UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF MICHIGAN
SOUTHERN DIVISION

NOVO NORDISK A/S and
NOVO NORDISK, INC.,

Plaintiffs,

v.

Case No. 05-40188
HON. AVERN COHN

CARACO PHARMACEUTICAL
LABORATORIES, LTD. and
SUN PHARMACEUTICAL INDUSTRIES, LTD.,

Defendants.

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DECISION

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I. INTRODUCTION

A. The Case

This is a patent case under the Hatch Waxman Act, 21 U.S.C. §.356, *et. seq*. The patent-in-suit, U.S. Patent No. 6,677,358B1, NIDDM REGIMEN (the '358 Patent) in the words of the abstract:

> . . .discloses a method of achieving improvement in glycemic control by combined use of repaglinide and metformin in NIDDM patients poorly controlled on metformin alone.

The patent is owned by assignment by plaintiffs Novo Nordisk A/S and Novo Nordisk, Inc. (Novo). Defendant, Caraco Pharmaceutical Laboratories, Ltd. (Caraco) asserts that Claim 4, the claim-in-suit of the '358 patent which reads

> A method for treating non-insulin dependent diabetes mellitus (NIDDM) comprising administering to a patient in need of such treatment repaglinide in combination with metformin is invalid as obvious and anticipated, and is unenforceable because of inequitable conduct and patent misuse.

Proceedings against defendant Sun Pharmaceutical Industries, Ltd., the second defendant of which Caraco is a partially owned subsidiary, have been stayed until further order of the Court (Doc. 346).

The issues of obviousness, anticipation and inequitable conduct were tried to the Court in June and August of 2010. The issue of patent misuse is the subject of a separate proceeding before the Court.

B. The Decision

For the reasons which follow, which constitute the findings of fact and conclusions of law required by Fed. R. Civ. P. 52(a), the Court finds that:

- The '358 Patent is not invalid because of anticipation
- The '358 Patent is invalid because of obviousness
- The '358 Patent is not enforceable because of inequitable conduct

II. BACKGROUND

A. Overview

This case has a long and complicated history. It began with the filing of a complaint by Novo charging Caraco with infringement of the '358 Patent on July 21, 2005 (Doc. 1), and Caraco responding with an answer and counterclaim asserting invalidity and unenforceability of the '358 Patent (Doc. 7). Since filing, the case has generated over 500 docket entries.

B. History

The history of the case is generally described in the following decisions of the Court and the Court of Appeals for the Federal Circuit as follows:

On August 31, 2009, the Court held that Caraco could challenge the incorrect use code narrative furnished by Novo for placement in the Orange Book maintained by the Food and Drug Administration on its application for approval of the new drug covered by the '358 Patent, and that Caraco could assert an affirmative defense to the charge of infringement because of this. *Novo v. Caraco*, 649 F. Supp. 2d 661 (E.D. Mich. 2009).

On September 24, 2009, the Court found that Novo improperly filed a use code narrative in its application for approval of the new drug. *Novo v. Caraco*, 656 F. Supp. 2d 729 (E.D. Mich. 2009).

On September 25, 2009, the Court entered an Order and Injunction (Doc. 423) requiring Novo to correct the use code narrative in the Orange Book.

On April 14, 2010, the Federal Circuit reversed the Order and Injunction, holding

that a counterclaim such as filed by Caraco challenging the Orange Book listing was not available under Hatch Waxman. *Novo v. Caraco*, 601 F.3d 1359 (Fed. Cir. 2010). On July 21, 2010, rehearing was denied. *Novo v. Caraco*, 615 F.3d 1374 (Fed. Cir. 2010). On December 23, 2010, Caraco applied to the Supreme Court for *certiorari.*

On June 9, 2010, the Court found that the relevant date for prior art in the challenge to validity of the '359 Patent was October 29, 1996. *Novo v. Caraco*, 2010 WL 2403041 (E.D. Mich. June 9, 2010)

On October 6, 2010, in a Memorandum and Order, the Court denied Novo's motion to dismiss the case for lack of subject matter jurisdiction premised on the grounds that Caraco had changed the nature of its Application For A New Drug (ANDA) with the Food and Drug Administration (FDA). *Novo v. Caraco*, 2010 WL 3492727 (E.D. Mich. Oct. 6, 2010).

On September 09, 2009, Caraco stipulated that its ANDA filed with the FDA infringed the '358 Patent (Doc. 309). On August 24, 2010, in a Notice of Lodging of Stipulation of Infringement, the stipulation was reaffirmed (Doc. 489).

III. THE TRIAL

On April 23, 2010, the Court entered an order (Doc. 459) reversing the order of proofs at trial. The trial extended over 11 days in June and August of 2010.

A. The Witnesses

Fourteen witnesses, as named in the List of Trial Witnesses (Doc. 490) filed by the parties post-trial, testified. The witnesses' direct testimony for the most part was presented in narrative form (see Doc. 459). A brief description by name and general nature of testimony of the witness follows.

1. Caraco

Name	General Nature of Testimony
Domenico Accili (Accili)	Expert in the field of endocrinology and diabetes research. Accili expressed the opinion that claim 4 of the '358 patent was invalid as obvious, and that there was a lack of unexpected results when repaglinide was combined with metformin.
Marcello Pagano (Pagano)	Expert in the field of biostatistics. Pagano expressed the opinion that there was a lack of statistical validity in Novo's studies with respect to the combination of repaglinide with metformin.

2. Novo

Name	General Nature of Testimony
· Robert Moses, M.D. (Moses)	Medical Director of an Australian research institute. Moses was one of the principal clinical investigators of a study of the combination of metformin and repaglinide (Moses Study)[1]. His research data and results were the foundation of the examples reported in the '358.
· Peter Müller, M.D. (Müller)	A research associate in Novo's research department in Denmark. Müller is the named inventor of the '358 patent. He designed the Moses Study to test the combination of repaglinide and metformin.
· Andreas Pfeiffer, M.D. (Pfeiffer)	A clinical specialist in the field of endocrinology. Pfeiffer conducted clinical research on the combination of repaglinide and metformin (Pfeiffer Study). He expressed the

[1]Appendix I contains a list of reports and articles referenced in this Decision, including the Moses Study, noted above. The appendix lists (1) the exhibit number for the report or article, (2) the full citation for the report or article, and (3) the Court's abbreviation for the report or article.

	opinion that the results of the combination were unexpected.
· Jeppe Sturis, Ph.D. (Sturis)	A principal scientist of Novo in Denmark. Sturis tested a combination of repaglinide and metformin in Zucker obese rats (Sturis Study). He expressed the opinion that the results of his testing were synergistic. The results were cited to the Patent Office in support of patentability of the combination of repaglinide and metformin.
· Howard Thaler, Ph.D. (Thaler)	An expert in biostatistics. Thaler reviewed the results of the Moses Study and the Sturis Study. He expressed the opinion that the studies showed synergistic results from the combination of repaglinide and metformin.
· Peter Damsbo, M.D. (Damsbo)	Novo's chief medical advisor. Damsbo's early work with repaglinide provided a foundation for a therapeutic approach for the combination of repaglinide and metformin.
· John Miller, M.D. (Miller)	Medical director of Novo in Australia. Miller coordinated and supervised the Moses Study. He described this work and said he was surprised by the results.
· Michael Mark, Ph.D. (Mark)	A German scientist. Mark discovered repaglinide and attempted to commercialize it. He was involved in its transfer to Novo.
· Arne Melander, M.D. (Melander)	Researcher in the clinical pharmacology of diabetes. Melander expressed the opinion that repaglinide was not interchangeable with sulfonylureas, and was not thought suitable for combination therapy with metformin.
· Brian Reisetter, Ph.D. (Reisetter)	An expert in medical marketing. Reisetter expressed an opinion about the commercial success of the repaglinide-metformin combination therapy.
· Alan Garber, M.D., Ph.D. (Garber)	An expert in clinical endocrinology and biochemistry. Garber expressed the

	opinion that claim 4 the '358 Patent is valid as nonobvious.
· Bharati Nadkarni (Nadkarni)	A senior manager at Sun Pharmaceutical. Nadkarni described Sun's activities in India and Mynamar with repaglinide and sulfonylureas.

B. Exhibits

Roughly over 360 exhibits were introduced in evidence at trial. A consolidated list of trial exhibits (Doc. 494) was filed by the parties post-trial. The exhibits beyond the '358 Patent (JX 1) and an abbreviated File History (JX 2A), include correspondence, chains of e-mails, articles, abstracts of articles, clinical trials reports, curriculum vitaes of scientific witnesses, data compilations and various graphic comparisons, as well as a miscellany of other written material.

IV. THE LAW

A. Anticipation

Anticipation exists only if, within the four corners of a single prior art document, every element of the claimed invention is described, expressly or inherently, such that a person of ordinary skill in the art could practice the invention without undue experimentation. *Callaway Golf Co. v. Acushnet Co.*, 576 F.3d 1331, 1346 (Fed. Cir. 2009).

B. Obviousness

A patent is presumed valid, 35 U.S.C. §282, and a party challenging its validity bears the burden of proving the factual elements of invalidity by clear and convincing evidence. *Pfizer v. Apotex*, 480 F.3d 1348, 1359 (Fed. Cir. 2007). Once the challenger has presented a prima facie case of invalidity, the patent owner has the burden of going

forward with rebuttal evidence. *Id*. at 1360. This requirement "does not in substance shift the burden of persuasion, because the presumption of validity remains intact and the ultimate burden of proving invalidity remains with the challenger throughout the litigation." *Id*. (case citations omitted).

Where the accused infringer relies only upon prior art considered by the patent examiner, the statutory presumption of validity includes deference to the examiner's decision based upon the Patent Office's expertise. *American Hoist & Derrick Co. v. Sowa & Sons*, 725 F.2d 1350, 1359-60 (Fed. Cir. 1984). In the Supreme Court's *KSR* decision, where the invalidity defense was based on prior art not considered by the Patent Office, the Court observed that "the rationale underlying the presumption – that the PTO, in its expertise, has approved the claim – seems much diminished here."[2] *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 446 (2007).

A valid patent may not be granted or upheld when "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S. C. §103(a). The ultimate question of patent validity is one of law, based on an underlying factual framework laid out by the Supreme Court in *Graham v. John Deere Co.*:

> Under §103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this

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[2]On November 29, 2010, the Supreme Court granted *certiorari* in *i4i Ltd. Partnership v. Microsoft Corp.*, 598 F.3d 831 (Fed. Cir. 2010) on the question whether the clear and convincing standard must be applied to the invalidity defense under these circumstances. *Microsoft Corp. v. i4i Ltd. Partnership*, 131 S.Ct. 647 (2010).

> background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. As indicia of obviousness or nonobviousness, these inquiries may have relevancy.

383 U.S. 1, 17-18 (1966).

Often, as here, it is necessary to utilize this framework to determine whether a patent claiming a combination of elements known in the prior art was obvious at the time of the claimed invention. Over the years, the Federal Circuit created and applied a test known as the "teaching, suggestion or motivation" (TSM) test. Under this test, a patent claim is proved obvious only if a motivation or suggestion to combine the prior art teachings can be found in the prior art. The Supreme Court in *KSR* held that the TSM test can provide a "helpful insight," but noted that

> [o]ften, it will be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. . . . As our precedents make clear, however, the analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.

Continuing:

> The obviousness analysis cannot be confined by a formalistic conception of the words, teaching, suggestion, and motivation, or by overemphasis on the importance of published articles and the explicit content of issued patents. The diversity of inventive pursuits and of modern technology counsels against limiting the analysis in this way. In many fields it may be that there is little discussion of obvious techniques or combinations, and it often may be the case that market demand, rather than scientific literature, will drive design trends.

550 U.S. at 418-19.

Known disadvantages of prior art elements that might have taught away from the claimed combination may be taken into account in determining obviousness. *Id*. at 416, citing *United States v. Adams*, 383 U.S. 39, 51-52 (1966).

In another step applicable here, *KSR* approved the selective use of the "obvious to try" test that had long been rejected by the Federal Circuit:

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

550 U.S. at 421.

The Federal Circuit subsequently elaborated on the obvious-to-try "rule of thumb," identifying two factual situations where it was inappropriate:

> First, an invention would not have been obvious to try when the inventor would have had to try all possibilities in a field unreduced by direction of the prior art. When "what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful" an invention would not have been obvious. *O'Farrell*, 853 F.2d at 903. This is another way to express the *KSR* prong requiring the field of search to be among a "finite number of identified" solutions. 550 U.S. at 421, 127 S.Ct. 1727; *see also Proctor & Gamble*, 566 F.3d at 996; *Kubin*, 561 F.3d at 1359. It is also consistent with our interpretation that KSR requires the number of options to be "small or easily traversed." *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008).
>
> Second, an invention is not obvious to try where vague prior art does not guide an inventor toward a particular solution. A finding of obviousness would not obtain where "what was 'obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." *O'Farrell*, 853 F.2d at 903. This expresses the same idea as the *KSR* requirement that the identified solutions be "predictable." 550 U.S. at 421, 127 S.Ct. 1727; *see also Proctor & Gamble*, 566 F.3d at 996-97; *Kubin*, 561 F.3d at 1359-60.

Bayer Schering Pharma AG v. Barr Labs, Inc., 575 F.3d 1341, 1347 (Fed. Cir. 2009). The Federal Circuit has declined to "cabin" the "obvious to try standard" to the "predictable arts" (as opposed to the relatively unpredictable biotechnology arts). *In re Kubin*, 561 F.3d 1351, 1360 (Fed. Cir. 2009).

Where, as here, all the elements of the claimed invention are found in a combination of prior art references, the party challenging validity must show by clear and convincing evidence (1) that a skilled artisan would have had a reason or motivation to combine the teachings of the prior art to achieve the claimed invention combination, or would have found it obvious to try the claimed combination, and (2) that such person would have had a reasonable expectation of success in doing so. *Pfizer v. Apotex*, 480 F.3d 1348, 1361 (Fed. Cir. 2007); *KSR*, 550 U.S. at 421.[3] The court in *Pfizer* elaborated on the "reasonable expectation of success:"

> [C]ase law is clear that obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success . . . . . [T]he expectation of success need only be reasonable, not absolute.

Id. at 1364.

