Nos. 24-1094, 24-1149

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

TEVA PHARMACEUTICALS INTERNATIONAL GMBH,

TEVA PHARMACEUTICALS USA, INC.,

Plaintiffs-Appellants,

v.

ELI LILLY AND COMPANY,

Defendant-Cross-Appellant.

On Appeal from the U.S. District Court for the District of Massachusetts,
The Honorable Allison D. Burroughs, Case No. 1:18-cv-12029-ADB

APPELLANTS' OPENING BRIEF

Gabriel B. Ferrante
GOODWIN PROCTER LLP
The New York Times Building
620 8th Ave
New York, NY 10018
(212) 813-8800

Kevin P. Martin
Elaine Herrmann Blais
Edwina B. Clarke
GOODWIN PROCTER LLP
100 Northern Avenue
Boston, MA 02210
(617) 570-1000

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Counsel for Plaintiffs-Appellants

PATENT CLAIM LANGUAGE

U.S. Patent No. 8,586,045

[17. A method for reducing incidence of or treating headache in a human, comprising administering to the human an effective amount of an anti-CGRP antagonist antibody, wherein said anti-CGRP antagonist antibody is a human monoclonal antibody or a humanized monoclonal antibody.]

30. The method of claim 17, wherein said anti-CGRP antagonist antibody is a humanized monoclonal antibody.

CERTIFICATE OF INTEREST

Undersigned counsel for Appellants certifies as follows:

1. The full name of every entity represented by undersigned counsel is:

Teva Pharmaceuticals International GmbH; Teva Pharmaceuticals USA Inc.

2. The name of the real party in interest for the entities is:

N/A

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

Teva Pharmaceuticals International GmbH: Teva Pharmaceutical Industries Ltd.

Teva Pharmaceuticals USA Inc.: Teva Pharmaceutical Industries Ltd.

4. The names of all law firms and the partners or associates that appeared for the entities in the trial court or agency or are expected to appear in this court (and who have not or will not enter an appearance) are:

Goodwin Procter LLP: Douglas J. Kline, I. Neel Chatterjee, Robert Frederickson III, Natasha E. Daughtrey, Molly Grammel, Eric T. Romeo, Alexandra S. Lu, Joshua S. Weinger, Kathleen A. McGuinness, Martin C. Topol, Shaobo Zhu, Madeline DiLascia, Sean M. Anderson, Tara R. Thigpen, Audie Soucy, Grace P. Truong

5. Other than the originating case(s) for this case, related or prior cases that meet the criteria under Fed. Cir. R. 47.5(a) are:

None.

6. Organizational victims and bankruptcy cases:

N/A.

/s/ *Kevin P. Martin*
Kevin P. Martin

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GLOSSARY

’045 patent	U.S. Patent No. 8,586,045 (Appx205-275)
’907 patent	U.S. Patent No. 9,884,907 (Appx276-353)
’908 patent	U.S. Patent No. 9,884,908 (Appx354-430)
CGRP	Calcitonin Gene-Related Peptide
G1/fmab	Fremanezumab
Gmab	Galcanezumab
IPR	*Inter partes* review
Lilly	Defendant-Cross Appellant Eli Lilly & Co.
POSA	Person of Ordinary Skill in the Art
PTAB	Patent Trial and Appeal Board
PTO	U.S. Patent & Trademark Office
Teva	Plaintiffs-Appellants Teva Pharmaceuticals International GmbH and Teva Pharmaceuticals USA, Inc.

STATEMENT OF RELATED CASES

The following cases are related to these consolidated appeals, as defined by Fed. Cir. R. 47.4(a)(5):

None.

INTRODUCTION

The inventors of the patents-in-suit discovered that a class of antibodies already well known to a POSA—murine (mouse) anti-CGRP antagonist antibodies—could, after humanization, be used to treat debilitating headaches such as migraine and cluster headache. This was a groundbreaking discovery, establishing that the blood-brain barrier does not preclude antibody-based treatments for headache and leading to preventative migraine medications from patent-owner Teva and patent-infringer Lilly. Lilly challenged Teva's patents at the PTO, which held that Teva's claims to the humanized antibodies were obvious but its claims to the use of those antibodies to treat headache were not. This Court affirmed.[1] Then, after a month-long trial, a jury found that Lilly is willfully infringing the method of treatment claims and that those claims pass § 112's written description and enablement tests. The district court, however, granted JMOL to Lilly on both § 112 defenses. The lower court's JMOL decision flowed from serious legal errors and this Court should reverse.

The invention in this case is a novel method of treatment using an already well-known class of antibodies, all of which will work in the claimed method. This Court repeatedly has rejected § 112 defenses, just like Lilly's, challenging method

[1] *Teva Pharms. Int'l GmbH v. Eli Lilly & Co.*, 8 F.4th 1349 (Fed. Cir. 2021); *Eli Lilly & Co. v. Teva Pharms. Int'l GmbH*, 8 F.4th 1331 (Fed. Cir. 2021); *Teva Pharms. Int'l GmbH v. Eli Lilly & Co.*, 856 F. App'x 312 (Fed. Cir. 2021).

claims that employ an already well-known genus. The invention here is not a novel class of antibodies, and so this case is nothing like the antibody cases on which the district court relied, in which claims to novel classes of antibodies were found inadequately described or enabled.

There was overwhelming evidence in this case that a POSA would have been very familiar with murine anti-CGRP antagonist antibodies and humanizing them would have been routine and predictable. Indeed, the jury learned that Lilly, in its successful IPR challenging Teva's antibody patents, had asserted to the PTAB that:

- "anti-CGRP antagonist antibodies were well known in the art";
- the "prior art" was "replete with exemplary disclosures of anti-CGRP antagonist antibodies, including humanized antibodies, to treat human diseases and conditions";
- "anti-CGRP antagonist antibodies that bound to and blocked the biological effect of CGRP were well known in the art"; and
- "the prior art already reported several monoclonal anti-CGRP antagonist antibodies, including those that bound to and blocked human CGRP."

Lilly's brief to this Court in its successful defense of the PTAB's decision emphasized the Board's conclusion "that anti-CGRP antagonist antibodies were well known in the art." Appx22642; Appx22627. And, in affirming the Board, this Court repeated that anti-CGRP antagonist antibodies were "known in the art" and "well known in the art." *Teva*, 8 F.4th at 1355-56.

The district court nonetheless found lack of written description and

enablement largely for this reason: because the many murine anti-CGRP antagonist antibodies known in the prior art had not *actually* been humanized, and the applicants described only one humanized antibody in the specification. The court confined its § 112 analysis to the one humanized antibody, refusing to consider the murine antibodies known in the art and disclosed in the specification. Relying on cases involving claims to novel classes of antibodies and methods of treatment with novel small-molecule compounds, the court held that the single humanized antibody was not enough to describe or enable the claimed method of treatment.

The district court's disregard of the known class of murine antibodies because they had not actually been humanized was legal error. Written description and enablement do not require actual reduction to practice, nor must a specification teach what a POSA already knows. Under those bedrock legal principles, the applicants did not need to humanize the murine antibodies known to a POSA—to actually reduce them to practice—or to describe them in the specification. And especially once the murine antibodies are taken into account (but even if they are not) there was ample evidence supporting the jury's verdict, including Lilly's admissions to the PTAB that anti-CGRP antagonist antibodies were "well known in the art" and that the prior art was "replete with exemplary disclosures of anti-CGRP antagonist antibodies[.]"

The district court also ran roughshod over the JMOL standard, usurping the

jury's right to resolve credibility issues. The most blatant example is this: Lilly's antibody expert Dr. McDonnell opined that the number of antibodies that would need to be generated and analyzed to describe and enable the invention can be calculated via a "thought experiment" involving *random substitution* of every amino acid in the antibody's variable chain. The jury, however, heard and could have credited contrary testimony: that if a mouse is repeatedly immunized with CGRP, its immune system will *selectively* produce antibodies responsive to CGRP. In fact, at summary judgment the district court found that Dr. McDonnell's random-substitution opinion was "not credible or persuasive." Appx4552. The jury clearly agreed. But, in its JMOL decision, the district court flip-flopped, relying on Dr. McDonnell's thought experiment to find that a "mind-bogglingly" large number of antibody candidates exist. That was error.

The district court should have let the jury verdict stand. This Court should reverse, or at a minimum vacate, the decision below.

JURISDICTIONAL STATEMENT

The district court had jurisdiction under 28 U.S.C. §§ 1331, 1338. That court entered final judgment on September 28, 2023. Appx1. Teva timely appealed. Appx4564-4567. This Court has jurisdiction under 28 U.S.C. § 1295(a)(1).

STATEMENT OF THE ISSUES

1. Whether the district court erred in granting Lilly JMOL that the asserted patent claims are invalid for lack of written description.

2. Whether the district court erred in granting Lilly JMOL that the asserted patent claims are invalid for lack of enablement.

STATEMENT OF THE CASE

I. The Zeller team discovers that anti-CGRP antagonist antibodies can be used to treat headache and patents its discovery.

A. By the 2006 priority date, the class of anti-CGRP antagonist antibodies was already well known to a POSA.

CGRP is a protein in the human body. Appx6. When it binds to CGRP receptors on certain cells, the cells expand and increase blood flow through blood vessels—a change associated with headache. *Id.*

Antibodies are proteins produced by the immune system that can fight disease and infection by identifying and binding to antigens, like CGRP, to neutralize them. Appx7. Antibodies are made up of amino acids that combine in chains to form a protein. *Id.* The shape of the protein determines the protein's function. *Id.*

Full-length anti-CGRP antagonist antibodies have four chains, and each chain has a constant region and a variable region. Appx7. The variable regions contain complementarity determining regions, or "CDRs," which have a distinct sequence of amino acids. Appx8. A CDR's shape is based on that sequence, and when the shape complements the shape of a particular binding site on an antigen, called an

"epitope," the antibody binds to the antigen. *Id.* When anti-CGRP antagonist antibodies bind to one of three epitopes on CGRP, they block CGRP from interacting with its receptor. Appx9.

