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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CSL BEHRING LLC, CSL BEHRING GMBH, and
CSL BEHRING RECOMBINANT FACILITY AG,
Petitioners,

v.

BIOVERATIV THERAPEUTICS INC.,
Patent Owner.

IPR2018-01345
Patent 9,623,091 B2

Before GEORGIANNA W. BRADEN, WESLEY B. DERRICK, and MICHELLE N. ANKENBRAND, *Administrative Patent Judges*.

DERRICK, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
35 U.S.C. § 314

I. INTRODUCTION

CSL Behring LLC, CSL Behring GmbH, and CSL Behring Recombinant Facility AG (collectively, "Petitioners")[1] request an *inter partes* review of claims 1–17, 20, 22, 24, and 28 of U.S. Patent 9,623,091 B2 (Ex. 1101, "the '091 patent"). Paper 3 ("Pet."). Bioverativ Therapeutics Inc. ("Patent Owner") filed a Preliminary Response. Paper 9 ("Prelim. Resp.").

We have authority to determine whether to institute an *inter partes* review. 35 U.S.C. § 314(b); 37 C.F.R. § 42.4(a). We may not institute an *inter partes* review "unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a). Applying that standard, for the reasons set forth below, we decline to institute an *inter partes* review because Petitioners have not shown a reasonable likelihood that they would prevail in establishing the unpatentability of any challenged claim.

II. BACKGROUND

A. Related Proceedings

Petitioners have filed a second petition for *inter partes* review of the '091 patent, IPR2018-01313. Pet. 6. The parties identify additional proceedings involving the '091 patent—*In the matter of Certain Recombinant Factor IX Prods.*, Inv. No. 337-TA-1066 (terminated) ("ITC

[1] Petitioners have updated the identified real-parties-in-interest in providing notice that "the real-parties in interest in this proceeding are: CSL Behring LLC, CSL Behring GmbH, CSL Behring Lengnau AG (successor in interest to CSL Behring Recombinant Facility AG), CSL Limited, and CSL Behring Beteilgungs- und Verwaltungs GmbH & Co. KG." Paper 4, 2.

investigation") and *Bioverativ Inc. v. CSL Behring LLC*, CA No. 17-914-GMS (D. Del.) (pending) ("district court litigation"). Pet. 6; Paper 7 (Patent Owner's Mandatory Notices).

B. The '091 Patent (Ex. 1101)

The '091 patent is directed to methods of administering Factor IX using chimeric polypeptides comprising Factor IX and an FcRn binding partner in order to treat hemophilia B in a human subject.[2] Ex. 1101, [57], 2:34–35, 79:25–35.

C. Illustrative Claim

Claim 1, the sole independent claim, is reproduced below:

> 1. A method of treating hemophilia B in a human subject in need thereof comprising intravenously administering to the subject multiple doses of about 50 IU/kg to about 100 IU/kg of a chimeric factor IX ("FIX") polypeptide comprising FIX and an FcRn binding partner ("FcRn BP") at a dosing interval of about 10 days to about 14 days between two doses, wherein the FcRn BP comprises Fc or albumin, wherein the administration maintains the plasma FIX activity of the subject above 1 IU/dL between the dosing interval, and wherein the administration treats the human subject by reducing the frequency of spontaneous bleeding.

Ex. 1001, 79:25–35.

[2] Factor IX is a serine protease required for normal *in vivo* blood coagulation, Ex. 1101, 1:52–54, and FcRn is the neonatal Fc receptor, Ex. 1142, 2057.

D. The Asserted Grounds of Unpatentability

Petitioners contend that the challenged claims are unpatentable under 35 U.S.C. § 103 over Peters 2007[3] (Ex. 1157) and the '956 Patent[4] (Ex. 1103) in view of Shapiro[5] (Ex. 1149) and Carlsson[6] (Ex. 1125).

Petitioners support the Petition with the testimony of Claude Negrier, M.D., Ph.D. (Ex. 1102).

III. ANALYSIS

A. Level of Skill in the Art

Petitioners, relying on the hypothetical person of ordinary skill in the art being a team of individuals, contend that the team would include

> an M.D. with experience treating hemophilia patients and/or researching hemophilia treatments; an M.D., Pharm.D., and/or Ph.D. in pharmacology or a related field with experience in pharmacokinetics and pharmacodynamics; and a Ph.D. in molecular biology or a related field with knowledge of fusion protein therapeutics and/or protein therapeutics for treating hemophilia.

Pet. 20–21 (citing Ex. 1102 ¶ 89).

Patent Owner agrees that the skilled artisan would be part of such a team. Prelim. Resp. 12–13.