A case of prima facie obviousness can be rebutted by "unexpected results," but "the results must be shown to be unexpected compared with the closest prior art." *Id*. at 1370. "[I]n order to properly evaluate whether a superior property was unexpected, the court should have considered what properties were expected." *Id*. at 1371. But

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[3]*Pfizer* was decided one month before *KSR*. In *KSR,* the Supreme Court held that the "obvious to try" standard may be applied in appropriate circumstances, as quoted above. 550 U.S. 398, 421 (2007).

even unexpectedly superior results may not be sufficient to overcome a strong prima facie case of obviousness. *Id*. at 1372.[4] *See also, Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010).

A strongly contested legal issue here is the relevance and meaning of *Asyst v. Techs. v. Emtrak, Inc.*, 544 F.3d 1310, 1316 (Fed. Cir. 2008), which Caraco relies upon for its holding that "objective evidence of non-obviousness [e.g., unexpected results and commercial success] must be commensurate in scope with the claims which the evidence is offered to support." Evidence of unexpected results, though based upon subject matter that lies within the scope of a patent claim, will not support the unobviousness of a claim whose breadth extends far beyond that evidence unless "the probative value of a narrow range of data can be reasonably extended to prove the unobviousness of a broader claimed range." *In re Clemens*, 622 F.2d 1029, 1036 (CCPA 1980); *see also* the MPEP §716.02(d), which cites *Clemens*; *In re Grasselli*, 713 F.2d 731, 743 (Fed. Cir. 1983) (cited in *Asyst*); *In re Tiffin*, 448 F.2d 791, 792 (CCPA 1971 (cited in Asyst).

Prima facie obviousness can also be rebutted by evidence of commercial

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[4]The parties have belabored the issue of whether the claimed combination produced synergistic, as well as unexpected and superior results. Synergy became part of the vocabulary in this case in an abstract written for publication describing the results of the Moses Study. See, DX 9; ¶ 96, infra.

The Supreme Court has endorsed the generally accepted definition of "synergistic," namely, "an effect greater than the sum of the several effects [of the constituent elements] taken separately." *Sakraida v. Ag Pro, Inc.*, 425 U.S. 273, 282 (1976). The Manual of Patent Examining Procedure (MPEP) states that "a greater than additive [i.e., synergistic] effect is not necessarily sufficient to overcome a prima facie case of obviousness because such an effect can either be expected or unexpected." §716.02(c).

success of the claimed invention. *Graham*, *supra*, 383 U.S. at 17-18.

C. Inequitable Conduct

The overall contours of the defense of patent unenforceability due to inequitable conduct have been summarized by Judge (now Chief Judge) Rader as follows:

> Applicants for patents have a duty to prosecute patent applications in the Patent Office with candor, good faith, and honesty; see also 37 C.F.R. § 1.56. A breach of this duty — including affirmative misrepresentations of material facts, failure to disclose material information, or submission of false material information — coupled with an intent to deceive, constitutes inequitable conduct. In determining whether inequitable conduct occurred, a trial court must determine whether the party asserting the inequitable conduct defense has shown by clear and convincing evidence that the alleged nondisclosure or misrepresentation occurred, that the nondisclosure or misrepresentation was material, and that the patent applicant acted with the intent to deceive the United States Patent and Trademark Office. The nondisclosure or misrepresentation must meet threshold levels of both materiality and intent. Once the threshold levels of materiality and intent have been established, the trial court must weigh materiality and intent to determine whether the equities warrant a conclusion that inequitable conduct occurred. Id. The more material the information misrepresented or withheld by the applicant, the less evidence of intent will be required in order to find inequitable conduct.

Honeywell Int'l Inc. v. Universal Avionics Sys. Corp., 488 F.3d 982, 999 (Fed. Cir. 2007) (internal citations omitted).

Even if a threshold level of both materiality and intent to deceive are proven by clear and convincing evidence, a court may still decline to render the patent unenforceable. *Star Scientific, Inc. v. R.J. Reynolds Tobacco Co.*, 537 F.3d 1357, 1365 (Fed. Cir. 2008).

The applicable definitions of materiality and intent, however, are less settled.[5]

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[5]The Federal Circuit granted a petition for rehearing en banc in *Therasence, Inc. v. Becton, Dickinson and Co.*, 593 F.3d 1289 (Fed. Cir. 2010), and requested briefing on all aspects of the current framework for determining and balancing materiality and intent. *See* 374 Fed. Appx. 35 (Fed. Cir. 2010). Oral argument was held on November

"Materiality" is defined by the Patent Office's current rule as follows:

> (b) Under this section, information is material to patentability when it is not cumulative to information already of record or being made of record in the application, and
>
> (1) It establishes, by itself or in combination with other information, a prima facie case of unpatentability of a claim; or
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> (2) It refutes, or is inconsistent with, a position the applicant takes in:
>
> (I) Opposing an argument of unpatentability relied on by the office, or
>
> (ii) Asserting an argument of patentability.
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> A prima facie case of unpatentability is established when the information compels a conclusion that a claim is unpatentable under the preponderance of evidence, burden-of-proof standard, giving each term in the claim its broadest reasonable construction consistent with the specification, and before any consideration is given to evidence which may be submitted in an attempt to establish a contrary conclusion of patentability.

37 C.F.R. §1.56(b) (2009).

The Federal Circuit has held that this current version, effective since 1992, was not intended to supplant the earlier "reasonable examine" standard or the case law interpreting it. *Digital Control v. Charles Machine Works*, 437 F.3d 1309, 1316 (Fed. Cir. 2006). The court further held that if a misstatement or omission is material under either test, or even under other previously applied tests, such as the "but for" test (the misrepresentation caused the examiner to approve claims he or she would not otherwise have approved) or the "but it may have" test (the misrepresentation may have influenced the examiner), then it is material. *Id*. at 1315-16. "To the extent that one standard requires a higher showing of materiality than another standard, the requisite finding of intent may be lower." *Id*. In fact, recent Federal Circuit decisions have applied the definition from the earlier version of 37 C.F.R §1.56, namely, information is

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9, 2010.

material "where there is a substantial likelihood that a reasonable examiner would consider it important in deciding whether to allow the application to issue as a patent."[6]

Some decisions have found it appropriate, when weighing inferences relevant to intent, to consider plausible reasons for the withholding of material information:

> The intent element of the offense is . . . in the main proven by inferences drawn from facts, with the collection of inferences permitting a confident judgment that deceit has occurred. . . . however, inequitable conduct requires not intent to withhold, but rather intent to deceive. Intent to deceive cannot be inferred simply from the decision to withhold [information] where the reasons given for the withholding are plausible.

McKesson Information Solutions, Inc. v. Bridge Medical, Inc., 487 F.3d 897, 913 (Fed. Cir. 2007) (reasons for withholding prior art patent and information from related applications held insufficient to negate inference of deceptive intent).

> An inference of intent to deceive is generally appropriate, however, when (1) highly material information is withheld; (2) "the applicant knew of the information [and] ... knew or should have known of the materiality of the information; and (3) the applicant has not provided a credible explanation for the withholding."

Praxair, Inc. v. ATMI, Inc., 543 F.3d 1306, 1313-14 (Fed. Cir. 2008) (no good faith explanation given for failure to disclose material prior art).

Another 2008 decision of the Federal Circuit raises an additional hurdle for inferring deceptive intent when alternative inferences can be drawn from the evidence.

> We have also held that because direct evidence of deceptive intent is rarely available, such intent can be inferred from indirect and circumstantial evidence. But such evidence must still be clear and convincing, and inferences drawn from lesser evidence cannot satisfy the deceptive intent requirement. Further the inference must not only be based on sufficient evidence and be reasonable in light of that evidence, but it must also be the single most reasonable inference

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[6] *E.g., Advanced Magnetic Closures, Inc. v. Rome Fastener Corp.*, 607 F.3d 817, 829 (2010); *Symantec Corp. v. Computer Assocs. Int'l*, 522 F.3d 1279, 1297 (2008).

> able to be drawn from the evidence to meet the clear and convincing standard. [internal cites omitted]

Star Scientific, *supra*, 537 F.3d at 1365 (emphasis added) (no deceptive intent found; withheld document found to be cumulative, and therefore not material). *See also, Advanced Magnetic Closures, supra*, 607 F.3d at 829. In *Star Scientific*, the Federal Circuit held that the existence of a reasonable alternative explanation completely precludes an inference of deceptive intent. A contemporaneous decision, however, gave the district court broad discretion to weigh the patentee's alternative explanations against the inference of deceptive intent, affirming a finding of deceptive intent, without imposing the "single most reasonable inference" standard. *Aventis Pharma S.A. v. Amphastar Pharmaceuticals, Inc*., 525 F.3d 1334, 1344 (Fed. Cir. 2008) (failure to disclose that half life studies were done at different doses).

V. THE PATENT

A. Technical Overview

For ease of reference, in Parts V through VIII the paragraphs are numbered.

1. This overview is essentially based on the Glossary of Terms lodged with the Court on June 20, 2010 by the parties. This overview is a brief tutorial of the underlying technology.

2. One of the byproducts of the body's digestion of food is **glucose** (sugar), which enters the bloodstream. A persistently too high level of bloodstream glucose is termed hyperglycemia, while a persistently too low glucose level is called hypoglycemia. Insulin is a hormone produced by beta cells in the pancreas, where it is stored until rising blood glucose levels cause it to be released. Insulin instructs the body's cells to take up

glucose from the blood for use as an energy source, and also instructs the liver to stop producing glucose and to instead take up glucose from the blood and store it as glycogen until needed by the body.

3. **Diabetes** is a glucose metabolism disorder characterized by hyperglycemia after meals and in the fasting state. About 24 million people in the United States have diabetes. Type I diabetes, represented by five percent of the diabetic population, occurs when the pancreas' beta cells fail to manufacture and secrete insulin in response to elevated blood glucose levels. The only therapy is treatment with exogenous (externally originated) insulin.

4. In **Type II diabetes**, representing the remaining 95 percent of the diabetic population, the beta cells fail to secrete sufficient insulin, and/or the body is resistant to the effects of insulin. Type II diabetes is also known as non-insulin dependent diabetes (NIDDM). It can be treated with orally administered antidiabetic drugs (**OADs**) in the form of monotherapy (a single OAD) or combination therapy (more than one OAD). **Insulin resistance** is a characteristic of Type II diabetes in which the cells and the liver are insensitive to the presence of insulin, and do not respond to the chemical message carried by insulin.

5. There are several groups of OADs. The two groups which are the primary focus of this lawsuit are insulin **secretagogues** and insulin **sensitizers**. The secretagogues stimulate insulin release from the pancreas' beta cells. Sensitizers reduce insulin resistance by acting on the liver to reduce glucose production from glycogen stored there, and improve insulin sensitivity in muscle and fat tissues.

6. **Repaglinide**,[7] one of the two ingredients specified in Claim 4 of the '358 Patent, is an insulin secretagogue. It is one of five members of the meglitinide class of secretagogues, only one other of which (nateglinide or A-4166) has been approved by the FDA. A second class of secretagogue consists of thirteen sulfonylureas.

7. **Metformin**, the other claimed ingredient in Claim 4, is an insulin sensitizer. It is the only one of three members of the **biguanide** class that has been approved by the FDA. A second class of sensitizer, the thiazolidinediones ("TZDs"), consists of five drugs.

8. Two measures of glucose control have been referred to in this lawsuit. The first is **HbA_{1c}** or glycosylated hemoglobin, a form of hemoglobin to which glucose in the blood binds. The glucose remains attached for the life of the hemoglobin cell (about four months). This parameter is not influenced by daily fluctuations in blood glucose, and shows the average glucose level in the recent past. It is therefore used to monitor the effect of diet, exercise and drug therapy on blood glucose. The second measure is **FPG** or **fasting plasma (blood) glucose**. This measurement is taken after a patient has not eaten for about eight hours (e.g., overnight). High levels of FPG can be caused by increased glucose production from glycogen stored in the liver, resulting from impaired insulin action in the liver.

9. As will be amplified below, **combination therapy**–using any two drugs having

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[7]At the time this case was filed, repaglinide was a patented pharmaceutical, U.S. Patent No. RE37,035E (the '035 Patent). The patent expired on March 14, 2009. It was in anticipation of the expiration of the '035 Patent that Caraco filed the ANDA that precipitated the filing of this case by Novo and the counterclaim by Caraco which is the subject matter of this case and the trial.

different mechanisms of action--will generally be more effective than **monotherapy**--using just one of those drugs. If monotherapy with a drug proves successful, a logical testing progression was to test that drug in combination therapy. Combination therapy using an insulin sensitizer and an insulin secretagogue was a well-known successful technique for treating Type II diabetes long before the invention claimed in the '358 Patent.

10. A combination of drugs is said to have an **additive** effect when the total effect equals the sum of the effect of each drug taken separately (e.g., Drugs A and B each reduce hypertension by 10% when administered separately, and reduce hypertension by 20% if administered together). If the combined effect exceeds the sum of the separately administered effects, the effect is said to be **greater-than-additive** or **synergistic** (e.g., Drugs A and B in the above example yield a 25% reduction in hypertension when administered together). If Drug B inhibits or counteracts the effect of Drug A, the drugs are said to be antagonistic (e.g., the combination of the same Drugs A and B reduce hypertension by only 5%).

B. Conception and Development of the Patented Combination

11. Novo is a large producer of drugs used to treat diabetes. In November, 1990, it acquired license rights to repaglinide, a known but still unapproved insulin secretagogue. Development of repaglinide became the exclusive focus of Müller, who joined Novo in Denmark as a clinical researcher in 1989. He is the patentee of the '358 Patent. During 1991-92, he treated Type II patients with repaglinide to determine proper dosages and prove its efficacy and safety. He also compared its performance

with sulfonylureas, a well-known class of insulin secretagogues. 6/7/10 Tr. at 186-95 (Müller).[8]

12. As Müller explained, in that time period there were sulfonylureas (secretagogues) and metformin, an insulin sensitizer that had been around for many years. He conceived the repaglinide/metformin combination at an unknown date before June of 1994, and did not study any other repaglinide combinations. *Id*. 192, 198. He thought "it would make more sense" to combine repaglinide with metformin than with sulfonylureas, because of metformin's complementary mechanism of action. "That's why my thought was a good idea to combine those two." *Id*. at 192-93. Relative to patients whose glucose levels were not adequately controlled on metformin alone, he therefore "expected some additional improvements in the glucose control of the patients treated with the combination." 6/8/10 Tr. at 18 (Müller)

13. Damsbo, who worked with Müller, testified that metformin was the first drug they tested in combination with repaglinide because repaglinide "was a natural thing to combine with a sensitizer . . . it's not more complicated than that." 8/5/10 Tr. at 49 (Damsbo). That combination "was the only relevant other angle for treating Type II diabetes . . . apart from the sulfonylureas." *Id*. at 52. The sensitizer metformin was chosen because, by attacking the disease from different angles, "you might get a better effect, a synergistic effect." *Id*. at 54 (emphasis added).