By November 2006, the priority date of the patents-in-suit, anti-CGRP antagonist antibodies had been described extensively in the scientific literature and "a great deal was known" about them. Appx4059; *see also* Appx4062-4069. Monoclonal antibodies were shown to antagonize CGRP by 1992. Appx4119-4120. That kicked off a flurry of activity, including researchers testing commercially-available anti-CGRP antagonist antibody "4901" in a variety of animal physiologies. Appx4120-4121. Several scientific publications reported that anti-CGRP antagonist antibodies blocked the effects of CGRP in animals. *E.g.*, Appx4067-4069; Appx51990-51994; Appx4120-4126; Appx17920; Appx52609 ("We have identified several MAbs which block a biological effect of CGRP."); Appx52306 ("Ten monoclonal antibody lines [binding CGRP] 4901-4910 were developed successfully.").

Teva's expert Dr. Hill recounted that his graduate student Keith Tan published on multiple anti-CGRP antagonist antibodies in 1994 and 1995, including four he made himself and seven that were a gift from another researcher. Appx4121-4126; *see also* Appx4209-4210 (Dr. Hale, agreeing with Dr. Hill that anti-CGRP antagonist antibodies were well known in the art based on, *inter alia*, Tan's papers).

Tan and Plourde (also published in the 1990s) cited earlier disclosures of anti-CGRP antagonist antibodies and demonstrated that anti-CGRP antagonist antibodies blocked the effects of CGRP *in vivo*. *E.g.*, Appx51190 (Tan); Appx18038 (Plourde). And the Sigma product catalog sold anti-CGRP antagonist antibody 4901. Appx18043-18046; Appx4061-4064. By the 2006 priority date, anti-CGRP antagonist antibodies were known that attached to all three epitopes of CGRP—the C-terminal, mid-region, and N-terminal—and blocked CGRP's activity wherever they bound. *See* Appx18046; Appx219998; Appx4216-4217; Appx3321-3324; Appx17918; Appx4125; Appx51187-51197; Appx18384-18386.

While anti-CGRP antagonist antibodies were well known, their uses for treating medical conditions had not been established. By the priority date, it was known that CGRP is connected to migraine—that CGRP causes acute migraine if injected into a human. Appx1276-1277. It also was known that small molecule drugs that block the CGRP receptor can alleviate migraine symptoms. Appx3977-3982. Those drugs, unfortunately, did not remain in the body long enough to prevent migraine. Appx1278-1279. Antibodies, on the other hand, can stay in the body long enough to serve as preventative treatments. *Id.* Many in the field, however, believed that antibodies could not treat headache because they could not cross the "blood-brain barrier." Appx4144-4145.

B. The Zeller team discovers that humanized anti-CGRP antagonist antibodies can treat headache.

In 2003, a team led by named inventor Joerg Zeller began researching whether anti-CGRP antagonist antibodies can treat headache despite the blood-brain barrier. To conduct its experiments, the Zeller team licensed an existing anti-CGRP antagonist antibody from UCLA to use as a benchmark, Appx1463, and also made its own antibodies by injecting CGRP into mice, Appx1337-1338. By the priority date, the generation of murine anti-CGRP antagonist antibodies by injecting mice with CGRP was a well-established process requiring little direct involvement by scientists. Appx4212-4214; Appx1469-1471; Appx2951-2952.

The Zeller team tested the antibodies for binding to CGRP, Appx1338-1339, and blocking ability, Appx1340-1342. These tests were routine. Appx4168-4169. The team then tested whether the antagonists would work in an animal model of migraine. Appx10. These tests demonstrated what other researchers did not think was possible: anti-CGRP antagonist antibodies will treat headache. Appx1286-1287.

The Zeller team "humanized" one of antibodies, "antibody 7[E]9," also referred to at trial as "antibody 79" and, in its humanized form, as antibody G1. Appx10. Humanization, necessary to avoid adverse reactions by the human immune system, was "well established in the field at the time" having been extensively described in the prior art, for example in the "Queen" reference. Appx1477;

Appx1481 (similar); *see also* Appx16526-16672 (Queen). Typically, humanization consists of transplanting the non-human antibody's CDRs, where "all the variability of antibodies is focused," Appx3118, into well-known human antibody templates, Appx21671-21672. By 2005, "a POSA that followed Queen's teachings would have readily been able to graft CDRs from a donor murine anti-CGRP antagonist antibody onto a human IgG scaffold, while maintaining the binding affinity and specificity for human CGRP." Appx18881.

The Zeller team's discovery that humanized anti-CGRP antagonist antibodies could be used to treat headache was groundbreaking—they succeeded where others were failing. Specifically, a team of researchers from Lilly also tested whether such antibodies could treat headache, including by purchasing the same commercially-available antibody the Zeller team purchased, and their tests failed. Appx2807-2808; Appx2814-Appx2817. The Lilly researchers therefore shelved their effort, switching their anti-CGRP antagonist antibody research to the treatment of different maladies. Appx2814-Appx2817. It was only after the Zeller team's patent applications published that the Lilly researchers returned to headache. *See* Appx2635-2638; Appx1366.

C. The Zeller team obtains patents to their novel method of treatment, which Teva purchases and commercializes.

The Zeller team applied for and obtained patents separately covering (1) humanized anti-CGRP antagonist antibodies and (2) methods of using such

antibodies to treat headache. The three patents-in-suit fall into the latter category. Five claims are at issue: claim 30 of the '045 patent, claims 5 and 6 of the '907 patent, and claims 5 and 6 of the '908 patent.

Claim 30 of the '045 patent, which is representative of the asserted claims, depends from claim 17, which recites:

> A method for reducing incidence of or treating headache in a human, comprising administering to the human an effective amount of an anti-CGRP antagonist antibody, wherein said anti-CGRP antagonist antibody is a human monoclonal antibody or a humanized monoclonal antibody.

Appx273(100:3-7). Claim 30 specifies that a humanized monoclonal antibody is used. Appx273(100:56-57). Claims 5 and 6 of the '907 and '908 patents specify particular types of headache to be treated. Appx353(103:43-48); Appx430(101:1-6).

The shared specification of the patents-in-suit reflects the extensive knowledge a POSA would have had about anti-CGRP antagonist antibodies. *Supra*, pp. 5-7. The specification acknowledges that "[a]nti-CGRP antagonist antibodies are known in the art," and points the reader to several of the prior art publications discussed above and to the Sigma catalog. Appx237(25:59-63) (citing "Tan et al., Clin. Sci. (Lond). 89:565-73, 1995; Sigma (Missouri, US), product number C7113 (clone #4901); Plourde et al., Peptides 14:1225-1229, 1993."). The specification explains that additional anti-CGRP antagonist antibodies can be made using "any

method known in the art." Appx238(27:41-42). It discloses that the Zeller team tested seven murine anti-CGRP antagonist antibodies, Appx250(51:5-27), and discloses the amino-acid sequence of the humanized antibody G1, Appx260-261(SEQ ID Nos. 1-12). Additional antibodies, the specification explains, can be made and then humanized using routine and predictable methods, such as described in Queen. Appx238-239(28:55-29:28); *see also* Appx16526-16672 (Queen).

As relevant to the asserted method of treatment claims, the specification teaches that anti-CGRP antagonist antibodies can treat headache, including migraine. It recounts that, in testing with rats, antibody G1 and several murine antibodies blocked the effects of CGRP in the "closed cranial window assay," Appx258-259(68:59-69:67), an assay that was "understood to be predictive of efficacy for treating migraine in humans," Appx4509 n.10. It also discloses that multiple anti-CGRP antagonist antibodies, including G1, were effective in the "rat saphenous nerve assay," another test the inventors determined to be predictive of migraine treatment efficacy. Appx252(55:27-57:12); Appx258(67:54-68:57); Appx4160-4162. It goes on to explain that "[t]hose skilled in the art will be able to determine appropriate dosage amounts for particular agents to be used in combination with an anti-CGRP antibody." Appx234(20:41-42). Dr. Hill confirmed that the specification, in conjunction with FDA guidelines, would allow a POSA to routinely arrive at an effective dose of an anti-CGRP antagonist antibody.

Appx4162-4166.

Teva purchased the rights to the patents-in-suit in 2014. Appx2139-2140. It began marketing its own anti-CGRP headache medicine, Ajovy, in September 2018. Appx1727. Ajovy is indicated for the preventive treatment of migraine. Appx16447. The active ingredient in Ajovy is fremanezumab or "fmab," which is the same as the humanized antibody G1 disclosed in the patent specifications. Appx16.

II. Lilly challenges Teva's patents at the PTAB, which upholds the method of treatment patents but not the patents to the antibodies themselves.

Lilly, which brought its own anti-CGRP headache medicine "Emgality" to market in October 2018, petitioned the PTAB to review Teva's antibody and method of treatment patents. The Board concluded that Teva's antibody genus claims were obvious, but its method of treatment claims were not.

Importantly, in its successful challenge to the antibody genus claims, Lilly repeatedly asserted that a POSA would have been very familiar with both anti-CGRP antagonist antibodies and humanization. According to Lilly and its expert witnesses, by 2006 the prior art was "replete with exemplary disclosures of anti-CGRP antagonist antibodies, including humanized antibodies, to treat human diseases and conditions." Appx21513. "[A]nti-CGRP antagonist antibodies were" therefore "well known in the art," Appx21417, having been described by "several publications," Appx21417; Appx18846, and were "commercially available,"

Appx22627. Lilly represented that "the prior art already reported several monoclonal antibodies that bind to human αCGRP." Appx21702; *see also* Appx21443 (similar). It asserted that "techniques for making" anti-CGRP antagonist antibodies "were extensively described in the prior art," Appx21442, and that "well known, standard immunization processes, such as those described in Tan, Wong, or Andrew, would have provided more than adequate guidance to a POSA on how to prepare murine anti-CGRP antagonist antibodies," Appx21696. Lilly also told the Board that "humanization was a well-established and routine procedure by 2005." Appx21407.