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[3] Peters & Bitonti, *Enhanced Pharmacokinetics of Factor IX as a Monomeric Fc Fusion*, 5(Suppl. 2) J. THROMB. HAEMOST. O-M-016 (July 9, 2007) (Ex. 1157).
[4] Peters et al., US 7,404,956 B2, issued July 29, 2008 (Ex. 1103).
[5] Shapiro et al., *The safety and efficacy of recombinant human blood coagulation factor IX in previously untreated patients with severe or moderately severe hemophilia B*, BLOOD 105(2):518–25 (Jan. 15, 2005) (Ex. 1149).
[6] Carlsson et al., *Multidose pharmacokinetics of factor IX: implications for dosing in prophylaxis*, HAEMOPHILIA 4(2):83–88 (Mar. 1998) (Ex. 1125).

On this record, we adopt Petitioners' uncontested definition of the level of ordinary skill. We further note that the prior art itself demonstrates the level of skill in the art at the time of the invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that "specific findings on the level of skill in the art . . . [are not required] 'where the prior art itself reflects an appropriate level and a need for testimony is not shown'" (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985))).

B. Claim Construction

For petitions requesting an *inter partes* review filed before November 13, 2018, the Board interprets claim terms in an unexpired patent according to their broadest reasonable construction in light of the specification of the patent in which they occur. 37 C.F.R. § 42.100(b) (2016).[7] Under that standard, we interpret claim terms using "the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in the applicant's specification." *In re Morris*, 127 F.3d 1048, 1054 (Fed. Cir. 1997). Only those terms that are in controversy need to be construed and only to the extent necessary to resolve the controversy. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013,

[7] The broadest reasonable construction standard applies to *inter partes* reviews with petitions filed before November 13, 2018. 77 Fed. Reg. 48,727 (Aug. 14, 2012) (codified at 37 C.F.R. § 42.100(b)), as amended at 81 Fed. Reg. 18,766 (Apr. 1, 2016); *see also* 83 Fed. Reg. 51,340 (Oct. 11, 2018) (to be codified at 37 C.F.R. pt. 42) (changing the standard for interpreting claims in *inter partes* reviews filed on or after November 13, 2018).

1017 (Fed. Cir. 2017); *see also U.S. Surgical Corp. v. Ethicon, Inc.*, 103 F.3d 1554, 1568 (Fed. Cir. 1997) (holding claim construction is not necessary when it is not "directed to, or has been shown reasonably to affect, the determination of obviousness").

Petitioners note that "Petitioners and Patent Owner agreed to a set of constructions" in the ITC investigation, but that "none . . . [are] critical here." Pet. 21; Ex. 1129.

Patent Owner contends that Petitioners' arguments do not turn on any disputed claim construction issue, but notes that the parties do "dispute whether 'comprising/comprises' requires construction" in the district court litigation. Prelim. Resp. 13 n.2 (citing Ex. 2133).

We determine that no claim term requires express construction for the purpose of determining whether to institute review.

C. Overview of Asserted Prior Art

1. Peters 2007 (Ex. 1157)

Peters 2007 is titled "Enhanced Pharmacokinetics of Factor IX as a Monomeric FC Fusion" and discloses recombinant fusion protein (FIXFc) containing a single molecule of Factor IX (FIX) attached to the constant region (Fc) of immunoglobulin G (IgG) and determining the half-life of intraveneously administered FIXFc, along with an unconjugated recombinant FIX control (rFIX). Ex. 1157. Testing was conducted in mice, FIX-deficient mice, rats, FIX-deficient dogs, and cynomolgus monkeys. *Id.* Measurements in FIX-deficient mice and dogs demonstrated longer plasma elimination half-lives, 52 hours (FIXFc), rather than 13 hours (rFIX), for FIX-deficient mice and 47 hours (FIXFc), rather than 14-18 hours (rFIX), for FIX-deficient dogs. *Id.* Peters 2007 reports that activity measurements

indicated a similar increase in half–life for FIXFc in both FIX-deficient mice and FIX-deficient dogs. *Id.* Peters 2007 further reports that the "whole blood clotting time in the dogs was corrected from pre-dose measurements of greater than 60 min. to approximately normal range of 12-15 min, returning to baseline levels after 144 hours." *Id.* Peters 2007 "predict[s] that the [plasma] elimination half-life of FIXFc in humans will be approximately 50 hr. i.e. more than two-fold longer than for rFIX and thus consistent with a once weekly dosing regimen." *Id.*

2. The '956 Patent (Ex. 1103)

The '956 Patent is titled "Immunoglobulin Chimeric Monomer-Dimer Hybrids" and discloses a hybrid protein formed of two polypeptide chains, the first including at least a portion of an immunoglobulin constant region and a biologically active molecule, and the second at least a portion of an immunoglobulin constant region. Ex. 1103, [57], 1:17–27. The portion of the immunoglobulin constant region can include an Fc fragment (*id.* at 19:48–52) and the biologically active molecule can be a clotting factor, including Factor IX (*id.* at 16:56–57, 60–62); that is, the hybrid protein can include one Factor IX-Fc polypeptide dimerized with a Fc fragment (monomer-dimer) or two Factor IX-Fc polypeptides dimerized together (homodimer) (*id.* 51:45–52:48).