14. Müller had another reason for studying the effect of the repaglinide/metformin combination on patients that were not adequately controlled on metformin alone. While

[8]References to the transcript will be cited in the following form: "Date, Tr. at __", followed by the witnesses name in parenthesis, where appropriate.

monotherapy with a new drug is necessary for regulatory review:

> you also try to keep a focus on how you can prove something new and exciting, not least for your marketing colleagues when they have to go out and sell your product after approval . . . [T]his would be an obvious -- not obvious, but a good idea of where to expand your market . . . . It would be a scientifically sound thing to do. It would not cannibalize on the markets we were already looking for. So in that respect, I think it made sense.

6/8/10 Tr. at 13-14 (Müller).

15. The protocol for a clinical trial of the repaglinide/metformin combination on patients failing on metformin alone was developed under Müller's direction. *Id*. at 22. The study was conducted in Australia during 1995-96 by a team of investigators led by Moses. 8/5/10 Tr. at 201 (Miller).

16. On June 13, 1997, Novo filed a patent application on this combination therapy in Denmark, and filed a provisional application in the United States on October 29, 1997. The '358 patent was granted on January 13, 2004. The critical date for prior art under 35 U.S.C. §102(b) is therefore October 29, 1996. The same critical date applies to prior art under §102(b)/103. *See* Memorandum of June 9, 2010 (Doc. 417).

17. Claim 4, the only claim in suit, reads as follows:

> 4. A method for treating non-insulin dependent diabetes mellitus (NIDDM) comprising administering to a patient in need of such treatment repaglinide in combination with metformin.

C. Prosecution History

18. The patent examiner issued four successive rejections of Müller's application as obvious over the prior art. The first rejection was based upon a 1996 written by one of Novo's expert witnesses, Melander. (Melander Article).[9] The examiner stated:

[9] *See* Appendix I and n.1, *supra*.

> Melander teaches combination therapy as a rational approach to the treatment of NIDDM comprising administering agents that have different mechanisms of action and different side-effect profiles. . . . One skilled in the diabetes art would have been motivated to combine two hypoglycemic agents as one pharmaceutical composition to treat NIDDM based on their onsets and durations of action in view of the teaching of Melander. Such would have been obvious in the absence of evidence to the contrary because it would have been reasonable to expect clinical efficacy to be additive, while dosage and side-effect profiles could be decreased, following the administration of clinically effective agents that demonstrate different modes of action.

JX 2A, Tab 3 at C0172889-90, Office Action dated 10/19/2000.

19. In response, Novo's' argument included reliance on Example 3 of the application, which contains the data from the Moses Study, as demonstrating an unexpected "synergistic effect." *Id*. at Tab 4, C0172904-05, Amendment and Response filed 1/15/2002.

20. The examiner then repeated her obviousness rejection based upon the Melander Article and made the rejection Final. *Id*. at Tab 6, C0172930-31, dated 3/15/2001.

21. Novo's next Amendment and Response argued that the Melander Article did not suggest the specific combination of repaglinide and metformin; that "obvious to try" is not a proper basis for rejection (KSR's endorsement of that basis had not yet occurred); and again argued that Example 3 in the application demonstrated an unexpected synergistic effect. *Id*. at Tab 8, C0172937-39, dated 7/6/2001.

22. The examiner withdrew the Final Rejection because she entered an additional ground of rejection, not here relevant. She further stated that the claims failed to recite a synergistic effect in quantitative terms, and repeated her position that Melander's teaching made the claimed combination obvious. *Id.* at Tab 9, C0172944-45, dated 7/23/2001.

23. Novo then repeated its earlier arguments, adding that the law does not require that the improved or unexpected properties relied upon be included in the claims. Id. at Tab 11, C0172955-57, dated 1/15/2002.

24. A fourth and final obviousness rejection of all claims followed:

> The prior art is replete with examples of combination therapy wherein side-effects are minimized, dosages are reduced and a more clinically beneficial outcome is observed as compared with monotherapy [additional prior art publications omitted]. One skilled in the diabetic art would have been motivated to combine metformin for its longer acting effects and its ability to reduce blood glucose levels with a shorter acting, insulin-releasing agent having a rapid onset of action, in view of the teachings of Melander. Repaglinide and A-4166, which are more rapid in their onset of action and are shorter-acting, and are specifically disclosed by Melander, would have reasonably been preferable to the older sulfonylureas.

Id. at Tab 13, C0173001-02, dated 4/16/2002.

25. Novo's next Amendment and Response reiterated its "unexpected and synergistic effect" arguments, and submitted a Declaration of Sturis (Sturis Declaration, PX 233). The Sturis Declaration reported the results of his study of the repaglinide/metformin combination on Zucker obese rats,[10] and concluded that his data showed:

> . . . synergistic effects on glucose tolerance in Zucker obese rats and that this data, taken together with the data presented in Example 3 of the present application, strongly suggests that the combination of repaglinide and metformin has synergistic properties in type 2 diabetic patients.

Id. at Tab 14, C0173015, 10/16/2002.

26. Although the Sturis Declaration did not itself conclude that the test results were either unexpected or surprising, the accompanying Remarks of Novo's attorney, Dr.

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[10]Zucker obese rats are a breed of rats specifically bred for use in research as models for obesity, diabetes and heart disease. See http://www.ratbehavior.org/RatSpecies.htm (last visited Jan. 13, 2011)

Richard Bork (Bork), asserted that the data contained in the application and in the Declaration "provides clear evidence of synergy . . . in the treatment of type II diabetes," and that any prima facie case of obviousness "is rebutted by the evidence of synergistic and surprising results achieved by the claimed combined therapy in humans." *Id*. at Tab 14, C0173010.

27. These submissions caused the examiner to withdraw her rejection of claims to the repaglinide/metformin combination. She unequivocally stated her reason:

> Based solely on the Declaration submitted by Dr. Sturis and reconsideration of the synergistic effects demonstrated in Example 3, pages 11-12 of the specification, and Table I, page 14, which are limited to the combination of metformin and repaglinide, this rejection of record is withdrawn for claims 25-29 and 31-33. Neither the Declaration nor the showing in the specification is directed to an unexpected synergistic effect resulting from the combination of compound AY4166 [nateglinide] and metformin. For the reasons of record, the rejection of record under 35 U.S.C. 103 is maintained with respect to claim 30.

Id. at Tab 17, C0173146. Although the examiner's first sentence is clear enough, the second sentence confirms that it was the presence or absence of evidence of the "unexpected synergistic effect" that was the sole basis of her decision. Although the examiner's first rejection opined that it was "reasonable to expect clinical efficacy to be additive" when drugs having differing modes of action were combined, the examiner cited no prior art describing or predicting synergistic (i.e., more than additive) results.

28. Additional Patent Office proceedings, not relevant to the issue of validity of Claim 4 in suit, followed the examiner's withdrawal of the rejection, and the '358 Patent issued on January 13, 2004. (JX 1). Claim 4 corresponds to application claim 29, which was never amended during the prosecution of the application.

VI. ANTICIPATION

A. Discussion

29. Caraco contends that Claim 4 is anticipated by the Rachman's 1995 article (Rachman). The article teaches the benefits of combination therapy for treatment of Type II diabetes, using insulin sensitizers and insulin secretagogues. It specifically identifies metformin as one of the first group and repaglinide as one of the second. Novo's expert, Garber, conceded that Rachman "suggests that metformin combined with repaglinide will give you additive effects [in diabetes patients]" 8/11/10 Tr. at 87 (Garber).

30. However, Rachman does not specifically describe the metformin/repaglinide combination in its listing of many individual drugs and drug types. The article also states that it is "uncertain" whether repaglinide will have clinical advantages, "and initial studies do not indicate a major effect" (Rachman at 471). Also, Rachman is listed in the '358 Patent as a reference that was considered by the examiner.

B. Conclusion

31. In sum, Rachman, though strongly probative on the issue of obviousness, does not fairly or directly teach the claimed metformin/repaglinide combination of Claim 4, and therefore does not anticipate Claim 4; the '358 patent is not invalid on grounds of anticipation.

VII. OBVIOUSNESS

A. Discussion

1. The Level of Skill in the Art

32. A person of ordinary skill in the art is a person having a medical degree with training in endocrinology and three years of clinical experience or laboratory research in the field of diabetes treatment. 6/1/10 Tr. at 100 (Accili). This definition, based on Accili's definition, is similar to Garber's except that the latter's definition would require that the three years of experience be in clinical treatment of diabetes. 8/10/10 Tr. at 109 (Garber). The inclusion of the alternative laboratory research experience is appropriate because excellent diabetes research on OADs has been done by laboratory researchers without clinical experience but having familiarity with OAD uses and combinations. 6/1/10 Tr. at 100 (Accili).

2. The Prior Art

33. The critical date for prior art under 35 U.S.C. §102(b)/103 is October 29, 1996. See, ¶ 16, *supra*.

34. Garber testified that the prior art taught "two drugs are better than one" when they have "different mechanisms of actions" and attack diabetes from different angles. 8/11/10 Tr. at 51 (Garber). In response to the Court's question, Garber also agreed that "in general any two drugs which have different mechanisms of action are better than one." *Id*. at 53. Melander testified that the logical progression in testing new diabetes drugs is to test it in monotherapy, including comparison with other monotherapy drugs; then, if successful in monotherapy, in most cases the "next logical step" is to test the drug in combination therapy. 8/9/10 Tr. at 183 (Melander).

35. The "most widely used and most extensively studied" OAD combination as of the critical date was metformin (an insulin sensitizer) combined with a sulfonylurea (a class of insulin secretagogues). (Consensus Statement at 1517); *see also* 6/1/10 Tr. at

125-26 (Accili). "[D]octors have been treating diabetes patients with combinations of metformin with secretagogues for about a half of a century." 8/11/10 Tr. at 44 (Garber). This combination had been prescribed both as separate and as co-formulated tablets. 6/1/10 Tr. at 128 (Accili); 8/11/10 Tr. at 44 (Garber).

36. The rationale for the metformin/secretagogue combination therapy is well summarized in the Melander Article[11] and was further explained by Accili at trial. Insulin secretagogues are OADs that act upon the pancreas' beta-cells to stimulate insulin secretion, thereby lowering blood glucose. OADs that reduce insulin resistance are "insulin sensitizers," because they increase receptivity of muscle and fat tissue to insulin's action. Thus, sensitizers improve glucose utilization by the body, and act on the liver to reduce glucose production there. 6/1/10 Tr. at 114-16 (Accili). Melander taught that if monotherapy with either of these types of drugs does not result in near-normal glucose levels:

> [C]ombination treatment seems rational for a number of reasons. These agents have different mechanism of action and different side-effects; hence the clinical efficacy would be additive while dosage and side-effects could be minimized.

(Melander Article at 146).

37. Other prior art reported the beneficial effect of combination therapy using the sensitizer metformin with secretagogues such as the sulfonylureas, because of their different mechanisms of action. A 1965 article stated that "[t]he two drugs thus act synergistically, the sulphonylureas to augment release and plasma activity of insulin,

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[11]The Melander Article was published in September, 1996, before the critical date, and is a survey of pre-1996 literature rather than an original study. 6/7/10 Tr. at 23-25 (Accili).

and the diguanides [biguanides, such as metformin] to potentiate its effect on the tissues. . . . The *apparent synergistic* effect of the sulphonylureas and diguanides is probably due to their different modes of hypoglycaemic action." (Clarke at 1251) (emphasis added); 6/1/10 Tr. at 127 (Accili).

38. In 1995, the Consensus Statement reported that "the availability of agents that act by differing mechanisms or may have differing side effects permits the design of individualized regimens that address the heterogeneity of the pathophysiology of NIDDM." (Consensus Statement at 1515). After discussing sulfonylureas and metformin, the Consensus Statement observed that where glycemic goals are not maintained with an initial medication, "in most patients, it is reasonable to consider combination therapy." *Id*. at 1517. Further, "[t]he most widely used and most extensively studied combinations are a sulfonylurea plus metformin or a sulfonylurea plus insulin." *Id*. *See also*, 6/1/10 Tr. at 125-26 and 148 (Accili).

39. Metformin is a member of the biguanide class, the oldest class of insulin sensitizers. Of the three members of that class known before the critical date, it was the only one currently available for clinical practice in most countries, the other two either having been withdrawn or never approved because of safety issues. 6/1/10 Tr. at 116 (Accili); Melander Article at 145. Metformin was approved by the FDA in 1995, and quickly became popular in the United States, both in monotherapy and combination therapy. 6/1/10 Tr. at 119 (Accili).

40. Two classes of insulin secretagogues were known before the critical date: sulfonylureas (used since the 1950s) and meglitinides (repaglinide and netaglinide). At that time, only the sulfonylureas were approved by a regulatory body for treatment of

NIDDM. The Melander Article identified two new non-sulfonylurea "insulin-releasing drugs," then under study: repaglinide and A-4166 (netaglinide, repaglinide's sister meglitinide). He described them as having similar action to sulfonylureas, though absorbed and eliminated more quickly. Although they had not yet been approved, Melander said they "look very promising" because possibly less likely than sulfonylureas to cause dangerously low blood sugar levels. (Melander Article at 145). *See also*, 6/1/10 Tr. at 114-15 (Accili); 8/9/10 Tr. at 145 (Melander). Melander himself admitted at trial that his article would have encouraged a person of ordinary skill in the art to scientifically study the combination of repaglinide with metformin. 8/9/10 Tr. at 197 (Melander).

41. A 1995 article also encouraged combining OADs having different mechanisms of action, because “the limited efficacy of sulphonylureas and metformin on their own . . . make polypharmacy inevitable in many cases.” (Rachman at 474). He added that it was “likely” that such therapy “will have additive effect.” *Id*. at 467. The article specifically described repaglinide as a “non-sulphonylurea secretagogue.” *Id*. at 471. Although Rachman did not specifically describe the repaglinide/metformin combination, Garber conceded that Rachman “suggests that metformin combined with repaglinide will give you additive effects [in diabetes patients].” 8/11/10 Tr. at 87 (Garber).