Accepting Lilly's arguments, the PTAB found that "anti-CGRP antagonist antibodies were well known in the art, and that the art encouraged the development of humanized anti-CGRP antibodies." Appx18535. And it found "that a [POSA] would have been able to create antibodies that bound both isoforms of human CGRP, as was performed by [the] Tan and Andrew [references]." Appx18819. It therefore held that Teva's patents to the genus of humanized anti-CGRP antagonist antibodies were invalid as obvious. Appx18778; Appx18949. This Court affirmed, noting the PTAB's finding—and the patents' specification's "conce[ssion] that 'anti-CGRP antagonist antibodies were well known in the art.'" *Teva*, 8 F.4th 1349, 1355-56; *see also Teva*, 856 F. App'x 312, 313.

With respect to the method of treatment claims, however, the PTAB rejected

Lilly's challenge. It held that a POSA would not have expected antibodies to treat headache due to the blood-brain barrier. Appx19259-19265. This Court affirmed that decision, noting that "the blood brain barrier raised uncertainty, unpredictability, and skepticism in using full-length anti-CGRP antibodies to reduce incidence of or treat headache such as migraine." *Eli Lilly*, 8 F.4th at 1338.

III. A jury finds that the method of treatment claims are valid under § 112, but the district court grants JMOL of invalidity to Lilly.

A. Teva sues Lilly for patent infringement, and Lilly counterclaims alleging that the patents are invalid under § 112.

Lilly's Emgality is marketed for the preventative treatment of migraine and cluster headache. Appx1611. Its active ingredient is the anti-CGRP antagonist antibody galcanezumab, or gmab. Appx17. While the district court decision emphasized certain differences between Lilly's gmab and antibody G1 disclosed in Teva's patents (and between the antibodies' respective commercial embodiments), the evidence showed that the two performed similarly in *in vivo* tests. *Compare* Appx35-36, *with* Appx2828-2830; Appx4242-4246.

Teva sued Lilly, alleging that using Emgality to treat headache directly infringes the asserted method of treatment claims and that Lilly willfully induces and contributes to that infringement. Lilly counterclaimed, asserting that Teva's method of treatment claims are invalid under § 112 for lack of written description and enablement. Lilly had the burden of proving invalidity by clear and convincing

evidence. *Ajinomoto Co. v. Int'l Trade Comm'n*, 932 F.3d 1342, 1352 (Fed. Cir. 2019).

B. The district court denies Lilly's summary judgment motion, specifically disparaging Lilly's antibody expert's key opinion

Following discovery, Lilly moved for summary judgment on its § 112 theories, which the district court denied. Appx4501-4553. As relevant to this appeal, in denying Lilly's motion the court disparaged one of the key opinions of Lilly's antibody expert, Dr. McDonnell, as essentially frivolous. Dr. McDonnell opined that, based on purely random substitution of amino acids in the antibody's variable chain, the number of antibody candidates that would need to be generated and tested to discover all the antibodies that work in the claimed methods of treatment is "enormous": "more than the number of stars in our galaxy…, atoms in the earth…, or hydrogen atoms in the universe." Appx4551. The district court rejected that opinion as "not credible or persuasive," because a POSA would not "engage in such a dramatic and disorganized substitution [of amino acids] in search of an antibody that binds to and antagonizes CGRP." Appx4551-4552.

C. The jury finds that the asserted claims are valid and Lilly is willfully infringing them.

At trial, Lilly stipulated that using Emgality to treat headache directly infringes the asserted claims, but disputed that it indirectly infringed or that its infringement was willful. Appx1207. The jury found for Teva on all the

infringement issues. Appx4555-4557. Lilly did not challenge those findings in its post-trial motions. The jury also found that Lilly had failed to prove that the asserted claims are invalid for lack of written description and enablement. Appx4558-4559. It awarded Teva $36.74 million in reasonable royalty damages, $90 million in lost profits, and $49.8 million in future lost profits. Appx4560-4562.

D. The district court enters JMOL for Lilly.

Lilly moved for JMOL and the district court granted Lilly's motion in part, holding that the jury should have found the asserted claims invalid for lack of both written description and enablement.

1. The district court acknowledges that the jury reasonably could have made numerous findings in favor of Teva

Importantly, even as it granted JMOL to Lilly, the district court agreed that a reasonable jury could have made numerous factual findings that, on a proper application of the law, should have been fatal to Lilly's § 112 theories.

First, the court acknowledged that numerous murine anti-CGRP antagonist antibodies already were known in the art, including "anti-CGRP antagonist antibodies that could bind to different epitopes of CGRP." Appx28. The court further acknowledged that the number of murine anti-CGRP antagonist antibodies that "could be humanized and treat headache" is "*not necessarily very large* or small." Appx27 (emphasis added).

Second, the court acknowledged that the patents' specification teaches a

POSA that "*all* humanized anti-CGRP antagonist antibodies would treat headache," no matter the epitope to which they bind. Appx28 (emphasis added); Appx33 ("a POSA would know that anti-CGRP antagonist antibodies could bind to different regions of CGRP and still accomplish the claimed function of treating headache"); Appx42 n.23 ("a POSA could have believed the anti-CGRP antagonist antibodies would treat headache based on knowledge about anti-CGRP antagonist antibodies that were known as of November 2006, in addition to the data from the animal test in the Zeller specification") (cleaned up).

And third, the court repeatedly acknowledged that humanizing murine antibodies for use in the claimed method would have been "routine" for a POSA—there was nothing inventive about humanization. *E.g.*, Appx11 ("a POSA would have known that humanization of the antibodies was routine"); Appx33 ("the disclosed murine anti-CGRP antagonist antibodies could be routinely humanized and a POSA would know they could treat headache"); Appx41 n.22 (same).

2. The district court rules that Lilly proved lack of written description as a matter of law.

In finding lack of written description, the district court considered whether the specification discloses either (1) a "representative number of species" of antibodies for use in the claimed method or (2) common structural features of such antibodies. Appx21. The court quickly held that no common structural features are disclosed, Appx43-44, and mainly focused on the representative number of species issue.

On that issue, the court treated humanized anti-CGRP antagonist antibodies as a novel genus of antibodies, of which antibody G1 was the only known species. Appx27 (in discussing the "Novelty of the Genus," stating "[t]he jury heard uncontroverted evidence that no humanized anti-CGRP antagonist antibodies were known in the prior art"); Appx40 ("Humanized anti-CGRP antagonistic antibodies were a new genus"); Appx42 ("a reasonable jury could only have found that … the Patents-in-Suit claimed a new genus of antibodies for a functional purpose"). The court refused to consider the many murine anti-CGRP antagonist antibodies already known to a POSA, even though humanizing them would have been routine and a POSA would know that they all would treat headache, because they had not *actually* been humanized: "The murine antibodies that Teva points to also could not fall within the scope of the Asserted Claims because they were not humanized." Appx28; *see also* Appx35 n.18 (similar).

As against antibody G1, the court emphasized that the genus of antibodies for use in the claimed method is potentially "very, very large," pointing to Dr. McDonnell's thought experiment involving random substitution of amino acids. Appx26-27. The court also found that there were "relevant differences" between G1 and Lilly's gmab such that G1 was not "representative" of the genus. Appx35-38. The court therefore concluded that "clear and convincing evidence supports a finding that the disclosure of the single species G1 was insufficient to claim the

entire genus of humanized anti-CGRP antagonist antibodies for the treatment of headache." Appx36.

3. The district court rules that Lilly proved lack of enablement as a matter of law.

Turning to enablement, the district court held that no reasonable jury could have found that a POSA would be able to practice the claimed method without "undue experimentation." Appx44-53. On this issue too, the court treated the invention as a novel genus of antibodies, rather than a novel method of treatment using a known class of antibodies. *See, e.g.*, Appx49. The court again relied on Dr. McDonnell's testimony that there is a "large" number of candidate antibodies to test, and it again refused to consider the murine anti-CGRP antagonist antibodies already known in the art on the basis that they had not been humanized. Appx49. Ultimately, the court concluded that the specification provided "nothing more than a 'roadmap' for a 'trial and error' process to identify and make antibodies within the scope of the Asserted Claims." Appx50.

SUMMARY OF THE ARGUMENT

This Court should reverse, or at a minimum vacate, the district court's decision on § 112.

I. The district court erred in overturning the written description verdict.

A. The jury reasonably found that Lilly failed to prove lack of written description. Antibody G1 was representative of the class for purposes of the claimed

method of treatment, and further murine anti-CGRP antagonist antibodies were well-known in the art and humanizing them would have been routine. The inventive aspect of the claims—the use of the humanized antibodies to treat headache—was described in detail, and the district court did not find differently.

B. The district court committed critical legal errors in analyzing written description.

1. The court disregarded prior art murine antibodies because they had not actually been humanized. This holding is contrary to the black-letter rules that actual reduction to practice is not required and a specification need not repeat what a POSA knows. The error was case dispositive: the court's decision rested on its conclusion that the single disclosed humanized antibody was insufficient, but Lilly did not prove that G1 together with the prior art murine antibodies constituted an insufficient number of representative species.

2. The court failed to view the evidence in the light most favorable to the verdict. The court relied on testimony from Lilly's expert Dr. McDonnell on hotly contested issues, including with respect to the number of antibody candidates, despite finding the same testimony not credible at summary judgment and despite contradictory opinions from Teva's witnesses. The jury reasonably could have found Dr. McDonnell not credible and so rejected his opinions.

3. The court erred in holding that representative species of antibodies must

be structurally similar to the accused antibody. This Court's caselaw with respect to method claims employing a well-known class of compounds does not require that representative examples have structural features common to the accused compound.

4. The court erred in approaching this case as if it concerned claims to a novel class of antibodies. It does not. It involves methods of treatment using a well-known class of antibodies—a type of claim this court has not previously invalidated on written description grounds. Precedent in more analogous cases demonstrates that the written description here was sufficient.

II. The district court erred in overturning the enablement verdict.

A. The jury reasonably found that Lilly failed to prove lack of enablement. The specification and prior art were replete with exemplary disclosures of anti-CGRP antagonist antibodies; the patent provided a working example in antibody G1; creating, testing, and humanizing antibodies was routine; and a POSA would have been able to properly dose the antibodies to treat headache.