3. Shapiro (Ex. 1149)

Shapiro is titled "The safety and efficacy of recombinant human blood coagulation factor IX in previously untreated patients with severe or moderately severe hemophilia B" and discloses the results of a clinical study testing the efficacy and safety of rFIX in treating hemophilia B. Ex. 1149, 518–519. The testing study included patients who received rFIX for

prophylaxis, some receiving routine infusions 2 or more times per week, and others receiving an infusion once a week. *Id.* at 521.

4. Carlsson (Ex. 1125)

Carlsson is titled "Multidose pharmacokinetics of factor IX: implications for dosing in prophylaxis" and discloses use of single-dose pharmacokinetic data for FIX to predict multidose pharmacokinetics with a particular purpose to obtain dosages and dosing intervals to maintain FIX activity at or above 1 U/dL (1% of normal activity). Ex. 1125, 83, 86; *see also id.* at 87–88. Carlsson discloses that "[t]he 1% level [1 IU/dL] is . . . adequate to prevent development of haemophilic arthropathy in most cases." *Id.* at 87. Carlsson also discloses dosing patients every two or three days to be suitable to maintain this threshold level, but that once weekly dosing, i.e., with patient 8, would not be suitable. *Id.*, Table 3.

D. Alleged Unpatentability over Peters 2007 and the '956 Patent in view of Shapiro and Carlsson

Petitioners assert that claims 1–17, 20, 22, 24, and 28 are unpatentable because the subject matter of those claims would have been obvious over Peters 2007, the '956 patent, Shapiro, and Carlsson. Pet. 22–45. Petitioners rely on Peters 2007 for disclosing the existence of a recombinant fusion protein rFIXFc, its intended purpose, animal testing demonstrating efficacy and an extended half-life, and a prediction based on the testing as to half-life in humans. *Id.* at 22 (citing Ex. 1102 ¶¶ 74–75; Ex. 1157). Petitioners rely on the '956 patent, which names Dr. Peters as a co-inventor, for disclosing that rFIXFc is "a chimeric protein comprised of two polypeptide chains, wherein the first chain contains Fc and Factor IX, and the second chain contains unmodified Fc" and that its purpose is to increase serum half-life.

Id. at 22–23 (citing Ex. 1102 ¶¶ 68–73; Ex. 1103, 1:21–27, 2:15–24; 16:56–62, 51:44–52:48). Petitioners rely on Shapiro and Carlsson for their teachings as to FIX prophylaxis regimens. *Id.* (citing Ex. 1102 ¶¶ 61–67; Ex. 1125, 83, 87; Ex. 1149, 521).

Petitioners contend that a person of ordinary skill in the art "would have been motivated to administer the extended half-life rFIXFc molecule described in Peters 2007 and the '956 patent in similar dose amounts [as] used for prophylaxis with rFIX but at longer intervals of about 10-14 days." *Id.* (citing Ex. 1102 ¶¶ 119–126); *see id.* at 34–35. Petitioners further contend that a person of ordinary skill in the art "would have had a reasonable expectation of success that such a regimen would maintain plasma FIX activity level above 1 IU/dL and reduce frequency of spontaneous bleeding" "[b]ased on the animal data in Peters 2007 and the teachings of Shapiro and Carlsson." *Id.* at 23–24 (citing Ex. 1102 ¶¶ 127–134).

More specifically, Petitioners contend that the prior art teaches or suggests all elements of claim 1, and set forth the basis for this contention as follows.

"Method of treating hemophilia B in a human subject in need thereof"

Petitioners maintain that Peters 2007, the '956 patent, Shapiro, and Carlsson teach methods of treating hemophilia B patients. *Id.* at 24–25 (citing Ex. 1102 ¶¶ 96–98; Ex. 1103, 33:18–54, 60–61, 34:4–10; Ex. 1125, 83, 84, 87; Ex. 1149, 643; Ex. 1149, 518, 519, 521–523; Ex. 1157). Petitioners cite Peters 2007 for its general disclosure of FIXFc, including that it "contain[s] a single molecule of Factor IX attached to the constant region (Fc) of immunoglobulin (IgG)," and that it was sought in order to

extend the half-life and, thus, enable less frequent infusions. *Id.* (citing Ex 1157). Petitioners cite the '956 patent, which also discloses rFIXFc and its use, as "'relat[ing] to a method of treating a subject having a hemostatic disorder,' specifically including hemophilia B." *Id.* at 25 (citing Ex. 1103, 33:18–54, 60–61). Petitioners cite Shapiro for "disclos[ing] successfully treating hemophilia B with one or more rFIX infusions per week." *Id.* (citing Ex. 519, 521–523). Petitioners cite Carlsson for its "'study . . . [relating to] cost-effective dosing of FIX concentrates in their prophylactic treatment of haemophilia B.'" *Id.* (citing Ex. 1124, 87).

