praised the administration schedule taught in claim 13 of the #284 patent or Lonsurf®'s label.

207) Based on the foregoing, I find that the industry praised Lonsurf® as a product. But like with long-felt need, I afford this finding little weight because there is no record evidence that the industry praised the administration schedule taught in claim 13 of the #284 patent.

4. Alleged Commercial Success of the Method of Treatment in Claim 13 of the #284 Patent

208) Taiho argues that "LONSURF® has been a marketplace success." D.I. 168 at 46.

209) I agree with Taiho that Lonsurf® is a commercially successful product. Lonsurf®'s net sales since launch have exceeded $1.6 billion. PTX 1718 at 2; Tr. 324:25–25:11 (Whitten); Tr. 467:9–10 (Rao). In recent years, Lonsurf® has outsold its two closest competitors, even though Lonsurf® has been on the market for less time. Tr. 468:2–9 (Rao); PTX 1727 at 4. And even after Taiho decreased Lonsurf® promotional spending, Lonsurf®'s sales continued to rise. Tr. 326:6–25 (Whitten).

210) Here, however, Lonsurf®'s financial success is not very probative because Taiho's other patents barred others from commercially testing the features taught in claim 13. As Mr. Hofmann credibly testified, the #475 patent created some economic disincentives for others to pursue a FTD/tipiracil oral

chemotherapy treatment. Tr. 498:25–99:9; 499:21–500:21.[4] Dr. Rao conceded that the #475 patent "covers Lonsurf," Tr. 475:12–14, and that because the #475 patent was listed on the Orange Book, "Taiho implicitly represented to FDA that [the #475 patent] read on Lonsurf," Tr. 475:15–20.

211) Moreover, the record does not demonstrate that Lonsurf®'s commercial success can be apportioned to the method of treatment claimed in claim 13 of the #284 patent.

212) Dr. Rao attributed Lonsurf®'s commercial success to four patents: the #284 patent and U.S. Patent Nos. 9,527,833 (the #833 patent); 10,457,666 (the #666 patent); and 10,456,399 (the #399 patent). Tr. 473:18–22. He further testified that "you can't apportion during the period all these patents were together because there's just no way -- there's no method known to us to apportion it." Tr. 491:19–22.

[4] Hofmann also testified that U.S. Patent No. 6,479,500 (the #500 patent) was a blocking patent. Tr. 499:24–500:4. But except for referring to the #500 patent as "another method of use patent that relates to the use of trifluridine and tipiracil," Tr. 500:3–4, and briefly showing the #500 patent on a slide, Tr. 501:20–23, Hofmann offered no testimony about the content of the #500 patent or explained how it acted as a blocking patent. I therefore find that Defendants have not shown that the #500 patent acted as a blocking patent.

213) I do not find credible Dr. Rao's testimony that based on his review of Dr. Goldberg's and Dr. Myerson's[5] reports, the #284 patent "describes Lonsurf's efficacy and side effect profile," the #833 and #666 patents "are related to Lonsurf's oral dosing and stability," and the #399 patent "relates to a method of dosing for patients with severe renal impairment." Tr. 459:1–10. First, as noted above, Dr. Goldberg agreed with Defendants that claim 1 of the #284 patent, which claim 13 depends from, is not directed towards efficacy; it is directed towards administration of TAS-102 in accordance with a dosage and dose administration schedule. *See* ¶ 198 (citing Tr. 441:8–12, 442:15–17). Second, during cross examination, Dr. Rao admitted that "there's nothing in the" portions of Dr. Myerson's report that Dr. Rao cited to with respect to the #833 and #666 patents "that has anything to do with oral dosage form or the stability of Lonsurf." Tr. 484:13–19. Third, Dr. Rao did not testify that the dosing schedule taught in claim 13 of the #284 patent describes Lonsurf®'s efficacy and side effect profile. On the contrary, he admitted that when he evaluated the #284 patent, he did not distinguish "between a method of use and the compound." Tr. 478:11–23. This

[5] Defendants concede that Dr. Myerson is expected to testify at a future trial with regards to the #833 and #666 patents. D.I. 159 ¶ 219. The parties agreed during the pretrial conference that for efficiency purposes, Dr. Rao and Mr. Hofmann could testify in part about the patents that would be the subject of the second trial and Dr. Rao and Mr. Hofmann could rely in part on the testimony of experts who were expected to testify at the later trial. D.I. 145 at 19:13–21:12.

finding is bolstered by Mr. Hofmann's testimony that the dosing schedule in Stivarga®, Lonsurf®'s competitor, was preferable to Lonsurf® and that Lonsurf®'s schedule was considered a barrier to Lonsurf®'s success. Tr. 502:17–05:14 (citing JTX 0139; JTX 0140 at 14; JTX 0138 at 2, 9); *see also* Tr. 363:24–25 (Dr. Goldberg testifying that Stivarga® is Lonsurf®'s "main competitor").