B. The court found lack of enablement only by committing critical legal errors.

1. The court again erred in refusing to consider the prior art murine antibodies because they were not humanized. Actual reduction to practice is not required for enablement. Undue experimentation would not be required to practice this invention because murine anti-CGRP antagonist antibodies already were well-known in the

art, the specification taught that the entire class would work to treat headache, and humanization was routine.

2. The court erroneously overruled the jury's credibility determinations. The court again relied on Dr. McDonnell's testimony that the universe of antibodies that must be tested is large, but a jury reasonably could have discredited that testimony. This error was case dispositive; without credible evidence regarding the number of antibody candidates or the size of the genus, the jury reasonably could find that Lilly had not carried its burden of proving undue experimentation. Lilly's failure of proof distinguishes this case from recent enablement decisions involving antibodies.

3. The court again erred by treating this case as if it involves claims to a novel class of antibodies. Where the claim is to a method of treatment using a well-known class of antibodies, the enablement inquiry properly focuses not on the antibodies but on the method. The cases on which the district court relied for its enablement analysis do not involve claims to methods of treatment using well-known genuses.

III. The district court's decision fails to advance the purposes of § 112 while robbing innovative methods of treatment of effective patent protection. The asserted claims claim no more than what the inventors discovered: that all humanized anti-CGRP antagonist antibodies will treat headache. These claims do not cover such antibodies for all purposes, nor did they cover everything that works to treat headache. Limiting method of treatment claims to species or sub-genus claims for

the specific antibodies an applicant generates with particular mice may make it impossible to prevent easy design-arounds.

STANDARD OF REVIEW

This Court reviews the district court's JMOL decision de novo. *Uniloc USA, Inc. v. Microsoft Corp.*, 632 F.3d 1292, 1301 (Fed. Cir. 2011). In the First Circuit, JMOL is warranted only where "the evidence points so strongly and overwhelmingly in favor of the moving party that no reasonable jury could have returned a verdict adverse to that party." *Id.* (quoting *Keisling v. SER-Jobs for Progress, Inc.*, 19 F.3d 755, 759-60 (1st Cir. 1994)).

In considering a JMOL motion, the district court "may not evaluate 'the credibility of witnesses, resolve conflicts in testimony, or evaluate the weight of the evidence,' but must view the evidence in the light most favorable to" the non-moving party—here, Teva. *Id.* (quoting *Gibson v. City of Cranston*, 37 F.3d 731, 735 (1st Cir. 1994)). Thus, all credibility issues and inferences must be resolved "in favor of the jury verdict." *Bezanson v. Fleet Bank-NH*, 29 F.3d 16, 22 (1st Cir. 1994); *accord Rodriguez-Quinones v. Jimenez & Ruiz, S.E.*, 402 F.3d 251, 254 (1st Cir. 2005) (similar).

The First Circuit is "especially reluctant" to support JMOL "in favor of a party with the burden of persuasion," which Lilly bore here. *Aggarwal v. Ponce Sch. of Med.*, 837 F.2d 17, 19 (1st Cir. 1988) (quoting *Insurance Co. of N.A. v. Musa*, 785

F.2d 370, 372 (1st Cir. 1986)).

ARGUMENT

I. The district court committed legal error by overturning the jury's written description verdict for Teva.

The Court should reverse, or at a minimum vacate, the district court's written description decision. The district court found lack of written description only by committing several critical errors: (1) requiring actual reduction to practice of representative species; (2) overriding the jury's credibility determinations; and (3) treating claims to a novel method of treatment using a *known* class of antibodies as if they were claims to a *novel* class of antibodies.

A. The jury reasonably found that Lilly failed to prove lack of written description.

1. Written description is an invention-specific factual inquiry requiring consideration of a POSA's background knowledge.

"[T]he critical inquiry" under the written description requirement "is whether the relevant artisan reading the specification would understand that the inventor was in possession of the claimed invention at the time of the filing." *BASF Plant Science, LP v. CSIRO*, 28 F.4th 1247, 1264 (Fed. Cir. 2022) (quotations and alteration omitted). "[T]he amount of disclosure necessary to satisfy the written-description requirement will necessarily vary depending on the context, considering such facts as the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, and the predictability of the aspect at

issue." *Ajinomoto*, 932 F.3d at 1359 (quotations omitted).

Importantly, "a patent need not teach, and preferably omits, what is well known in the art." *McRo, Inc. v. Bandai Namco Games Am. Inc.*, 959 F.3d 1091, 1102 (Fed. Cir. 2020) (quotations omitted); *see also Immunex Corp. v. Sandoz Inc.*, 964 F.3d 1049, 1064 (Fed. Cir. 2020) ("It is well-established that a patent specification need not re-describe known prior art concepts."). As the Court has observed, "the forced recitation of known sequences in patent disclosures would only add unnecessary bulk to the specification." *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1368 (Fed. Cir. 2006). Therefore, "a patentee may rely on information that is well-known in the art for purposes of meeting the written description requirement." *Ajinomoto*, 932 F.3d at 1359 (quotations omitted).

2. There was ample evidence supporting the jury's written description verdict.

The jury considered the asserted claims in light of the specification and a POSA's background knowledge of anti-CGRP antagonist antibodies and humanization and reasonably found that Lilly had failed to meet its burden of proving, by clear and convincing evidence, that the inventors lacked possession of the claimed method. The jury reasonably could have decided that the applicants did not need to include numerous examples of humanized anti-CGRP antagonist antibodies in the specification because antibody G1 was representative of the already well-known class of antibodies for use in the claimed method. Moreover, both

murine anti-CGRP antagonist antibodies and humanization were already well-known to a POSA and are not themselves the invention. The invention is the novel method of treating headache, not the class of antibodies that antagonize CGRP, and the district court did not find that the *treatment* aspects of the claim were inadequately described.

To start, there was overwhelming evidence that murine anti-CGRP antagonist antibodies were already well known to a POSA. The specification expressly acknowledged that the class of antibodies was already known, citing scientific journal articles and a commercial source for an antibody. *Supra*, pp. 10-12. The jury learned that Lilly had argued to the PTAB that "anti-CGRP antagonist antibodies were well known in the art" and that the prior art was "replete with exemplary disclosures of anti-CGRP antagonist antibodies," and that the PTAB had agreed, finding that "anti-CGRP antagonist antibodies were well known in the art." *Supra*, pp. 12-14. The testimony at trial was no different, with expert and lay scientific witnesses testifying that anti-CGRP antagonist antibodies were known to a POSA and available for purchase. *Supra*, pp. 5-7. These included anti-CGRP antagonist antibodies that attached to all three epitopes of CGRP—the C-terminal, the mid-region, and N-terminal—and blocked CGRP's activity wherever they bound. *Supra*, p. 7. And if a POSA wanted to make their own anti-CGRP antagonist antibodies, it would have been easy for them to do so. *Supra*, pp. 6-9.

The district court's JMOL decision brushed aside the PTAB's finding, made at Lilly's urging, that "anti-CGRP antagonist antibodies were well known in the art," because it was made in the context of Teva's antibody claims rather than the method of treatment claims: "as Teva concedes, the IPRs discussed in the record and in its brief did not relate to a method of treatment, but instead covered the underlying antibodies themselves." Appx28 n.13 (cleaned up). That point of distinction makes no sense whatsoever: The class of antibodies at issue in the IPRs was *identical* to the class of antibodies at issue in this case. And the district court found lack of written description because it thought the *class of antibodies* was inadequately disclosed, not the process for humanizing those antibodies or their use in treating headache. Appx42; Appx44. Lilly's admissions and the Board's findings concerning a POSA's background knowledge of anti-CGRP antagonist antibodies therefore go straight to the heart of the case and a reasonable jury could have given them great weight.

Because the underlying class of murine antibodies was well known, there was no need for the specification to teach it—after all, a specification "preferably omits" what is already known. *McRo*, 959 F.3d at 1102. And there was evidence from which the jury reasonably could have found that a representative number of such antibodies already were known, including not only antibody G1 disclosed in the specification, but also Lilly's statement to the PTAB that the prior art was "replete

with *exemplary disclosures* of anti-CGRP antagonist antibodies[.]" Appx21436 (emphasis added). The district court expressly acknowledged that "anti-CGRP antagonist antibodies that could bind to different epitopes of CGRP" were already known in the art and that a POSA would understand that they all would work in the claimed method of treatment. *Supra*, pp. 16-17.

There also was an avalanche of evidence that humanizing the known class of murine antibodies would not have been inventive, but was instead entirely routine for a POSA—as the district court agreed: "a jury could have concluded that a POSA would have known that humanization of the antibodies was routine." Appx11. The evidence was that the results of humanization would be predictable—humanization would not fail. Appx4221-4228. One expert witness testified that prior art humanization techniques could be performed commercially with a "money-back guarantee." Appx4227. Therefore humanization, too, did not need to be fully described in the specification. Nonetheless, the specification described humanization techniques and cited the prior art, such as the Queen reference. Appx238(28:55-64). The district court did not find lack of written description for humanization.

Because the class of antibodies was already well known and humanization was routine, the inventive aspect of the claims-in-suit—the proper focus of the written description issue—was the novel method of treating headache. This method

of treatment was inventive in light of doubts that using antibodies to treat headache would work given the blood-brain barrier. *Supra*, p. 7. The specification describes in detail the evidence that the method of treatment works, using antibody G1 as an example—the district court did not find any differently. And once the inventors discovered that treating headache with antibody G1 would work, the evidence showed that a POSA would understand that *all* anti-CGRP antagonist antibodies will treat headache. Appx4174; Appx4272. Again, the district court expressly acknowledged this. *Supra*, pp. 16-17.

B. The district court committed legal error by disregarding the known murine antibodies because they had not actually been humanized.

The district court's decision largely turned on its view that the murine anti-CGRP antagonist antibodies known in the art did not count because they had not actually been humanized. The district court's written description analysis thus treated antibody G1 as the *only* species for determining whether a "representative number" of species were disclosed. *Supra*, pp. 17-19.

