IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

LIPOCINE INC., Plaintiff, v. CLARUS THERAPEUTICS, INC., Defendant.	C.A. No. 19-622 (WCB)

MEMORANDUM OPINION AND ORDER*

Defendant Clarus Therapeutics, Inc., has moved for summary judgment of invalidity as to all the patent claims asserted by plaintiff Lipocine Inc. in this action. Dkt. Nos. 184, 185. Lipocine has responded, Dkt. No. 200, and Clarus has replied, Dkt. No. 211. Clarus argues that the asserted claims are invalid for failure to satisfy the written description and enablement requirements of 35 U.S.C. § 112. In addressing the motion for summary judgment, I have considered the briefs, the oral arguments, and those portions of the exhibits that the parties have submitted in support of and in opposition to the motion. Clarus's motion is GRANTED, and summary judgment of invalidity will be entered as to all of the asserted claims of the four patents in suit.

BACKGROUND

The four patents at issue in this case are U.S. Patent Nos. 9,034,858 ("the '858 patent"), 9,205,057 ("the '057 patent"), 9,480,690 ("the '690 patent"), and 9,757,390 ("the '390 patent").

* This order was filed under seal on May 25, 2021. The parties were permitted to request that portions of the order remain sealed. The order has now been issued in unredacted form.

The four patents share the same specification. Lipocine has asserted a total of 24 claims from those patents. The asserted claims are directed to methods of treating hypogonadal males, i.e., men deficient in naturally produced testosterone. The methods consist of administering testosterone undecanoate ("TU") to subjects according to an initial regimen, measuring their resulting serum testosterone levels, and adjusting the dosage level to obtain certain designated pharmacokinetic ("PK") results. The text of the 24 asserted claims is set forth in Appendix A to this opinion.

I. The Asserted Claims

While the limitations of the asserted claims vary somewhat, the claims have much in common. They are all directed to methods for increasing the serum concentration of testosterone in a hypogonadal male through the oral delivery of a TU formulation or composition.[1] All but two of the 24 asserted claims recite methods that begin with the administration of an initial dose of a composition containing between 14% and 35% TU by weight, the exceptions being claims 22 and 26 of the '858 patent, which do not specify the percentage weight of TU in the initial dose.

With respect to the other claim limitations, the 24 asserted claims can be divided into a few general categories. *See* Appendix B (chart summarizing the limitations in the asserted claims). The recited initial TU dose levels in each of the claims fall into three groups. The first group recites an initial daily dose of 360–480 mg of TU.[2] That initial daily dose is recited in claims 1,

[1] In the patents, "the terms 'formulation' and 'composition' are used interchangeably and refer to a mixture of two or more compounds, elements, or molecules." '858 patent, col. 3, ll. 49–51.

[2] The abbreviation "mg" refers to milligrams. The abbreviation "mcg" refers to micrograms. The abbreviation "ng" refers to nanograms. The abbreviation "dL" refers to deciliters. The abbreviation "mL" refers to milliliters. The term "wt %" refers to percent by weight. The term "C_{max}" refers to the maximum level of serum concentration of a drug in a dosing interval. The terms "C_{ave}" and "C_{avg}" refer to the steady state average serum concentration of a drug over the dosing interval.

2, 14, and 17 of the '858 patent; claims 2, 4, 5, 7, 9, and 21 of the '057 patent; and claims 7, 8, and 21 of the '690 patent. The second group recites an initial daily dose of 350–650 mg of TU. That initial daily dose is recited in claims 22 and 26 of the '858 patent; claim 17 of the '057 patent; and claims 11, 12, 17, and 18 of the '690 patent. The third group recites an initial daily dose of either about 450 mg or about 480 mg of TU. That initial daily dose is recited in all four asserted claims of the '390 patent, claims 1, 4, 7, and 11.

Many of the claims recite the same PK limitation. The most common PK limitation is the requirement that the method result in a C_{ave} serum testosterone level between 300 ng/dL and 1100 ng/dL in the subject. That range is referred to as the "eugonadal range," i.e., the range that is regarded as normal for adult males. '858 patent, col. 1, ll. 39–43. That PK limitation is found in all the asserted claims of the '057 patent, the '690 patent, and the '390 patent.

The asserted claims of the '858 patent have several different PK limitations. Claims 1, 2, and 17 of the '858 patent require that the method result in a serum testosterone concentration C_{ave} within the "target range" for a hypogonadal male subject (i.e., the eugonadal range or some subset thereof) and either a ratio of C_{max} to C_{ave} of 2.7 or less, or a dose-normalized serum testosterone C_{ave} of about 1.9×10^{-6}/dL or more. Claim 14 of the '858 patent contains the same PK limitations, except that in place of the "target range" limitation, claim 14 requires that the method provide a steady state serum testosterone C_{ave} within the narrower range of 350 to 800 ng/dL. Claim 26 of the '858 patent requires a C_{ave} serum testosterone level of 300 to 1100 ng/dL in at least 75% of a group of hypogonadal male subjects and either (1) a C_{max} serum testosterone level of less than 1500 ng/dL in at least 85% of the subjects, (2) a C_{max} serum testosterone level of about 1800 ng/dL to about 2500 ng/dL in 5% or fewer of the subjects, or (3) a C_{max} serum testosterone level greater than 2500 ng/dL in about 1% or fewer of the subjects. Claim 22 of the '858 patent is the only one

of the asserted claims that contains no express numerical PK requirement. It requires a serum concentration of testosterone in the subject that is "within a target serum testosterone concentration C_{ave} range for a hypogonadal male subject having testosterone deficiency."

Most of the claims provide for a single dose adjustment (i.e., a titration) from the initial daily dose. The adjusted daily dose is described as the "maintenance regimen." The amount of permissible dose adjustment in each of the claims is between a 40% increase in the dose amount to a 40% decrease in the dose amount, depending on the results of testing done during the initial regimen. Only two of the 24 asserted claims provide for more than one titration: claims 2 and 22 of the '858 patent. Claim 2 provides that a dose titration metric can be determined based on the subject's serum testosterone concentration following the first titration, and that a second maintenance regimen can be established based on that determination. Those steps can be repeated if needed, leading to a third titration. Claim 22 of the '858 patent provides for establishing a second maintenance regimen in which the daily dose of TU is within ±40% of the daily dose of TU administered after the first titration.

Various claims recite that the daily TU doses are to be given with a meal, or given with a meal containing certain fat content, and/or administered twice a day. *See* '858 patent, claims 1, 2, 14, and 17; '057 patent, claims 7 and 17; '690 patent, claims 7, 8, 17, and 18; and '390 patent, claim 4. And several of the claims recite components of the carriers in the TU formulations. Those claims require that the carrier comprise oleic acid ('057 patent, claim 4), polyoxyethylene hydrogenated vegetable oil ('057 patent, claim 5), a solubilizer in an amount from about 50 wt % to about 86 wt % of the composition ('057 patent, claim 9), "a triglyceride, a sterol derivative, an ionic hydrophilic surfactant, a non-ionic hydrophilic surfactant, an alcohol or a combination thereof" ('057 patent, claim 21), "a fatty acid and a polyoxyethylene hydrogenated vegetable oil"

('690 patent, claims 7, 8, 11, 17, and 18), "a fatty acid and a polyoxyethylene hydrogenated vegetable oil" and "a triglyceride" ('690 patent, claim 12), "a monoglyceride, a diglyceride, a triglyceride, an antioxidant or a combination thereof" ('690 patent, claim 21), "one or more of: a fatty acid, a monoglyceride, a diglyceride and a polyoxyethylene hydrogenated vegetable oil" ('390 patent, claim 11), or "a monoglyceride, a diglyceride, a fatty acid, a polyoxyethylene hydrogenated vegetable oil or a combination thereof" ('057 patent, claim 17).

II. The Specification

Following the Background of the Invention and the Summary of the Invention, the common specification for the four patents contains a Detailed Description, which is divided into two parts.[3] The first part consists of a lengthy list of definitions of terms used in the specification and the claims. *See* '858 patent, col. 3, line 37, through col. 9, line 29. The second part, titled "Invention," lists a series of what the specification refers to as "embodiments" or "aspects" of the invention. The discussion of those embodiments is very general in nature and lacks any disclosure regarding which compositions produce the results set forth in the patents' claims. *See id.*, col. 9, line 30, through col. 26, line 40.

The first embodiment described in the "Invention" portion of the specification is "a pharmaceutical capsule for oral delivery" that "can include a solubilizer and about 14 wt % to about 35 wt % testosterone undecanoate based on the total weight of the capsule fill." *Id.*, col. 9, ll. 39–43. The specification states that "the oral dosage capsule is such that when a single oral administration [sic] to a male subject of one or more capsules with a total testosterone undecanoate daily dose of about 350 mg to about 650 mg it provides a ratio of serum testosterone C_{max} to serum

[3] All references to the common specification for the four asserted patents are to the text of the specification for the '858 patent.

testosterone C_{ave} of about 2.7 or less." *Id.*, col. 9, ll. 44–48; *see also id.*, col. 26, ll. 14–16. The specification does not suggest that all formulations containing a daily dose of between 350 mg and 650 mg of TU will produce that pharmacokinetic result, nor does it define the contents of the capsule that will produce such a result. Instead, it simply states that the oral dosage capsule "is such" that a daily dose of between 350 mg and 650 mg of TU provides the specified ratio of serum testosterone C_{max} to serum testosterone C_{ave}. The specification further states that a method of administering such oral dosage capsules can result in a ratio of serum testosterone C_{max} to serum testosterone C_{ave} of 2.7 or less based on a single administration. *Id.*, col. 26, ll. 15–17.

Another embodiment is described as a "method for providing a serum concentration of testosterone within a target serum testosterone concentration C_{ave} range for a male subject." *Id.*, col. 9, ll. 52–56. The method "includes the step of orally administering to the male subject a daily dose of a testosterone undecanoate-containing composition" comprising "about 14 wt % to about 35 wt %" TU, in which "the daily dose provides about 350 mg to about 420 mg" of TU to the subject with no titration. *Id.*, col. 9, ll. 56–62. The specification adds that the TU can be present in different percentage amounts in the composition, such as from about 15 wt % to about 30 wt %, from about 18 wt % to about 25 wt %, or from about 14 wt % to about 18 wt % of the total composition. *Id.*, col. 9, ll. 62–65; *id.*, col. 12, ll. 43–61. The discussion of those embodiments contains no reference to the resulting serum testosterone concentration in the subject, except for the allusion to the "target" range.

After a discussion of the conditions for which testosterone therapy is appropriate, the specification states that a TU composition can provide therapeutically effective treatment without the need for oils, triglycerides, or hydrophilic surfactants. *Id.*, col. 12, ll. 3–42. The specification then turns to a lengthy listing of a wide range of excipients, including solubilizers, dispersants,

surfactants, and solidifying agents, that can be used in the TU composition. *Id.*, col. 13, line 10, through col. 17, line 52.

Following the listing of excipients, the specification states that oral capsules "can be formulated such that they have distinctive release profiles." *Id.*, col. 18, ll. 6–7. The specification reports that as a result of *in vitro* testing, oral TU dosage capsules were found to have release profiles between 75 wt % of the TU during the first 120 minutes, to up to 85 wt % of the TU in the first 30 minutes. *Id.*, col. 18, ll. 6–35. The specification also states that the TU dosage capsules can be formulated so that the TU can begin releasing at various times after ingestion. *Id.*, col. 18, ll. 36–55; *see also id.*, col. 20, ll. 49–65.

The specification next provides that the dosage capsules "can be formulated such that . . . they provide a serum total testosterone C_{avg} ranging [from] about 300 ng/dL to about 1100 ng/dL." *Id.*, col. 19, ll. 9–12. That statement is followed by a number of other statements that the oral dosage capsules "can be formulated" to produce different serum total testosterone concentrations in male subjects, including a serum total testosterone C_{ave} ranging from about 400 ng/dL to about 600 ng/dL, a serum TU C_{ave} of about 1.5 ng/mL to about 1 mcg/mL, a serum TU C_{ave} of about 3 ng/mL to about 850 ng/mL, and a serum TU C_{ave} of about 10 ng/mL to about 850 ng/mL. *Id.*, col. 19, ll. 12–32. In other embodiments, according to the specification, a single dose can provide a dose-normalized serum testosterone C_{max} of about 3 x 10^{-6}/dL or higher, about 1.9 x 10^{-6}/dL or higher, or about 2.7 x 10^{-6}/dL or higher. *Id.*, col. 19, ll. 32–41.

The specification further states that the TU compositions "can be formulated" so that the capsules provided to a group of hypogonadal men will produce a serum testosterone C_{ave} between 300 ng/dL and 1100 ng/dL in at least 75% of the men, and that at least one of the following will also be true: there will be a serum testosterone C_{max} of less than about 1500 ng/dL in at least 85%

of the group; there will be a serum testosterone C_{max} of about 1800 ng/dL to about 2500 ng/dL in 5% or fewer of the men; or there will be a serum testosterone C_{max} greater than 2500 ng/dL in about 1% or fewer of the men. *Id.*, col. 21, ll. 19–34; *see also id.*, col. 25, line 64, through col. 26, line 15.

The specification notes that the claimed TU compositions can be taken with meals containing various numbers of calories and fat content, and can be taken at various times during the day. The specification does not say what consequences flow from those differing treatment regimens, however. *Id.*, col. 20, ll. 14–48; *id.*, col. 26, ll. 17–40.

The specification then describes various titration schemes involving a maintenance regimen consisting of a maintenance daily dose ranging from 45% to 155% of the initial daily dose, depending on the results of the initial regimen. *Id.*, col. 21, line 35, through col. 22, line 29; *see also id*., col. 25, ll. 12–24. In order to provide "a serum concentration of testosterone within a target serum testosterone concentration C_{ave} range," the specification states that after administering a particular daily dose of TU, a titration metric is determined based on a measurement of the serum testosterone concentration in the subject during the initial regimen. *Id.*, col. 24, line 27, through col. 25, line 11. The described method, according to the specification, "can provide desirable pharmacokinetic parameters based on administration to a group of subjects." *Id.*, col. 25, ll. 62–64.

The next section of the common specification, titled "Examples," contains a list of what are referred to as 55 examples, which are described as being "provided to promote a more clear understanding of certain embodiments of the present invention, and are in no way meant as a limitation thereon." *Id.*, col. 26, ll. 44–46. The reference to "examples" is somewhat confusing because the first 47 "examples" consist simply of a listing of 49 TU formulations. Those

formulations are numbered 1–47, plus 15A and 39A. The last eight "examples" report the results of clinical tests and simulations involving some of those formulations.[4]

The specification describes six of the formulations—Composition Examples 15A, 40, 41, 44, 45, and 47—as having been the subjects of certain clinical studies and simulations. The results of those clinical studies and simulations, which are reported in Data Examples 48–55, purport to show that certain of those six Composition Examples satisfied various PK limitations set forth in the asserted claims. Data Examples 48 and 49 are the only parts of the specification that provide actual PK results achieved by the administration of any of the TU compositions to subjects; the data reported in Data Examples 50–55 are the results of simulations that were based on the clinical test results from Data Examples 48 and 49.