42. Further evidence of the state of the art as of the October 29, 1996 critical date is found in a November 12, 1996 publication (Kaku). Although published two weeks after the critical date, Garber agreed that the article was “just recapping the prior art” and that

it had been written and submitted for publication 2-6 months earlier.[12] 8/11/10 Tr. at 78, 83-84 (Garber). Kaku described repaglinide as a "new insulin secretagogue" that is rapid and short-acting, and stated that "it is expected to be used" to improve postprandial hyperglycemia and to reduce delayed hypoglycemia (Kaku at NOVO-6741638). He also stated that that "combination therapy using these agents will be performed largely, because these agents have individual unique characteristics" *Id*. at NOVO-6741641, Figure 2 of the article displayed secretagogues as being combined with biguanide sensitizers (such as metformin). *Id*. at NOVO-6741644.

43. Garber acknowledged that, before the critical date, one of ordinary skill in the art "may" have considered repaglinide an appropriate candidate for combination therapy for at least some patient populations (namely, those whose "post-prandial," or after-meal, glucose levels were not under control.) 8/11/10 Tr. at 94 (Garber).

44. As part of the argument that it would not have been obvious to try combining repaglinide with metformin, Novo asserted that in 1996 there were at least 44 known OADs that provide at least 900 possible two-drug OAD combinations. *See* PX 477. This list includes seven insulin sensitizers (one biguanide, i.e., metformin and six TZDs), twenty insulin secretagogues (fifteen sulfonylureas and five meglitinides, including repaglinide), five glucose absorption inhibitors, six gluconeogenesis inhibitors and six weight-loss agents. Appropriately, Novo listed but did not count among the 44 OADs two other biguanides that were widely recognized as unsafe.

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[12] "The fact of near-simultaneous invention, though not determinative of statutory obviousness, is strong evidence of what constitutes the level of ordinary skill in the art." *Ecolochem, Inc. v. So. Cal. Edison Co.*, 227 F.3d 1361, 1379 (Fed. Cir. 2000).

45. Accili, however, disagreed that each of these 44 OADs was appropriate for treatment of Type II diabetes. He considered the list "the proverbial kitchen sink," including drugs whose use would be considered malpractice. He named seven of the 44 that he could not in good conscience prescribe to anyone. 6/3/10 Tr. at 21 (Accili). In response to the Court's questions, Accili stated that Novo's expanded list included drugs that had been considered as potential OADs at some time before 1996, but had been "totally discredited" by 1996. *Id*. at 21-22. He gave specific reasons, such as limited efficacy, discontinued availability, toxicity or other concerns for long-term safety. Id. at 8-13, 18, 24. Even Garber admitted that there were "no reputable weight-loss agents" due to "either limited efficacy or . . . concerns about their long-term safety." 8/11/10 Tr. at 75 (Garber). Similarly, he admitted that development of gluconeogenesis inhibitors "had been hampered by toxicity," and that none had reached the market even as of today. *Id*.

46. Later, again in response to the Court's questions, Accili stated that Novo's expanded list was the "potential universe" but it would have to be modified to show the "effective universe." 6/7/10 Tr. at 22-23 (Accili). At the Court's request, Accili prepared a chart showing the effective universe of OAD drugs. PX 477A, a copy of which is found in Appendix II. The chart lists (1) five sensitizers, including one biguanide (metformin) and four TZDs; (2) nine insulin secretagogues, including seven sulfonylureas and two meglitinides (repaglinide and nateglinide); and two glucose absorption inhibitors. As of the critical date, the TZDs were still in the testing stage, some having been withdrawn. Only two were considered viable, and none was approved by the FDA until 1997. 6/1/10 Tr. at 119 (Accili). Glucose absorption

inhibitors interfere with the conversion of carbohydrates to glucose in the small intestine. As of the critical date it was known that this class of drugs does not directly treat either of the two causes of NIDDM, i.e., decreased insulin secretion or impaired insulin action. One of these, acerbose, was used before the critical date, but was known to have a modest effect relative to metformin and the sulfonylureas. 6/1/10 Tr. at 119-20 (Accili).

47. According to the Consensus Statement, the metformin/sulfonylurea combinations had already been widely studied and used, and several other potential combinations had been examined and used to a lesser extent. Consensus Statement at 1517. Thus, the untested candidates for combination therapy represented only a fraction of the seventeen OADs comprising the effective universe charted on PX 477A. Melander explained that it would have been "more interesting scientifically and clinically to examine combination therapies with metformin and repaglinide," as well as some others, than the already studied combinations of metformin and sulfonylureas. 8/9/10 Tr. at 195-96 (Melander).

48. Accili's testimony regarding the effective universe of candidates for combination therapy was credible. As of the critical date, this universe of potential or previously combined OADs included a "finite number of identified, predictable solutions." *KSR*, supra. The guidance provided by the prior art's teaching of the benefits of combining insulin secretagogues and insulin sensitizers created a reasonable expectation of success in achieving at least additive results from combination of these candidate OADs. *See Bayer Schering* and *Pfizer*, *supra*. In other words, the Court is not persuaded by Novo's argument that it was not obvious by the prior art to try combining repaglinide and metformin. Indeed, as explained above and below, quite the opposite

was true.

49. Novo also asserts that prima facie obviousness is precluded because the prior art taught away from the claimed combination. Specifically, repaglinide was known to have a small impact on fasting plasma glucose (FPG) due to its short biological activity life.

50. According to Melander because repaglinide was quick-acting and quickly eliminated from the body, it was viewed as a “niche compound” useful for only a "narrow and very specific patient population." 8/9/10 Tr. at 84 (Melander). However, Melander's own article, after citing these properties, stated that repaglinide would lessen certain risks and looked “very promising.” (Melander Article at 145). He also admitted that his article taught that a short-acting sulfonylurea (glipizide) could be combined with metformin in some circumstances, without problem; that all sulfonylureas, in principle, achieve the same results; that “sulfonylurea and repaglinide are alternatives if you're looking for an insulin secretagogue;” and that the article encouraged a person of ordinary skill to study the metformin/repaglinide combination. 8/9/10 Tr. at 177-78, 182, 193-94, 197-98 (Melander); *see also* 8/11/10 Tr. at 64-66 (Garber). And Garber admitted that even if repaglinide were not beneficial for high-FPG patients, Rachman still suggested that its combination with metformin could produce additive effects and be useful for patients with elevated post-prandial glucose. *Id*. at 87, 94 (Garber); Rachman.

51. The examiner, as more fully quoted above (¶¶18, 24), also cited the Melander Article to support her view that rapid and short-acting repaglinide “would have reasonably been preferable to the older sulfonylureas” for combination with

longer-acting metformin. PX 2A at Tab 13, C0173001-02, dated 4/16/2002.

52. In sum, the prior art as a whole did not teach away from combining repaglinide with metformin, even if beneficial results might not be obtained for all Type II diabetes patients.

3. Prima Facie Obviousness

53. As presented in detail above, the record clearly and convincingly establishes that the prior art supplied the teaching, suggestion and motivation to combine repaglinide with metformin as combination therapy for Type II diabetes. The prior art taught that two drugs having different mechanisms of action in treating Type II diabetes are better than one.

54. The combination of metformin (an insulin sensitizer) and a sulfonylurea (a class of insulin secretagogues) had been widely studied and successfully used because of their differing mechanisms of action. This drug combination was the closest prior art. The prior art described the effect of this combination therapy as additive and synergistic.

55. Repaglinide was a known insulin secretagogue having a similar mechanism of action to sulfonylureas, especially the fast-acting sulfonylureas, and hence was known to have a different mechanism of action than metformin.

56. It was a logical testing progression to try combination therapy once monotherapy with a new drug (here, repaglinide) proved successful. Clinical efficacy would be additive while dosage and side-effects could be minimized.

57. Whether looking for a secretagogue to combine with metformin, or a sensitizer to combine with repaglinide, a finite number of identified predictable solutions existed among the OADs in the effective universe of candidates for combination therapy.

58. Metformin was the most widely used insulin sensitizer, and the only one available in most countries. The effective universe of insulin secretagogues to combine with it comprised a maximum of seven sulfonylureas (several of which had already been successfully so combined), and two new meglitinides (repaglinide and nateglinide).

59. The effective universe of insulin sensitizers to combine with repaglinide comprised a maximum of four TZDs and one biguanide (metformin, the most widely used sensitizer). This universe qualifies as a "finite number of identified, predictable solutions." *KSR*, 550 U.S. at 421.

60. Novo's experts admitted that the prior art suggested to persons of ordinary skill in the art that the combination of repaglinide and metformin be studied (Melander), and that such combination would produce additive effects in the control of glucose levels in Type II diabetes patients (Garber). There was a reasonable expectation of successful and beneficial results from the claimed combination, including reduction in HbA1c, FPG and insulin resistance.

61. Market pressure motivated Müller to expand Novo's market for repaglinide by incorporating it in combination therapy as well as in monotherapy.

62. Müller, who was charged with developing repaglinide for the market, considered it a good idea to combine it with metformin because of their complementary mechanisms of action. He expected such combination therapy to provide additional improvement in glucose control for patients inadequately controlled on metformin alone.

63. Metformin was the first and only sensitizer chosen by Müller for combination therapy testing with repaglinide. His colleague, Damsbo, considered it the “natural” combination, and the only relevant angle for treatment other than a sulfonylurea.

64. These facts are reinforced by the repeated rulings of the examiner, quoted above, regarding the teaching, suggestion and motivation provided by the prior art, based primarily upon the same Melander Article. Significantly, the examiner did not have the benefit of the testimony Müller and Damsbo as to their motivation to make the claimed combination, and their expectations for its results. Those expectations were consistent with those taught by the prior art.

65. In view of these facts, established by clear and convincing evidence, a person of ordinary skill in the art, as of the critical date, would have found it obvious to try the combination of metformin with repaglinide as a potential treatment for Type II diabetes. As such, the Court finds that a prima facie case of obviousness exists.

4. Secondary Considerations

(a) Background and Relevant Precedents - Unexpected Results

66. Before reaching the ultimate conclusion on the issue of obviousness, the evidence and assertions of unexpected and surprising results, as well as synergistic results, must be considered. The case law has sometimes referred to this factor as a "secondary" consideration, placing it in the category with commercial success, copying, failure of others and long-felt but unsolved need. These sources of evidence provide only an indirect bases for inferring nonobviousness, whereas the Court views evidence of surprising or expected properties as more direct and technological evidence bearing more directly on the statutory inquiry as to "the differences between the subject matter sought to be patented and the prior art."[13] 35 U.S.C. §103(a). Because in patent law,

[13]On this and other points, the thorough and insightful analysis of Professor Rebecca S. Eisenberg in her article, *Pharma's Nonobvious Problem*, 12 LEWIS & CLARK

"a compound and all of its properties are inseparable," evidence of the properties of the claimed compound is directly relevant to show what the claimed invention is. *In re Papesch*, 315 F.2d 381, 391 (C.C.P.A 1963).

67. In response to a question by the Court, Novo's counsel provided a useful definition: "a surprising result or surprise in the context of this case would be if there is a result that is inconsistent with what was known in the art, inconsistent with an expectation of a person of skill in the art based on the literature or the accumulated knowledge . . . ." 8/5/10 Tr. at 29.

68. Two contrasting Federal Circuit decisions involving allegedly unexpected results provide a useful perspective and framing for the present issue. First, in *McNeil-PPC, Inc. v. L. Perrigo, Co.*, 337 F.3d 1362 (Fed. Cir. 2003), McNeil was faced with the expiration of its patent on loperamide, the active ingredient in its best-selling antidiarrheal product. McNeil sought to patent an improvement to extend its market-leading position. *Id*. at 1364. The patent had composition and method claims drawn to loperamide (or one of a specified group of other antidiarrheal compounds) in combination with the known antiflatulent simethicone for the treatment of diarrhea and flatulence (gas). The prior art described many combinations of various antidiarrheal drugs with simethicone, and the court found it obvious to substitute loperamide in the combination with simethicone, *id*. at 1367). Thus, the Federal Circuit found the patents invalid. The Federal Circuit also found that the district court had properly discounted the secondary indicia of nonobviousness, in that McNeil had commercial motivation to make

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L. REV. 375, 418 (2008) should be considered.

the combination; the evidence commercial success was obscured by massive advertising; and the proffered clinical studies were too inconsistent and lacking in appropriate comparative tests to demonstrate unexpected or synergistic effects. *Id*. at 1370.[14]

69. In *Ortho-McNeil v. Mylan Laboratories*, 520 F.3d 1358 (Fed. Cir. 2008), the patent was directed to a new chemical compound that has had substantial commercial success as a significant epilepsy drug. The new compound was created as an intermediate byproduct in the course of the inventor's search for a new antidiabetes drug. The record showed that it was unlikely that a person of ordinary skill would have started with the formulation that the inventor started with; there were no clues as to what properties that the claimed intermediate might have; and no reason to interrupt the development process and test this intermediate "for properties far afield from the purpose for the development in the first place (epilepsy rather than diabetes)." *Id*. at 1364. The court observed that "this clearly is not the easily traversed, small and finite number of alternatives that *KSR* suggested might support an inference of obviousness. *Id.* The record also showed "powerful unexpected results," skepticism of experts,

[14]Caraco strongly relies on *Richardson-Vicks, Inc. v. Upjohn Co., et al*, 122 F.3d 1476 (Fed. Cir. 1997), where obviousness was found, notwithstanding unexpected and unchallenged synergism. While that case has many factual similarities to the present case, a careful reading reveals that the only difference between the claimed combination and the prior art was that the same two prior art drugs that were claimed in the patent as a "combinatory immixture" (i.e., in a single tablet) had been prescribed together but as separate tablets. Id. at 1480, 1483-84. Relevant to the issue of claim scope discussed in Part VI(A)(4)(a)(iv), infra, the examiner allowed the claims only when a new claim set limited in scope to the specific dosages used in the synergy-proving tests was submitted. *Id*. at 1482. Thus, this case is not particularly illuminating to the issue at hand.

copying and commercial success. *Id*. at 1365. Accordingly, the Federal Circuit affirmed the holding of nonobviousness.[15]

70. These cases illustrate that determining whether an unexpected result exists requires a detailed factual analysis of the trial record.

(b) The Trial Record - Unexpected Results

71. The question of unexpected and surprising results was extensively and vigorously contested by the experts at trial. All of them, including Garber, aided in an understanding of this complex subject matter. However, on the particular issue of unexpected results, Garber was frequently required to retreat from opinions expressed in his direct testimony when confronted by his earlier deposition testimony and his own and others' prior contradictory publications.