The district court's disregard of the known murine antibodies because they had not been humanized was legal error. The background legal principle is incontrovertible. The "critical inquiry" for written description "is whether the relevant artisan reading the specification would understand that the inventor was in possession of the claimed invention at the time of filing." *BASF Plant Science*, 28

F.4th at 1264 (quotations and alterations omitted). In conducting this inquiry, "the written description requirement does not demand either examples or an actual reduction to practice; a constructive reduction to practice may be sufficient if it identifies the claimed invention and does so in a definite way." *Centrak, Inc. v. Sonitor Techs., Inc.*, 915 F.3d 1360, 1367 (Fed. Cir. 2019) (quotations omitted). The Court has "repeatedly stated" in its written description precedents "that the invention does not actually have to be reduced to practice." *Nuvo Pharms. (Ir.) Designated Activity Co. v. Dr. Reddy's Lab'ys Inc.*, 923 F.3d 1368, 1380 (Fed. Cir. 2019).

Moreover, as recited above, this Court's precedents are chockful of statements that a specification need not repeat what already is known to a POSA—"a patentee may rely on information that is well-known in the art for purposes of meeting the written description requirement." *Supra*, p. 25 (quoting *Ajinomoto*, 932 F.3d at 1359 (quotations omitted)). This principle works hand-in-glove with the principle that an actual reduction to practice is not required; a constructive reduction to practice can take account of what already is known to a POSA. For example, in *Streck, Inc. v. Research & Diagnostic Systems, Inc.*, an alleged infringer argued that a claim covering the use of "true reticulocytes" in a hematology control technology lacked written description because the specification only disclosed actual reductions to practice using "reticulocyte analogs." 665 F.3d 1269, 1285-86 (Fed. Cir. 2012). This Court affirmed summary judgment for the patentee, explaining "[g]iven the

language in the patents-in-suit" that true reticulocytes could be used, "coupled with the well-known use of true reticulocytes in the prior art, a person of ordinary skill would understand the patent to include integrated controls using true reticulocytes." *Id*. at 1287.

Here, of course, the Zeller team *did* actually reduce one antibody that could be used in the claimed method to practice—they created murine antibody 7E9 and humanized it, resulting in antibody G1. But they also constructively reduced to practice the entire class of anti-CGRP antagonist antibodies. That class was already well-known and extensively described; at least one such antibody was available commercially (indeed, Lilly researchers purchased it, Appx2817); and generating more members of the class was easy. *Supra*, pp. 6-9. A POSA would have understood that "the disclosed anti-CGRP antagonist antibodies could be routinely humanized," as the district court acknowledged. *Supra*, p. 17. A POSA would have further understood from the test data disclosed in the specification for antibody G1 that "all humanized anti-CGRP antagonist antibodies would treat headache," Appx28, and "that anti-CGRP antagonist antibodies could bind to different regions of CGRP and still accomplish the claimed function of treating headache," Appx33; *see also* Appx41 n.22. That is a reduction to practice of the entire class for the invention: a method of treating headache with a humanized anti-CGRP antagonist antibody.

Consequently, the applicants did not need to *actually* reduce more murine antibodies to practice—to actually humanize them—or to disclose their humanized versions in the specification, in order to "possess" them for purposes of describing their invention. The district court's failure to grasp this point of law is exemplified by the following passage:

> The Court finds that the jury could not have found that the inventors were in possession of anti-CGRP antagonist antibodies that could bind to all three regions of CGRP. The jury could have credited testimony, however, that a POSA would know that anti-CGRP antagonist antibodies could bind to different regions of CGRP and still accomplish the claimed function of treating headache.

Appx33; *see also* Appx42 ("the inventors … at the very least did not possess species that bound to all three epitopes of CGRP"). As a matter of law, the second sentence contradicts the first. If a POSA would have known that anti-CGRP antagonist antibodies binding to different regions of CGRP will all work in the invention, then the applicants *did* constructively possess those antibodies for purposes of the invention.[2]

Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559 (Fed.

[2] To the extent relevant, there was evidence from which a reasonable jury could have concluded that the Zeller team did not actually reduce antibodies binding to all three epitopes to practice *not* because they were incapable of it, but for commercial reasons. Dr. Zeller testified that by the time of filing, he had generated mid-region and N-terminal anti-CGRP antibodies. Appx1442. The team focused on bringing G1 into the clinic rather than developing other antibodies because it was their best clinical candidate. Appx1473-1474; Appx1486-1487.

Cir. 1997), on which the district court relied (at Appx29-30), is readily distinguishable. In that case, the Court held that disclosures of rat cDNA and human protein were not sufficient to disclose the claimed human cDNA. 119 F.3d at 1567. But the evidence was that getting from either rat cDNA or human protein to human cDNA was not even obvious at that time, much less routine. *Id.* By contrast, the district court acknowledged that getting from a murine anti-CGRP antagonist antibody to a humanized antibody by transplanting the murine antibody's CDRs to a human scaffold would have been merely routine by the Zeller filing date. *Supra*, p. 17.

The district court's disregard of the prior art murine antibodies was case dispositive. The court's ultimate written description opinion was that "clear and convincing evidence supports a finding that the disclosure of the single species G1 was insufficient to claim the entire genus of humanized anti-CGRP antagonist antibodies for the treatment of headache." Appx36. But there was ample evidence—not least Lilly's admissions to the PTAB—from which the jury could have found that, if G1 alone were not enough, then the prior art's further disclosure of murine antibodies amounted to a representative number of species. *Supra*, pp. 6-7, 12-14. Indeed, Lilly had the burden of proof, yet it did not, *e.g.*, compare the commercially-available murine anti-CGRP antagonist antibody 4901 to Lilly's own gmab, nor did its expert Dr. McDonnell mention that antibody in his discussion of the prior art.

See generally Appx3132-3134; Appx62522. The jury therefore reasonably could have found that Lilly did not meet its burden of proof, and the district court should not have disturbed the verdict.

C. The district court failed to view the evidence in the light most favorable to Teva in evaluating representative species.

In considering a JMOL motion in the First Circuit, "it is assumed that issues of credibility are resolved, and inferences from evidence drawn, in favor of the non-moving party." *Combustion Eng'g, Inc. v. Miller Hydro Grp.*, 13 F.3d 437, 441 (1st Cir. 1993); *Bezanson*, 29 F.3d at 22. The district court did the opposite here; its JMOL order relied on the testimony of Lilly's antibody expert Dr. McDonnell on several issues, even where Teva's experts and scientific witnesses offered contrary opinions. Without Dr. McDonnell's testimony, Lilly did not come close to meeting its burden of proving lack of written description by clear and convincing evidence.

The most egregious example of the district court's reliance on Dr. McDonnell pertains to the representative species issue. The court's holding was premised on its conclusion that the jury needed to find that a "very, very large" and "mind-bogglingly" large number of antibody candidates must be generated and tested to see if they are anti-CGRP antagonist antibodies. Appx 18; Appx23 n.12; Appx24; Appx26-27. And that conclusion was based on Dr. McDonnell's testimony concerning his random-substitution "thought experiment." *See* Appx18 (citing

Appx3142-3145).[3]

This was error. As recounted above, at summary judgment, the district court itself had disparaged Dr. McDonnell's "thought experiment" as "not credible or persuasive." *Supra*, p. 15. Having itself previously concluded that Dr. McDonnell's reasoning was "not credible," the court could not reasonably decide for purposes of JMOL that the jury *needed* to credit it, *especially* under the clear and convincing evidence standard. The court never acknowledged its flip-flop with respect to Dr. McDonnell's testimony, and never tried to explain it.

The district court's reliance on Dr. McDonnell's "thought experiment" testimony was especially improper because there was credible testimony from Teva's lay and expert scientific witnesses that immunizing mice with CGRP results in the *selective* generation of anti-CGRP antibodies, not the *random* generation of junk amino acid sequences and antibodies responsive to other substances:

> [W]hen you use a mouse to generate the antibodies by immunizing it with the target or a form of the target, the mouse launches an immune response, and therefore, any antibodies that you generate have already been screened through its own biochemistry and its own biophysics. So

[3] Elsewhere, the court pointed to testimony from one of Teva's witnesses concerning the processing speed of assay equipment for the proposition that a "very large" number of antibodies would need to be screened for antagonism. Appx27 (citing Appx4215-4216). That testimony concerning the *equipment* was not clear and convincing evidence of how many different antibodies will be generated through murine immunization with CGRP or the relative proportion of anti-CGRP antagonists, much less that the numbers are "very large."

> the antibodies they produce are generally kind of pretty good binders because the mouse has already done the equivalent of the pannings and the selections in vivo.

Appx1523-1524; *see also* Appx1524 ("Q. If you immunize a mouse with CGRP, are you going to get those cancer antibodies? A. Absolutely not."). While Dr. McDonnell hyperbolically asserted that finding anti-CGRP antagonist antibodies is like looking for a needle in a "galaxy-sized haystack," Appx3200, Dr. Hale credibly responded that "the anti-CGRP antagonist antibodies, … once you've boosted the mouse and boosted the mouse, there's going to be lots of those antibodies, so it's like having lots of needles in the haystack." Appx4240. The jury was permitted to credit Teva's witnesses over Dr. McDonnell, and the district court erred in "substitut[ing] its judgment for that of the fact finder." *Union Oil Co. of California v. Atl. Richfield Co.*, 208 F.3d 989, 997 (Fed. Cir. 2000).