The clinical tests described in Data Example 48 were designed to determine whether the tested formulations satisfied one of the two alternative PK limitations in claim 1 of the '858 patent and its dependent claims: the requirement that the claimed method provide, upon single dose administration, a ratio of the serum testosterone C_{max} to the mean serum testosterone C_{ave} of 2.7 or less. The specification reported that four of the five tested Composition Examples (Composition Examples 15A, 40, 41, and 45) satisfied that alternative PK limitation. *See id.*, col. 37, ll. 10–40 & Table XX.[5]

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[4] Because Examples 1–47 in the specification consist of a list of TU compositions and Examples 48–55 report clinical results or estimates of the performance of certain of those compositions with regard to different PK parameters and other data, the examples numbered 1 through 47 are referred to here as "Composition Examples." The remainder of the "examples," numbered 48 through 55, are referred to here as "Data Examples."

[5] Composition Example 44 is not included in Data Example 48. The dose amounts for Composition Examples 45 and 47 reported in Data Example 48 do not fall within the initial dose range set forth in claim 1 of the '858 patent, but the dose amounts for those two Composition Examples would fall within the claimed range after a titration of ±40% of the initial dose.

Data Example 49 reports the results of four Composition Examples that were purportedly tested to determine whether they satisfied the other alternative limitation of claim 1 of the '858 patent and its dependent claims: the requirement that the recited method provide a dose-normalized serum testosterone C_{ave} of about 1.9 x 10^{-6}/dL or higher. The specification reports that two of the four tested Composition Examples (Composition Examples 40 and 41) satisfied that alternative PK limitation. *See id.*, col. 37, line 41, through col. 38, line 6, & Table XXI.

Data Examples 50 through 53 of the specification present estimated PK results generated from computer simulations run on different groupings of Composition Examples 41, 44, 45, and 40 (along with several variants of Composition Example 40).[6] Those simulations were designed to estimate PK performance parameters for various subsets of those formulations before titration (Data Example 50), after one titration (Data Example 51), after two titrations (Data Example 52), and after three titrations (Data Example 53). *See id.*, col. 38, line 7, through col. 41, line 23, & Tables XXII through XXV.

Data Example 55 is a simulation based on five different initial daily TU doses of an unspecified formulation with between zero and three titrations. In each case, according to Data Example 55, where the titrations were between 25% and 55% greater or less than the previous

[6] The specification identifies six variants of Composition Example 40. Those variants, denominated Composition Examples 40 through 40E, represent different but sometimes overlapping daily TU dose levels of the same formulation. Composition Example 40A represents a daily TU dose of 150 mg; Composition Example 40B represents a daily TU dose of 360–420 mg; Composition Example 40C represents a daily TU dose of 430 mg; Composition Example 40D represents a daily TU dose of 1000 mg; and Composition Example 40E represents a daily TU dose of 360–460 mg. Thus, Composition Example 40 (daily TU dose of 430–460 mg) and variant 40C overlap, and variants 40B and 40E are effectively the same, as they represent substantially overlapping amounts of the same components. The specification states that Composition Example 40 represents a daily TU dose of 430–460 mg, but counsel for Lipocine has acknowledged that Composition Example 40 was tested at a daily TU dose of 450 mg. It is therefore reasonable to treat Composition Example 40 as identical to variants 40B and 40E.

daily dose, the simulations for all five formulations resulted in a C_{ave} greater than 300 ng/dL and less than 1500 ng/dL. *See id.*, col 42, line 33, through col. 43, line 13, & Table XXVII.[7] While the specification does not report which formulation or formulations were used in the simulations represented by Data Example 55, counsel for Lipocine has represented that all of the formulations in Data Example 55 were based on different amounts of Composition Example 40.

DISCUSSION

I. The Written Description Requirement: Legal Standards

Section 112(a) of the Patent Act, which contains the written description, enablement, and best mode requirements, provides as follows:

> The specification shall contain a written description of the invention, and of 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, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

35 U.S.C. § 112(a) (2012).[8] The written description requirement requires that the specification "describe the invention sufficiently to convey to a person of skill in the art that the patentee had possession of the claimed invention at the time of the application, i.e., that the patentee invented what is claimed." *LizardTech, Inc. v. Earth Res. Mapping, Inc.*, 424 F.3d 1336, 1345 (Fed. Cir. 2005). A patentee "can lawfully claim only what he has invented and described, and if he claims

[7] Data Example 54 has little, if any, relevance to the asserted claims. That Data Example provides what it refers to as "clinical practice titration metrics" suggesting that certain levels of serum testosterone in a subject at particular times following a single TU administration indicate that either up titration or down titration is appropriate in amounts between ±25% and ±55% of the initial dose. '858 patent, col. 41, line 25, through col. 42, line 32, & Table XXVI.

[8] The cited version of section 112 incorporates amendments to the prior version made by section 4(c) of the Leahy-Smith America Invents Act, Pub. L. No. 112-29, § 4(c), 125 Stat. 284, 296 (2011). The prior version of section 112 applies to the '858 patent because that patent was filed before September 16, 2012, the date on which the America Invents Act's amendments to section 112 took effect. The differences between the two versions are, however, immaterial for the purposes of this case.

more his patent is void." *Carnegie-Mellon Univ. v. Hoffman-LaRoche Inc.*, 541 F.3d 1115, 1122 (Fed. Cir. 2008) (citing *O'Reilly v. Morse*, 56 U.S. (15 How.) 62, 121 (1853)).

The written description requirement is satisfied if "the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). That is, the description of the invention in the patent "must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed." *In re Alton*, 76 F.3d 1168, 1172 (Fed. Cir. 1996).

The purpose of the written description requirement is to "ensure that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the inventor's contribution to the field of art as described in the patent specification." *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 920 (Fed. Cir. 2004) (quoting *Reiffin v. Microsoft Corp.*, 214 F.3d 1342, 1345 (Fed. Cir. 2000)); *see also Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1561 (Fed. Cir. 1991). As the Federal Circuit explained in *AbbVie Deutschland GmbH v. Janssen Biotech, Inc.*, 759 F.3d 1285 (Fed. Cir. 2014), a question "regarding the written description requirement has been raised when a genus is claimed but the specification only describes a part of that genus that is insufficient to constitute a description of the genus." *Id.* at 1299.

A sufficient description of a genus requires the specification to disclose "either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can 'visualize or recognize' the members of the genus." *Ariad*, 598 F.3d at 1350 (quoting *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1568–69 (Fed. Cir. 1997)). If the genus is not large, or if the specification "discloses species representing the genus throughout its scope, the [written description]

requirement may be met. On the other hand, . . . if the disclosed species only abide in a corner of the genus, one has not described the genus sufficiently to show that the inventor invented, or had possession of, the genus. He only described a portion of it." *AbbVie*, 759 F.3d at 1299–1300. As the Federal Circuit explained in *Ariad*, "merely drawing a fence around the outer limits of a purported genus is not an adequate substitute for describing a variety of materials constituting the genus and showing that one has invented a genus and not just a species." 598 F.3d at 1350. Instead, "[o]ne needs to show that one has truly invented the genus, i.e., that one has conceived and described sufficient representative species encompassing the breadth of the genus. Otherwise, one has only a research plan, leaving it to others to explore the unknown contours of the claimed genus." *AbbVie*, 759 F.3d at 1300; *see also Pernix Ireland Pain DAC v. Alvogen Malta Operations Ltd.*, 323 F. Supp. 3d 566, 626 (D. Del. 2018), *aff'd*, 945 F.3d 1184 (Fed. Cir. 2019) ("Absent a description of the class of formulations that will work, . . . a patent merely describes the problem to be solved and claims all solutions to it.").

In the pharmaceutical and other medical arts, applications claiming new methods of treatment are typically supported by test results. *In re '318 Patent Infringement Litig.*, 583 F.3d 1317, 1324 (Fed. Cir. 2009). To be sure, actual reduction to practice and the results of clinical trials are not required in every instance. *See Ariad*, 598 F.3d at 1352; *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1366–67 (Fed. Cir. 2006); *Univ. of Rochester*, 358 F.3d at 926. However, the specification must demonstrate that the inventor possessed the invention as claimed, i.e., the specification must "describe the claimed subject matter in terms that establish that the applicant was in possession of the claimed invention, including all of the elements and limitations." *Univ. of Rochester*, 358 F.3d at 926 (cleaned up) (quoting *Hyatt v. Boone*, 146 F.3d 1348, 1353 (Fed. Cir. 1998)). Simply presenting a "laundry list" of compositions that might or might not satisfy the

claims is not sufficient. *See Novozymes A/S v. DuPont Nutrition Biosciences APS*, 723 F.3d 1336, 1345–46 (Fed. Cir. 2013); *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571 (Fed. Cir. 1996); *Purdue Pharma L.P. v. Iancu*, 767 F. App'x 918, 924 (Fed. Cir. 2019); *FWP IP ApS v. Biogen MA, Inc.*, 749 F. App'x 969, 974 n.5 (Fed. Cir. 2018).

A description of an invention in purely functional terms has frequently been found inadequate to satisfy the written description requirement. *See, e.g.*, *Regents of the Univ. of Cal.*, 119 F.3d at 1568 ("A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is."); *Ariad*, 598 F.3d at 1349 ("The [written description] problem is especially acute with genus claims that use functional language to define the boundaries of a claimed genus. In such a case, ... the specification must demonstrate that the applicant has made a generic invention that achieves the claimed result and do so by showing that the applicant has invented species sufficient to support a claim to the functionally-defined genus."). Functional claim language can meet the written description requirement when the art has established a correlation between structure and function. *See Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 964 (Fed. Cir. 2002) (written description requirement would be met if the functional characteristics at issue "were coupled with a disclosed correlation between that function and a structure that is sufficiently known or disclosed").

The question whether a patent satisfies the written description requirement is treated as a question of fact, judged from the perspective of a person of ordinary skill in the art as of the relevant filing date. *Immunex Corp. v. Sandoz Inc.*, 964 F.3d 1049, 1063 (Fed. Cir. 2020); *Quake v. Lo*, 928 F.3d 1365, 1373 (Fed. Cir. 2019); *Ariad*, 598 F.3d at 1355. A judgment of invalidity for lack of written description can be entered only if the adjudicator is satisfied by clear and convincing evidence that the claims in question are not supported by adequate written description

in the patent. *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1338 (Fed. Cir. 2016); *Cordis Corp. v. Medtronic AVE, Inc.*, 339 F.3d 1352, 1364 (Fed. Cir. 2003); *Abbott Labs. v. Syntron Bioresearch, Inc.*, 334 F.3d 1343, 1356 (Fed. Cir. 2003).

Summary judgment (or judgment as a matter of law) of invalidity for failure to satisfy the written description requirement can be entered only if no reasonable finder of fact could find that the written description requirement was satisfied. *Atl. Rsch. Mktg. Sys. v. Troy*, 659 F.3d 1345, 1353 (Fed. Cir. 2011); *Crown Packaging Tech., Inc. v. Ball Metal Beverage Container Corp.*, 635 F.3d 1373, 1379–80 (Fed. Cir. 2011); *PowerOasis, Inc. v. T-Mobile USA, Inc.*, 522 F.3d 1299, 1307 (Fed. Cir. 2008). Nonetheless, compliance with the written description requirement is "amenable to summary judgment in cases where no reasonable fact finder could return a verdict for the non-moving party." *Boston Sci. Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1361 (Fed. Cir. 2011) (quoting *PowerOasis*, 522 F.3d at 1307).

Because the factual issues underlying a written description determination often turn on the text of the specification, courts have been more willing to entertain summary judgment motions on written-description issues than on other issues. *See Centocor Ortho Biotech, Inc. v. Abbott Labs.*, 636 F.3d 1341, 1347 (Fed. Cir. 2011) ("A patent also can be held invalid for failure to meet the written description requirement based solely on the face of the patent specification."); *Univ. of Rochester*, 358 F.3d at 927 ("[A]lthough compliance with the written description requirement is a question of fact, . . . [the] argument that a patent may not be held invalid on its face is contrary to our case law." (citation omitted)); *Stored Value Sols., Inc. v. Card Activation Techs., Inc.*, 796 F. Supp. 2d 520, 527 (D. Del. 2011) (Jordan, J.) ("Whether a patent meets the written description requirement . . . . is amenable to determination at the summary judgment stage and may be based 'solely on the face of the patent specification.'" (quoting *Centocor*, 636 F.3d at 1347)). On

numerous occasions, the Federal Circuit has upheld or directed grants of summary judgment or judgment as a matter of law on the question whether the written description requirement was satisfied.[9]

II. Analysis

Clarus argues that the asserted claims are invalid for lack of written description. According to Clarus, the asserted claims are very broad, and the specification, although lengthy and discursive, provides only limited and narrowly circumscribed support for the claims. As a result,

[9] *See*, *e.g.*, *Idenix Pharms. LLC v. Gilead Scis. Inc.*, 941 F.3d 1149, 1163–65 (Fed. Cir. 2019) (directing entry of JMOL of no written description); *Novozymes*, 723 F.3d at 1338 (upholding summary judgment of no written description); *Streck, Inc. v. Research & Diagnostic Sys.*, 665 F.3d 1269, 1284–87 (Fed. Cir. 2012) (upholding summary judgment that written description requirement was satisfied); *Boston Sci. Corp.*, 647 F.3d at 1356 (upholding summary judgment of no written description); *Billups-Rothenberg, Inc. v. Associated Reg'l & Univ. Pathologists, Inc.*, 642 F.3d 1031, 1032 (Fed. Cir. 2011) (upholding grant of summary judgment of no written description); *In re Katz Interactive Call Processing Patent Litig.*, 639 F.3d 1303, 1318–20 (Fed. Cir. 2011) (upholding grant of summary judgment of no written description); *Centocor*, 636 F.3d at 1344 (directing entry of JMOL of no written description); *Crown Packaging*, 635 F.3d at 1379–83 (directing entry of summary judgment that written description requirement was satisfied); *Ariad*, 598 F.3d at 1340 (directing entry of JMOL of no written description); *ICU Med., Inc. v. Alaris Med. Sys., Inc.*, 558 F.3d 1368, 1379 (Fed. Cir. 2009) (upholding summary judgment of no written description); *Carnegie Mellon*, 541 F.3d at 1120 (upholding summary judgment of no written description); *LizardTech*, 424 F.3d at 1337 (Fed. Cir. 2005) (upholding summary judgment of no written description); *Space Sys./Loral, Inc. v. Lockheed Martin Corp.*, 405 F.3d 985, 989–90 (Fed. Cir. 2005) (overturning summary judgment of no written description and holding that written description requirement was satisfied); *Univ. of Rochester*, 358 F.3d at 917 (upholding summary judgment of no written description); *All Dental Prodx, LLC v. Advantage Dental Prods., Inc.*, 309 F.3d 774, 779 (Fed. Cir. 2002) (directing entry of summary judgment that written description requirement was satisfied); *PIN/NIP, Inc. v. Platte Chem. Co.*, 304 F.3d 1235, 1237–38 (Fed. Cir. 2002) (directing entry of JMOL of no written description); *Cooper Cameron Corp. v. Kvaerner Oilfield Prods., Inc.*, 291 F.3d 1317, 1322–23 (Fed. Cir. 2002) (holding, as a matter of law, that claims were not invalid for inadequate written description); *TurboCare Div. of Demag Delaval Turbomachinery Corp. v. Gen. Elec. Co.*, 264 F.3d 1111, 1113 (Fed. Cir. 2001) (upholding summary judgment of no written description); *Realtime Data, LLC v. Morgan Stanley*, 554 F. App'x 923, 936–37 (Fed. Cir. 2014) (upholding summary judgment of no written description); *Stored Value Sols.*, 499 F. App'x at 12–14 (upholding summary judgment of no written description); *MessagePhone, Inc. v. SVI Sys., Inc.*, 2000 WL 1141046, *6–8 (Fed. Cir. Aug. 11, 2000) (upholding summary judgment of no written description).