"intraveneously administering to the subject multiple doses of about 50 IU/kg to about 100 IU/kg"

Petitioners maintain that "Peters 2007, the '956 patent, Shapiro, and Carlsson disclose intraveneous administration of FIX replacement therapy." *Id.* at 25–26 (citing Ex. 1102 ¶¶ 99–100; Ex. 1103, 12:52–63, 21:63–65, 34:55–59; Ex. 1125, 87; Ex. 1049, 519; Ex. 1157). Petitioners rely on Shapiro as "disclos[ing] effective prophylaxis with rFIX injections of 72.5±37.1 (35.4-109.6) IU/kg two times a week or more, and once weekly injections of 75.9±17.9 (58-93.8) IU/kg," and also as "disclos[ing] a [broader] range of prophylaxis doses between 9.7 and 230.4 IU/kg." *Id.* at 26 (citing Ex. 1102 ¶¶ 100–101; Ex. 1149, 518, 519, 521, 523, Table 2). Petitioners contend that "Shapiro's once weekly dose of 75.9±17.9 IU/kg falls squarely within the range of about 50-100 IU/kg, [and] render[s] the claimed range obvious" and that "[i]t would have been obvious for a [person of ordinary skill in the art] to administer rFIXFc, which Peters 2007 reported as having good had established good in vivo clotting activity." *Id.* at 26–27 (citing Ex. 1102 ¶ 102, Ex. 1157). Petitioners cite, in particular, Peters 2007 as reporting that "whole blood clotting time in [FIX-deficient] dogs was

corrected from pre-dose measurements of greater than 60 min to approximately normal range of 12-15 min, returning to baseline levels after 144 hours." *Id.* at 27.

Petitioners further contend that a person of ordinary skill in the art would "start with an established FIX dose in IU/kg and identify the specific dose for an individual patient through routine optimization" and then conclude that "it would have been obvious based on Peters 2007, the'956 patent, and Shapiro for a [person of ordinary skill in the art] to treat hemophilia B using about 50-100 IU/kg doses of rFIXFc as claimed." *Id.* at 28 (citing Ex. 1102 ¶¶ 36, 102; Ex. 1149, 523).

"a chimeric factor IX ('FIX') polypeptide comprising FIX and an FcRn binding partner ('FcRn BP') . . . wherein the FcRn BP comprises Fc or albumin"

Petitioners maintain that "Peters 2007 teaches . . . a chimeric FIX polypeptide, *i.e.*, rFIXFc, which 'contain[s] a single molecule of Factor IX attached to the constant region (Fc) of immunoglobulin G (IgG)' . . . that when tested in animal models, . . . had good clotting activity and an extended half-life." *Id.* at 28 (citing Ex. 1102 ¶ 104; Ex. 1157).

Petitioners maintain that "[t]he '956 patent teaches the same rFIXFc fusion protein to extend half-life of rFIX." *Id.* at 28–29 (citing Ex. 1102 ¶ 103; Ex. 1003, 1:21–27, 2:18–22, 12:27–51, 54–62, Fig. 2b (SEQ ID NO:8), Fig. 3b (SEQ ID NO:9). Petitioners further maintain that "[t]he '956 patent . . . explains the mechanism of half-life extension" is grounded on FcRn recycling and teaches "preparation of the rFIXFc monomer-dimer hybrid and testing of rFIXFc including administration to rats." *Id.* at 29 (citing Ex. 1102 ¶ 103; Ex. 103, 2:32–36, 41:34–42:7 (Example 4), 51:44–

52:48 (Example 14), 56:5–67 (Examples 22–23), Fig. 2b (SEQ ID NO:8), Fig. 3b (SEQ ID NO:9)).

"*at a dosing interval of about 10 days to about 14 days between two doses*"

Petitioners contend that "Peters 2007 and the '956 patent in view of Shapiro and the knowledge of a [person of ordinary skill in the art] suggest administering rFIXFc at a dosing interval of about 10–14 days." *Id.* Petitioners rely on Shapiro as teaching effective prophylaxis with once weekly doses of 75.9±17.9 IU/kg" of rFIX. *Id.* at 29–30 (citing Ex. 1102 ¶ 105; Ex. 1149, 521–523). Petitioners rely on Peters 2007 as disclosing data "showing that rFIXFc is efficacious and has a half-life approximately 3- to 4-times longer than rFIX" and for "expressly predict[ing] that the elimination half-life of rFIXFc will be more than two-fold longer than rFIX in humans." *Id.* at 30 (citing Ex. 1102 ¶ 106; Ex. 1149). Petitioners rely on the '956 patent as "teach[ing] that rFIXFc has an extended half-life because of FcRn recycling" and "instruct[ing] that dosing information can be extrapolated from dose response curves obtained from animal models." *Id.* at 30–31 (citing Ex. 1002 ¶¶ 72, 107; Ex. 1103, 2:32–36, 12:31–39, 54–62, 34:56–35:11).