72. Although the examiner cited the Melander Article as suggesting that combination therapy should be additive, she cited no predictions or reports of synergistic results from the closest prior art. As noted above (¶27), the examiner ultimately withdrew her rejection of Claim 4 "solely" on the basis of the evidence of the unexpected synergistic effects of the claimed combination. However, the examiner:

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[15]Novo strongly relies upon *Sanofi-Synthelabo v. Apotex*, 550 F.3d 1075 (Fed. Cir. 2008), where nonobviousness was found. Unlike Müller's combination of two prior art drugs, following the roadmap of the prior art, the patent in *Sanofi* was on an entirely new compound for preventing blood-thrombotic events such as heart attacks and strokes. It resulted from a very complex, costly and unpredictable process of separating components of a compound that itself had been the result of years of costly trial and error research. The physical properties of the separated components, even if they could be obtained, were not only unpredictable, but were most likely to have an unpredictable blend of beneficial and toxic properties. The component that became the subject of the patent had the "rare" characteristic of possessing only favorable activity and no toxicity. *Id.* at 1080-81, 1087-90. Thus, this case is not analogous.

· did not have the benefit of the testimony of Müller and Damsbo as to the results they expected (¶¶ 12-13, *supra*);

· was unaware that several prior art publications described or predicted synergistic results from combination therapy with metformin and secretagogues of the sulfonylurea type (¶¶ 71-75 *infra*);

· did not have the benefit of expert testimony concerning reasonable expectations for, and explanation of the results of, the claimed combination (¶¶ 34-36, 40-43, 50 *supra*; 83-85, *infra*);

· was unaware of the undisclosed conclusions of the Sturis Declaration (¶ 141, infra).

70. Repaglinide was known to have properties and effects similar to those of the sulfonylureas in the context of combination therapy. The teachings of several prior art or contemporaneous publications have been described above. (Melander Article, Rachman and Kaku). Moreover, the examiner herself observed that, because of its properties, repaglinide "would have reasonably been preferable to the older sulfonylureas" in combination with metformin. JX 2A at Tab 13, C0173002.

71. Indeed, a 1995 article discussing the results of clinical trials stated that the differing mechanisms of action of metformin and sulfonylureas "can be used alone or together to produce synergistic, if not complementary, actions in various clinical situations." "When metformin and sulfonylureas are used in dual therapy, there is an apparent synergy of action . . . . Such synergy should produce adequate glycemic control in all but the most severe or advanced cases of NIDDM." Karlsson/Garber (DX 307 at 78, 81) (emphasis added).

72. Referring to the results of other clinical trials involving the diguanide (or biguanide) metformin and a sulfonylurea, Clarke, in 1965, see, ¶ 37, supra, states that "[t]he two drugs thus act synergistically, the sulphonylureas to augment release and plasma activity of insulin, and the diguanides to potentiate its effect on the tissues. . . . The apparent *synergistic* effect of the sulphonylureas and diguanides is probably due to their different modes of hypoglycaemic action." (Clark at C0173325 emphasis added).

73. A 1995 article by Novo's expert, Garber, states that:

> Combination therapy with both sulfonylureas and metformin is the next logical step to control NIDDM patients not adequately treated with either agent alone. Additive or synergistic action to control hyperglycemia should be anticipated . . . .

(Garber at 84 emphasis added).

74. Another 1995 article by Garber refers to the extensive clinical experience with metformin in Europe and Canada in the past 30 years, and states that "[i]t may also be used in combination with a sulfonylurea in patients not responding adequately to sulfonylurea or metformin monotherapy, because these agents work by different mechanisms and appear to have a *synergistic* effect when used concomitantly." (Garber II at 568, emphasis added, *see also* at 578-80).

75. Similarly, a 1995 Bristol-Myers Squibb Company product monograph describing its Glucophage brand metformin drug states that it is "synergistic in combination with a sulfonylurea." (Bristol-Myers at 3, emphasis added).

76. As of the critical date, a person of ordinary skill in the art would have reasonably expected success in the form of beneficial, and even synergistic, results in the control of glucose levels by combination therapy using metformin and repaglinide. This finding is

based upon the evidence described above establishing that: (1) the closest prior art was combination therapy using metformin and a sulfonylurea; (2) combination therapy using metformin and one of the sulfonylurea class of secretagogues was well known in the art to produce beneficial and even synergistic results in controlling glucose levels in Type II diabetes patients; (3) repaglinide was known as an insulin secretagogue having a similar mechanism of action to the sulfonylurea class of secretagogues.

77. As part of its counterargument, Novo relies on three studies to support its claim of substantial and unexpected improvements in glucose control and insulin sensitivity resulting from metformin/repaglinide combination therapy: the Moses Study, that was the basis for data found in the '358 Patent, the Sturis Study, and the Pfeiffer Study. Each study is discussed in turn below.

(i) The Moses Study

78. For the Moses Study, patients failing on metformin monotherapy were chosen for the test population. One test parameter was HbA_{1c} or glycosylated hemoglobin, which shows the average glucose level in the recent past. Combination therapy reduced that level by 1.41%, about twice the drop produced by the two monotherapy treatment results combined. 8/5/10 Tr. at 124 (Miller); Moses Study at table 8-1, Figure 8-1; top half of DX 393, page 2.

79. Novo particularly emphasizes the dramatic reductions in fasting plasma glucose (FPG) levels resulting from metformin/repaglinide combination therapy for the patients in the Moses Study. Novo's witnesses testified that little or no reduction in FPG was expected in patients who were failing on metformin monotherapy because of repaglinide's known short duration of action. 8/10/14 Tr. at 148 (Garber); 6/7/10 Tr. at

91, 97-98 (Moses). Yet the combination therapy test results showed a reduction in FPG of more than eight times the reduction achieved by metformin alone. (Moses Study at Table 8-3, Figure 8-2; top half of DX 393, page 1). This result was asserted to be even more surprising because achieved with lower repaglinide dosages than given to the repaglinide monotherapy patients in the study, i.e. an unexpected "dose-sparing effect."

80. Various Novo witnesses and documents described the Moses Study results as "suggestive" of synergy, or showing synergistic "effects" or "properties" in the metformin/repaglinide combination. These qualifications were appropriate, because it was agreed that the Moses Study was not designed to show, and could not show, statistically significant synergy because ethical reasons precluded removing the sick patients from all therapy in order to perform the required placebo-placebo control group arm of a more comprehensive test. *See e.g.*, 6/7/10 Tr. at 120 (Pagano); 6/10/10 Tr. at 54-55 (Thaler); 6/7/10 Tr. at 89 (Moses).

81. Novo contends that, to this day, there is no explanation for the unexpected improvements in HbA_{1c} and FPG resulting from this combination therapy, and no explanation for the "dose-sparing effects" from such therapy.

82. However, the dispositive fact in this analysis of Novo's various study test results, however, is whether the results were unexpected, not whether they were suggestive of synergism or even statistically synergistic. *See* MPEP §716.02(c), quoted in footnote 3, supra. If synergistic results were expected, they would not negate obviousness. Moreover, a convincing explanation for the Moses Study test results was offered at trial.

83. Accili explained that the patients in the Moses Study, chosen because they were failing on metformin monotherapy, were therefore experiencing the effects of glucose

toxicity and insulin resistance, wherein the body resists insulin's action. 6/1/10 Tr. at 110-12 (Accili). In this condition, the pancreas no longer can compensate for this insulin resistance. Both post-prandial and fasting hyperglycemia result, the former because the body is unable to process glucose from the meal, and the latter because of increased glucose production by the liver resulting from impaired insulin action there. The resulting hyperglycemia is self-perpetuating and extremely dangerous. On the other hand, lowering hyperglycemia in such patients "jump-starts a virtuous cycle that tends to improve glucose metabolism." Id. at 111-12. *See also*, 8/1/10 Tr. at 141-43 (Garber).

84. The patients in the Moses Study had been suffering from uncontrolled glycemic levels for three years. 6/3/10 Tr. at 61-62 (Accili). The prior art taught that glucose toxicity interferes with any OAD's effectiveness, including metformin's ability to improve insulin sensitivity. And reducing glucose toxicity will increase insulin sensitivity. 8/11/10 Tr. at 142-44 (Garber). Garber admitted that the prior art Clark article taught that patients suffering from glucose toxicity, upon receiving combination therapy with metformin and an insulin secretagogue (a sulfonylurea in Clark's study), saw their glucose toxicity wane, allowing the metformin to work as it should to increase insulin sensitivity. That in turn lowered their fasting plasma glucose levels below what it had been with either drug alone. *Id*. at 139-44 (Garber); Clark.

85. Garber was not surprised by Clark's explanation for the increased insulin sensitivity, as that phenomenon was understood even before that prior art article. *Id*. at 140. Clark's conclusion supplies the explanation for the "unexpected" reductions in the HbA_{1c} and FPG level improvements in the patients in the Moses Study once the secretagogue repaglinide was combined with their formerly insufficient metformin

therapy. The repaglinide “jump-started a virtuous cycle” that caused their glucose toxicity to wane so that the metformin could work.

86. Similarly, the result achieved by combination therapy on the patients in the Moses Study, using lower dosages of repaglinide than used in the monotherapy, was the known "dose-sparing" consequence of combination therapy. The examiner cited the Melander Article as support for her view that “[t]he prior art is replete with examples of combination therapy wherein side-effects are minimized, dosages are reduced and a more clinically beneficial outcome is observed as compared with monotherapy.” JX 2A, Tab 13, C0173001-02; Melander Article at 146; Hermann/Melander at 1107.

87. The evidence does not establish that the claimed combination therapy produces clinical results superior to those produced by the closest prior art. The evidence is to the contrary. Two prior art studies reported greater reductions in HbA_{1c} and FPG than those of the Moses Study. The Hermann/Melander study, using metformin and the sulfonylurea glyburide, yielded a 2.3% reduction in HbA_{1c} and 6.1 mmol/l reduction in fasting plasma glucose for patients inadequate controlled on metformin monotherapy; a 2.0% reduction in HbA1c and 4.8 mmol/l reduction in fasting plasma glucose for patients inadequately controlled on glyburide monotherapy; and a 2.2% reduction in HbA1c and 6.1 mmol/l reduction in fasting plasma glucose for naïve patients treated with the metformin/glyburide combination. Hermann/Melander, Table 4.

88. The DeFronzo study of the same metformin/glyburide combination yielded a 1.7 % drop in HbA1c and 3.5 mmol/l reduction in FPG. DeFronzo; 6/2/10 Tr. at 25 (Accili). These reductions are all greater than those of the Moses Study (a 1.4% reduction in HbA1c and 2.18 mmol/l reduction in FPG).

89. The probative value of these comparative numerical results is challenged by Novo, because of differences in the patient populations and treatment parameters, and the associated expectations for the treatments. Both Novo and Caraco have stressed the important role of the particular characteristics of various Type II diabetes patient sub-populations in predicting and explaining the results of OAD therapy. While these numerical comparisons may therefore not establish that clinical results of the claimed combination were inferior to those of the closest prior art, neither does the record contain any comparative test results establishing superiority of the claimed combination.

90. But there is other less challengeable evidence that is persuasive of the fact that the clinical efficacy of the claimed combination therapy is not superior to the efficacy of the closest prior art. First, Garber is a practicing physician who has spent his entire 35-year career focused on the treatment and management of diabetes, both treating patients and conducting clinical studies. 8/10/10 Tr. at 100-01 (Garber). Garber testified that he "rarely prescribe[d]" the claimed combination, and "the situations in which I would normally use repaglinide would not be situations in which I'd normally use metformin." 8/11/10 Tr. at 132, 134 (Garber). He also testified that he was "probably not" offering an opinion that the claimed combination is superior in terms of efficacy to the prior art metformin/sulfonylurea combination. *Id*. at 112-13.

91. Second, and by contrast, Accili has spent 24 years doing research in diabetes in academia, administrative agencies and clinical capacities. He also treats patients and supervises diabetes-related clinical trials. 6/1/10 Tr. at 95-96 (Accili). Accili testified that he prescribes combination therapy with metformin and sulfonylureas about 20 times more often than with the metformin/repaglinide combination. 6/7/10 Tr. at 37.

92. Third and finally, a Novo-financed literature review published in 2008 discusses the Moses Study and Pfeiffer Study, along with studies of metformin/sulfonylurea combinations. The author concludes that "[c]ollectively, these data indicate that combination therapy with repaglinide plus metformin may provide efficacy *comparable* to other combinations plus a favorable safety profile in the early treatment of type 2 diabetes." Raskin, at 1172 (emphasis added). Thus, twelve years after the Moses Study, Raskin was unable to conclude that the claimed combination produced results superior to those provided by the closest prior art.

93. These specific examples are reinforced by the overall market's reaction to the claimed combination. As presented more fully in Part VII(A)(4)(c) Commercial Success, *infra*, only a small and declining percentage of Type II diabetes patients taking OADs are taking the claimed combination therapy. The record as a whole therefore does not support a conclusion that the claimed combination yields superior results to those of the closest prior art.

94. Notwithstanding that several Novo witnesses testified as to their surprise at the Moses Study results, the weight of published prior art and expert testimony compels the conclusion that one of ordinary skill in the art should have expected successful, and perhaps even synergistic, results from the combination therapy given to the patients in the Moses Study.

95. Further, the trial testimony in 2010 of Novo's witnesses proclaiming their surprise in 1966 concerning the unexpected and "synergistic" results of the Moses Study is unsupported by contemporaneous documents. The 1996 Clinical Trial Report of the Moses Study, signed by Moses, stated that the combination therapy "produced

statistically superior glycemic control" compared to monotherapy with the two constituent drugs. There is no mention of synergism or even suggestions of synergistic effects in the Report. Nor does the Moses Study use the words "unexpected" or "surprising" anywhere in its discussion of Efficacy Results, Conclusions, Efficacy Evaluation, Efficacy Conclusions, Discussion, Overall Conclusions or anywhere else. Miller, who supervised all of Novo's clinical studies in Australia, testified in response to the Court's question that he did not know of any contemporaneous Novo document that mentioned synergism. 8/5/10 Tr. at 194-96 (Miller).

96. The only contemporaneous document in the record is a December, 1996, draft abstract prepared by Novo in Denmark for upcoming medical society meetings, and stating that the data from the Moses Study "suggest" that the claimed combination "*may* have synergistic properties in this type of patients." DX 9 (emphasis added); 6/7/10 Tr. at 84-85 (Moses); *see also* DX 12, PX 206, PX 207. Garber, who studied the paper trail, stated in response to a question by the Court that he did not recall anything exclusive of the trial record that described the results of the Moses Study as surprising and unexpected. 8/11/10 Tr. at 189-90 (Garber). As such, the Moses Study does not support Novo's contention that the claimed combination produces unexpected results in Type II diabetes patients.