Clarus contends, the specification fails to provide an adequate written description for the full breadth of the claims. I agree.

A. The Breadth of the Asserted Claims

The asserted claims are directed to methods of using oral TU formulations to achieve certain PK targets. The claimed methods consist of administering an oral TU composition to a subject, measuring the resulting serum testosterone level in the subject, and then adjusting the dose of the composition, if necessary, to achieve a designated PK result. The claims are largely defined by functional limitations and contain minimal formulation restrictions.

To begin with, the formulation and dosage limitations in the asserted claims are broad. Most of the asserted claims recite daily TU doses from about 360 mg to about 480 mg, or from about 350 mg to about 650 mg. Only the four asserted claims of the '390 patent have narrow ranges of daily TU doses. Those claims recite a formulation containing a daily TU dose of 450 mg or 480 mg (claims 1, 4, and 11) or about 480 mg (claim 7). The asserted claims also cover a broad range in the recited percentage-by-weight amounts of TU used in the formulations. Most of the claims call for the percentage by weight of TU in the formulations to fall between 14% and 35%. The two exceptions, claims 22 and 26 of the '858 patent, contain no restrictions at all on the concentration of TU in the formulations.

The range of doses to be administered upon dose adjustment (i.e., titration) renders the claims even broader. The asserted claims uniformly recite that after the initial dosage regimen is assessed, adjustments may be made in any amount ranging from 40% less than the initial dosage regimen to 40% more than the initial dosage regimen.

As for the PK limitations, the broadest of the asserted claims, claim 22 of the '858 patent, contains no specific PK requirement at all. In that claim, the inventors sought patent protection

for a treatment method in which a daily TU dose of between 350 mg and 650 mg is administered to a subject for the purpose of achieving an unspecified "target serum testosterone concentration C_{ave} range for a hypogonadal male subject having testosterone deficiency" after two titrations. There is a similar limitation in claims 1, 2, and 17 of the '858 patent, requiring that the claimed treatment method result in a serum testosterone concentration C_{ave} within the "target range" for a hypogonadal male subject. At Lipocine's behest, I construed the term "target range" to mean the range selected by a treating physician for a particular patient, which may vary somewhat from the 300–1100 ng/dL eugonadal range, i.e., the average testosterone concentration for a healthy male, and in particular may be some subset within that range. *See* Dkt. No. 119, at 10.

The remaining claims contain PK limitations that must be satisfied following one titration (or up to three titrations in the case of claim 2 of the '858 patent). Those PK limitations are also broad. In addition to the "target range" C_{ave} limitation, claim 1 and its dependent claims 2 and 17 of the '858 patent require either (1) that the ratio of C_{max} to C_{ave} be 2.7 or less, or (2) that the method provide a dose-normalized serum testosterone C_{ave} level of about 1.9×10^{-6}/dL or higher. Those PK parameters would cover any oral treatment method with 360–480 mg of TU that either did not produce an unsafe spike in serum testosterone levels, or resulted in an acceptable minimum level of serum testosterone in the subject, as long as the steady state serum testosterone concentration C_{ave} ended up somewhere within the "target range." In short, because claims 1, 2, and 17 of the '858 patent merely limit C_{max} in the alternative, and because a steady state C_{ave} within the "target range" does not exclude an unsafe spike in serum testosterone (i.e., a high C_{max}), the PK parameters of those claims essentially cover any oral TU treatment method that is effective, but not necessarily safe, involving compositions within a wide range of dosage amounts and concentrations of TU, regardless of which excipients are contained within those compositions.

Like the PK parameters of claim 1, the PK parameters of claim 26 of the '858 patent are quite broad, requiring that the method produce (1) a serum testosterone C_{ave} of 300 to 1100 ng/dL in at least 75% of a group of hypogonadal male subjects and (2) either a serum testosterone C_{max} of less than 1500 ng/dL in at least 85% of the subjects in the group, or a serum testosterone C_{max} of about 1800 ng/dL to about 2500 ng/dL in 5% or fewer of the subjects in the group, or a serum testosterone C_{max} greater than 2500 ng/dL in about 1% or fewer of the subjects in the group.

Claim 14 of the '858 patent is somewhat narrower than the other claims of the '858 patent but is still quite broad. In addition to incorporating the two alternative PK parameters from claim 1, claim 14 requires a steady state serum testosterone C_{ave} of between 350 ng/dL and 800 ng/dL.

The PK limitations of the asserted claims of the '057, '690, and '390 patents are even broader than those of claim 1 of the '858 patent. The only PK limitation set forth in the asserted claims of those three patents is the requirement that the claimed method produce a serum testosterone C_{ave} in a hypogonadal male within the eugonadal range, i.e., between about 300 ng/dL and about 1100 ng/dL. Some of those claims cover any formulation that satisfies those requirements, regardless of what excipients are contained within the formulation and regardless of what quantities of TU are used, within the broad ranges set forth in those claims.

As for limitations directed to the excipients used in the formulations, ten of the asserted claims do not require the compositions to contain any particular excipients at all. Those are the following: all six asserted claims of the '858 patent; claim 7 of the '057 patent; and claims 1, 4, and 7 of the '390 patent. The claims that contain limitations on the excipients in some form are claims 2, 4, 5, 9, 17, and 21 of the '057 patent; all seven asserted claims of the '690 patent; and claim 11 of the '390 patent.

Even those claims that limit their excipients employ broad categories when doing so. Claim 2 of the '057 patent recites a carrier "comprising a solubilizer and a dispersant"; claim 9 of the '057 patent recites a carrier "comprising a solubilizer in an amount of from about 50 wt % to about 86 wt % of the pharmaceutical composition"; claim 17 of the '057 patent recites a carrier "comprising a monoglyceride, a diglyceride, a fatty acid, a polyoxyethylene hydrogenated vegetable oil *or* a combination thereof" (emphasis added); claim 21 of the '057 patent recites a carrier "comprising a triglyceride, a sterol derivative, an ionic hydrophilic surfactant, a non-ionic hydrophilic surfactant, an alcohol *or* a combination thereof" (emphasis added); and claim 11 of the '390 patent recites a carrier that comprises "one or more of: a fatty acid, a monoglyceride, a diglyceride and a polyoxyethylene hydrogenated vegetable oil." Other than the range set forth in claim 9 of the '057 patent, none of the claims contain any meaningful limitation on the amounts of the excipients used in the formulations.

While the excipient limitations in the remaining claims are somewhat more specific, those claims still cover an expansive range of compositions. Claim 4 of the '057 patent recites a carrier "comprising oleic acid," but does not further confine its components. Similarly, claim 5 of the '057 patent recites a carrier "comprising a polyoxyethylene hydrogenated vegetable oil," but does not further confine its components. Claims 7, 8, 11, 17, and 18 of the '690 patent recite a carrier "comprising a fatty acid and a polyoxyethylene hydrogenated vegetable oil," while claim 12 of the '690 patent, which depends from claim 11, recites that the carrier "further comprises a triglyceride." However, "fatty acid" is a broad category of solubilizers, as demonstrated by the specification's description of "non-limiting examples" of fatty acids, which spans three paragraphs. *See* '858 patent, col. 13, line 27, through col. 14, line 34. Likewise, "triglyceride"

encompasses a broad subcategory of solubilizers within the category of fatty acids. *See id.*, col. 13, line 57, through col. 14, line 6.

Only one of the 24 asserted claims provides any meaningful degree of specificity regarding the identity of the excipients. That is claim 21 of the '690 patent, which recites "oleic acid and Cremophor RH 40" in addition to "a monoglyceride, a diglyceride, a triglyceride, an antioxidant or a combination thereof." Yet even that claim is not highly specific with respect to its formulation, because it covers any composition that includes oleic acid and Cremophor RH 40, and *at least one of* a monoglyceride, a diglyceride, a triglyceride, and an antioxidant, as well as any other components, without restriction. And no amounts of any of those excipients are recited in the claim; the claimed excipients can be in any quantity, along with any quantity of unclaimed excipients, so long as the formulation achieves effective treatment of hypogonadism with an initial daily TU dose between 360 mg and 480 mg and a percentage by weight of between 14% and 35% TU in the composition.

The claims that appear to be the narrowest in terms of PK limitations—claims 14 and 26 of the '858 patent—contain no restrictions at all regarding the nature or quantity of excipients. The breadth of the formulations covered by those claims is problematic because the specification emphasizes that solubilizers play a crucial role in achieving effective treatment of hypogonadism. The background section of the specification states that "[i]t is generally believed that in order to promote lymphatic absorption for better safety profile and to facilitate effective oral delivery of testosterone undecanoate, the testosterone undecanoate must be presented in a bioacceptable solubilizer. Accordingly, research continues into the development of testosterone oral delivery products that can have high drug load and provide for practical unit oral dosage forms." '858 patent, col. 2, ll. 2–9. The specification adds: "The solubilizers used in the pharmaceutical

compositions and oral dosage capsules of the present invention play role [sic] in the ability of the formulation to provide the desired therapeutic characteristics. Solubilizers that can be used can be selected from a variety of compounds and mixtures of compounds that have the ability to facilitate loading of testosterone undecanoate." *Id.*, col. 13, ll. 10–16. And it states: "Examples 30 through 35 demonstrate the importance of the choice of the solubilizers of the current invention and their levels to achieve greater testosterone undecanoate loading and yet maintain the solubilization of the testosterone undecanoate in the composition and/or the dosage form." *Id.*, col. 34, ll. 1–5.

Thus, in spite of the emphasis in the specification on the importance of the choice of excipients to the invention's ability to achieve the recited therapeutic objectives, the asserted claims of the '858 patent and many of the asserted claims of the other three patents are devoid of meaningful limitations directed to the excipients.

B. Lack of Support in the Specification

The specification support for the asserted claims is severely deficient. Although the specification is lengthy, it does not contain a written description sufficient to demonstrate that the inventors possessed the full scope of the claimed inventions. The specification contains a detailed discussion of matters known in the art, such as the nature of various excipients that can be used in TU formulations. The specification also contains a long list of TU formulations. But with very few exceptions, the specification does not identify which of those formulations can satisfy the recited functional limitations when administered in the amounts specified in the claims. In fact, the 55 examples and 43 columns of disclosure in the specification consist mainly of background information, not a description demonstrating that the inventors were in possession of the claimed inventions. Although the specification contains some examples that might have supported claims limited to the data set forth in the specification and reasonable extrapolations from that data, the

claims are much broader—so much so that the specification cannot reasonably be said to support the full scope of those claims.

1. The Data Examples

The 49 Composition Examples set forth in the specification contain specific amounts of particular components, but for the great majority of those examples there is no data or other indication of which, if any, can be used successfully in the claimed methods. The eight Data Examples, on the other hand, purport to demonstrate the efficacy of the claimed methods and thus provide support for the claims. Yet upon closer examination, it is apparent that the Data Examples provide little written description support for the full scope of the asserted claims.

In light of the paucity of clinical testing results reported in the specification, a detailed examination of the Data Examples is necessary. The problem is that the results set forth in the Data Examples, and in particular the results of the clinical tests represented by Data Examples 48 and 49, support the PK limitations for only a small subset of the genus of formulations covered by the asserted claims.

Data Examples 48 and 49 contain information regarding clinical tests purportedly performed on six of the 49 formulations set forth in the specification: Composition Examples 15A, 40, 41, 44, 45, and 47. Upon inquiry by the court, however, Lipocine's counsel admitted that two of the listed Composition Examples—Composition Examples 15A and 41—were not actually tested. Instead, according to Lipocine's counsel, the inventors "built the formulation Examples 15A and 41" based on a study of a different formulation, which was not included in the specification. Dkt. No. 266, at 2 (redacted version of Dkt. No. 263).[10] In addition, counsel for

[10] The specification is misleading when it represents that "clinical testing" was conducted on "the select inventive composition examples" set forth in Data Example 48, '858 patent, col. 37, ll. 13–14, and it is simply false when it states that for Data Example 49, "Examples 40, 41, 44, and

Lipocine disclosed that the clinical tests of Composition Examples 40 and 45 were conducted at a daily TU dosage level of 450 mg and 632 mg, respectively, not across a range of 430–460 mg and 600–650 mg, as represented in the specification. Dkt. No. 264-1, Exh. A, at 21:1–22:3.

Moreover, nothing in the specification suggests that either the six listed formulations or the four that were actually tested are representative of the full range of compositions covered by the asserted claims. In fact, as Clarus points out, Composition Examples 40 and 41 are very similar formulations, as they consist of nearly identical amounts of nearly identical components. Those two compositions are highly comparable to a prior art composition developed by Lipocine.[11] Composition Examples 44 and 45 are also very similar to one another, as they contain very similar amounts of identical components.[12] Those two compositions were based on a prior art patent application owned by Clarus and a related prior art publication by Yin et al. *See* Dkt. No. 187-2, Exh. G; Dkt. No. 187-3, Exh. H. In addition, Composition Example 15A is very similar to Composition Examples 40 and 41.[13] Therefore, for practical purposes, the six formulations for

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45 were clinically tested," *id.*, col 37, line 44.