Petitioners contend that it would have been obvious, therefore, for a person of ordinary skill in the art "to treat hemophilia B in humans with rFIXFc with doses similar to the ones already used with rFIX but administered over a longer interval." *Id.* at 31 (citing Ex. 1002 ¶¶ 108–110). Relying on the expectation that "a FIX therapeutic exhibiting longer half-life in animal models would . . . do so in humans as well" (citing Ex. 1102 ¶¶ 108, 113; Ex. 1103, 35:2–11; Ex. 1157), Petitioners reiterate that "Shapiro discloses successful prophylaxis with once weekly rFIX" and that

"Peters 2007 establishes a 3- to 4-fold longer half-life for rFIXFc in animals." *Id.*; *see also id.* at 35 (relying on an "[u]nderstanding from Shapiro that rFIX at 75.9±17.9 IU/kg once weekly provided successful prophylaxis . . . [and] Peters 2007 showing . . . at least a two-fold half-life extension" as motivating dosing rFIXFc "at similar doses but at longer dosing intervals than rFIX, *i.e.*, about every 10–14 days").

Petitioners also contend that a person of ordinary skill in the art "would have relied on experience with established FIX therapeutics, starting with an established FIX dose in IU/kg and identifying the most appropriate dosing interval for an individual patient through routine optimization." *Id.* at 31 (citing Ex. 1102 ¶¶ 36, 108; Ex. 1149, 523).

In sum, Petitioners contend that it would have been obvious "to treat hemophilia B by administering rFIXFc at similar doses but a longer interval than rFIX, i.e., about once every 10–14 days as claimed. *Id.* at 31–32 (citing Ex. 1102 ¶ 110).

"wherein the administration maintains the plasma FIX activity of the subject above 1 IU/dL between the dosing interval"

Petitioners rely on Carlsson's disclosure that "[p]rophylactic treatment . . . aims to prevent bleeding and maintain normal joint status" and that a "strategy to achieve this is to 'keep the plasma level of factor . . . IX procoagulant activity . . . at or above 1 U dL^{-1} at all times,'" and that this was "'adequate to prevent development of haemophilic arthropathy in most cases.'" *Id.* at 32 (citing Ex. 1002 ¶ 111; Ex. 1125, 83, 84, 86, 87).

Petitioners then maintain that "effectively managing spontaneous bleeding generally entails maintaining FIX activity levels above 1 IU/dL between doses" and that a person of ordinary skill in the art would therefore understand that Shapiro's once weekly regimen of 75.9±17.9 IU/kg rFIX

successfully maintained FIX activity levels above 1IU/dL." *Id.* (citing Ex. 1002 ¶ 112).

Petitioners contend that "it would have been obvious that patients such as those successfully treated on Shapiro's once weekly regimen would successfully maintain FIX activity levels above 1 IU/dL when administered about 50-100 IU/kg of rFIXFc about every 10–14 days." *Id.* at 32–33 (citing Ex. 1102 ¶ 113; Ex. 1103, 2:32–36, 12:54–62, 33:18–55, 60–61, 34:4–10, 34:56–35:11; Ex. 1157); *see id.* at 35.

"wherein the administration treats the human subject by reducing the frequency of spontaneous bleeding"

Petitioners rely on Carlsson for teaching that the aim of prophylactic treatment is "to prevent bleedings" (citing Ex. 1102 ¶ 115; Ex. 1125, 83, 87), on Shapiro as "disclos[ing] that prophylaxis doses between 50-100 IU/kg rFIX once weekly reduced spontaneous bleeding" (citing Ex. 1102 ¶ 182; Ex. 1149, 518, 519, 521, 522–524), and on both Peters 2007 and the '956 patent as "indicat[ing] that rFIXFc is effective and can be administered at a longer dosing interval than rFIX" (citing Ex. 1102 ¶¶ 116–117; Ex. 1003, 2:32–36, 12:54–62, 33:18–55, 60–61, 34:4–10; Ex. 1157). Pet. 33.

Petitioners contend that "it would have been obvious that patients such as those successfully treated on Shapiro's once weekly regimen of 75.9±17.9 IU/kg rFIX would experience reduced frequency of spontaneous bleeding when administered about 50-100 IU/kg rIX-FP about every 10-14 days." *Id.* at 33–34 (citing Ex. 1002 ¶¶ 117–118).