More generally, the district court's reliance on Dr. McDonnell's testimony for numerous propositions, including on other highly-contested issues such as a functional comparison between Emgality and Ajovy,[4] was improper because the jury reasonably could have concluded that Dr. McDonnell was just not a credible witness *at all*. "Even uncontradicted opinion testimony is not conclusive if it is intrinsically

[4] *Compare* Appx36-37 (citing McDonnell at Appx3170 for supposed differences in potency), *with* Appx3303. Teva's expert Dr. Blumenfeld testified that Emgality's cluster headache approval benefited from a fortuitous study design and still only "just made it" to statistical significance. Appx4021. The jury also heard that Emgality was not approved to treat cluster headache in Europe. Appx3011-3012.

nonpersuasive." *Sternberger v. United States*, 401 F.2d 1012, 1016 (Ct. Cl. 1968). "Exaggeration, inherent improbability, self-contradiction, omissions in a purportedly complete account, imprecision and errors may all breed disbelief and therefore the disregard of even uncontradicted nonopinion testimony." *Id.*

Dr. McDonnell's frivolous "thought experiment" is just one example of testimony that may have caused the jury to discredit him. As another example, after testifying on direct that humanization was not routine, Dr. McDonnell repeatedly professed that he did not know the Queen reference. Appx3290; Appx3295; Appx3296-3297; Appx3300-3301. Yet a mountain of evidence showed a POSA would be intimately familiar with Queen, a landmark reference that Lilly itself had called the "gold standard" for humanization in the IPRs. *E.g.*, Appx4221-4225 (Hale); Appx21785; Appx21524. Indeed, Queen's teachings are cited by both the patents-in-suit and Lilly's own patent covering Emgality. Appx49611(7:61-65); Appx238(28:55-64). Similarly, after telling the jury that antibodies binding to CGRP's mid-region were unknown in the prior art, Dr. McDonnell was forced to concede that a prior art reference with which he was previously unfamiliar claimed to disclose such an antibody. *Compare* Appx3138, *with* Appx3319-3324; *see also* Appx4216-4217 (Teva's expert Dr. Hale discussing the same reference). The jury reasonably could have decided that Dr. McDonnell's ignorance of important prior art contradicting his opinions showed a lack of expertise, candor, and/or seriousness.

As yet another example, Dr. McDonnell was not Lilly's expert in its successful challenge to Teva's patents at the PTAB; Lilly used a different expert, Dr. Vasserot. *See* Appx21649. Dr. McDonnell apparently never familiarized himself with the positions Lilly had taken at the PTAB. Appx3286. He then offered opinions at trial that were contrary to Lilly's positions in the IPR on pivotal issues, such as whether anti-CGRP antagonist antibodies were "well known" in the prior art and whether humanizing those antibodies would have been "routine." *E.g.*, Appx62522 (demonstrative disparaging prior art disclosures of murine antibodies); Appx3214-3215 (disagreeing that humanization is "routine").

Lilly bore the burden of proof by clear and convincing evidence. Yet it chose to present an antibody expert—a different expert than it had used in the IPR—whose key opinion was based on a frivolous "thought experiment," who was unfamiliar with the "gold standard" teaching in the field of humanization (Queen), and who offered opinions on important issues that were contrary to those Lilly had successfully advanced before the PTAB. A reasonable jury easily could have decided to discredit him. The district court therefore should not have relied on his testimony in granting JMOL to Lilly, particularly on contested issues.

D. Representative species need not be structurally similar to the accused antibody.

In considering the representative species question, the district court relied on *AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.*, 759 F.3d 1285 (Fed.

Cir. 2014), for the proposition that at least one representative species of antibodies must be structurally similar to the accused antibody, and held that antibody G1 is not a representative species because it is structurally different from Lilly's gmab. *See* Appx37-38.

Since *AbbVie* issued in 2014, however, this Court consistently has described the written description standard for genus claims in *disjunctive* terms: "[a] sufficient description of a genus … requires the disclosure of either a representative number of species falling with the scope of the genus *or* structural features common to the members of the genus." *Ajinomoto*, 932 F.3d at 1358 (quotations omitted, emphasis added); *see also Juno Therapeutics, Inc. v. Kite Pharma, Inc.*, 10 F.4th 1330, 1335 (Fed. Cir. 2021) (same); *Idenix Pharms. LLC v. Gilead Sciences Inc.*, 941 F.3d 1149, 1164 (Fed. Cir. 2019) (same); *Amgen Inc. v. Sanofi*, 872 F.3d 1367, 1373 (Fed. Cir. 2017) (same). The Court has repeated *AbbVie's* statement that there must be a representative example that is structurally similar to the accused antibody only once, and then to distinguish the case. *See Ajinomoto*, 932 F.3d at 1360.

Indeed, in the context of method of treatment claims employing a well-known class of compounds, this Court has *not* previously treated structural similarity as the sole determining factor for representativeness. In *Ajinomoto*, the Court considered a claim to a method of modifying bacterium by "replacing the native promoter … with a more potent promoter," and rejected a written description challenge centered

on the "more potent promoter" genus limitation. 932 F.3d at 1347. In addressing the representative species issue, the Court did not discuss whether the examples in the patent and prior art were structurally similar to the "more potent promoter" of the accused product (although the Court *separately* upheld a finding of structural similarity). *Id.* at 1359-60. Instead, the Court emphasized a finding that "enhancing promoter activity was well-known and that a skilled artisan would have been able to identify more potent promoters by employing common tools for measuring RNA transcription." *Id.* at 1359 (quotations omitted). Because "the genus of more potent promoters was already well explored in the relevant art by the time of the … invention," and the invention was not the genus of more potent promoters itself but rather the use of that genus in creating modified bacterium, the Court affirmed a determination that representative species existed. *Id*.

Here too, whatever the degree of structural similarity between G1 and gmab, a reasonable jury could have concluded that the specification and prior art disclosed a representative number of species of anti-CGRP antagonist antibodies for use in the claimed method of treatment. As in *Ajinomoto*, the invention was not the well-known class of antibodies itself, but rather the class's use in another invention: treating headache. In addition to antibody G1, the prior art was "replete with exemplary disclosures" of the class, which were "well known in the art." *Supra*, pp. 6-7, 12-14. A POSA would have understood that *all* such antibodies, whatever their

different structures, will work in the claimed method of treatment. *Supra*, pp. 16-17. This is true no matter the epitope to which the antibody binds, and the prior art disclosed at least one anti-CGRP antagonist antibody binding to the same epitope as gmab (a fact of which Dr. McDonnell was unaware when offering his representativeness opinion). *Supra*, pp. 7, 37. Whatever their differences, antibody G1 and gmab performed similarly in *in vivo* testing (another fact of which Dr. McDonnell was unaware). *Supra*, p. 14; Appx3303. There also was evidence that Ajovy and Emgality have similar clinical outcomes. Appx1829-1835. Lilly presented no evidence that the same would not be true with respect to the prior art murine antibodies (such as the commercially-available antibody its researchers had purchased), or any of them. On these facts, a jury reasonably could have found that Lilly failed to prove a lack of sufficient representative examples.

E. Precedents concerning novel classes of antibodies or methods of using novel small-molecule drugs are not controlling with respect to novel methods of treatment using known classes of antibodies.

At bottom, the district court erred by approaching this case involving a novel method of treatment using an already well-known class of antibodies, all of which work in the claimed method of treating headache, as if it concerned claims to a novel class of antibodies, or a well-known class of antibodies where it is uncertain which species will work in the claimed method.

Most of this court's written description cases concerning antibodies involve

claims to novel antibodies, or methods employing a novel class of antibodies or where it is uncertain which antibodies will work. *See Juno*, 10 F.4th 1330; *Amgen*, 872 F.3d 1367; *AbbVie*, 759 F.3d 1285. The court has never specifically addressed antibody claims like those here: claims to a novel method of using an existing, well-known class of antibodies, where what is inventive are not the antibodies themselves, but the discovery that the entire class of antibodies can be used in the novel method. This Court has therefore never deemed a method of treatment claim using an already well-known class of antibodies invalid on written description grounds due to an allegedly inadequate disclosure of the underlying antibodies.

The Court has issued two § 112 decisions involving methods of treatment using antibodies, and neither is on point. *In re Alonso*, on which the district court relied, *see* Appx40, involved human-human hybridomas developed from cancer cells where, because "heterogeneity of tumors both between patients and metastatic sites within a single patient is to be expected" and the target antigens "vary substantially," the disclosure of one antibody for one patient provided inadequate written description for a claim to treat all patients. 545 F.3d 1015, 1019-20 (Fed. Cir. 2008) (internal quotation omitted). *Alonso* explained that "a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated." *Id*. at 1020

(quotations omitted). But on the facts of this case, the jury reasonably could have found that such "unpredictability" does not exist—the district court acknowledged that a POSA would know that humanization was routine and that *all* humanized anti-CGRP antagonist antibodies will work in the invention. *Supra*, pp. 16-17. The other case, *Tobinick v. Olmarker*, considered whether a specification adequately disclosed a claimed method of administration, and this Court held that it did. 753 F.3d 1220, 1225-27 (Fed. Cir. 2014). That case has no bearing here.

Outside the antibody context, precedents from this Court and its predecessor demonstrate that method claims employing an already well-known genus should not be treated the same as claims involving a novel genus. *Ajinomoto* was already discussed above. *Supra*, pp. 39-40. As another example, in *In re Herschler*, this Court's predecessor rejected an argument that disclosure of a single species of steroids inadequately described the class of "steroidal agents" usable in a claimed method. 591 F.2d 693, 701 (C.C.P.A. 1979). The court explained that "claims drawn to the Use of Known chemical compounds in a manner auxiliary to the invention must have a corresponding written description *only so specific* as to lead one having ordinary skill in the art to that class of compounds." *Id.* at 702 (emphasis added); *see also Erfindergemeinschaft UroPep GbR v. Eli Lilly & Co*., 276 F. Supp. 3d 629, 648 (E.D. Tex. 2017) (Bryson, J.), *aff'd*, 739 F. App'x 643 (Fed. Cir. 2018) ("[W]hen a genus is well understood in the art and not itself the invention but is

instead a component of the claim, background knowledge may provide the necessary support for the claim."). The court emphasized that all steroidal agents, whatever their other differences, would work in the claimed method: "steroids, when considered as a class of compounds carried through a layer of skin by DMSO, appear on this record to be chemically quite similar." 591 F.2d at 701. The court distinguished the claims before it from claims to "New compounds per se or claims drawn to processes Using those New compounds," and cautioned that "[w]ere this application drawn to novel 'steroidal agents,' a different question would be posed." *Id.* at 701-02.

Similarly, in *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313 (Fed. Cir. 2003) ("*Hoechst*"), this Court considered claims to a method of using vertebrate or mammalian host cells to produce recombinant erythropoietin (a hormone). The Court held that the specification need not identify specific representative species or common structural characteristics of the genus of vertebrate and mammalian cells, "because the claim terms at issue here ["vertebrate cells" and "mammalian cells"] are not new or unknown biological materials that ordinarily skilled artisans would easily miscomprehend." *Id*. at 1332.