[11] Composition Example 40, which represents Lipocine's product TLANDO, is described as being identical to Composition Example 17. '858 patent, col. 36, ll. 14–16. As such, it consists of 15% TU; 63% maize oil glycerides (Maisine 35-1); 16% polyoxyl 40 hydrogenated castor oil (Cremophor RH40); and 6% polyethylene glycol 8000. *See id.*, cols. 30–31, Table XII; *id.*, col. 36, Table XVII. Composition Example 41 consists of 18% TU; 68% monoglycerides, for example maize oil monoglycerides such as Maisine 35-1; 8% hydrophilic surfactants such as Cremophor RH40 or Cremophor EL; and 6% solidifying agent such as polyethylene glycol 8000. *Id.*, col. 36, ll. 10–27 & Table XVIII.

[12] Composition Example 44 consists of 18% TU; 17% hydrophilic surfactants such as Cremophor RH40 or Cremophor EL; 53% fatty acids such as linoleic acid, linolenic acid, or oleic acid; and 12% triglyceride, such as castor oil, maize oil, borage seed oil, lauroglycol, or corn oil. Composition Example 45 consists of 20% TU; 16% hydrophilic surfactants such as Cremophor RH40 or Cremophor EL; 52% fatty acids such as linoleic acid, linolenic acid, or oleic acid; and 12% triglyceride, such as castor oil, maize oil, borage seed oil, lauroglycol, or corn oil. '858 patent, col. 36, Table XIX.

[13] Composition Example 15A consists of 18% TU; 63% maize oil glyceride (Maisine 35-1); 16% polyoxyl 40 hydrogenated castor oil (Cremophor RH40); and 12% glyceryl distearate

which results are given in Data Examples 48 and 49 actually represent only three different groups of formulations—the group consisting of Composition Examples 15A, 40, and 41 (of which only Composition Example 40 was tested); the group consisting of Composition Examples 44 and 45; and Composition Example 47.

Data Example 50 contains estimated PK performance parameters for the formulations of Composition Examples 40A, 40B, 40C, 40D, 41, and 45 with no dose titration. Data Example 50 reports that of those six formulations, only Composition Example 41 and variant 40B were estimated to produce a C_{ave} serum testosterone concentration satisfying the PK limitations of claim 26 of the '858 patent. Composition Example 45 and the other variants of Composition Example 40 did not satisfy the PK limitation requiring a serum testosterone C_{ave} from 300 to 1100 ng/dL in at least 75% of the subjects. '858 patent, col. 38, ll. 9–67 & Table XXII.

Data Example 51 contains estimated PK performance parameters for the formulations of Composition Examples 40A, 40E, 40D, and 45 after one titration within a range of ±40% of the initial daily TU dose. That Data Example reports that of those four formulations only variant 40E was estimated to produce a C_{ave} serum testosterone concentration satisfying the PK limitations of Claim 26. The simulations run on Composition Examples 40A, 40D, and 45 all resulted in an estimated serum testosterone C_{ave} from 300 to 1100 ng/dL in fewer than 75% of the subjects, which takes those formulations outside the scope of claim 26. *Id.*, col. 39, ll. 1–41 & Table XXIII.

(Percirol ATO 5), which the specification identifies as a solidifier. '858 patent, cols. 30–31, Table XII; *id.*, col. 17, line 36. Composition Example 40 consists of 15% TU; 63% maize oil glycerides (Maisine 35-1); 16% polyoxyl 40 hydrogenated castor oil (Cremophor RH40); and 6% polyethylene glycol 8000. And Composition Example 41 consists of 18% TU; 68% monoglycerides, for example maize oil monoglycerides such as Maisine 35-1; 8% hydrophilic surfactants such as Cremophor RH40 or Cremophor EL; and 6% solidifying agent such as polyethylene glycol 8000. *See id.*, cols. 30–31, Table XII; *id.*, col. 36, Tables XVIII and XIX.

Data Examples 48, 49, 50, and 51 report that several formulations did not satisfy the limitations pertaining to the PK parameters to which the asserted claims are directed. With respect to the two alternative PK limitations in claim 1 of the '858 patent and its dependent claims, the results set forth in Data Example 49 show that only Composition Example 40 and untested Composition Example 41 satisfied the minimum level of dose-normalized C_{ave} per deciliter required by the first alternative PK limitation of those claims. Similarly, the clinical results set forth in Data Example 48 show that only Composition Examples 15A, 40, 41, and 45 satisfied the mean C_{max} to C_{ave} ratio required by the second alternative PK limitation of those claims.[14] As noted, however, Lipocine admits that Composition Examples 15A and 41 were not actually tested.[15] Therefore, of the formulations that were actually tested for purposes of Examples 48 and 49, only Composition Example 40 satisfied the first alternative PK limitations set forth in claim 1 of the '858 patent and its dependent claims, and only Composition Examples 40 and 45 satisfied the second alternative PK limitation of those claims.

The method of dependent claim 14 of the '858 patent not only must satisfy the PK limitations from claim 1, but also must result in a serum testosterone C_{ave} between 350 ng/dL and 800 ng/dL. Of the four Composition Examples meeting at least one of the two alternative PK limitations in claim 1—Composition Examples 15A, 40, 41, and 45—none is shown by Data

[14] Although the range of doses given in Data Example 48 for Composition Example 45 (600 to 650 mg) is outside the dosage range for the initial dosage regimen set forth in claims 1, 2, and 17 of the '858 patent (360 to 480 mg), the range of doses in Composition Example 45 would be within the permissible maintenance dosage range after one titration in an amount up to 40% more than the initial dosage regimen, as provided for in claims 1, 2, and 17 of the '858 patent.

[15] Even if the results reported for Composition Examples 15A and 41 are taken into account, they can only be counted once, as Lipocine admits that the results for both Composition Examples 15A and 41 were taken from clinical results for a single formulation, which was not disclosed in the specification.

Examples 50 and 51 to produce a serum testosterone C_{ave} within that range.[16] While Data Examples 50 and 51 show that a simulation involving Composition Example 40E resulted in 75% of subjects having a serum testosterone C_{ave} between 300 ng/dL and 1100 ng/dL, that report does not show that the steady state serum testosterone C_{ave} of "a hypogonadal male subject" would fall within the narrower range of 350 to 800 ng/dL.

The PK limitation in claim 26 of the '858 patent, which permits a single titration, corresponds to the simulation results reported in Data Examples 50 and 51, which provide for no titration and a single titration, respectively. Those Data Examples report that only three of the formulations for which simulations were conducted, Composition Examples 40B, 40E, and 41, satisfied the PK limitation of claim 26. And two of those formulations (variants 40B and 40E) are identical formulations with substantially overlapping TU dose amounts, while the third (Composition Example 41) is almost exactly the same formulation as Composition Example 40 and its variants.

The asserted claims of the remaining three patents in suit share the same PK limitation, requiring that the method result in a serum testosterone C_{ave} in the subject from about 300 ng/dL to 1100 ng/dL after one titration.[17] Yet the only Data Examples that reasonably provide any support for that PK limitation are Data Examples 50 and 51. Data Example 50 reports the simulated results for Composition Examples 40A, 40B, 40C, 40D (which simply vary the TU dose

[16] Data Examples 52 and 53 are not relevant to claim 14 of the '858 patent, because those examples allow for two and three titrations, respectively, while claim 14 allows for only one titration. The same is true with respect to claim 26 of the '858 patent.

[17] Because claim 22 of the '858 patent provides for a serum concentration of testosterone "within a target serum testosterone concentration C_{ave} range," which I construed to be generally within the eugonadal range, I have treated the PK limitation of claim 22 as essentially equivalent to the PK limitations in the asserted claims of the '057, '690, and '390 patents. The same is true with respect to the PK limitation in claims 1, 2, and 17 of the '858 patent that requires a serum testosterone concentration C_{ave} within the "target range."

amounts of Composition Example 40), 41, and 45, all without titration. Data Example 51 reports on simulated results for Composition Examples 40A, 40D, 40E, and 45, with one titration. Only Composition Example 41 and variants 40B and 40E of Composition Example 40 produced simulated results showing that more than 75% of the subjects had a serum testosterone C_{ave} in the range of 300 to 1100 ng/dL after either no titrations or one titration, giving rise to an inference that a hypogonadal male taking those TU formulations according to the methods recited in the asserted claims of the '057, '690, and '390 patents would have a serum testosterone C_{ave} between 300 ng/dL and 1100 ng/dL.

Data Examples 52 and 53 provide simulated results for certain Composition Examples following multiple titrations. Those Data Examples are relevant to only two of the asserted claims—claims 2 and 22 of the '858 patent—which are the only two claims that provide for more than one titration. Data Example 52 contains estimated PK performance parameters for simulations run on the formulations of Composition Example 45 and variants 40A, 40E, 40D of Composition Example 40, after two titrations within a range of ±40% of the initial daily TU dose and the first maintenance dose.[18] That Data Example reports that only the simulations run on Composition Example 45 and variant 40E resulted in a serum testosterone C_{ave} from 300 to 1100 ng/dL in at least 75% of the subjects. *Id.*, col. 39, line 42, through col. 40, line 33, & Table XXIV. Data Example 53 reports on the estimated results of simulations run on the formulations of Composition Examples 41, 44, and 45, and variants 40A, 40D, and 40E of Composition Example 40, after three titrations within a range of ±40% of the initial daily TU dose and the subsequent

[18] The specification reports that variant 40C was one of the Composition Examples for which simulated results were derived in Data Example 52, but counsel for Lipocine acknowledged that the reference to variant 40C was a typographical error and that variant 40D was supposed to have been cited instead.

maintenance doses. Data Example 53 is pertinent only to claim 2 of the '858 patent, which is the only asserted claim that provides for three titrations. The simulations reported in Data Example 53 show that only the formulations of Composition Examples 40E, 41, 44, and 45 resulted in an estimated serum testosterone C_{ave} from 300 to 1100 ng/dL in at least 75% of the subjects. *Id.*, col. 40, line 38, through col. 41, line 23, & Table XXV. Because claim 2 of the '858 patent incorporates the alternative PK limitations of claim 1, which are addressed in Data Examples 48 and 49, the combined results from Data Examples 52 and 53 indicate that only three formulations—Composition Examples 40, 41, and 45—satisfied the PK limitations of claim 2. As for claim 22 of the '858 patent, Data Example 52 indicates that only Composition Example 45 and variant 40E satisfied the PK limitation of claim 22.

Finally, Data Example 55 appears to provide little if any support for any of the asserted claims. That Data Example reports simulated results for five formulations, following between zero and three titrations. There are several problems with Data Example 55, however. First, Lipocine represents that those five formulations all represent different doses of the same formulation: Composition Example 40. Accepting Lipocine's representation, the scope of any support provided by Data Example 55 is limited to that single formulation. Second, the titration range for Example 55 (±25–55%) is different from the titration range recited in the asserted claims (±40%). Third, the range of predicted serum testosterone C_{ave} after the designated number of titrations (between 300 ng/dL and 1500 ng/dL) differs from the range of serum testosterone C_{ave} recited in the PK limitations of the asserted claims of the '057, '690, and '390 patents (about 300 to 1100 ng/dL), and it differs from the "target range" in claim 1 of the '858 patent and its dependent claims, as well as in claim 22 of the '858 patent. That range also differs from the range of serum testosterone C_{ave} recited in claim 14 of the '858 patent (350 to 800 ng/dL).

In short, although Lipocine states that Data Examples 50–55 show "titration simulations of clinical data of four different formulations under various dosing regimens," Dkt. No. 200, at 3, the actual disclosures of those Data Examples are more limited. Data Example 50 discloses just two working examples, one of which is Composition Example 41, which Lipocine admits was not clinically tested. Data Example 51 discloses only one working example. Data Example 52 provides two working examples for the PK limitations of claims 2 and 22 of the '858 patent. And Data Example 53 provides three working examples, including Composition Example 41, that fall within one of the PK limitations of claim 2. Data Example 55 provides data only for Composition Example 40, and the data provided is of little value, because it does not line up with the PK limitations of any of the asserted claims.

The disclosures provided by the Data Examples with respect to the PK limitations of the asserted claims can be summarized as follows:

Claim 1 of the '858 patent and its dependent claim 17: Data Example 48 reports that only Composition Examples 15A, 40, 41, and 45 satisfied one of the alternative PK limitations of claim 1 of the '858 patent and its dependent claim 17. Data Example 49 shows that only Composition Examples 40 and 41 satisfied the other alternative PK limitation of those claims. However, of the Composition Examples that satisfied at least one of those alternative PK limitations, only Composition Example 41 and variants 40B and 40E of Composition Example 40 (which are essentially identical) are reasonably shown by the simulations in Data Examples 50 (no titrations) and 51 (one titration) to have satisfied the additional PK limitation in those claims requiring a steady state testosterone C_{ave} within the "target range." Because Lipocine concedes that Composition Examples 15A and 41 were not actually tested, and that the results for those Composition Examples are based on a single formulation that was not disclosed in the

specification, those two Composition Examples cannot be counted as two separate formulations for purposes of assessing the written description in the specification. Moreover, the clinical results reported for Composition Example 41 in Data Examples 48 and 49 can, at most, be treated as estimates, not the products of clinical testing of that formulation. Treating Composition Example 40 (450 mg daily TU dose) as equivalent to Composition Example 40E (360–460 mg daily TU dose)—which is required to piece together the disclosures from Data Examples 48 through 51—only tested Composition Example 40 and untested Composition Example 41 satisfied all the limitations of claim 1 and its dependent claim 17.

Claim 2 of the ’858 patent: Claim 2 has the same PK limitations as claim 1 except that it permits up to three titrations, the first of which has an explicit range of ±40% of the initial daily dose. Because of those permitted titrations, claim 2 find some additional support in Data Examples 52 (two titrations) and 53 (three titrations). All in all, Composition Examples 40, 41, and 45 satisfied all the limitations of claim 2 of the ’858 patent. Again, however, the “clinical” results reported for Composition Example 41 in Data Examples 48 and 49 must be treated as mere estimates.

Claim 14 of the ’858 patent: The additional PK limitation of dependent claim 14 (a steady state testosterone C_{ave} between 350 ng/dL and 800 ng/dL) finds no support in the specification. Data Examples 48 and 49 contain no data that supports that limitation, and the pertinent simulations in Data Examples 50 and 51 also provide no support for that limitation, as those Data Examples provide estimated results for the C_{ave} range of 300 to 1100 ng/dL, which is significantly broader than the range in the additional PK limitation of claim 14.