Petitioners contend that a person of ordinary skill in the art "would have had a reasonable expectation of success in maintaining plasma FIX activity above 1 IU/dL between doses and reducing the frequency of spontaneous bleeding, thus treating hemophilia B, by administering 50-100

IU/kg rFIXFc at about every 10-14 days." *Id.* at 35 (Ex. 1102 ¶¶ 127, 134). Petitioners ground their contentions on a person of ordinary skill in the art knowing, from Shapiro, that "once weekly doses between 50-100 IU/kg rFIX reduced the frequency of spontaneous bleeding" (citing Ex. 1102, ¶¶ 129–131; Ex. 1149, 521–523) and knowing, from Carlsson, that "effective prophylactic treatment generally maintains FIX activity above 1 U/dL to reduce the frequency of spontaneous bleeding" (citing Ex. 1102 ¶ 128; Ex. 1125, 83, 87). *Id.* at 36. Petitioners, in effect, maintain that a person of ordinary skill in the art would have recognized that the level of FIX activity was maintained at or above 1 IU/dL with once weekly doses between 50–100 IU/kg.

Petitioners then rely on the disclosure in Peters 2007 that "rFIXFc had *in vivo* clotting efficacy" and its predicted elimination half-life of FIXFc in humans being "approximately 50 hr, i.e., more than two-fold longer than for rFIX," and on the disclosure in the '956 patent "that 'effective doses may be extrapolated from dose-response curves obtained from animal models' and that '[i]n vito assays may be employed to determine optimal dose ranges and/or schedules for administration.'" *Id.* at 36–37 (citing Ex. 1102 ¶ 133; Ex. 1103, 35:2–11; Ex. 1157). Petitioners further maintain that a person of ordinary skill in the art "would have a reasonable expectation of success in treating hemophilia B by administering 50-100 IU/kg [rFIXFc] at . . . about every 10-14 days as claimed." *Id.* at 37 (citing Ex. 1102 ¶ 134). Further, Petitioners cite to *Biomarin Pharm., Inc. v. Genzyme Therapeutic Prods., LP*, IPR2013-00537, Paper 79 at 13–21 (PTAB Feb. 23, 2015).

Petitioners also maintain that arriving at a 10–14 day interval would have required no more than routine optimization. *Id.* at 38 (citing Ex. 1102 ¶¶ 36, 102, 108; Ex. 1113, 5).

In response, Patent Owner contends the asserted ground fails because it is grounded "on the false premise that Shapiro discloses effective weekly dosing of recombinant FIX to maintain a patient's plasma FIX activity levels above 1 IU/dL" and because it

> ignores that (1) Peters 2007 reports that FIXFc could improve clotting in animal models for ***only six days***; (2) Peters 2007 does not disclose what doses were administered to the animals in these studies; and (3) Peters 2007 merely speculates that the results of these studies are consistent with ***once weekly*** dosing in humans.

Prelim. Resp. 14–15.

As to Shapiro and once weekly FIX dosing, Patent Owner maintains that Petitioner fails to cite a single reference that supports its contention that weekly FIX dosing is capable of maintaining a FIX activity of above 1% in a patient, including Petitioners' own work subsequent to Peters 2007. *Id.* 15–16 (citing Ex. 1134; Ex. 1136, 634; Ex. 1148, S6). Patent Owner's expert, Dr. Pasi, maintains "Shapiro does not disclose that ***any*** patient was able to maintain a plasma FIX activity level of at least 1% during any of the disclosed dosing regimens." *Id.* at 19 (citing Ex. 2101 ¶ 92); *see* Ex. 2101 ¶¶ 89–93, 97; *see* Prelim. Resp. 22–23 (citing Ex. 2101 ¶¶ 38, 91; Ex. 2125, 3; Ex. 2140, 100). As Patent Owner highlights, it was understood that more frequent dosing, *i.e.*, 2 to 3 doses a week, was required to maintain the recited FIX activity level, as Petitioners' own work evidences, including: (1) Peters 2007, which "states that prophylaxis treatment of hemophilia B 'generally requires multiple infusions per week with the currently available

drugs'" (Ex. 1157); (2) Metzner, which states that "prophylactic treatment requires an i.v. application approx. every two to three days to keep trough levels above 1%'" (Ex. 1136, 634); and (3) Schulte, which "state[s] that '[p]rophylactic therapy with FIX concentrates usually requires regular intraveneous infusions every 2-3 days to maintain FIX clotting activity >1% and to prevent spontaneous bleeding'" (Ex. 1148, S6). Prelim. Resp. 20–21.