(ii) The Sturis Study

97. Novo also relies upon the Sturis Declaration, which was submitted to the examiner to reinforce the results of the Moses Study in demonstrating unexpected and synergistic results from the claimed combination therapy. Sturis stated in his Declaration that his test results showed ". . . synergistic effects on glucose tolerance in

Zucker obese rats and that this data, taken together with the data presented in Example 3 of the present application, strongly suggests that the combination of repaglinide and metformin has synergistic properties in type 2 diabetic patients." JX 2A at Tab 14, C0173015, 10/16/2002.

98. Sturis used Zucker obese rats for his tests. These rats are an accepted animal model with excellent predictive capabilities for humans with Type II diabetes.[16] Sturis, however, admitted at trial that his test results may not translate to humans, and that was why he relied upon the Moses Study's results as well to support his conclusion of "strongly suggest[ed]" synergy in humans. 6//9/10 Tr. at 22-24, 88-89 (Sturis). Notably, the final draft of his abstract of his study stated that "[t]he presence of greater-than additive effects *may* be of relevance to the clinical efficacy of the claimed combination." PX 242 (emphasis added). Three days after his Declaration, Sturis' PowerPoint presentation to Novo's core group in charge of repaglinide development stated with respect to the Moses Study that it was "not possible to assess whether REP/MET combination is additive, synergistic or antagonistic," by which he meant that it was not statistically possible to so assess. DX 56 at 105702; 6/9/10 Tr. at 91-93, 97 (Sturis). These two documents were not provided to the examiner. Sturis was unwilling to testify that the two studies together proved synergism in Type II patients. Id. at 99.

99. Caraco attacks several aspects of the Sturis Study, including the statistical analysis and his selection of a data point that departed from his test protocol. These issues are addressed below in Part VIII(A)(1)(a), dealing with the inequitable conduct

[16] *See* ¶ 25, n.10, *supra*.

issues.

100. The Sturis Study, while pertinent to the synergy debate, is not probative on the question of whether the claimed combination produces unexpected results in Type II diabetes patients.

(iii) The Pfeiffer Study

101. Novo also relies upon a 2003 Novo-funded study by Pfeiffer. The study compared the insulin sensitivity of patients taking only metformin with that of the same patients after they had taken the metformin/repaglinide combination. Because repaglinide is an insulin secretagogue and not an insulin sensitizer, Novo contends that one of ordinary skill in the art would not have expected the results observed by Pfeiffer: the insulin sensitivity of the patients taking both drugs was 35% greater than when those same patients were taking metformin alone. Pfeiffer Study, Pfeiffer II Study, 6/8/10 Tr. at 106-10 (Pfeiffer). Pfeiffer testified that the extent of this increase was extraordinary, statistically significant, clearly synergistic and unexplainable even today. *Id*. at 102, 110, 118.

102. Accili questioned the reliability of conclusions that can be drawn from the Pfeiffer Study, based upon the small number of patients (eleven) and the wide range of their base line characteristics, such as body mass and changes in insulin sensitivity. 6/2/10 Tr. at 38 (Accili). *See also*, 8/11/10 Tr. at 151-52 (Garber). Caraco also asserts that Pfeiffer's results were fully predicted by the prior art Clark article, which taught that even monotherapy with an insulin secretagogue could increase insulin sensitivity. Clark at 9243; 6/8/10 Tr. at 144-49 (Pfeiffer). In response, Pfeiffer pointed out that Clark's study was with a very different type of patient. In contrast to Clark'' patients, who were

suffering from glucose toxicity, the Pfeiffer Study patients were well controlled on metformin. Pfeiffer testified that reduction in glucose toxicity could therefore not fully explain the 35% increase in sensitivity; it would only account for about a 10% increase in sensitivity. *Id*. at 144-46, 179-83 (Pfeiffer).

103. Pfeiffer's trial testimony is inconsistent with the explanation found in his contemporaneous report of his 2004 Study. There, he discussed two possible explanations for the improved insulin sensitivity. He admitted at trial that he copied his first explanation, almost verbatim, from the Clark article. 6/8/10 Tr. at 155-58 (Pfeiffer). The texts of Clark and of Pfeiffer are shown below (and in DX 416):

> The extrapancreatic effects – glucose metabolized per unit of insulin – of glimepiride treatment observed in this study are likely to be secondary to the improved glycemic control during the week of therapy. The latter would be associated with an increase in insulin mediated glucose disposal.

Clark at C0209243.

> This extrapancreatic effect may be related to the improved glycemic control during the one week of treatment hence to the reduction of hyperglycemia-induced insulin resistance (Yki-Jarvinen, 1992). The latter would be associated with an increase in insulin mediated glucose disposal.

Pfeiffer at NOVO-0005433.

104. This discussion describes the glucose toxicity issue, for which Pfeiffer cited Yki-Jarvinen but not Clark's article, which he admittedly copied. 6/8/10 Tr. at 155-58 (Pfeiffer); *see also*, 8/11/10 Tr. at 148-49 (Garber). Pfeiffer's report included "an alternative explanation" for which he cited prior art sources (including Clark), but he concluded that it was "*incredibly likely* that the improvement of insulin sensitivity is related to a waning of glucose toxicity." (Pfeiffer Study at NOVO-0005433, emphasis added).

105. Pfeiffer's contemporaneous explanation that he copied from Clark's prior art article (i.e., waning of glucose toxicity) for the increased insulin sensitivity found in his test results is entitled to greater credibility and weight than his trial testimony that those results were unexpected and unexplainable.

106. Aside from the issue of unexpected results, Pfeiffer's testimony concerning his study contradicts Novo's position that the study is evidence supporting the nonobviousness of the claimed invention. Pfeiffer contended that his study's patient population was not suffering from glucose toxicity because they were well controlled on metformin at the time therapy with the metformin/repaglinide combination began. But Novo asserts that Claim 4 of the '358 Patent is explicitly limited to use for patients "in need of such treatment," i.e., in need of the combination therapy (Post-Trial Brief at 34, emphasis added). If Pfeiffer's patients were already well controlled, and therefore not "in need," then his test results cannot be probative of a "dramatic and unexpected effect of the [claimed] combination therapy" on those in need. *Id*. at 25. Thus, the Pfeiffer Study does not support a finding that the results of the combination was unexpected.

(iv) Scope of Claim 4

110. Also relevant to obviousness in terms of expected results is a determination as to the scope of Claim 4 of the '358 Patent, which specifies a method "for treating non-insulin dependent diabetes mellitus (NIDDM) comprising administering to a patient in need" the claimed combination (emphasis added). As previously stated, the examiner ultimately granted Claim 4 "solely" on the basis of the Sturis Declaration concerning his rat study and "reconsideration of the synergistic effects demonstrated in Example 3, pages 11-12 of the specification, and Table I, page 14." JX 2A, Tab 17 at

C0173146.

111. During discovery, Novo admitted that Claim 4 covers "all instances in which repaglinide is administered in combination with metformin to treat NIDDM." 6/8/10 Tr. at 84-85 (Novo Response to Request for Admission No. 203) (emphasis added). Now, Novo contends that Claim 4 is limited to use for patients "*in need of such treatment*." Novo Post-Trial Br. at 34 (emphasis by Novo). Other than stating that it does not assert that the claimed combination therapy is needed by all Type II diabetes patients, Novo does not specify who is "in need of such treatment" or how to determine whether such need exists.

112. To the extent that there is a difference in scope between "all instances" of administration and administration only to those "in need," Novo should be bound by its earlier admission. Further, Novo would presumably assert that all administrations of the claimed combination would be an infringement, without inquiring into whether the patient really was "in need" of that particular treatment.

113. By Novo's admission, Claim 4 necessarily covers administration of the combination to, e.g., patients who are drug-naïve who start on the metformin/repaglinide combination without previously having taken any OADs. Drug-naïve patients are a known and quantifiable sub-population of NIDDM patients who have received the claimed combination therapy. *See* PX 175 at NOVO-6900704, 6900707 (showing monthly totals of drug-naïve patients starting on such combination therapy).[17]

[17]PX 175 is a compilation of historical prescription data (including, e.g., prescriptions for repaglinide, metformin and the combination thereof) published by IMS, the industry standard source for pharmaceutical market data. 8/10/10 Tr. at 22 (Reisetter).

114. Novo presented no evidence that the claimed combination therapy produced unexpected or synergistic results in drug-naïve patients. In fact, the evidence is to the contrary. In one Novo Integrated Clinical Trial Report where 56% of the tested patients were drug-naïve ("OHA-naïve" or oral antiglycemic agent-naïve, in that Report), "the synergistic effect of combination therapy observed by Moses et al was not consistently seen in this trial." (AGEE-3010, dated 12/2/02 at NOVO-0029328-29). In another, where all of the tested patients were drug-naïve, the conclusion was that "the combined therapy has not shown statistically better results than the drugs used in monotherapy." (AGEE-1411, dated 2/20/06, at NOVO-1008845 and 1008897).

115. The '358 Patent Abstract and the Field of the Invention both identify just one group: "NIDDM patients poorly controlled on metformin alone." The Moses Study was designed to compare the results of metformin/repaglinide combination therapy with monotherapy with either drug "in NIDDM patients inadequately controlled on MET alone." JX 1, at col. 7:66 to 8:3. The specification summarized the results by saying that: "the data also suggest that the combination of REP and MET may have synergistic properties in this type of patient." *Id*. at col. 8:30-31 (emphasis added). Novo's other unexpected-result evidence was confined to Zucker obese rats (the Sturis Study) and patients whose glucose levels were adequately controlled on metformin (the Pfeiffer Study).[18]

116. The type of NIDDM patient involved in the Moses Study (those failing on

[18]It would appear that the latter group, being adequately controlled, were not "in need" of combination therapy. If, as Novo belatedly asserts, the scope of Claim 4 is confined to patients "in need," then the Pfeiffer Study cannot be evidence of unexpected results achieved by the claimed invention. Novo cannot have it both ways.

metformin alone) represents less than 25% of Type 2 diabetes patients. 8/11/10 Tr. at 127 (Garber). Müller admitted that the Moses Study results could not be extrapolated to other patient populations. 6/8/10 Tr. at 77. See also, 6/2/10 Tr. at 29 (Accili). Other Novo studies conducted on other patient sub-populations yielded results that were "inconsistent" with, and even "contrary to," those of the Moses Study. AGEE-3018 at 57; AGEE-3011 at 62, AGEE-1411 at 54. When Damsbo was asked how important the characteristics of a tested patient population is, he answered:

> You have to remember that Type II diabetes is a disease where you have different categories. People have different levels of the disease. So *it's very important* that the population you pick out for a starting is the same, meaning that they have the same weight, the same body mass index, the same glucose levels and the same – that the match each other. *That's critical*.

8/5/10 Tr. at 90-91 (emphasis added).

117. Consistent with Damsbo's testimony, Novo has argued that the Moses test results cannot properly be directly compared with those of the prior art DeFronzo and Hermann/Melander studies because of differences in the tested patient populations.

118. The Moses Study, and the evidence submitted to the Patent Office was limited to one type of patient (not counting the Zucker obese rats). Solely on the basis of that evidence, the examiner allowed Claim 4. Other patients might well have different results from the same treatment. 8/5/10 Tr. at 108 (Damsbo).

119. Thus, even if the Moses Study results in one narrow NIDDM patient sub-population were found to be unexpected, the record does not support a conclusion that the claimed combination would generate unexpected results in "all instances" of administration of that combination to NIDDM patients. In fact, the record is to the contrary, as exemplified by the evidence described above. Therefore, this is not a case

where "one having ordinary skill in the art could ascertain a trend in the exemplified data which would allow him to reasonably extend the probative value thereof." *In re Clemens*, 622 F.2d 1029, 1036 (C.C.P.A. 1980). Novo could have, but did not seek a patent claim restricted in scope to patients failing on metformin alone, or even to those failing on insulin sensitizers generally.

120. Just as a broad independent claim cannot be unobvious when a narrower dependent claim is invalid as obvious, *see Comaper Corp. v. Antec. Inc.*, 596 F.3d 1343, 1350 (Fed. Cir. 2010), so here, when the evidence concerning a subset of Claim 4 (drug-naïve patients) showed no improvement over monotherapy, then prima facie obviousness of Claim 4 has not been overcome by Novo's evidence of alleged unexpected results confined to one narrow subset of patients.

(c) Commercial Success

121. Novo's claim of commercial success of the claimed invention is "a short horse soon curried."[19]

122. Only about 0.5% of NIDDM patient prescriptions for oral anti-diabetes drugs are for the claimed repaglinide/metformin combination. PX 262; 8/10/10 Tr. at 33, 35 (Reisetter). Further, from 2003 to 2007, the number of prescriptions for the claimed combination dropped from 1.24% to 0.71% of the total NIDDM patients taking OADs. PX 175; 8/10/10 Tr. at 41 (Reisetter). Reisetter, Novo's commercial success expert, agreed that use of the claimed combination dropped by 25% from 2003 to 2007. PX

[19]According to the Oxford Dictionary of Proverbs, this centuries-old saying means "A slight task is soon completed. Curried here means 'groomed with a curry-comb.'"

366A; 8/10/10 Tr. at 44-45, 92-93.

123. As cited above, both Garber and Accili stated preference for other combination therapies in their practice.

124. As evidence of commercial success or copying, Novo cites the fact that six major generic drug manufacturers have filed ANDAs for repaglinide. That argument has been rejected by the Federal Circuit. *See Purdue Pharma Prods. L.P. v. Par Pharm., Inc.*, Nos. 2009-1553, 2009-1592, 2010 WL 2203101, at *4 (Fed. Cir. June 3, 2009) ("we do not find compelling Purdue's evidence of copying in the ANDA context where a showing of bioequivalency is required for FDA approval"). Here, the record shows that to the extent that Caraco and other generic manufacturers are seeking to market the combination, they are doing so only under duress because of a belief that Novo had manipulated the FDA Orange Book. This conduct has prevented them from carving out the combination from their proposed labels for repaglinide, the patent on which has expired. Novo's expert on commercial success conceded that these activities of the generic manufacturers should not be characterized as evidence of commercial success of the claimed combination. 8/10/10 Tr. at 69 (Reisetter).