Claim 22 of the ’858 patent: The simulated results reported in Data Examples 50–52 provide some support for the PK limitation of claim 22, as it is reasonable to infer that that the

"target serum concentration" PK limitation of that claim is met when more than 75% of subjects have a serum testosterone C_{ave} level between 300 ng/dL and 1100 ng/dL. That support is limited to Composition Examples 45, the overlapping variants 40B and 40E of Composition Example 40, and untested Composition Example 41.

Claim 26 of the '858 patent: Data Examples 50 and 51 provide support for the PK limitation of claim 26, but that support is limited to untested Composition Examples 41 and the overlapping variants 40B and 40E of Composition Example 40. Those are the only formulations for which it was estimated that more than 75% of subjects would have a serum testosterone C_{ave} level between about 300 ng/dL and 1100 ng/dL, and that (1) at least 85% of subjects would have a serum testosterone C_{max} of less than 1500 ng/dL, or (2) 5% or fewer of subjects would have a serum testosterone C_{max} between 1800 ng/dL and 2500 ng/dL, or (3) 1% or fewer of subjects would have a C_{max} of greater than 2500 ng/dL.

The asserted claims of the '057, '690, and '390 patents: As for the asserted claims of the other three patents, only Data Examples 50 and 51 reasonably provide any support for the PK limitations in those claims, which require a serum testosterone C_{ave} level within the range from about 300–1100 ng/dL after one titration. That support, moreover, is limited to two very similar formulations: untested Composition Example 41 and the overlapping variants 40B and 40E of Composition Example 40.[19]

Thus, with regard to the asserted claims of the '858 patent, the data support in the specification for the PK limitations in those claims is limited to between zero and three

[19] Although the TU dose amounts recited in the asserted claims of the '390 patent (about 450 mg or about 480 mg) do not fall within the ranges given in Data Example 50 for Composition Examples 40B (360 to 420 mg) and 41 (340 to 400 mg), those dose amounts would fall within the ranges given for Composition Examples 40B and 41 in Data Example 50 after one titration in an amount up to ±40% of the initial dose, as provided for in the '390 patent.

formulations (treating the overlapping variants 40B and 40E as a single formulation). And for the asserted claims of the '057, '690, and '390 patents, the specification support for the PK limitation in those claims is confined to two closely related and overlapping formulations (treating the overlapping variants 40B and 40E as a single formulation). *See* Appendix B (summarizing the Data Examples and Composition Examples relevant to each asserted claim).

2. The Lack of Representative Species

As noted above, the written description requirement does not require a patentee wishing to claim a genus to provide written description support for every species within that genus. To do so would be impossible in many instances, such as for a claim to a pharmaceutical product that is defined by features spanning a numerical range of dose amounts, dosing frequency, or concentration of components. Rather, what is required is for the specification to provide either a sufficient number of representative species to show that the inventor has possession of the entire genus, or for the described species to have structural features characteristic of the genus from which a person of skill in the art could infer that the inventor has possession of the entire genus, not just isolated species within the broader genus. *Idenix Pharms. LLC v. Gilead Scis., Inc.*, 941 F.3d 1149, 1164 (Fed. Cir. 2019); *Ariad*, 598 F.3d at 1350.

No specific number of species must be disclosed in order to satisfy the requirement of describing a genus. What is required is that the species be representative and that possession of the genus can be reasonably inferred from the demonstrated possession of the described species.

The Federal Circuit has pointed to the Patent and Trademark Office's Guidelines for Examination of Patent Applications Under the 35 U.S.C. § 112, ¶ 1 "Written Description" Requirement, 66 Fed. Reg. 1099 (Jan. 5, 2001), as providing "an accurate description of the law by the agency responsible for examining patent applications, and thus persuasive authority."

Carnegie Mellon, 541 F.3d at 1124. In the portion of the Guidelines quoted by the Federal Circuit in *Carnegie Mellon*, the Patent and Trademark Office explains that the written description requirement may be satisfied through a sufficient description of a "representative number of species"; the Guidelines then define a representative number of species to mean that "the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus." *Carnegie Mellon*, 541 F.3d at 1124 (quoting 66 Fed. Reg. at 1106).

Using the metaphor of trailblazing, the Federal Circuit has described the task of providing an adequate written description as being akin to providing "blaze marks which single out particular trees" in a forest, rather than simply "pointing to trees." *Idenix*, 941 F.3d at 1164; *Fujikawa*, 93 F.3d at 1570; *In re Ruschig*, 379 F.2d 990, 994–95 (C.C.P.A. 1967). Continuing with the metaphor, the Federal Circuit has explained:

> As *Ruschig* makes clear, one cannot disclose a forest in the original application, and then later pick a tree out of the forest and say here is my invention. In order to satisfy the written description requirement, the blaze marks directing the skilled artisan to that tree must be in the originally filed disclosure.

Purdue Pharma L.P. v. Faulding Inc., 230 F.3d 1320, 1326–27 (Fed. Cir. 2000).

In this case, the claims of the asserted patents are very broad, and the number of operative species disclosed in the specification is very small. And there is no evidence in the patents, or otherwise in the record, that the few operative species are representative of the broad genus that the inventors sought to cover with each claim. In short, the claims are directed to a forest, and the specification contains very few blaze marks identifying the particular formulations that can be used to satisfy the functional limitations of the claims. What is more, the species that are shown to be operative are not representative of the entire claimed genus; in effect, the blaze marks are confined to a few trees at one edge of the forest.

This point is illustrated most clearly by claim 14 of the '858 patent, which has no support in the specification at all. That is because claim 14 requires a steady state serum testosterone C_{ave} between 350 ng/dL and 800 ng/dL, and the Data Examples report PK results only in terms of a percentile distribution across a broader C_{ave} range of 300 to 1100 ng/dL. The remaining claims of the '858 patent fare only slightly better. Treating the overlapping variants 40B and 40E as a single formulation, those claims find, at most, support from three Composition Examples, and in some cases support from only two Composition Examples. Furthermore, there is little diversity among those supporting Composition Examples. As noted, Composition Examples 40 and 41 are almost identical. Both have TU concentrations at the low end of the claimed range (between 15% and 18%), and both contain the same or similar excipients in similar quantities. Further, Composition Examples 15A and Example 41 cannot both be counted; not only were they not clinically tested, but Lipocine represented that both were based on a single tested formulation, so at most those two Composition Examples count as one. Most importantly, the asserted claims of the '858 patent do not limit the composition of the TU formulations in any way, either by designating any of the carrier components or the amounts of any such components.

The Composition Examples that satisfy the limitations of the asserted claims of the '057, '690, and '390 patents are likewise not representative of the entire claimed genus. The PK limitation in those claims reasonably finds support in two Composition Examples tested in Data Examples 50 and 51—Composition Examples 41, and variants 40B and 40E of Composition Example 40. The two variants of Composition Example 40 are identical formulations with substantially overlapping dosages, and Composition Example 41 is very similar to Composition Example 40.

In contrast to the narrow range of the formulations supported by the specification, the formulation limitations in the asserted claims from the '057, '690, and '390 patents are very broad. And the problem of the lack of support for the formulations spanning the breadth those claims is underscored by what the specification refers to as "the importance of the choice of the solubilizers of the current invention and their levels to achieve greater testosterone undecanoate loading." '858 patent, col. 34, ll. 1–2. Claims 1, 4, and 7 of the '390 patent and claim 7 of the '057 patent, for example, do not limit the components of the claimed formulations in any way beyond requiring that the formulation consist of 14–35% by weight of TU. Another claim, claim 9 of the '057 patent, confines the amount of the carrier in the recited formulation: The carrier must comprise a solubilizer in an amount from about 50–86% by weight of the formulation. But even with that restriction, claim 9 finds limited support in the specification because the universe of solubilizers is immense, *see* '858 patent, cols. 13–14, and the Data Examples demonstrate only that a formulation containing two such solubilizers, maize oil and the broader category of "monoglycerides," can produce the PK parameters recited in claim 9.

The other asserted claims of the '057 and '390 patents are just as broad and similarly lack support in the specification. Some of those claims require specific excipients, e.g., the "oleic acid" in claim 5 of the '057 patent. However, those claims contain no restriction on the amount of the required excipients. Accordingly, they cover any combination of other excipients that can achieve effective treatment of hypogonadism in conjunction with the specified TU doses as long as at least some amount of the claimed excipients is included in the formulations. Further, the only support for those claims, Composition Example 41 and overlapping variants 40B and 40E, is qualified by the fact that the TU concentration in those Composition Examples (18%, 15%, and 15%, respectively) are near the bottom of the 14–35% TU concentration range recited in those claims.

A similar conclusion can be reached with respect to the asserted claims of the '690 patent, which specify certain excipients (e.g., "a fatty acid and a polyoxyethylene hydrogenated vegetable oil"). Those claims impose no limitation on the amount of their required excipients. In short, the asserted claims of the '057 and '690 patents cover a vast forest, but the specification discloses only a small number of relevant trees—overlapping variants 40B and 40E of Composition Example 40 and untested Composition Example 41.

All things considered, the few operative Composition Examples relied on by Lipocine to justify the broad genus claims in the patents in suit are not sufficiently representative to satisfy the written description requirement. In the words of the Federal Circuit, the examples "abide in a corner of the genus." *AbbVie*, 759 F.3d at 1300.

C. Lipocine's Response

Although the specification discloses only a few compositions that, when used in the recited titration methods, were shown to satisfy the PK limitations set forth in the claims, Lipocine argues that the specification provides support for the much broader range of compositions and titration schemes covered by the claims. In support of that contention, Lipocine makes four principal arguments. First, Lipocine asserts that oral TU formulation was a mature field as of the priority date, thus easing the task of providing a sufficient written description of the invention. Dkt. No. 200, at 2–3, 4–9. Second, Lipocine points to the numerous examples in the specification, which Lipocine contends provide "representative formulations suitable for the claimed titration method." *Id.* at 2–3, 9–12. Third, Lipocine notes that the claims are directed to "specific dose titration methods that achieve certain PK results using oral TU formulations." *Id.* at 3, 12–13. Fourth, based on the specification, the level of knowledge of persons skilled in the art, and the predictability of the art, Lipocine argues that skilled artisans would understand how to formulate

an oral TU composition that would work in the claimed dose titration methods. *Id.* at 3, 13–16. In light of those arguments, Lipocine contends that the specification satisfies the written description requirement because a person of skill in the art would understand that the inventors possessed the full breadth of the claimed methods of using oral TU formulations to obtain the recited pharmacokinetic results. *Id.* at 19–33.

1. The maturity of the field

In arguing that the specification provides sufficient support for the claims, Lipocine relies heavily on statements in its experts' declarations regarding the state of the art. In particular, Lipocine argues, the specification provides sufficient guidance, when viewed in light of the knowledge of persons of skill in the art in the well-known field of TU formulations, to support the broad claims in each of the asserted patents.

The problem with the experts' declarations is that much of what they have to say is that a person of skill in the art, armed with the information in the specification, would know what clinical testing and other experimentation would have to be done to show that particular embodiments of the claimed methods would work to achieve the treatment objectives set forth in the patents. That evidence goes to whether a person of skill in the art could devise studies that would likely lead to successful methods of drug formulation and treatment. But it falls short of demonstrating that the inventors had possession of the claimed invention.

Lipocine argues that methods of formulating oral TU compositions were well known in the art, so it was not necessary for the specification to set out in detail which particular excipients should be used and in what quantities. In addition, Lipocine argues, the prior art "provided useful teachings for correlating formulation changes to existing clinical data." Dkt. No. 200, at 8. And Lipocine contends that the specification revealed the inventors' discovery of "novel methods of

orally administering TU twice a day using TU compositions such that certain desired PK results are achieved." *Id.* at 9. But even though Lipocine asserts that the specification "describes nearly 50 unique examples (i.e., Examples 1–47)," *id.*, nothing in the specification (or in Lipocine's brief) suggests that all the examples would work to achieve the PK goals set forth in the claims. To the contrary, as noted above, the Data Examples address only a small number of those compositions, and only a subset of those compositions have been shown to satisfy the PK limitations set forth in the claims.

Lipocine next argues that its expert, Dr. Cory J. Berkland, will testify that "the distinct exemplary formulations tested each represent a different combination of excipients." *Id.* at 11. In support of that statement, Lipocine cites only Composition Examples 40, 41, 44, and 45. But the problem is not with those compositions and the PK parameters associated with them, as shown in Data Examples 48 and 49. The problem is that the claims are not limited to those compositions and their close equivalents, but cover a much wider field of compositions. Lipocine does not point to anything that suggests which, if any, of the compositions within that wider field would work to achieve the functional limitations of the claims, i.e., the PK limitations. And other than simply listing the components of the Composition Examples, the specification offers no reason to believe that many of the listed compositions—or any other compositions, for that matter—would satisfy the PK limitations of the asserted claims.

Through its experts, Lipocine contends that the field of oral TU compositions was mature and predictable as of the date of the invention, and that the maturity of the field serves to fill in the gaps in the specification's disclosure. But it is not enough to point out that the field was mature and that persons of skill in the art could determine, with appropriate experimentation, which embodiments would satisfy the claim limitations and which would not.

It is true, as Lipocine argues, that "the background knowledge of those skilled in the art can supplement the teaching in the specification to provide written description support" for the claims. *Rivera v. Int'l Trade Comm'n*, 857 F.3d 1315, 1322 (Fed. Cir. 2017). But that is not to say that the background knowledge in the art provides the written description support for particular limitations. As the *Rivera* court put it, "[t]he knowledge of ordinary artisans may be used to inform what is actually in the specification . . . but not to teach limitations that are not in the specification." *Id.* In *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565 (Fed. Cir. 1997), the Federal Circuit set forth that distinction clearly. Addressing the written description issue in the context of whether a later-filed claim had written description support in an earlier-filed specification, the court wrote:

> It is the disclosures of the applications that count. Entitlement to a filing date does not extend to subject matter which is not disclosed, but would be obvious over what is expressly disclosed. It extends only to that which is disclosed. While the meaning of terms, phrases, or diagrams in a disclosure is to be explained or interpreted from the vantage point of one skilled in the art, all the limitations must appear in the specification.

Id. at 1571–72. *See also Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1309 (Fed. Cir. 2015) (district court erred by relying on an undisclosed clinical protocol to support its written description determination: "The clinical protocol is not part of the specifications of the asserted patents. It should not form the basis of the written description inquiry, even if it shows that the inventors had invented the claimed invention before the time of filing. The written description requirement requires possession *as shown in the specification*, not as shown by prior experimental work."); *TurboCare Div. of Demag Delaval Turbomachinery Corp. v. Gen. Elec. Co.*, 264 F.3d 1111, 1119 (Fed. Cir. 2001).