Dr. Negrier does not squarely address these contrary teachings of the art, including that of Petitioners, in reaching his opinion as to Shapiro maintaining FIX activity above 1 IU/dL with once weekly doses. *See* Ex. 1102 ¶¶ 111–113. Accordingly, we give Dr. Negrier's opinion that Shapiro would be recognized as maintaining a level of FIX activity above 1 IU/dL little weight. *See Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 294 (Fed. Cir. 1985) ("Lack of factual support for expert opinion going to factual determinations" is sufficient to "render the testimony of little probative value in a validity determination.").

Moreover, the contended reduction in bleeding or prophylaxis in Shapiro with once weekly doses does not support the contention that the FIX activity level was maintained at a level of at least 1 IU/dL. First, although Carlsson teaches maintaining a level of FIX activity above 1 IU/dL as a strategy for prophylactic treatment, that only establishes that such a level suffices, not that it is necessary for prophylaxis. Ex. 1125, 83. Thus, even if Shapiro did maintain a prophylactic effect with once weekly dosing, it does not reasonably support that the levels of FIX activity necessarily were maintained above 1 IU/dL. Second, as discussed above, the prevailing consensus, even after Shapiro, was that at least twice-weekly dosing was

required to maintain a FIX activity level of at least 1 IU/dL in a patient. *Id.* at 22 (citing Ex. 2101 ¶ 93).

As to Peters 2007 and its disclosed animal testing, Patent Owner contends that the reported results are contrary to maintaining a patient's plasma FIX activity levels above 1 IU/dL over a 10–14 day interval. *Id.* at 24 (citing Ex. 1157; Ex. 2101 ¶ 99). In particular, as Patent Owner highlights, "Peters 2007 only tests the efficacy of FIXFc to control bleeding in a single animal model—FIX deficient dogs . . . [and that] when such FIX-deficient dogs are administered FIXFc, the ability of their blood to clot 'returned to baseline levels after 144 hours [6 days].'" *Id.* The Petition is lacking in that, although it reproduces the text reporting that the ability to clot returns to baseline in citing to Peters 2007 for its teaching that rFIXFc has good *in vivo* clotting activity (Pet. 27), it fails to address how the limited duration of clotting effect, which returns to FIX-deficient baseline levels in six days, is consistent with maintaining plasma FIX activity levels above 1 IU/dL over a 10–14 day interval (*see generally id.*).

Moreover, although Peters 2007 does not disclose the administered FIXFc dose, Patent Owner highlights that Peters 2010, a later publication by Peters, "reported similar data showing that when such dogs are administered a dose of 140 IU/kg FIXFc . . . their plasma FIX activity level drops below 1 IU/dL, and their ability to clot returns to baseline less than 7 days after the dose is administered." *Id.* at 24–25 (citing Ex. 1142, 2061–2062; Ex. 2101 ¶ 100). Peters 2010 reasonably supports that doses according to the claims would not provide the recited activity of 1 IU/dL over the recited range of 10–14 days in FIX-deficient dogs. Petitioners' awareness of Peters 2010, relied on in its Petition in this proceeding, as well as in earlier-filed

IPR2018-01313, underscores the deficiency in the Petition failing to squarely address the ability of the FIX-deficient dogs to clot returning to baseline in six days after dosing with rFIXFc in Peters 2007. *See generally* Pet.

Relying on the deficiencies in Petitioners' treatment of Shapiro and Peters 2007, Patent Owner also contends that the Petition fails to establish a reasonable expectation of success. Prelim Resp. 27–29. Patent Owner relies on deficiencies in Petitioners' positions that Shapiro teaches that once weekly doses between 50–100 IU/kg rFIX maintain FIX activity above 1 IU/dL and that Peters 2007 supports a 10–14 day dosing regimen, including in Petitioners' reasoning that "Peters 2007 animal data would be predictive for a human dosage regimen." *Id.* Petitioners' reasoning grounded on Shapiro teaching that the FIX activity is maintained above 1 IU/dL with 50–100 IU/kg rFIX once weekly is not well founded, as explained above. Similarly, the animal data from Peters 2007, and associated reasoning as to its predictive value, falls short in the absence of an explanation how the data relating to the ability of the FIX-deficient dogs to clot is not contrary to a dosing interval of 10–14 days. *See* Ex. 2101 ¶ 105.

Patent Owner further contends that the Petition fails to establish that routine or predictable optimization of existing regimens would have led to the dosing regimen claimed. Prelim. Resp. 31–39. Patent Owner highlights Petitioners' unfounded reliance on Shapiro's once weekly dosing maintaining FIX activity levels at 1 IU/dL and providing prophylaxis. *Id.* at 32–33. Patent Owner also highlights that Petitioners "ignore that Peters 2007's optimistic speculation of 'more than two-fold longer than rFIX in

humans' was accompanied by statements that this was '***thus consistent with a once weekly dosing regimen***.'" *Id.* at 33 (citing Ex. 1157). Patent Owner also contends that the '956 patent's disclosure to administer doses "at any interval" is insufficient to invite routine optimization. *Id.* at 34–35 (citing Ex. 1103, 34:65–35:2; Ex. 2101 ¶ 96).