214) Taiho's commercial success evidence also offers limited probative value because Lonsurf® was granted five-year New Chemical Entity exclusivity that did not expire until 2020. Tr. 511:6–9 (Hofmann).

215) I accordingly find that Taiho's commercial success evidence is entitled to little weight.

K. Written Description

216) TAS-102 is described in the #284 patent's written description as "a composition" containing FTD and tipiracil in a molar ratio of 1:0.5. #284 patent at 2:61–66.

217) TAS-102 is also described as the treatment that was orally administered in Examples 1–4. #284 patent at 6:63–9:2.

218) The #284 patent's written description also states that the claimed "method of invention is intended for cancers including, but not limited to," colorectal cancer, and "preferably malignant solid cancers such as gastric,

pancreatic, breast, colorectal, head and neck, gallbladder-bile duct and lung cancers." #284 patent at 5:44–52.

219) The #284 patent's written description does not describe a study in which colorectal or digestive cancer patients were orally administered TAS-102 in twice-daily doses for a period of five days followed by two days of rest. *See* #284 patent; Tr. 124:3–12 (Ratain).

220) But, as noted above, the #284 patent's written description does include "Example 3" and "Example 4," which respectively describe the 9805 and 9804 studies that Taiho conducted. *See* ¶¶ 177, 179.

221) In one of the clinical trials disclosed in Example 3, patients with digestive cancer received TAS-102 by oral administration thrice-daily at a daily dose of 70 mg/m^2/d in terms of FTD. #284 patent at 7:54–57.

222) Colorectal cancer is a type of digestive cancer. *See* #284 patent at claim 13; Tr. 119:11–15 (Ratain).

223) In one of the clinical trials disclosed in Example 4, patients with breast cancer received TAS-102 by oral administration twice-daily at a daily dose of 60 mg/m^2/d in terms of FTD. In the other trial, patients with breast cancer received TAS-102 by oral administration twice-daily at a daily dose of 50 mg/m^2/d in terms of FTD. #284 patent at 8:43–49.

224) In both Example 3 and Example 4, TAS-102 was administered every five days followed by two days off treatment. #284 patent at 8:26–27, 8:52–57.

225) Dr. Ratain testified that the 9804 and 9805 studies involve "two completely different diseases, and so you can't draw any conclusions comparing studies across diseases about whether a particular schedule is more useful than another one." Tr. 125:8–12 (Ratain).

226) I have already stated in paragraph 188 that I find credible Dr. Ratain's testimony that the probative value of comparing the 9804 and 9805 studies is diminished by the fact that the patients in the studies had different cancers, Tr. 125:8–12, 126:5–8; but I also find credible Dr. Goldberg's testimony that "Phase I studies are often" conducted with a "collection of patients with many types of primary, including breast and GI cancers," Tr. 357:15–22; and breast and colorectal cancer are both solid tumors that "commonly respond to cytotoxic agents," Tr. 376:2–24.

227) Dr. Ratain also offered the following conclusory testimony that specifically addressed the written description requirement:

> Q: And based on your review of the specification and the entire disclosure of the [#]284 patent, Dr. Ratain, is there any indication at all that would tell our [artisan of ordinary skill] that in January of 25 -- January of 2005, the applicants were in possession of a method where colorectal cancer patients are given a dose of TAS-102 two times a day, when this application was filed?

> A. There's no description that the inventors had actually done that, that they ever administered TAS-102 twice a day for two [sic] patients with colorectal cancer.
>
> Q. And do you have an opinion, Dr. Ratain, as to whether, then, this specification supports, in its written description, the dosing of colorectal patients two times a day?
>
> A. Well, I think it would be obvious to administer the drug in such a way. And while certainly [an artisan of ordinary skill] would know how to do that, there's no description that the inventors actually did it.

Tr. 203:21–04:13.