Dr. Berkland's report states that a skilled artisan could use the prior art to "prioritize" excipients and determine which would be preferred. Such an artisan, according to Dr. Berkland, could run "factorial design experiment[s]" to "expose information about the most important

features of the formulation" and then do "further development, including correlation to existing clinical results and/or additional clinical testing." Berkland Rebuttal Report, Dkt. No. 187-2, Exh. E, at ¶¶ 132–133; Dkt. No. 201-2, Exh. 2, at 82:17–85:17.

In response, Clarus argues that the inventors should have done that work and should have included proof of that work in the specification to demonstrate possession of the claimed inventions. A skilled artisan, Clarus argues, would need to test thousands of formulations to determine which excipients would be preferred. The experiments that would have to be conducted, Clarus contends, are the experiments that Lipocine should have conducted as part of its invention. *See* Dkt. No. 185, at 24–27.

I agree. Lipocine's specification merely defines the problem to be solved and does not disclose a solution to the full breadth of that problem. As the Federal Circuit explained in *Ariad*, the written description requirement guards against claims that "merely recite a description of the problem to be solved while claiming all solutions to it and . . . cover any compound later actually invented and determined to fall within the claim's functional boundaries—leaving it to the pharmaceutical industry to complete an unfinished invention." 598 F.3d at 1353.

That problem dovetails with the problem created by the fact that the claims rely on functional limitations. The consequence of the way the inventors drafted their claims is that any oral composition for which the daily doses of TU fall within the broad ranges of the claims is covered by the claims if it produces the recited PK results. The recited PK result for each of the claims, either directly or indirectly, is to produce a serum testosterone concentration level in the subject that is in the eugonadal range, i.e., 300 to 1100 ng/dL or a subset of that range. For that reason, the effect of the claims is to cover any oral method using almost any formulation administered within that broad range of doses, followed by titration if needed, as long as the

method works. But that kind of functional claiming runs afoul of the written description requirement. The Federal Circuit in *Ariad* made that clear. There, the court explained that:

> a generic claim may define the boundaries of a vast genus of chemical compounds, and yet the question may still remain whether the specification, including original claim language, demonstrates that the applicant has invented species sufficient to support a claim to a genus. The problem is especially acute with genus claims that use functional language to define the boundaries of a claimed genus. In such a case, the functional claim may simply claim a desired result, and may do so without describing species that achieve that result.

Id. at 1349.

What matters is what the inventor contributed to the art. The inventor cannot rely solely on the art itself to support the breadth of the limitations in the claims. That is because a patent is not a summary of what is known in the art. Instead, it is a contribution of a fully described improvement on what was previously known.

2. The large number of examples and long lists of excipients

Lipocine contends that the large number of examples in the specification and the lengthy and detailed listings of various excipients that can be used in TU formulations provide written description support for the asserted claims. That argument misunderstands the relevance of the examples in the specification. The great majority of the Composition Examples in the specification do not provide written description support for the asserted claims, for several reasons. First, nothing in the specification indicates that all of the Composition Examples could be used successfully in the claimed methods. Nor does Lipocine assert that the specification shows that they could. In fact, the specification repeatedly states that pharmaceutical compositions and oral dosage capsules of the present invention "can be formulated such that" they could successfully be used to achieve the PK limitations recited in the asserted claims. *See, e.g.*, '858 patent, col. 19, ll. 9–32, 42–54; *id.*, col. 21, ll. 19–34. But that recitation leaves out a critical step. What is missing

is a description of the particular formulation or formulations that would produce those results and some indication that those results would be achieved by employing the recited method with such formulations.

As discussed at length above, while the specification presents a laundry list of Composition Examples, only a small number of those Composition Examples were shown to satisfy the PK limitations of any of the asserted claims. Moreover, Lipocine has not shown that the few compositions that satisfy the PK limitations are representative of the entire range of TU formulations covered by the claims. Nor does Lipocine argue that the specification demonstrates that those few compositions have structural features that are common to compositions that would work across the full scope of the claims.

The long list of excipients that can be used with TU compositions contributes little to help satisfy the written description requirement. The list of excipients, which covers several columns of the specification, may be testimony to the diligence of the inventors in assembling a variety of possible ingredients for oral TU formulations, but it fails to demonstrate, or even contribute to demonstrating, that the inventors invented what they have claimed. What is lacking in the list of excipients is the critical step of showing which of those excipients, in combination with other components of the TU formulations, will satisfy the PK limitations of the claims.

The list of excipients might well be of use to a researcher setting out to formulate an oral TU pharmaceutical, but that merely provides a starting point for a research program; it falls far short of demonstrating a completed invention, which is what the written description requirement demands. In the words of the specification itself, "research continues." '858 patent, col. 2, ll. 6–7. Rather than describing and claiming the particular compositions and dosage regimens that were shown to satisfy the recited PK limitations, the inventors' answer to the problem that only a few

compositions were shown to work is that the other compositions could be tested to determine which would work and which would not. But that is exactly what the written description requirement is intended to avoid: allowing an inventor to obtain broad patent protection merely by describing a problem and outlining the research that would be necessary to achieve a solution to the problem. To demonstrate possession of the invention, the inventor must provide enough description in the specification to demonstrate that he "actually invented" the full scope of what has been claimed; "a mere wish or plan for obtaining the claimed invention" is not enough. *Nuvo Pharms. (Ireland) Designated Activity Co. v. Dr. Reddy's Labs. Inc.*, 923 F.3d 1368, 1380–81 (Fed. Cir. 2019) (cleaned up); *Centocor*, 636 F.3d at 1348 (cleaned up); *see also Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1330 (Fed. Cir. 2003) ("The purpose of the written description requirement is to prevent an applicant from later asserting that he invented that which he did not.").

The same answer applies to Lipocine's argument that skilled artisans would use "their knowledge of *in vitro* / *in vivo* correlation" to estimate the PK results of other formulations. Dkt. No. 200, at 14. As Clarus notes, the specification does not identify any such *in vitro* / *in vivo* correlation or explain how to determine one. Lipocine's argument amounts to an assertion that enough testing of different formulations and titration strategies could have revealed which compositions would have worked to satisfy the PK limitations recited by the claims. But under well-established Federal Circuit precedent, that is not sufficient to satisfy the written description requirement of section 112. In sum, the few operative species of the invention in this case do not show that the inventors have "'truly invented the genus' as opposed to 'a research plan, leaving it to others to explore the unknown contours of the claimed genus.'" *Ajinomoto Co. v. Int'l Trade Comm'n*, 932 F.3d 1342, 1359 (Fed. Cir. 2019) (quoting *AbbVie*, 759 F.3d at 1300).

3. The titration schemes and methods of formulation

Lipocine argues that an important aspect of the contribution made by its patents was to demonstrate the role of titration in treatments using oral TU compositions. Of course, titration—the adjustment of the dose of a medication in order to obtain maximum benefits without undue adverse effects—has been known in medicine since drugs were first administered. If a dose of a drug is insufficient to achieve the intended result, the physician will consider increasing the dose; if the amount initially administered is greater than the minimum necessary or causes unacceptable side effects, the physician will consider reducing the dose.

Several of the prior art references cited by the parties discuss the use of titration in oral TU treatment regimens. In an article by N.M. Maisey et al., submitted by Lipocine, the authors noted that the dose of TU was increased "if there had been no clinical response, unchanged if there had been a good response and decreased . . . if the response had been regarded as excessive during the initial period." Dkt. No. 201-11, Exh. 11, at 626. Similarly, the patent application filed by Dudley et al. and owned by Clarus reported promising results of an oral TU regimen that resulted in many subjects achieving an average serum testosterone level within the normal range; for those that did not achieve that level, all were close enough to that level to indicate "that a modest increase in the TU dose would have been effective oral T replacement therapy in these subjects." Dkt. No. 201-4, Exh. 4, at ¶ 110.

Dr. John K. Amory, one of Clarus's witnesses, testified that titration is "sort of a universal concept. . . . [I]f you're being treated for blood pressure, hypothyroidism, periodically you . . . check levels and manage dose adjustments based upon what's going on with patients." Dr. Amory added that he was not "aware of any testosterone replacement therapies that do not require titration." He explained, "it's all about treating the patient's symptoms, minimizing the risk of

side effects. . . . So this is what we do in internal medicine, really, is give people medications to treat their symptoms or diseases and then monitor the therapy over time to make sure it's working and that it's safe." Deposition of John K. Amory, PhD, Dkt. No. 201-20, Exh. 20, at 235:8–236:1.

In the asserted patents, the recited range of titration, ±40%, is very large. The effect of such a large titration range is to increase the range of TU doses that can qualify for inclusion within the asserted claims. That is, for a claim such as claim 1 of the '858 patent, which provides for an initial dose of 360 mg to 480 mg of TU, the effect of the limitation allowing for a single titration is to provide that the claim will read on the administration of a dose 40 percent higher or lower than that range, i.e., between 216 mg and 672 mg of TU, as long as the initial dosage regimen is within the narrower range. The effect of the titration limitations in the claims that allow for more than one titration is to increase the TU dose range even more. Thus, for claim 22 of the '858 patent, which permits two titrations, the final range of doses can be from 126 mg to 1274 mg of TU. For claim 2 of the '858 patent, which permits three titrations, the final range of doses can be any range that proves "sufficient to provide a serum testosterone plasma concentration within the target range." Other than allowing for a broader range in the amount of the dose of TU, the description of the titration process in the specification offers nothing to show which formulations will work and which will not.

The titration limitations are thus equivalent to limitations setting the TU dose range at the maximum that would be allowed after titration, accompanied by a preference to begin with a dose level generally in the middle of that range. For the great majority of the Composition Examples, there is no showing that they would satisfy the PK limitations of the asserted claims, with or without titration. The titration limitations therefore do not help establish that the asserted claims satisfy the written description requirement.

4. The specification, literature, and predictability of the art

Lipocine contends that when the patents in suit are read in the context of the breadth of the literature in the field, skilled artisans would be able to practice the full scope of the claimed methods without "'many thousands' of experiments." Dkt. No. 200, at 13–14. Lipocine relies on its expert, Dr. Berkland, who stated in his deposition that a skilled artisan, when determining the formulation suitable for the claimed dose titration methods, would "be thinking about the particular compositions that are disclosed and how to achieve the desired pharmacokinetic and titration parameters." *Id.* at 14, quoting Dkt. No. 201-2, Exh. 2, at 52:14–19. For such a person, according to Dr. Berkland, the specification would provide "a guidebook with clinical examples of successful formulations that meet the claim limitations." Dkt. No. 201-2, Exh. 2, at 55:16–18.

There are several problems with that argument. First, the contention that the specification would allow skilled artisans to practice the full scope of the claimed methods without undue experimentation is an argument directed to enablement, not written description, and the Federal Circuit has made clear that "to satisfy the statutory requirement of a description of the invention, it is not enough for the specification to show how to make and use the invention, i.e., to enable it." *Amgen Inc. v. Sanofi, Aventisub LLC*, 872 F.3d 1367, 1377 (Fed. Cir. 2017); *see also Amgen Inc. v. Hoechst Marion Rousel Inc.*, 314 F.3d 1313, 1334 (Fed. Cir. 2003) ("The enablement requirement is often more indulgent than the written description requirement."). Moreover, Lipocine's heavy reliance on the background and literature in the field is at odds with the requirement that, for the purposes of written description, the specification itself must demonstrate that the inventor has invented the full scope of the invention. It is not enough that a skilled artisan could use the specification, together with literature in the field, to discover what compositions could be used with the claimed methods to achieve the recited PK results. The background

knowledge of those skilled in the art cannot substitute for the teachings in the specification necessary to demonstrate possession of the invention. Instead, the written description inquiry looks to "the four corners of the specification" to discern the extent to which the inventor had possession of the invention. *Ariad*, 598 F.3d at 1351; *Rivera*, 857 F.3d at 1322. "'A description that merely renders the invention obvious does not satisfy' the written description requirement." *Idenix*, 941 F.3d at 1165 (quoting *Ariad*, 598 F.3d at 1352).

Second, as discussed above, the few examples for which PK results were given in the specification are not sufficient to show that the inventors had possession of the full breadth of the subject matter recited in the asserted claims. Dr. Berkland's report and testimony do not grapple with the fact that the number of compositions that were shown to satisfy the PK limitations of the asserted claims was both very small and not representative of the full range covered by those claims.

Finally, as Clarus points out, Lipocine's contention that the science of oral TU formulations was well understood at the time of the invention and that the field of oral TU formulation development was predictable, Dkt. No. 200, at 2, 4–9, 13–16, is in tension with arguments Lipocine made during the prosecution of the patents in suit and in the specification itself. For example, the specification states that "the effective oral delivery of testosterone as testosterone and its esters remains a challenge . . . due to extremely poor bioavailability." '858 patent, col. 1, ll. 46–49. "Accordingly, research continues . . . ." *Id.*, col. 2, ll. 6–9. And during prosecution, the inventors argued to the examiner that oral TU formulations "are not obtainable by routine optimization," Dkt. No. 187-4, Exh. O, at LPCN00001198, and that the administration of oral TU formulations "is not a simple matter with finite solutions and predictable results," Dkt. No. 212-1, Exh. S, at LPCN00001978–79. Even in the course of this litigation, Lipocine's experts have testified that

"significant clinical research and study would be required for a POSITA to determine the effective dosing and titration scheme for an oral TU [testosterone replacement therapy]," Dkt. No. 201-13, Exh. 13, at ¶ 176 (Rebuttal Expert Report of Irwin Goldstein, M.D.), that a "difference in formulation impedes the comparability of the pharmacokinetics between formulations," Dkt. No. 212-1, Exh. T, at ¶ 105 (Rebuttal Expert Report of Dr. Daniel Weiner, Ph.D.), and that skilled artisans could not rely on the prior art to "predict the pharmacokinetic results" of formulations, *id.* at ¶ 119.

Lipocine relies on the fact that some of the asserted claims include particular classes of excipients as proof that, for those claims at least, the written description requirement was satisfied. It is true that some claims contain references to broad classes of excipients,[20] and some claims contain more specificity with respect to the excipients.[21] But there is nothing in the specification to indicate that compositions containing those particular excipients in varying amounts and in combination with various other excipients can achieve the PK parameters recited by the claims. Although Dr. Berkland stated that a person of skill in the art would "look to the specifications for specific examples," and would "be using the prior art, [and] using references to understand in this range which [excipient] might be preferred," Dkt. No. 200, at 14 (citing Dkt. No. 201-2, Exh. 2, at 59:15–60:2), that is not support for the full breadth of the claims—it is simply an assertion that a person of skill in the art would be able to use experimentation and background knowledge to conduct the research necessary to design compositions that would work.