125. The record falls far short of establishing commercial success of the combination therapy of Claim 4.

B. Conclusion

126. Claim 4 of the '358 Patent is invalid because the claimed combination was obvious to a person of ordinary skill in the art at the time the invention was made. Whether measured against the teaching/suggestion/motivation test or the obvious-to-try test, the record contains an abundance of clear and convincing evidence establishing a

strong prima facie case of obviousness.

127. That strong prima facie case of obviousness has not been overcome by Novo's attempt to prove unexpected results and commercial success. Clear and convincing evidence establishes that the results of the claimed combination therapy said by Novo to be unexpected and unexplainable were, to the contrary, expected and explainable in light of the state of the art as of the critical date. Further, the scope of Claim 4 substantially exceeds the scope of the evidence of allegedly unexpected results, and the record clearly and convincingly precludes extending the probative value of those results beyond the small Type II diabetes patient sub-population that experienced them. Finally, the record fails to establish that the claimed invention has been commercially successful.

VIII. INEQUITABLE CONDUCT

A. Discussion

1. Materiality

128. Caraco contends that material information concerning the Moses Study and Sturis Study was, with an intent to deceive the patent examiner, omitted and misrepresented by Sturis and Bork, the attorney who prosecuted the ‘358 patent. Attention is primarily directed to their communications to the examiner on October 16, 2002. JX 2A at Tab 14.

129. As more fully quoted above (¶ 27, supra), the examiner's decision to allow Claim 4 of the ‘358 Patent was “[b]ased solely on the Sturis Declaration and reconsideration of the synergistic effects demonstrated in Example 3, pages 11-12 of the specification, and

Table I, page 14." *Id*. at Tab 17, C0173146. In light of the examiner's previous four rejections based on obviousness, it is clear that the examiner considered the representations of Sturis and Bork concerning synergy (along with Example 3 of the specification) to be highly material to her decision on patentability.

130. The question of unexpectedness of results, rather than the fact or degree of synergism of those results, is the relevant inquiry as to whether prima facie obviousness has been overcome (see n 4, *supra*). It is not necessary to delve any deeper into the thicket of disputed evidence and arguments relating to whether mathematical proof of synergism was established by either the Moses Study or Sturis Study. Nevertheless, representations to the Patent Office by Sturis and Bork about alleged synergism are relevant to the issue of inequitable conduct, in view of the examiner's focus on synergism as the sole basis for the allowance of Claim 4.

(a) The Sturis Declaration

131. Caraco asserts that the Sturis Declaration: (1) highlighted a statistically significant[20] test data point (the two-hour point) that, unknown to the examiner, was not part of his original test protocol; (2) failed to tell the examiner that the area under the glucose vs. time curve, which proved to be statistically insignificant, was the test protocol's primary endpoint; (3) failed to tell the examiner that the rat study alone did not establish that the claimed combination is synergistic in humans; (4) failed to tell the

[20]Statistical analyses that result in "p" values of 0.05 or less are, by accepted standards, considered statistically "significant," while values greater than 0.05 are not. 6/7/10 Tr. at 173-74 (Pagano). The p-value is a value that statisticians use to show the uncertainty in the results of a study. Values of 0.05 or less mean that there is 5 percent or less likelihood that the outcome is the result of pure chance. *Id*. at 126-27.

examiner that, as he reported to a Novo team responsible for repaglinide development, it was "*not possible* to assess whether rep/met combination additive, synergistic or antagonistic" based on the Moses Study, and that the Moses Study was not designed to show synergy. 6/9/10 Tr. at 74, 82-84, 130 (Sturis); DX 56 at NOVO-1015702 (emphasis added).

132. At the time of his Declaration, Sturis was a non-physician Principal Scientist at Novo Nordisk. Responding to the Court's questions, he testified that he knew that mathematical proof of synergy is helpful in getting a patent, and that the Patent Office is interested in knowing whether there is mathematical proof of synergy. 6/9/10 Tr. at 47 (Sturis). For him to be satisfied that there is synergy, he "needed statistical evidence." Id. at 49. Sturis knew that the Moses Study did not demonstrate synergy from a statistical point of view. *Id.* Before the filing of his Declaration, Sturis told Bork that the Moses Study did not demonstrate synergy with statistical proof, and that "you needed mathematical proof" to argue synergy to the Patent Office. *Id*. at 52; see also, *Id*. at 42-43, 47, 53.

133. At trial, Sturis further acknowledged that viewing the Moses Study and his rat study together, he would not say that they "prove[d]" that the claimed combination has synergistic properties in human Type II diabetic patients. *Id*. at 99. Nevertheless, Sturis declared to the Patent Office that his rat study data showed:

> . . . synergistic effects on glucose tolerance in Zucker obese rats and that this data, taken together with the data presented in Example 3 of the present application, strongly suggests that the combination of repaglinide and metformin has synergistic properties in type 2 diabetic patients.

Id. at Tab 14, C0173015, 10/16/2002 (emphasis added).

134. Accili testified that Sturis' use of the qualifier "suggests" was appropriate, and that he had no disagreement with this qualified statement. Pagano, a biostatistics expert, acknowledged that the Sturis Declaration informed the examiner of the p-values for both the area-under-the-curve and the two-hour test results, and that the tests were performed on rats rather than humans. 6/7/10 Tr. at 150-51.

135. However, Pagano criticized the fact that the two-hour data point, though statistically significant, was post hoc and "cherry-picked," in that it was not part of the original test protocol. Pagano explained that biostatisticians base their analyses on an established protocol, to avoid result-oriented conclusions. Calculation of p-values based upon a single data point that was not part of the original protocol should include a correction factor. However, Sturis did not do so with regard to the 0.02 p-value that he obtained for the two-hour test point. *Id.* at 128-32, 172-73 (Pagano).[21] Nor did Sturis inform the examiner that such data point was post hoc, or in the alternative submit the protocol so that the examiner could determine that on her own. *Id*. at 177 (Pagano); 6/9/10 Tr. at 83-84 (Sturis). Therefore, Pagano considered it "statistically unsound" for Sturis to conclude, as he expressly did with respect to that test point, that the p-value of 0.02 "shows that significant synergy exists" at that data point for the combination therapy. JX 2A at Tab 14 at C0173015, ¶6B; 6/7/10 Tr. at 130-32.

136. Second, Pagano considered as incorrect Sturis' statement that the p-value of

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[21]Thaler testified that there is a "strict set of well-accepted guidelines for correcting or adjusting analysis obtained from the 'post hoc' analysis." 6/10/10 Tr. at 49-50 (Thaler). The Bonferroni correction is a method used in statistics to address the problems of multiple comparisons performed simultaneously. http://wikipedia.org/wiki/Bonferroni_correction (last visited Jan. 18, 2011).

0.061 for the protocol's original end-point of the area-under-the-curve "indicates a synergistic effect," because that p-value is greater than the 0.05 standard. Id. at 176-77. JX 2A, Tab 14 at C0173014, ¶6A. That assertion of "synergistic effect" is also contrary to Sturis' own standards requiring statistical proof. Sturis admitted that he did not disclose to the examiner that this data point was not statistically significant or that it was the protocol's primary endpoint. 6/9/10 Tr. at 63-65, 82 (Sturis).

137. Because Sturis himself admitted that the Moses Study did not prove synergism, and his rat study did not prove synergism in rats, Pagano found “no statistical support” for Sturis’ stated conclusion that the combined rat and Moses Study “strongly suggests that the combination of repaglinide and metformin has synergistic properties in type 2 diabetic patients.” 6/7/10 Tr. at 130-31.

138. Thaler’s testimony that the Moses Study “support[s] the finding that a synergism exists between repaglinide and metformin,” and that the Sturis Study “demonstrates that repaglinide and metformin have a synergistic effect,” 6/10/10 Tr. at 36, is weakened by his acknowledgment that what he was saying was “[no]thing more than that the effect of the combination of the drugs that were used was greater than the sum of the effects of the individual drugs when given alone.” *Id*. at 97.

139. Sturis did not represent to the examiner that synergism in humans was mathematically proven. He also knew that his “strongly suggests” statement could make the difference between Novo getting or not getting the patent. 6/9/10 Tr. at 85-86 (Sturis). His “strongly suggests” qualified conclusion concerning the combined effect of the two studies was aggressive advocacy. However, it must be said that it has not been shown by clear and convincing evidence to be false. Nonetheless, to the extent that the

examiner drew further conclusions from the Sturis Declaration per se, they were not warranted.

140. Rather, it was the material omissions from the Sturis Declaration that violated his duty to disclose material information, not the representations. Undisclosed to the examiner were the facts that the two-hour data point was not part of the test protocol, and that a correction factor had not been applied to that p-value. That data point was the only one in his rat test that appeared to produce a statistically significant p-value of less than 0.05. Also undisclosed were Sturis' opinions (listed below) that, by his own standards requiring mathematical proof, neither his rat study nor the Moses Study alone proved synergy in humans.

141. Clearly, the examiner, focused as she was on the Sturis Declaration and the "synergistic effects" described in the patent specification, would have wanted to consider Sturis' expressed negative views on synergism, inconsistent as they were with the conclusions expressed or "strongly suggest[ed]" in his Declaration, and with Bork's exaggerated arguments based on Sturis' view. Undisclosed to the examiner were Sturis' conclusions that:

(1) the Moses Study "*did not demonstrate synergy"* with statistical proof. 6/9/10 Tr. at 42-43, 53, 129-30 (Sturis) (emphasis added). He expressed this opinion to Bork a few months before his Declaration to the Patent Office;

(2) it is "*not possible* [based on Moses' Study] to assess whether rep/met combination is additive, synergistic or antagonistic." DX 56 at NOVO-0105702 (emphasis added); 6/9/10 Tr. at 130 (Sturis). He expressed this conclusion to the Novo core repaglinide development group just a few days after his

Declaration;

(3) his rat study was not designed to test for synergy in humans, and the results "do not necessarily translate into humans;" 6/9/10 Tr. at 74. Indeed, in the abstract of his rat study report he was only willing to state that "[t]he presence of greater-than-additive effects may be of relevance to the clinical efficacy of the REP-MET combination." DX 74; PX 242 (emphasis added); *Id*. at 77;

(4) his rat study alone does not prove that the claimed combination is actually synergistic in humans. Id.

(5) even viewing the Moses Study and Sturis study together, Sturis would not say that they "prove[d]" that the claimed combination has synergistic properties in human Type II diabetic patients. *Id*. at 99.

142. Clear and convincing evidence is present that the opinions of Sturis were highly material to the patentability of Claim 4, because they refuted or were inconsistent with the opinions expressed in his Declaration in support of patentability. 37 C.F.R. §1.56(b)(2). A reasonable examiner, focused on the issue of synergism as was the examiner here, would have wanted to consider any qualifications or reservations held by Sturis concerning the conclusions he expressed in his Declaration.

> The fact that the conduct here consists of an omission rather than a *misrepresentation* does not compel a different result, as either may mislead an examiner. An examiner must be able to evaluate information in an affidavit in context, giving it proper weight . . . . Affidavits are inherently material, even if only cumulative. The affirmative act of submitting an affidavit must be construed as being intended to be relied upon.

Refac Intern., Ltd. v. Lotus Development Corp., 81 F.3d 1576, 1582-83 (Fed. Cir. 1996) (emphasis in original). Indeed, the examiner's explicit reliance on the Sturis Declaration

warrants the conclusion that the Declaration satisfied the alternative "but for" materiality test. *Digital Control*, 437 F.3d at 1315-16.

(b) The Bork Representations

143. In support of the Sturis Declaration, Bork asserted in response to the Final Rejection:

> Applicant therefore submits that the data presented in the application, in combination with the data presented in the Declaration of Dr. Sturis, provides *clear evidence of synergy* for the use of the claimed combination of repaglinide and metformin in the treatment of type II diabetes.
>
> . . . a prima facie case [of obviousness] is rebutted by the evidence of *synergistic and surprising results* achieved by the claimed combination therapy in humans (Example application) and in Zucker obese rats (Sturis' Declaration).

JX 2A, Tab 14 at C0173010 (emphasis added).[22]

144. In light of what Bork then knew, his representations to the examiner go beyond aggressive advocacy; the representations were known by him to be unsupported by the Sturis Declaration, and known to be untrue. With respect to synergistic results in humans, the Sturis Declaration never went beyond "strongly suggests." More importantly, Sturis had previously told Bork directly that the Moses Study did not mathematically or statistically demonstrate synergy in humans. 6/9/10 Tr. at 53-54 (Sturis). Bork's representations, however, asserted "clear evidence of synergy" and "synergistic and surprising results" in humans (emphasis added). There is no evidence that Bork's exaggerations were based on any sources other than the Sturis Study and

[22]The patent specification states that, with respect to NIDDM patients, "[I]t has been found that there is a synergism between repaglinide and metformin." JX-1 at col. 3, lines 11-12 (emphasis added). Sturis testified that such statement was talking about humans, not rats, and that he has seen no evidence proving synergism with the combination in humans. 6/9/10 Tr. at 128 (Sturis).

the Moses Study.

145. In addition to the contrary information possessed by Bork at the time of his representations to the examiner, he later received explicit contrary information from Sturis. On January 1, 2003 (the '358 Patent issued a year later, on January 13, 2004), Sturis sent an e-mail to Bork, enclosing a final draft of the repaglinide/metformin abstract. The abstract sent to Bork stated: "The presence of greater-than-additive effects *may* be of relevance to the clinical efficacy of the REP-MET combination." DX 74; PX 242; 6/9/10 Tr. at 77 (Sturis) (emphasis added). Bork's duty to disclose this highly qualified statement, inconsistent with his own earlier representations to the examiner, continued until the issuance of the patent, over one year later:

> The duty to disclose information exists with respect to each pending claim until the claim is cancelled or withdrawn from consideration, or the application becomes abandoned.

37 C.F.R. §1.56(a).

146. The evidence is clear and convincing that Bork's representations of October 16, 2002, as well as his failure to correct them in light of the later-received information described above, went beyond acceptable advocacy because they did not contain the limitations and qualifications communicated to him by Sturis. Further, they were highly material to patentability, because their absolute and unqualified character "refutes, or is inconsistent with, a position the applicant takes in . . . asserting an argument of patentability." *Id*. at §1.56(b)(2). As in the case of the Sturis Declaration, they also satisfy the alternative "but for" materiality test. *Digital Control*, 437 F.3d at 1315-16.