228) Based on this record, I find that Defendants have not adduced clear and convincing evidence that the #284 patent's written description would not have conveyed to an artisan of ordinary skill that the inventor possessed the claimed subject matter.

III. LEGAL STANDARDS

A. Obviousness

Under § 103 of the Patent Act, a patent "may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103 (2006).

As the Supreme Court explained in the seminal case *Graham v. John Deere Company*, under § 103, "[a]n invention which has been made, and which is new in the sense that the same thing has not been made before, may still not be patentable if the difference between the new thing and what was known before is not considered sufficiently great to warrant a patent." 383 U.S. 1, 14 (1966). Section 103 ensures that "the results of ordinary innovation are not the subject of exclusive rights under the patent laws." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 427 (2007). "Were it otherwise patents might stifle, rather than promote, the progress of useful arts." *Id.* (citing U.S. Const. art. I, § 8, cl. 8).

The Court reaffirmed in *KSR* that the "framework" set out in the following paragraph from *Graham* governs the application of § 103, *id.* at 406:

> While the ultimate question of patent validity is one of law, the [§] 103 condition [of patentability] . . . lends itself to several basic factual inquiries. Under [§] 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. As indicia of obviousness or nonobviousness, these inquiries may have relevancy.

Graham, 383 U.S. at 14–15 (citations omitted).

It is clear that under this framework, a district court must consider in an obviousness inquiry the three primary factors identified by the Court in *Graham*: (1) the scope and content of the prior art, (2) the differences between the prior art and the claims at issue, and (3) the level of ordinary skill in the pertinent art. Less clear is the role, if any, secondary considerations should play in the analysis.

The logical—some would say necessary—implication of the Court's use of the word "secondary" in *Graham* and its holding that the secondary considerations "might be utilized" and "may have relevancy" is that a district court is permitted—but not required in all cases—to examine such considerations in evaluating an obviousness-based invalidity challenge. The Court seemed to confirm as much in *KSR*, when it noted that "*Graham* set forth a broad inquiry and *invited* courts, where appropriate, to look at any secondary considerations that would prove instructive." *KSR*, 550 U.S. at 415 (emphasis added).

But a district court ignores *Graham*'s "invitation" to examine secondary considerations at its peril. One legal scholar, Harmon, has observed that under Federal Circuit law "[w]e are able now safely to strike the 'may' in the . . . sentence" in *Graham* in which the Court stated that secondary "indicia of obviousness and nonobviousness . . . may have relevancy." Robert Harmon, Cynthia Homan & Laura Lydigsen, *Patents and the Federal Circuit* 245 (13th ed. 2017). Harmon correctly notes that "[t]he Federal Circuit has emphatically and

repeatedly held that objective evidence of non-obviousness must be taken into account always and not just when the decisionmaker is in doubt." *Id.* In *Stratoflex, Inc. v. Aeroquip Corp.*, for example, the Federal Circuit held that "evidence rising out of the so-called 'secondary considerations' must always when present be considered en route to a determination of obviousness." 713 F.2d 1530, 1538 (Fed. Cir. 1983). And in *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litigation*, 676 F.3d 1063 (Fed. Cir. 2012), the Federal Circuit reaffirmed that holding, *id.* at 1079, and it went on to say that the Supreme Court in *Graham* "did not relegate . . . to 'secondary status'" the "objective factors" the Supreme Court had explicitly identified in *Graham* as "secondary considerations." *Id.* at 1078.

True, less than a month after *In re Cyclobenzaprine*, a different Federal Circuit panel held in *Otsuka Pharmaceutical Co. v. Sandoz, Inc.*, that because it found that the defendants had "failed to prove that [the challenged patent claim] would have been *prima facie* obvious over the asserted prior art," it "need not address" the "objective evidence" of commercial success, long felt need, and the failure of others. 678 F.3d 1280, 1296 (Fed. Cir. 2012). But the safer course for a district court faced with an obviousness challenge is to treat *Graham*'s invitation to look at secondary considerations like a subpoena.