The decisions in *Ajinomoto*, *Herschler*, and *Hoechst* should control here. Here too, what is claimed is not a novel genus or a method of using a novel genus, but a novel method of using a well-known genus. As in *Ajinomoto*, the "already

well explored" genus was not the invention itself; instead that genus was merely being employed in the claimed method. 932 F.3d at 1359. Whatever differences may exist among anti-CGRP antagonist antibodies, "when considered as a class of compounds" for use in the claimed method, *Herschler*, 591 F.2d at 701, anti-CGRP antagonist antibodies function the same: "a POSA would know that anti-CGRP antagonist antibodies could bind to different regions of CGRP and still accomplish the claimed function of treating headache." Appx33. Moreover, as in *Hoechst*, anti-CGRP antagonist antibodies are not "new or unknown biological materials that ordinary skilled artisans would easily miscomprehend." 314 F.3d at 1332. Rather, there was ample evidence that, as Lilly argued to the PTAB, "anti-CGRP antagonist antibodies were well known in the art." *Supra*, pp. 12-14.

In contrast, the cases on which the district court relied look nothing like this one. In *Juno,* the narrowest claim at issue was to a composition comprising single-chain antibody variable fragments (scFvs) binding to a particular protein on lymphoma cells called CD19. *See* 10 F.4th at 1333-34. "An scFv is made by taking two pieces of an antibody, one from the heavy chain of an antibody's variable region and one from the light chain of an antibody's variable region, and linking them together with a linker sequence"; different scFvs will bind to different target antigens. *Id.* at 1333. The patentholder does not appear to have argued that the subclass of scFvs binding to CD-19 was well-known, only that scFVs *generally* were

well-known. *Id.* at 1336 ("Juno responds that scFvs were well-known"); *id*. at 1337 ("Juno argues that … scFvs, in general, were known"). At best a handful of scFvs binding to CD19 were known in the prior art, but it was *undisputed* that "millions of billions" of scFvs would need to be generated through the complex process described above to determine which bind to CD19. *Id.* at 1340. That is not this case, where Lilly successfully argued to the PTAB that the class of anti-CGRP antagonist antibodies was already "well known in the art"; a POSA would understand from the specification that all members of the class will work in the claimed method; and Dr. McDonnell's testimony concerning the number of antibody candidates that would need to be tested was both "not credible or persuasive" and hotly contested by Teva's witnesses. *Supra*, pp. 12-14, 15, 34-38.

AbbVie is likewise distinguishable. That case too did not involve a novel method of treatment using an existing, well-known class of antibodies—the claims were to the class of antibodies, which the patentholder described as "rare and difficult to obtain." 759 F.3d at 1298. Generating the class of antibodies required researchers either to "genetically engineer fully human IL-12 antibodies that are derived from human DNA"—"creating a large library of human DNA fragments and screening for those fragments that encoded an antibody fragment with IL–12 binding affinity" followed by "site-directed mutagenesis" ("a trial and error approach to modify individual amino acids in order to improve the IL-12 binding affinity")—or

to genetically engineer mice that would express human antibodies. *Id.* at 1291-92, 1301. This Court affirmed denial of JMOL for the patentholder because the claims covered all antibodies with IL-12 binding affinity, but "the patents do not describe any example, *or even the possibility*, of fully human IL-12 antibodies having heavy and light chains other than the V_H3 and Lambda types." *Id.* at 1300 (emphasis added). That is not this case, where a POSA would have been generally familiar with the class of anti-CGRP antagonist antibodies, including antibodies binding to all three CGRP epitopes, and would understand that *all* antibodies in the class would work for purposes of the claimed method of treatment. *Supra*, pp. 6-7, 16-17.

II. The district court committed legal error by overturning the jury's enablement verdict for Teva.

The jury reasonably found that practicing the claimed method of treatment did not require undue experimentation and so the claims are enabled. The district court granted JMOL to Lilly only by making many of the same legal errors that infected its written description analysis, so this Court should reverse or vacate the judgment.

A. The jury reasonably found that Lilly did not prove lack of enablement.

"To prove that a claim is invalid for lack of enablement, a challenger must show by clear and convincing evidence that a person of ordinary skill in the art would not be able to practice the claimed invention without undue experimentation." *Amgen Inc. v. Sanofi, Aventisub LLC*, 987 F.3d 1080, 1084 (Fed. Cir. 2021)

(quotations omitted). "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). The factors include "the quantity of experimentation necessary," "the amount of direction or guidance presented," "the presence or absence of working examples," and "the predictability … of the art," among others. *Id.*

"What is reasonable in any case" in terms of experimentation "will depend on the nature of the invention and the underlying art." *Amgen Inc. v. Sanofi*, 598 U.S. 594, 612 (2023). Thus, "the mere fact that the experimentation" needed to practice an invention "may have been difficult and time consuming does not mandate a conclusion that such experimentation would have been considered to be 'undue'" if "great expenditures of time and effort were ordinary in the field." *Falko-Gunter*, 448 F.3d at 1365 (quotations omitted). Even a "considerable amount of experimentation is permissible, if it is merely routine." *PPG Indus., Inc. v. Guardian Indus. Corp*., 75 F.3d 1558, 1564 (Fed. Cir. 1996) (quotations omitted); *see also Cephalon, Inc. v. Watson Pharms., Inc.*, 707 F.3d 1330, 1338 (Fed. Cir. 2013) (allowing for the "repetition of known or commonly used techniques").

Here, the asserted claims are method of treatment claims, so the question is whether the method is enabled. The jury reasonably concluded that Lilly failed to meet its burden of proving lack of enablement.

The relevant evidence is similar to that discussed above with respect to written description. The claimed method of treating headache requires the use of anti-CGRP antagonist antibodies, which as a class were already "well-known" by the priority date, with the prior art "replete with exemplary disclosures." *Supra*, pp. 12-13. The patent provided a "working example" in antibody G1; in addition, Lilly obtained the cancellation of Teva's antibody genus claims because it argued that a POSA "would have sought to humanize Tan's [prior art] antibodies," Appx53934, and the PTAB agreed that "Tan's [prior art] C4.19 antibody is a working example of an anti-CGRP antagonist antibody." Appx18878-18879; Appx18534 (same). At least one more such antibody was available for commercial purchase. *Supra*, pp. 6-7. In addition, if someone wanted to make their own antibodies, it would have been entirely routine to do so—a mouse immunized with CGRP will selectively generate antibodies responsive to CGRP and the anti-CGRP antagonists can be quickly identified. *Supra*, pp. 7-8, 17, 35-36. Teva's expert Dr. Hale walked the jury through the routine, non-labor intensive steps that a POSA could have undertaken to make antibodies for use in the claimed method. *See* Appx4213-4214 (antibodies); Appx4250 (same); Appx4220-4228 (humanization). Making them did not require a global pharmaceutical company's resources; indeed, graduate students could generate them and researchers were willing to just give them away. *Supra*, pp. 6-7.

A POSA would have further understood, from the test data reported in the

patents' specification, that the *entire* class of anti-CGRP antagonist antibodies will treat headache. The specification explains that tested antibodies were successful in an animal model that is predictive of "efficacy for treating migraine in humans," Appx4509 n.10; Appx258(68:59-69:39), and as the district court acknowledged, a POSA would have understood from the Zeller team's experimental data that all other anti-CGRP antagonist antibodies would work too, *see supra*, pp. 16-17.

The claim requires the antibodies to be humanized, and that would have been routine for a POSA too, with certainty of success. *Supra*, pp. 8-9, 17. Lilly even asserted to the PTAB that because "humanization was a well-established and routine procedure by the time Teva filed its application," the concept "does not and cannot provide any patentable weight" to the Zeller patents. Appx21746.

The specification further explains that a POSA "will be able to determine appropriate dosage amounts for particular agents to be used in combination with an anti-CGRP antibody." Appx234(20:41-43). Dr. Hill confirmed that the animal data in the specification, in conjunction with FDA guidelines, would allow a POSA to routinely arrive at an effective dose of an anti-CGRP antagonist antibody. Appx4162-4166. The district court nowhere held in its JMOL decision that Teva failed to enable the *treatment* aspects of the method of treatment claims.

B. The district court committed legal error in granting Lilly JMOL of lack of enablement.

The district court's opinion that the patents' specification provided "nothing

more than a 'roadmap' for a 'trial and error' process to identify and make antibodies within the scope of the Asserted Claims," Appx50, rested on a series of legal errors.

1. The district court erred in refusing to consider the prior art murine antibodies because they were not humanized.

Actual reduction to practice is not required for enablement, just as it is not required for written description. *Alcon Research Ltd. v. Barr Lab'ys, Inc.*, 745 F.3d 1180, 1189 (Fed. Cir. 2014) (in analyzing an enablement challenge, explaining "[i]t is well settled that an invention may be patented before it is actually reduced to practice"). Instead, constructive reduction to practice can be enough.

In considering whether the claimed method of treatment in this case is enabled, however, the district court again refused to consider the prior art's extensive disclosures concerning murine antibodies because they had not actually been humanized, focusing its analysis solely on the humanized antibody G1. Appx49 ("the specification disclosed only one covered antibody").

That was error. There was ample evidence from which a reasonable jury could have found that the claimed method of treating headache was constructively reduced to practice for the entire class of anti-CGRP antagonist antibodies, not just antibody G1. *Supra*, pp. 7-9, 10-11, 16-17. And the jury reasonably could have taken that constructive reduction to practice into account when applying the *Wands* factors and found that the amount of additional experimentation necessary to practice the full scope of the invention was not "undue." The district court therefore should not have

brushed aside the prior art's extensive disclosures concerning murine antibodies in its enablement analysis.

2. The district court erred in overruling the jury's credibility determinations.

In analyzing enablement, the district court again relied on a finding that the universe of antibodies that must be tested in order to identify anti-CGRP antagonist antibodies within the scope of the claims is "large." Appx49 ("there are a large number of antibodies that could potentially antagonize CGRP"). Here too the district court cited Dr. McDonell's random-selection "thought experiment." Appx49 (citing McDonnell's testimony at Appx3142-3145 and Appx3200-3201). But for the reasons already given, a jury reasonably could have concluded that Dr. McDonnell's testimony was not credible. *Supra*, pp. 34-38.