[20] An example is claim 2 of the '057 patent, which requires that the TU formulation contain a solubilizer and a dispersant.

[21] An example is claim 4 of the '057 patent, which requires that the formulation contain oleic acid.

Dr. Berkland stated in his declaration and deposition testimony that a skilled artisan could use the prior art to "prioritize" excipients. According to Dr. Berkland, such an artisan could run "factorial design experiments" to "expose information about the most important features of the formulation," and then do "further development, including correlation to existing clinical results and/or additional clinical testing." Dkt. No. 187-2, Exh. E, at ¶¶ 132–133; Dkt. No. 201, Exh. 2, at 82:17–85:17. As Clarus responds, however, that is work the inventors should have done and should have included in the specification to demonstrate their possession of the claimed inventions.

The underlying problem with the claims that require different combinations of excipients is that there is no basis from which to conclude that the functional limitations of any of those claims will be satisfied, except with respect to the few specific formulations that were the subjects of the clinical tests and simulations reported in the Data Examples. In theory, the inventors could have added a series of claims naming each of the various excipients that were discussed in the specification, if only to "cover the waterfront" by listing as many variations on TU formulation as an examiner would allow. That approach would not have helped satisfy the written description requirement; instead, it would simply have underscored the failure of the specification to identify a category of operable embodiments other than the few embodiments for which empirical evidence was provided. While the inventors did not take that approach, and thus did not draw attention to the unsupported breadth of their claims, the asserted claims are in effect just as broad and are just as lacking in written description.

D. Analogous Precedents

The Federal Circuit has decided several cases involving written description issues generally similar to the one in this case. In *Idenix Pharmaceuticals LLC v. Gilead Sciences Inc.*, 941 F.3d 1149 (Fed. Cir. 2019), for example, the patent in suit claimed a method of treatment for the

hepatitis C virus ("HCV") by using a particular pharmaceutical drug. The patent claimed the drug in a generic manner that included a large number of related compounds, although the specification identified only a small subset of four compounds from the entire genus of compounds as being effective. The Federal Circuit directed the entry of judgment as a matter of law for the defendant, holding that the patent failed to satisfy the written description requirement. The court ruled that the patent failed to demonstrate that the patentee had possession of the members of the genus outside of those species disclosed in the specification as being effective in treating HCV. The court explained that the specification provided "lists or examples of supposedly effective nucleosides, but [did] not explain what makes them effective, or why. As a result, a POSA is deprived of any meaningful guidance into what compounds beyond the examples and formulas, if any, would provide the same result." *Id.* at 1164. The same is true in this case with respect to those members of the claimed genus of compounds that were not shown to be effective in treating hypogonadism.

Two other Federal Circuit cases are particularly instructive: *Boston Scientific Corp. v. Johnson & Johnson*, 647 F.3d 1353 (Fed. Cir. 2011), and *Carnegie Mellon University v. Hoffman-La Roche Inc.*, 541 F.3d 1115 (Fed. Cir. 2008). In both of those cases, the claims were directed to a large genus, while the patent's specification or the prior art disclosed only a small number of species within that genus. In both cases, the court concluded that the narrowly disclosed species were not shown to be representative of the genus and thus did not provide written description support for the broadly claimed genus. *See Boston Scientific*, 647 F.3d at 1364–65; *Carnegie Mellon*, 541 F.3d at 1126. In both cases, the court distinguished the Federal Circuit's prior decision in *Capon v. Eshhar*, 418 F.3d 1349 (Fed. Cir. 2005), on which Lipocine relies. In *Capon*, the Board of Patent Appeals and Interferences cancelled all the claims of both parties to an interference

on the ground that neither party had satisfied the written description requirement. The Federal Circuit in *Boston Scientific* and *Carnegie Mellon* characterized *Capon* as a case in which the prior art contained extensive knowledge of the structure of the relevant genus, and in which the parties' specifications, viewed in light of the existing knowledge in the field, were sufficient to satisfy the written description requirement. That was not true in *Boston Scientific* and *Carnegie Mellon*, the court held, because in each of those cases there were only a small number of known operative species within the claimed genus. The court in those cases held that, as in this case, the disclosed species did not provide sufficient written description support for the claims that covered the entire genus. *See also Pernix*, 323 F. Supp. 3d at 626 (single operative embodiment did not provide written description support for generic claims, because it provided "no guidance as to which of [the claimed] formulations would satisfy the functional limitations of the claims and which would not.").

In sum, as Clarus contends and as the precedents confirm, Lipocine is seeking broad patent protection despite having made, at most, only a "minimal contribution to the art." Dkt. No. 185, at 27. Lipocine's patents would block others from using "almost any oral TU composition to achieve desired PK results if the dose is adjusted at any point somewhere in the broad range of within ±40% of the previous dose." *Id.* Yet the specification provides only simulated results for two very similar formulations to support the asserted claims of the '057, '690, and '390 patents, and a combination of clinical and simulated results for only three or fewer formulations to support the various asserted claims of the '858 patent. That limited showing of operative species does not provide adequate support for the broad generic claims of the four asserted patents. Because no reasonable jury could find the written description requirement to be satisfied by clear and

convincing evidence under these circumstances, Clarus is entitled to summary judgment of invalidity.

CONCLUSION

As a consequence of the grant of summary judgment, all of the asserted claims of the four patents in suit have been held invalid. It is therefore unnecessary to reach Clarus's motion for summary judgment of non-enablement that, if granted, would result in the same relief. Moreover, the summary judgment of invalidity renders moot Lipocine's claims of infringement and Clarus's counterclaims of non-infringement with respect to the claims asserted by Lipocine.

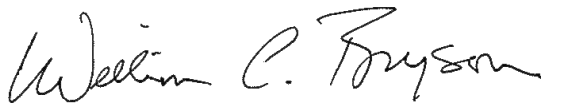
The remaining claims before the court are the following: Clarus's counterclaim of inequitable conduct; Clarus's counterclaim of patent misuse; Clarus's counterclaim seeking to have this case adjudged an "exceptional case"; and Clarus's counterclaims of patent invalidity with regard to the claims of the four patents in suit that were not asserted by Lipocine. A finding of inequitable conduct or patent misuse would result in a broader judgment than the summary judgment of no written description—unenforceability of all the claims of all four of Lipocine's patents, as opposed to invalidity of only the asserted claims. *See Therasense, Inc. v. Becton, Dickinson & Co.*, 649 F.3d 1276, 1287 (Fed. Cir. 2011) (en banc); *Zenith Elecs. Corp. v. PDI Commc'ns Sys., Inc.*, 522 F.3d 1348, 1367 (Fed. Cir. 2008); *Weatherchem Corp. v. J.L. Clark, Inc.*, 163 F.3d 1326, 1336 (Fed. Cir. 1998). Accordingly, the counterclaims of inequitable conduct and patent misuse are not rendered moot by the summary judgment of no written description. *See Fort James Corp. v. Solo Cup Co.*, 412 F.3d 1340, 1348 (Fed. Cir. 2005) ("Accordingly, the jury verdict holding that [defendant] did not infringe [plaintiff's] patents did not moot [defendant's] counterclaim for unenforceability nor did it act to divest the district court of jurisdiction to hear

that unlitigated counterclaim."). Clarus's exceptional case counterclaim is also not rendered moot by the summary judgment of no written description.

The parties are directed to file a joint report within 21 days of the date of this order setting out how they recommend the court should proceed in this case. In particular, the parties should address whether there is a continuing case or controversy between the parties with regard to Clarus's counterclaims of invalidity against Lipocine's unasserted patent claims. *See, e.g.*, *Ameranth, Inc. v. Domino's Pizza, LLC*, 792 F. App'x 780, 783–85 (Fed. Cir. 2019); *Voter Verified, Inc. v. Premier Election Sols., Inc.*, 698 F.3d 1374, 1382 (Fed. Cir. 2012); *Prasco, LLC v. Medicis Pharm. Corp.*, 537 F.3d 1329, 1338–41 (Fed. Cir. 2008). The parties should also address whether the court has jurisdiction over Clarus's counterclaims of non-infringement as to those unasserted claims. Unless the parties suggest a different course of action, this case will be set for trial on Clarus's remaining counterclaims at the earliest practicable date.

IT IS SO ORDERED.

SIGNED this 1st day of June, 2021.



WILLIAM C. BRYSON
UNITED STATES CIRCUIT JUDGE

APPENDIX A

The 24 asserted claims are excerpted or summarized below:

The ’858 Patent

Lipocine asserts six claims from the ’858 patent, three of which are dependent from claim 1, and two of which are dependent from claim 20. Asserted claims 1 and 2 read as follows:

> **1.** A method for providing a serum concentration of testosterone within a steady state target serum testosterone concentration C_{ave} range for a hypogonadal male subject having testosterone deficiency, comprising the steps of,
>
> 1) orally administering to the male subject twice a day with a meal an initial regimen including a daily dose of a testosterone undecanoate-containing composition, wherein the testosterone undecanoate comprises about 14 wt % to about 35 wt % of the testosterone undecanoate-containing composition and wherein the daily dose provides about 360 mg to about 480 mg of testosterone undecanoate to the male subject;
>
> 2) determining a dose titration metric based on a measurement of serum testosterone concentration for the male subject on at least one titration node day within the initial regimen said measurement of serum testosterone concentration made from 1 to 8 hours after single dose administration of said testosterone undecanoate-containing composition at steady state; and
>
> 3) orally administering to the male subject twice a day with a meal a maintenance regimen including a daily dose of a testosterone undecanoate-containing composition, wherein the testosterone undecanoate-containing composition comprises about 14 wt % to about 35 wt % of the testosterone undecanoate-containing composition and wherein the maintenance regimen provides a daily dose of testosterone undecanoate within ±40% of the amount of testosterone undecanoate of the initial regimen daily dose to the subject based on the titration metric determined on the at least one titration node day of the initial regimen sufficient to provide a serum testosterone plasma concentration within the target range
>
> wherein the testosterone undecanoate-containing composition provides upon single dose administration a ratio of serum testosterone C_{max} to C_{ave} of 2.7 or less or provides a dose-normalized serum testosterone C_{ave} of about 1.9×10^{-6} dL^{-1} or higher.

> **2.** The method of claim **1**, further comprising the steps of:
>
> 4) determining a dose titration metric based on a measurement of serum testosterone concentration for the male subject on at least one titration node day within the maintenance regimen;
>
> 5) orally administering to the male subject a second maintenance regimen including a daily dose of a testosterone undecanoate-containing composition, wherein the testosterone undecanoate-containing composition comprises about 14 wt % to about 35 wt % of the testosterone undecanoate-containing composition and

> wherein the second maintenance regimen provides a daily dose of testosterone undecanoate to the subject based on the titration metric determined on the at least one titration node day of the maintenance regimen sufficient to provide a serum testosterone plasma concentration within the target range; and optionally
>
> 6) repeating steps 4 and 5, if needed.

'858 patent, col. 43, line 31, through col. 44, line 18.

Asserted claim 14 of the '858 patent depends from claim 1 and adds "wherein the method provides a steady state serum testosterone C_{ave} of from 350ng/dL to 800 ng/dL." *Id.*, col. 45, ll. 4–6. Asserted claim 17 of the '858 patent also depends from claim 1 and adds "wherein said meal has from about 10 g to about 50 g fat." *Id.*, col. 45, ll. 13–14.

Claim 20 of the '858 patent is not asserted, but claims 22 and 26, which depend from claim 20, are asserted. Claim 20 provides as follows:

> **20**. A method for providing a serum concentration of testosterone within a target serum concentration C_{ave} range for a hypogonadal male subject having testosterone deficiency, comprising the steps of,
>
> 1) orally administering to said hypogonadal male subject an initial regimen including a daily dose of a testosterone undecanoate-containing composition having from about 350 mg to about 650 mg of testosterone undecanoate; and
>
> 2) orally administering to the male subject a first maintenance regimen including a daily dose of a testosterone undecanoate-containing composition that is within ±40% of the amount of testosterone undecanoate of the initial regimen daily dose wherein the daily dose of the maintenance regimen is determined by the serum concentration of testosterone at time t (Ct) at steady state during the initial regimen wherein Ct is correlated to the Cmax and Cave values of a population of hypogonadal men receiving said initial regimen to determine the maintenance regimen daily dose said serum testosterone concentration determined from 1 to 8 hours after single dose administration of said testosterone undecanoate-containing composition at steady state.

Id., col. 45, line 23, through col. 46, line 5.

Asserted claim 22 of the '858 patent depends from claim 20 and adds "further comprising administering a second maintenance dose regimen having a daily dose of testosterone undecanoate

that is within ±40% of the amount of testosterone undecanoate of the first maintenance regimen daily dose." *Id.*, col. 46, ll. 10–14.

Asserted claim 26 of the '858 patent depends from claim 20 and adds "wherein said method (i) provides a serum testosterone C_{ave} of 300 ng/dL to 1100 ng/dL in at least 75% of a group of hypogonadal male subjects and (ii) provides a) a serum testosterone C_{max} of less than 1500 ng/dL in at least 85% of the subjects in the group; b) a serum testosterone C_{max} of about 1800 ng/dL to about 2500 ng/dL in 5% or less of the subjects in the group; or c) a serum testosterone C_{max} greater than 2500 ng/dL in about 1% or less of the subjects in the group." *Id.*, col. 46, ll. 26–38.

The '057 Patent

Lipocine asserts seven claims from the '057 patent, six of which are dependent on claim 1 and the remaining one of which is dependent on claim 11. Claim 1 of the '057 patent, which is not asserted, provides as follows:

> **1**. A method for replacement therapy in a male having a condition associated with a deficiency or absence of endogenous testosterone said method comprising:
>
> (a) Orally administering to said male a daily dosing regimen of a pharmaceutical composition comprising about 14 weight % (wt %) to about 35 wt % testosterone undecanoate and a carrier, that provides from about 360 mg to about 480 mg of testosterone undecanoate to said male per day;
>
> (b) Determining the serum level of testosterone of said male during the daily dosing regimen at from 1-8 hours after single dose administration of said pharmaceutical composition at steady state; and
>
> (c) Orally administering a maintenance daily dosing regimen of pharmaceutical composition comprising about 14 wt % to about 35 wt % testosterone undecanoate and a carrier, that provides within plus or minus 40% of

> from about 360 mg to about 480 mg of testosterone undecanoate to said male based on the serum testosterone level determined in step (b),
>
> to provide a serum testosterone Cave in said male in the range of from about 300-1100 ng/dL.

'057 patent, col. 42, ll. 2–23.