Obviousness is assessed based on the perspective of an artisan of ordinary skill at the time of the invention. *Unigene Labs., Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1360 (Fed. Cir. 2011). The court therefore needs to guard against "hindsight bias" that infers from the inventor's success in making the patented invention that the invention was obvious. *In re Cyclobenzaprine*, 676 F.3d at 1079. The ultimate question in the obviousness analysis is "whether there was an apparent reason [for an artisan of ordinary skill] to combine [at the time of the invention] the known elements in the fashion claimed by the patent at issue." *KSR*, 550 U.S. at 418. "The analysis is objective." *Id.* at 406. Thus, a court must determine whether an artisan of ordinary skill "would have had reason to combine the teaching of the prior art references to achieve the claimed invention, and . . . would have had a reasonable expectation of success [in] doing so." *In re Cyclobenzaprine*, 676 F.3d at 1069.

The party challenging the patent's validity bears the burden of proving obviousness by clear and convincing evidence. *Id.* at 1068–69. In weighing the *Graham* factors to decide whether the party has met that burden, the district court must be guided by common sense. *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1238 (Fed. Cir. 2010). Indeed, "the legal determination of obviousness may include recourse to logic, judgment, and common sense, in lieu of expert testimony." *Id.* at 1239. In *KSR*, the Supreme Court warned lower courts to avoid

"[r]igid preventative rules that deny factfinders common sense" and to employ instead "an expansive and flexible approach" under the *Graham* framework. *KSR*, 550 U.S. at 415, 421. Thus, the district court may "reorder[] in any particular case" the "sequence" in which it considers the *Graham* factors. *Id.* at 407. And although a court should consider carefully the published prior art, "[t]he obviousness analysis cannot be confined by . . . overemphasis on the importance of published articles and the explicit content of issued patents." *Id.* at 419.

"[A]ny need or problem known in the field of endeavor at the time of the invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *Id.* at 420. And "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *Id.* at 416. "[T]he fact that a combination was obvious to try might show that it was obvious under § 103." *Id.* at 421. But a combination is obvious to try only "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions" in the prior art at the time of the invention. *Id.* And the court must also be mindful that "when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious." *Id.* at 416.

B. Written Description

Section 112 of the Patent Act requires that the specification of a patent "contain a written description of [(1)] the invention, and of [(2)] the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains . . . to make and use the same." 35 U.S.C. § 112 (2006). Courts refer to these two requirements respectively as adequate written description and enablement.

The "hallmark" of an adequate written description is "disclosure." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). A patent must "reasonably convey[] to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date" to satisfy the written description requirement. *Id.* An applicant establishes it was in possession of the invention "by describing the invention[] with all its claimed limitations." *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997) (emphasis omitted). This description can be made using "words, structures, figures, diagrams, formulas, etc." *Id.* A patentee can also "rely on information that is 'well-known in the art' to satisfy written description." *Streck, Inc. v. Rsch. & Diagnostic Sys., Inc.*, 665 F.3d 1269, 1285 (Fed. Cir. 2012) (citation omitted). A challenger to the patent must prove invalidity based on inadequate written description by clear and convincing evidence. *Invitrogen Corp. v. Clontech*

Lab'ys, Inc., 429 F.3d 1052, 1072 (Fed. Cir. 2005). Whether the written description requirement has been met is a question of fact. *Id.*

IV. CONCLUSIONS OF LAW

A. Obviousness

Defendants contend that they have proven by clear and convincing evidence that claim 13 of the #284 patent is invalid for obviousness.

I disagree. I did find above as a factual matter that every element of claim 13 except for twice-daily dosing is explicitly disclosed in the prior art. But I also found that twice-daily dosing is not explicitly disclosed in the art and that Defendants did not adduce clear and convincing evidence that based on Dwivedy, Emura II, the #535 patent, and the state of the art, an artisan of ordinary skill would have been motivated to administer TAS-102 in two divided portions per day.

Accordingly, I conclude as a matter of law that Defendants have not proven by clear and convincing evidence that claim 13 of the #284 patent is invalid for obviousness.

B. Written Description

Defendants contend that claim 13 of the #284 patent is invalid because it has an inadequate written description.

I disagree. I have already found above as a factual matter that Defendants have not adduced clear and convincing evidence that the #284 patent's written

description would not have conveyed to an artisan of ordinary skill that the inventor possessed the claimed subject matter.

Accordingly, I conclude as a matter of law that Defendants have not proven by clear and convincing evidence that claim 13 of the #284 patent is invalid for lack of an adequate written description.

V. CONCLUSIONS OF LAW

For the reasons discussed above, I find that Defendants have not proven that claim 13 of the #284 patent is invalid.

The Court will issue an Order directing the parties to submit a proposed order by which the Court may enter final judgments consistent with this Opinion.