When it comes to enablement, "[f]acts control." *Amgen*, 987 F.3d at 1086. Without a credible expert opinion that the number of antibodies that will be generated through murine immunization is so large as to render the amount of experimentation "undue," a jury reasonably could have found that Lilly failed to meet its burden of proof. *Cephalon*, 707 F.3d at 1339 (reversing judgment of no enablement where defendant failed to "show that the resulting experimentation in this case would be excessive, *e.g.*, that it would involve testing for an unreasonable length of time").

That conclusion is only strengthened by the district court's acknowledgement

that Lilly did not demonstrate that the genus of anti-CGRP antagonist antibodies is "*necessarily very large* or small." Appx27 (emphasis added). If the numerator and denominator are both small (or even if the numerator—the number of anti-CGRP antagonists—is large, but the denominator—the total number of antibodies generated through immunization—is small), and the experiments used to identify members of the genus are routine and automated, then a reasonable jury could conclude that any further experimentation would not be "undue." *In re Angstadt*, 537 F.2d 498, 503 (C.C.P.A. 1976).

Lilly's failure of proof distinguishes this case from the recent enablement decisions involving claims to classes of antibodies on which the district court relied (which also are distinguishable because they concern claims involving novel antibodies, not methods of treatment employing a well-known class of antibodies, as discussed *infra*). For example, in *Baxalta Inc. v. Genentech, Inc.*, there was evidence of "*millions* of potential candidate antibodies," of which "only 1.6%" might embody the claims. 81 F.4th 1362, 1364, 1366 (Fed. Cir. 2023). In *Amgen*, the evidence was that a "vast" number of antibodies would need to be tested to see if they bound to the specified residues on PCSK9 and blocked its function—"at least millions of candidates"—and empirical testing was needed for every antibody. 598 U.S. at 613-14. In *Wyeth & Cordis Corp. v. Abbot Laboratories*, a small-molecule chemical compound case, the field was "unpredictable and poorly understood," and

"there [was] no genuine dispute that practicing the full scope of the claims would require synthesizing and screening *each* of at least tens of thousands of compounds." 720 F.3d 1380, 1385-86 (Fed. Cir. 2013). And in *Idenix*, another small-molecule case, there were "many, many thousands" of compounds to screen. 941 F.3d at 1162-63.

In comparison to those cases, in this case Lilly failed to adduce credible expert testimony concerning the number of antibody candidates and the size of the genus. Under the demanding JMOL standard, the jury certainly was not *required* to credit Dr. McDonnell's testimony that a "mind-bogglingly" large number of antibody candidates would need to be screened to identify the members of the genus. The district court therefore should not have disturbed the verdict.

3. The district court erred by treating this case as if it involves claims to a novel class of antibodies.

Finally, as with written description, the district court erred by treating this case involving an innovative method of treatment employing a well-known class of antibodies as if it concerned a claim to a novel of class of antibodies. This Court has never held that a method of treatment claim employing a well-known class of antibodies is invalid for lack of enablement with respect to the underlying antibodies. Most of the cases to which the district court compared this case in its enablement analysis instead concerned claims involving a novel genus of antibodies or chemical

compositions. *E.g.*, *Baxalta*, 81 F.4th at 1363; *Amgen*, 872 F.3d at 1372; *Idenix*, 941 F.3d at 1161; *Wyeth*, 720 F.3d at 1385.

Enablement cases involving claims to a novel class of antibodies are simply not comparable, because in such cases the inventors are *necessarily* asserting that the *class itself* is inventive—that the class was not known or even obvious to a POSA. In such a case, because the class is the invention, the inquiry properly focuses on the experimentation necessary to enable the class of antibodies. In this case, on the other hand, because the class of antibodies was already "well known" and not the invention, the enablement inquiry properly is focused on the claimed method of treatment. The Zeller team claimed exactly what the specification teaches a POSA to do: to use the already well-known class of anti-CGRP antagonist antibodies to treat headache, which will work no matter the epitope to which a particular anti-CGRP antibody binds, because all members of the class will work in the method. *Supra*, pp. 16-17. For the reasons given above, Lilly failed to prove lack of enablement of that invention.

To be sure, the outcome could be different if the class of antibodies for use in the claimed method were *not* already "well known" in the art, or if it were not known that all members of the class would work in the claimed method. Under such circumstances, a jury applying the *Wands* factors could decide that the amount of experimentation needed to enable full practice of the invention—to determine the

composition of the class that will work in the invention—is undue.

Thus, in *Idenix*, the claim was to a method of treatment of hepatitis C using small molecule nucleotides to which "substituent atoms or groups of atoms" were selectively added in "either the 'up' or 'down' position" at each of five carbon atoms; the claimed method involved treatment with those compositions that worked to treat hepatitis C. 941 F.3d at 1154. There was no indication that the class of compounds meeting that description was already "well known" in the art; indeed, the specification of the patent disclosed several thousand compositions that would *still* need to be tested to determine if they fell within the scope of the claim. *Id.* at 1161. The Court therefore cast "[t]he key enablement question" as "whether a [POSA] would know, without undue experimentation, which 2'-methyl-up nucleosides would be effective for treating HCV," and answered that question "no." *Id.* at 1156, 1162.

Similarly, in *Wyeth*, the claim was to a method of treatment using small molecule compounds: "a method of treating or preventing 'restenosis in a mammal ... which comprises administering an antirestenosis effective amount of rapamycin to said mammal.'" 720 F.3d at 1382. There is no indication that the class of compounds usable in the claimed method was already "well known" to a POSA or that the specification taught that all members of the class would work in the invention—to the contrary, "[t]he specification offers no guidance or predictions

about particular substitutions that might preserve the immunosuppressive and antirestenotic effects observed in sirolimus." *Id.* at 1386.

For all the reasons given above, however, *Idenix* and *Wyeth* are nothing like this case. Here, the class of antibodies was already well known and a POSA would understand that all members of the class, which can be very easily generated, will work in the invention. On the specific facts of this case, it certainly was not *unreasonable* for the jury to decide that undue experimentation is not necessary to practice the full scope of the claimed method of treating headache.

III. The district court's reasoning fails to advance § 112's policies.

Stepping back, the district court's approach to written description and enablement fails to advance the purposes of § 112 while robbing innovative methods of treatment of effective patent protection. "[T]he 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." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1353-54 (Fed. Cir. 2010) (quotations omitted). Likewise, "[t]he purpose of" the enablement requirement "is to ensure that the public knowledge is enriched by the patent specification to a degree at least commensurate with the scope of the claims." *Warner-Lambert Co. v. Teva Pharms. USA, Inc.*, 418 F.3d 1326, 1336–37 (Fed. Cir. 2005) (quotations omitted).

Those purposes are satisfied here. The Zeller team's innovation is not in doubt. They started with an existing, indisputably well-known class of antibodies, overcame doubts that the class can be used to treat headache, and disclosed their groundbreaking discovery to the public. A POSA would understand from the specification's disclosures that whatever differences exist between antibodies in the class, they *all* will work in the claimed method of treating headache. The district court did not find that the treatment aspects of the claims are inadequately disclosed or enabled. And the antibodies for use in the method can be readily and easily generated and identified by a POSA, using methods taught in the specification and otherwise known in the art. In these patents, the Zeller team claimed only what they discovered—*not* the use of humanized anti-CGRP antibodies for all purposes, and *not* every antibody that treats headache, but *only* the use of humanized anti-CGRP antibodies to treat headache. The claims are consistent with "the scope of the inventor's contribution to the field of art," *Ariad*, 598 F.3d at 1353-54, and "the public knowledge is enriched by the patent specification to a degree at least commensurate with the scope of the claims." *Warner-Lambert*, 418 F.3d at 1337.

The district court ruled for Lilly on both § 112 issues because it thought the claims should be limited only to use of the humanized antibody the Zeller team created, or to the use of structurally similar antibodies. But when the invention is a novel method of treatment using a class of well-known and easily generated

antibodies, and the specification teaches that all members of the class will work, there is no § 112 rationale for limiting the inventors to species or sub-genus claims. As in cases like *Ajinomoto*, *Herschler*, and *Hoechst*, the applicants should be able to claim use of the entire class in the claimed method, because that is what they have constructively reduced to practice and what they have taught the public.

Under the district court's approach to method of treatment claims covering a genus of antibodies, effective patent protection for novel methods of treatment employing well-known and easily generated classes of murine antibodies may be impossible. Having learned from the inventor that *all* such antibodies will work in the claimed method, a competitor can quickly design around any narrower species or sub-genus claim by the simple expedient of immunizing more mice until one generates an antibody with a sufficiently different antibody sequence. Doing so will not require "undue experimentation"—it is something a graduate student can do with minimal effort. *Supra*, pp. 6-7.

Take this case. As recounted above, Lilly's researchers were already working with anti-CGRP antagonist antibodies but failed to discover that they can treat headache. *Supra*, p. 9. It was only after the Zeller team taught the public that anti-CGRP antagonist antibodies can treat headache that Lilly went back to headache. *Id.* The jury therefore unsurprisingly found that Lilly's infringement was willful. Appx4557. Section 112 does not exist so that a willful infringer can learn an

innovative method of treatment from a competitor's patent and blatantly copy it, just by selecting a different antibody from within an already well-known and easily-generated class of antibodies. The district court therefore should have let the jury verdict stand.

CONCLUSION

The judgment of the district court entering JMOL for Lilly on lack of written description and enablement should be reversed, or at a minimum vacated.

Respectfully submitted,

/s/ Kevin P. Martin

Kevin P. Martin
Elaine Herrmann Blais
Edwina B. Clarke
GOODWIN PROCTER LLP
100 Northern Avenue
Boston, MA 02210
(617) 570-1000

Gabriel B. Ferrante
GOODWIN PROCTER LLP
The New York Times Building
620 8th Ave
New York, NY 10018
(212) 813-8800

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Counsel for Plaintiffs-Appellants