Petitioners' reliance on Dr. Negrier's explanation that arriving at a 10–14 day interval would have required no more than routine experimentation is similarly insufficient on this record. Pet. 38 (citing Ex. 1102 ¶ 108). Although paragraph 108 does discuss that clinicians commonly tailor dose and/or the dosing interval based on patient response and the risk of bleeding, it also relies on rFIXFc exhibiting "a longer half-life than rFIX in standard animal models" and on Peters 2007 as supporting that "it would be expected to do so in humans as well." Ex. 1102 ¶ 108. As to this expectation, Petitioners further rely on the Dr. Negrier's testimony that "skilled artisans would have understood that efficacy and half-life extension in animal models were reasonably predictive of efficacy and half-life extension in humans." Pet. 14 (citing Ex. 1002 ¶¶ 74 n.10, 78 nn.12 & 13, 83 n.15, 108). The cited portions of Dr. Negrier's declaration, however, are directed in the main to efficacy, not half-life. Moreover, as discussed above, Dr. Negrier, fails to address the limited length of therapeutic effect reported in Peters 2007 (and Peters 2010) relative to the purported therapeutic effect and activity level in Shapiro despite the extended half-life for rFIXFc over rFIX in the FIX-deficient dog model.

Patent Owner further maintains that contrary to the *Biomarin* case, "where the prior art disclosed a treatment regimen based on human clinical experience, there is ***no clinically supported data*** as to the half-life of FIXFc

in humans in Peters 2007 or in any of [Petitioners'] cited references." *Id.* at 35. Patent Owner contends that "the *Biomarin* case involved an obviousness analysis of a dosing regimen for Pompe disease using human GAA [α-glucosidase] in light of a ***clinically supported*** prior art dosing regimen for treatment of Gaucher disease." *Id.* (citing *Biomarin*, Paper 79 at 15).[8]

Although it is not manifest how the circumstance in *Biomarin* differs based on Patent Owner's argument, the argument highlights how Petitioners' citation to pages 13 to 21 of *Biomarin* and characterization of the case, with quotation of several short phrases, does not sufficiently establish the similarity of the facts of that case and, absent that, *Biomarin* is not shown to fairly support Petitioners' challenge. Pet. 37–38; Prelim. Resp. 35.

Moreover, Patent Owner notes that the Notice of Allowability (Ex. 1117) includes the Examiner's reasoning that "optimization is not routine or predictable to arrive at what is claimed in the absence of human data" where there is "evidence that dosing studies in animal models are often different from what occurs in humans." *Id.* at 36 (citing Ex. 2102, 32); Ex. 1117, 3. Citing *In re Stepan*, 868 F.3d 1342, 1346 (Fed. Cir. 2017), for the proposition that articulated rationale is required to support routine optimization argument, Patent Owner further maintains that neither Petitioners nor Dr. Negrier provide evidence or persuasive analysis sufficient to meet this requirement in view of evidence indicating discrepancies in the animal models. Prelim. Resp. at 36–37.

Patent Owner's argument again highlights Petitioners' failure to establish sufficiently that the animal data relied on in the challenge

[8] Patent Owner may have intended to cite page 16 rather than page 15, as its relation to the argument is more readily apparent.

reasonably supports the conclusions and inferences of Petitioners and Dr. Negrier, particularly the failure to address the data from Peters 2007 (and Peters 2010) relating to the return to base-line FIX-deficient levels following administration of rFIXFc.

As to the dependent claims challenged, we discern nothing that remedies the deficiencies as to the challenge to claim 1, discussed above. For example, Petitioners' additional argument for the more specific dosing intervals that claims 6–11 require similarly relies on Shapiro and animal testing data, and further relies on adjusting the dosing interval within the range of 10–14 days, the range contended to have been obvious on the basis of Petitioners' challenge to claim 1. Pet. 40–41; Ex. 1102 ¶¶ 36, 108, 142–145.

Accordingly, we are not persuaded that Petitioners establish a reasonable likelihood of prevailing in showing that the subject matter of any of claims 1–17, 20, 22, 24, and 28 is unpatentable over Peters 2007 and the '956 Patent in view of Shapiro and Carlsson.

IV. CONCLUSION

Petitioners have not established a reasonable likelihood of prevailing on its assertion that claims 1–17, 20, 22, 24, and 28 are unpatentable.

V. ORDER

For the reasons given, it is:

ORDERED that the Petition is *denied* as to all challenged claims of the '091 patent and no trial is instituted.

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