(c) Novo's Post-Clinical Trials

147. Caraco also relies upon Novo's failure to disclose to the Patent Office the

unfavorable results of several clinical trials of the repaglinide/metformin combination Novo conducted while the application for the '358 Patent was pending. In two of the trials that had been completed before the patent issued, "the synergistic effect of combination therapy observed by Moses et al was not consistently seen" (AGEE-3018 at 57; AGEE-3018 at 62). The former study concluded that "[t]he results observed in this study were *contrary* to the study by Moses et al." AGEE-3018 at 57 (emphasis added).

148. Although Müller was Novo's lead scientist in connection with repaglinide's development, and these studies were conducted out of Novo's New Jersey facility during his tenure there, he was "surprised" that he knew nothing of them until this litigation. 6/8/10 Tr. at 53 (Müller). There is no contradictory evidence concerning his unawareness of these test results in the record. And there is no evidence that Novo informed Bork of the existence or content of these test results.

149. These two Novo post-clinical trials were highly material to patentability because they refuted or were inconsistent with Novo's representations to the Patent Office concerning the synergistic results of the Moses Study. 37 C.F.R. §1.56(b)(2).

150. Admittedly, there is no evidence that Müller, Sturis or Bork were aware of these test results, or that Novo deliberately concealed that information from them. Under the applicable Patent Office Rules, those were the only three Novo individuals to whom the duty of candor and disclosure applied, there being no record of any other inventors, attorneys or other persons substantively involved in the preparation or prosecution of the patent application. *Id*. at §1.56(c). *Compare, Synthon IP, Inc. v. Pfizer, Inc.,* 472 F. Supp. 2d 760, 779-80 (E.D. Va. 2007), *aff'd per curiam on inequitable conduct* (Fed. Cir.

2008) (non-precedential):

> [T]he duty of candor cannot be avoided by willful ignorance or compartmentalization of knowledge within a company in an effort to insulate the patent applicants and their attorneys from information unfavorable to patentability.

See also, Ranbaxy Laboratories Ltd. v. Abbott laboratories, 2005 WL 30503608, at *8 (N.D.Ill. Nov. 10, 2005). Further, the bare fact that undisclosed material information existed within a patent assignee company is insufficient to impose an obligation of disclosure. *Nordberg, Inc. v. Telsmith, Inc.*, 82 F.3d 394,397 (Fed. Cir. 1996).

151. Overall, it must be said that Caraco did not establish by clear and convincing evidence that there was any inequitable conduct relating to Novo's failure to disclose these post-clinical trials to the Patent Office.

2. Intent

152. Sturis, as discussed above, withheld from the Patent Office the opinions he expressed to Bork and to Novo's core repaglinide development group concerning the individual significance of each of the Moses Study and his own study. Sturis also withheld his opinion, expressed at trial, that synergistic properties in humans were not proven even when these two study results are viewed together. Before the filing of his Declaration, Sturis was already aware that a showing of synergy was helpful in securing a patent, and that the examiner would be interested in knowing if there were mathematical proof of synergy. DX 79; 6/9/10 Tr. at 43-47, 85-86 (Sturis).

153. There is clear and convincing evidence in the record justifying the inference that Sturis had the intent to deceive the Patent Office by withholding his opinions and conclusions respecting the significance of the results of the Moses Study and the Sturis

Study. He knew of the importance of synergism to the examiner's consideration of the patentability of the claimed invention. The close relationship of his withheld opinions and conclusions to those in his Declaration was inescapable. No plausible reason for his omissions, other than an intent to deceive, has been offered. Under the circumstances, no other reason would be credible. *McKesson*, *supra*, 487 F.3d at 913; *Praxair*, *supra*, 543 F.3d at 1313-14. An intent to deceive is the "single most reasonable inference able to be drawn from the evidence." *Star Scientific*, *supra*, 537 F.3d at 1365.

154. As previously stated, Bork was fully informed by Sturis himself of the qualified and contrary opinions he held. Bork's exaggerated arguments to the examiner in support of the Sturis Declaration went beyond aggressive advocacy; they misstated key conclusions. As a patent attorney, he had to have known of the materiality of his representations and the significance attached to them by the examiner. As in the case of Sturis, no plausible explanation, other than an intent to deceive, was offered, and none would be reasonable or credible under the circumstances. It is important to note that although Novo brought to trial witnesses from across this country and several from Europe and Australia, it did not bring Bork (presumably still in New Jersey) to testify concerning his role in the prosecution of the patent application.

155. Additional evidence of Novo's less than rigorous attitude toward its duty of candor arises from its untimely filing of the Ajinomoto Opposition papers that were filed against Novo's corresponding European application. That opposition, filed in February, 2002, presented prior art based arguments against the patentability of the European application. Novo filed its response in the European Patent Office in February, 2003.

JX 2A at Tab 22, C0173163, item 4. It did not disclose the papers to the examiner until May 6, 2003. Id. at C0173162, items 1 and 4 and attached Form PTO-1449 at C0173167. Novo's submission to the Patent Office did not occur until 15 months after the filing of the European Opposition, and four months after the Patent Office had allowed Claim 4 (application claim 29).

156. Applicable Patent Office rules require that an information disclosure statement (IDS), if not filed within three months of the application's filing date or before the mailing of a first Office action, will still be considered if accompanied by a statement that the disclosed item "was first cited in a communication from a foreign patent office in a counterpart application not more than three months prior to the filing of the [IDS]," or that "to the knowledge of the person signing the certification after making reasonable inquiry," no person subject to the duty of disclosure was aware of such item more than three months prior to the filing of the IDS. 37 C.F.R. §§(d) and (e). Bork failed to file the required statement, and Novo failed to provide the Court with any explanation for its long delay in filing the opposition evidence until after the examiner had allowed Claim 4.

157. The MPEP makes several references to the importance of timely filing of material information. Section 609 states that the relevant rules "are designed to encourage individuals to submit information to the Office "*promptly*" (emphasis added). Section 2001.06(a) focuses on the duty to disclose material information from "related foreign applications." Suggestion No. 12 of Section 2004's list of "Aids to Compliance with Duty of Disclosure" advises that "potentially material information discovered late in the prosecution should be *immediately* submitted." (emphasis added).

158. Based upon Sturis' omissions of clearly material information, the similar

omissions and misrepresentations by Bork, and the unexplained and therefore apparently calculated delay in filing the Ajinomoto opposition papers, an inference of intent to deceive the examiner is appropriately inferred. *Praxair*, *supra*, 543 F.3d 1306, 1313-14.

159. It is clear, however, that the finding of materiality is not the basis for finding intent. Indeed, the Federal Circuit has recently emphasized that

> . . . materiality and intent are separate requirements, and intent to deceive cannot be found based on materiality alone. *Larson Mfg. Co. of S.D., Inc. v. Aluminart Prods. Ltd.*, 559 F.3d 1317, 1340 (Fed .Cir. 2009). A court cannot simply infer that an applicant "should have known" the materiality of withheld information and thus intended to deceive the PTO because the applicant knew of the information and the information is material. A district court must find some other evidence that indicates that the applicant appreciated the information's materiality.

Cancer Research Technology Ltd. v. Barr Laboratories, Inc., 625 F.3d 724, 733-34 (Fed. Cir. 2010). As explained above, there is more than just the fact that the materials withheld from the Patent Office were material which establishes intent.

B. Conclusion

159. Under prevailing law, the evidence compels the conclusion that the '358 Patent is unenforceable due to inequitable conduct in the prosecution of the patent application before the Patent Office. Sturis withheld from his Declaration highly material information with intent to deceive the patent examiner. Bork both misrepresented and withheld highly material information with intent to deceive the examiner. The violations of the duties of disclosure by both men exceeds the necessary threshold levels of materiality and intent, and the equities warrant the conclusion that inequitable conduct occurred, and therefore the '358 patent is unenforceable.

IX. CONCLUSION

A.

Based on the findings of fact and the governing law as above, Claim 4 of the '358 patent is invalid. The claimed combination of metformin with repaglinide was obvious to a person of ordinary skill in the art at the time of the invention. Whether measured against the teaching/suggestion/motivation test or the obvious to try test, the record of the trial contains clear and convincing evidence establishing a prima facie case of obviousness. The prima facie case of obviousness was not overcome by proof of unexpected results and commercial success. The results of the combination claimed to be unexpected and unexplainable were, to the contrary, to be expected and were explainable in light of the state of the art as of the critical date. The scope of Claim 4 substantially exceeds the scope of the evidence of the asserted unexpected results, and the record clearly and convincingly precludes extending the probative value of the results beyond the small Type II diabetes patient sub-population that experienced them. Finally, the evidence in the record did not establish that the claimed invention has been commercially successful.

B.

Also, based on the findings of fact and the governing law above, Claim 4 of the '358 patent is unenforceable because of inequitable conduct in its prosecution. Sturis withheld from his Declaration highly material evidence which misled the patent examiner. Bork misrepresented and withheld highly material information from the patent examiner. The conclusion to be drawn from what Sturis and Bork did and did not do is that, with deceptive intent, they were successful in misleading the patent examiner to approve the application, which resulted in the issuance of the '358 patent.

C.

The Court is mindful of the attendant consequences of this decision. While Novo argued vigorously to sustain the '358 patent, at the end of the day the record simply does not support its arguments. Rather, the record shows, quite clearly**,** that the patent should never have issued. The idea to combine repaglinide with metformin was natural. Moreover, the results of the combination were not at all unexpected.

Novo knew the obstacles to obtaining a patent, as seen by the several rejections. Knowing what was needed to be shown to establish patentability, in what would be Novo's final attempt before the Patent Office, Novo omitted material information. The only inference which can be drawn from its conduct was that it was done with the intent to deceive the examiner and obtain a patent.

Perhaps market forces drove Novo to do what it did; the Court can only speculate. In the end, however, the patent cannot be sustained. An appropriate judgment will enter.

Dated: January 19, 2011

S/Avern Cohn
AVERN COHN
UNITED STATES DISTRICT JUDGE

I hereby certify that a copy of the foregoing document was mailed to the attorneys of record on this date, January 19, 2011, by electronic and/or ordinary mail.

S/Julie Owens
Case Manager, (313) 234-5160

Appendix I
Reports and Articles Referenced in Decision

DX 52 – AGEE-3018 Integrated Clinical Trial Report, "Repaglinide A 3-month, open-label, randomized multi-center study of repaglinide in combination with metformin as compared to metformin or repaglinide given as monotherapy for the treatment of type 2-diabetes" (9/29/2003) ("AGEE-3018").

DX 53 – AGEE-3010 Integrated Clinical Trial Report, "NovoNorm A 16-week, multi-centre, open-labeled study on type 2 diabetic patients treated with repaglinide and repaglinide in combination with metformin" (12/2/2003) ("AGEE-3010).

DX 54 – AGEE-1411 Integrated Clinical Trial Report, "Multicentre, randomized, comparative, open, three armed parallel group study on the use of metformin, repaglinide or the combination of both in type 2 diabetic patients after failure of dietary measures" (2/20/06) ("AGEE-1411").

DX 61 – DeFronzo et al, "Efficacy of Metformin in Patients with Non-Insulin-Dependent Diabetes Mellitus," N. Engl. J. Med. (1995) ("DeFronzo").

DX 200 – Rachman et al, "Drugs on the Horizon for Treatment of Type 2 Diabetes," Diabetic Medicine (1995) ("Rachman").

DX 202 – The American Diabetes Association, "Consensus Statement: The Pharmacological Treatment of Hyperglycemia in NIDDM," Diabetes Care (1995) ("Consensus Statement").

DX 203 – Melander, "Oral Antidiabetic Drugs: an Overview," Diabetic Medicine (1996) ("Melander").

DX 212 – Kaku et al, "Possibility of the Appearance of New Antidiabetic Agents (1): Oral Antidiabetic Agents," Practice (1996) ("Kaku").

DX 246 –Hermann and Melander, "Therapeutic Comparison of Metformin and Sulfonylurea, Alone and in Various Combinations, A Double-Blind Controlled Study," Diabetes Care (1994) ("Hermann/Melander")

DX 307 – Karlsson and Garber, "Metformin Comes to America: What to Do Now," Clinical Diabetes (1995) ("Karlsson/Garber").

DX 311 – Clarke et al, "Combined Metformin-Chlorpropamide Therapy in 108 Diabetic Sulphonylurea Failures," The Lancet (1965) ("Clarke").

DX 319 – Rudovich, Pfeiffer et al, "Enhancement of Early- and Late-Phase Insulin Secretion and Insulin Sensitivity by the Combination of Repaglinide and Metformin in Type 2 Diabetes Mellitus," Exp. Clin. Endocrinal Diabetes, Vol. 112, No. 7, pp. 395-400

(2004) ("Pfeiffer Study").

DX 350 – Garber, "Incremental Therapy for NIDDM," Clinical Diabetes (1995) ("Garber I").

DX 351 – Garber, "Metformin Therapy for Type II Diabetes Mellitus," P&T (1995) ("Garber II").

DX 361 – Bristol-Myers Squibb Product Monograph, "Glucophage, Metformin Hydrochloride Tablets" (1995) ("Bristol-Myers").

DX 369 – Raskin, "Oral combination therapy: repaglinide plus metformin for treatment of type 2 diabetes," Diabetes, Obesity and Metabolism, 10:1167-77 (2008) ("Raskin").

DX 383 – Clark et al, "The Effect of Glimepiride on Pancreatic -Cell Function Under Hyperglycaemic Clamp and Hyperinsulinaemic, Euglycaemic Clamp Conditions in Non –Insulin-Dependent Diabetes Mellitus," Horm. Metab. Res. (1996) ("Clark").

PX 138 – Rudovich, Pfeiffer et al, "Enhancement of Early and Late Phase Insulin Secretion and Insulin Sensitivity by the Combination of Repaglinide and Metformin in Type 2 Diabetes Mellitus," Exp. Clin. Endocrinal Diabetes, Vol. 112, No. 7, pp. 395-400 (2004) ("Pfeiffer Study").

PX 201 – AGEE-053 Integrated Clinical Trial ("Moses Study" or "Australian Study").

PX 401 – Sturis et al, "Combination of repaglinide and metformin results in greater than additive (synergistic) effects on glucose tolerance in obese Zucker (fa/fa) rats" ("Sturis Study").

PX 438 – Roudavitch et al, "Repaglinide plus Metformin: effects on insulin secretion and sensitivity in type 2 diabetes" ("Pfeiffer II Study").

APPENDIX II
05-40188
Novo Nordisk A/S, et al
v.
Caraco Pharmaceutical, et al