Asserted claim 2 of the '057 patent depends from claim 1 and adds "said carrier comprising a solubilizer and a dispersant." *Id.*, col. 42, ll. 24–25.

Asserted claim 4 of the '057 patent depends from claim 1 and adds "said carrier comprising oleic acid." *Id.*, col. 42, line 40.

Asserted claim 5 of the '057 patent depends from claim 1 and adds "said carrier comprising a polyoxyethylene hydrogenated vegetable oil." *Id.*, col. 42, ll. 41–42.

Asserted claim 7 of the '057 patent depends from claim 1 and adds "said daily dosing regimen or maintenance daily dosing regimen comprises twice daily dosing with said pharmaceutical composition." *Id.*, col. 42, ll. 45–47.

Asserted claim 9 of the '057 patent depends from claim 1 and adds "said carrier comprising a solubilizer in an amount of from about 50 wt % to about 86 wt % of the pharmaceutical composition." *Id.*, col. 42, ll. 51–53.

Asserted claim 21 of the '057 patent depends from claim 1 and adds "said carrier comprising a triglyceride, a sterol derivative, an ionic hydrophilic surfactant, a non-ionic hydrophilic surfactant, an alcohol or a combination thereof." *Id.*, col. 44, ll. 21–24.

Claim 11 of the '057 patent, which is not asserted, provides as follows:

> **11**. A method for replacement therapy in a male having a condition associated with a deficiency or absence of endogenous testosterone said method comprising:
>
> (a) Orally administering to said male a daily dosing regimen of a pharmaceutical composition comprising about 14 wt % to about 35 wt %

testosterone undecanoate and a carrier to provide from about 350 mg to about 650 mg testosterone undecanoate to said male per day;

(b) determining the serum level of testosterone of said male during the daily dosing regimen at a single time point from 1-8 hours after single dose administration of said pharmaceutical composition at steady state, C_t; and

(c) orally administering a maintenance daily dosing regimen of a pharmaceutical composition comprising about 14 wt % to about 35 wt % testosterone undecanoate and a carrier, that provides within plus or minus 40% of from about 350 mg to about 650 mg of testosterone undecanoate to said male based on the serum testosterone level determined in step (b),

said carrier comprising a monoglyceride, a diglyceride, a fatty acid, a polyoxyethylene hydrogenated vegetable oil or a combination thereof,

to provide a serum testosterone Cave in said male in the range of from about 300-1100 ng/dL.

Id., col. 42, line 57, through col. 43, line 14.

Asserted claim 17 of the '057 patent depends from claim 11 and adds "said daily dosing regimen or maintenance daily dosing regimen comprises twice daily dosing with said pharmaceutical composition." *Id.*, col. 43, ll. 26–28.

The '690 Patent

Lipocine asserts seven claims from the '690 patent, two of which are dependent from claim 1, four of which include claim 11 and three claims dependent from claim 11, and one of which is dependent from claim 20.

Claim 1 of the '690 patent, which is not asserted, provides as follows:

1. A method for replacement therapy in a male having a condition associated with a deficiency or absence of endogenous testosterone said method comprising:

(a) Orally administering to said male a daily dosing regimen of a pharmaceutical composition comprising about 14 weight % (wt %) to about 35 wt % testosterone undecanoate and a carrier, that provides from about 360 mg to about 480 mg of testosterone undecanoate to said male per day;

(b) Determining the serum level of testosterone of said male during the daily dosing regimen at from 1-8 hours after a single dose administration of said pharmaceutical composition at steady state; and

(c) Orally administering a maintenance daily dosing regimen of a pharmaceutical composition comprising about 14 wt % to about 35 wt % testosterone undecanoate and a carrier, that provides within plus or minus 40% of

> from about 360 mg to about 480 mg of testosterone undecanoate to said male based on the serum testosterone level determined in step (b),
>
> to provide a serum testosterone C_{ave} in said male in the range of from about 300-1100 ng/dL,
>
> wherein said carrier comprises a fatty acid and a polyoxyethylene hydrogenated vegetable oil.

'690 patent, col. 43, ll. 44–67.

Asserted claim 7 of the '690 patent depends from claim 1 and adds "wherein said daily dosing regimen or maintenance daily dosing regimen comprises twice daily dosing with said pharmaceutical composition." *Id.*, col. 44, ll. 24–26.

Asserted claim 8 of the '690 patent depends from claim 1 and adds "wherein said orally administering comprises administration of the pharmaceutical composition with a meal." *Id.*, col. 44, ll. 27–29.

Asserted claim 11 of the '690 patent reads as follows:

> **11**. A method for replacement therapy in a male having a condition associated with a deficiency or absence of endogenous testosterone said method comprising:
>
> (a) Orally administering to said male a daily dosing regimen of a pharmaceutical composition comprising about 14 wt % to about 35 wt % testosterone undecanoate and a carrier to provide from about 350 mg testosterone undecanoate to about 650 mg of testosterone undecanoate to said male per day;
>
> (b) determining the serum level of testosterone of said male during the daily dosing regimen at a single time point from 1-8 hours after a single dose administration of said pharmaceutical composition at steady state, C_i; and
>
> (c) orally administering a maintenance daily dosing regimen of a pharmaceutical composition comprising about 14 wt % to about 35 wt % testosterone undecanoate and a carrier, that provides within plus or minus 40% of

> from about 350 mg to about 650 mg of testosterone undecanoate to said male based on the serum testosterone level determined in step (b),
>
> said carrier comprising a fatty acid and a polyoxyethylene hydrogenated vegetable oil, to provide a serum testosterone C_{ave} in said male in the range of from about 300-1100 ng/dL.

Id., col. 44, ll. 36–61.

Asserted claim 12 of the ’690 patent depends from claim 11 and adds “wherein said carrier further comprises a triglyceride.” *Id.*, col. 44, ll. 62–63.

Asserted claim 17 of the ’690 patent depends from claim 11 and adds “wherein said daily dosing regimen or maintenance daily dosing regimen comprises twice daily dosing with said pharmaceutical composition.” *Id.*, col. 45, ll. 6–8.

Asserted claim 18 of the ’690 patent depends from claim 11 and adds “wherein said orally administering comprises administration of the pharmaceutical composition with a meal.” *Id.*, col. 45, ll. 9–11.

Claim 20 of the ’690 patent, which is not asserted, provides as follows:

> **20**. A method for replacement therapy in a male having a condition associated with a deficiency or absence of endogenous testosterone, said method comprising:
>
> (a) Orally administering to said male a daily dosing regimen of a pharmaceutical composition comprising about 14 % to about 35 % testosterone undecanoate and a carrier to provide from about 360 mg testosterone undecanoate to about 480 mg testosterone undecanoate to said male per day;
>
> (b) determining the serum level of testosterone of said male during the daily dosing regimen at a single time point from 1-8 hours after single dose administration of said pharmaceutical composition at steady state, C_i; and
>
> (c) orally administering a maintenance daily dosing regimen of a pharmaceutical composition comprising about 14 wt % to about 35 wt % testosterone undecanoate and a carrier, that provides within plus or minus 40% of

> from about 350 mg to about 650 mg of testosterone undecanoate to said male subject based on the serum testosterone level determined in step (b),
>
> said carrier comprising oleic acid and Cremophor RH 40, to provide a serum testosterone C_{ave} in said male in the range of from about 300-1100 ng/dL.

Id., col. 46, ll. 14–16.

Asserted claim 21 of the '690 patent depends from claim 20 and adds "wherein said carrier further comprises a monoglyceride, a diglyceride, a triglyceride, an antioxidant or a combination thereof." *Id.*, col. 46, ll. 14–16.

The '390 Patent

Lipocine asserts four claims from the '390 patent, which consist of claim 1 and three claims that depend from claim 1.

Asserted claim 1 of the '390 patent provides as follows:

> **1.** A method for replacement therapy in a male having a condition associated with a deficiency or absence of endogenous testosterone said method comprising:
>
> (a) Orally administering to said male a daily dosing regimen of a pharmaceutical composition comprising about 14 weight % (wt %) to about 35 wt % testosterone undecanoate and a carrier, that provides from about 450 mg or about 480 mg of testosterone undecanoate to said male per day;
>
> (b) Determining the serum level of testosterone of said male during the daily dosing regimen at from 1-8 hours after single dose administration of said pharmaceutical composition at steady state; and
>
> (c) Orally administering a maintenance daily dosing regimen of a pharmaceutical composition comprising about 14 wt % to about 35 wt %

> testosterone undecanoate and a carrier, that provides within plus or minus 40% of from about 450 mg or 480 mg of testosterone undecanoate to said male per day to provide a serum testosterone Cave in said male in the range of from about 300-1100 ng/dL.

'390 patent, col. 43, ll. 44–64.

Asserted claim 4 of the '390 patent depends from claim 1 and adds "wherein in [sic] said orally administering is twice a day administration." *Id.*, col. 44, ll. 15–16.

Asserted claim 7 of the '390 patent depends from claim 1 and adds "wherein said orally administering of step (a) provides about 480 mg of testosterone undecanoate per day." *Id.*, col. 44, ll. 22–24.

Asserted claim 11 of the '390 patent depends from claim 1 and adds "wherein said carrier comprises one or more of: a fatty acid, a monoglyceride, a diglyceride and a polyoxyethylene hydrogenated vegetable oil." *Id.*, col. 44, ll. 35–37.

APPENDIX B

Patent No.	**9,034,858**					
Claim No.	**1**	**2_1**	**14_1**	**17_1**	**22_{20}**	**26_{20}**
Titrations	One	Two or Three	One	One	Two	One
Initial dosage TU	360-480 mg				350-650 mg	
Weight perc. TU	14-35 %				Any	Any
Composition	Any				Any	Any
PK limitation	(Cmax to Cave ratio of <= 2.7 **OR** dose-normalized serum Cave of ~ 1.9×10^{-6} dL^{-1} or higher) **AND** (Cave within target serum concentration range (i.e., serum Cave of 350 ng/dL to 1100 ng/dL))		(Cmax to Cave ratio of <= 2.7 **OR** dose-normalized serum Cave of ~ 1.9×10 -6 dL-1 or higher) **AND** (serum Cave of 350 ng/dL to 800 ng/dL)	(Cmax to Cave ratio of <= 2.7 **OR** dose-normalized serum Cave of ~ 1.9×10^{-6} dL or higher) **AND** (Cave within target serum concentration range (i.e., serum Cave of 350 ng/dL to 1100 ng/dL))	Within a target serum concentration Cave range (i.e., serum Cave of 350 ng/dL to 1100 ng/dL)	(Serum Cave of 300 ng/dL to 1100 ng/dL in at least 75% of a group of hypogonadal male subjects) **AND** (serum Cmax of less than 1500 ng/dL in at least 85% of the subjects **OR** serum Cmax of about 1800 ng/dL to about 2500 ng/dL in 5% or less of the subjects **OR** serum Cmax greater than 2500 ng/dL in about 1% or less of the subjects)
Relevant Data Examples	Ex. 48 (XX) Ex. 49 (XXI) Ex. 50 (XXII) Ex. 51 (XXIII)	Ex. 48 (XX) Ex. 49 (XXI) Ex. 50 (XXII) Ex. 51 (XXIII) Ex. 52 (XXIV) Ex. 53 (XXV)	Ex. 48 (XX) Ex. 49 (XXI) Ex. 50 (XXII) Ex. 51 (XXIII)	Ex. 48 (XX) Ex. 49 (XXI) Ex. 50 (XXII) Ex. 51 (XXIII)	Ex. 50 (XXII) Ex. 51 (XXIII) Ex. 52 (XXIV)	Ex. 50 (XXII) Ex. 51 (XXIII)
Comps. Disclosed	40, 41*	40, 41*, 45	None	40, 41*	40(B & E), 41*, 45	40(B & E), 41*

*Composition Example 41 was not actually tested in the clinical tests represented by Data Examples 48 and 49 but was instead "based on" a similar formulation that Lipocine represents was clinically tested.

Patent No.	**9,205,057**						
Claim No.	**2_1**	**4_1**	**5_1**	**7_1**	**9_1**	**17_{11}**	**21_1**
Titrations	One						
Initial dosage TU	360-480 mg					350-650 mg	360-480 mg
Weight perc. TU	14-35 %				14-35 % TU 50-86 % carrier	14-35 %	
Composition	carrier comprising a solubilizer and a dispersant	carrier comprising oleic acid	carrier comprising a polyoxyethylene hydrogenated vegetable oil	carrier	carrier comprising a solubilizer in an amount from about 50-86 wt % of the pharmaceutical composition	carrier comprising a monoglyceride, a diglyceride, a fatty acid, a polyoxyethylene hydrogenated vegetable oil or a combination thereof	carrier comprising a triglyceride, a sterol derivative, an ionic hydrophilic surfactant, a non-ionic hydrophilic surfactant, an alcohol or a combination thereof
PK limitation	Serum Cave in said male in the range of from about 300-1100 ng/dL						
Relevant Data Examples	Ex. 50 (XXII) Ex. 51 (XXIII)						
Comps. Disclosed	40(B & E), 41*						

Patent No.	**9,480,690**						
Claim No.	**7_1**	**8_1**	**11**	**12_{11}**	**17_{11}**	**18_{11}**	**21_{20}**
Titrations	One						
Initial dosage TU	360-480 mg		350-650 mg				360-480 mg
Weight perc. TU	14-35 %						
Composition	carrier comprises a fatty acid and a polyoxyethylene hydrogenated vegetable oil			carrier comprising a fatty acid and a polyoxyethylene hydrogenated vegetable oil; carrier further comprises a triglyceride.	carrier comprising a fatty acid and a polyoxyethylene hydrogenated vegetable oil		carrier comprising oleic acid and Cremophor RH 40; carrier further comprises a monoglyceride, a diglyceride, a triglyceride, an antioxidant or a combination thereof
PK limitation	Serum Cave in said male in the range of from about 300-1100 ng/dL						
Relevant Data Examples	Ex. 50 (XXII) Ex. 51 (XXIII)						
Comps. Disclosed	40(B & E), 41*						

Patent No.	**9,757,390**			
Claim No.	**1**	**4_1**	**7_1**	**11_1**
Titrations	One			
Initial dosage TU	450 or 480 mg		480 mg	450 or 480 mg
Weight perc. TU	14-35 %			
Composition	carrier			carrier comprises one or more of: a fatty acid, a monoglyceride, a diglyceride and a polyoxyethylene hydrogenated vegetable oil
PK limitation	Serum Cave in said male in the range of from about 300-1100 ng/dL			
Relevant Data Examples	Ex. 50 (XXII) Ex. 51 (XXIII)			
Comps. Disclosed	40(B & E), 41*			