SUPERIOR COURT OF CALIFORNIA, COUNTY OF LOS ANGELES

Civil Division

Central District, Spring Street Courthouse, Department 10

JCCP4574
BYETTA CASES

April 6, 2021
2:58 PM

Judge: Honorable William F. Highberger
Judicial Assistant: A. Lim
Courtroom Assistant: None

CSR: None
ERM: None
Deputy Sheriff: None

APPEARANCES:

For Plaintiff(s): No Appearances

For Defendant(s): No Appearances

NATURE OF PROCEEDINGS: Ruling on Submitted Matter

The Court issues its Rulings on Submitted Matters on this date.

The Court's ruling is uploaded on the File & ServeXpress website on this date.

Further Status Conference is scheduled for 04/22/21 at 01:30 PM in Department 10 at Spring Street Courthouse on cases 37-2009-00099619-CU-PL-CTL, 37-2013-00030709-CU-PL-CTL, 37-2013-00075106-CU-PO-CTL, 37-2014-00005178-CU-PL-CTL, 37-2014-00007542-CU-PL-CTL, 37-2014-00009053-CU-PL-CTL, 37-2014-00016847-CU-PL-CTL, 37-2014-00024380-CU-PO-CTL, 37-2014-00026026-CU-PO-CTL, 37-2014-00030205-CU-PO-CTL, BC409306, BC415326, BC423725, BC424056, BC440822, BC463524, BC464632, BC465473, BC471562, BC475571, BC483878, BC486666, BC489119, BC505303, BC548302, and BC611229.

Clerk is ordered to give notice.

A copy of this minute order will append to the following coordinated cases under JCCP4574: 37-2009-00099619-CU-PL-CTL, 37-2013-00030709-CU-PL-CTL, 37-2013-00075106-CU-PO-CTL, 37-2014-00005178-CU-PL-CTL, 37-2014-00007542-CU-PL-CTL, 37-2014-00009053-CU-PL-CTL, 37-2014-00016847-CU-PL-CTL, 37-2014-00024380-CU-PO-CTL, 37-2014-00026026-CU-PO-CTL, 37-2014-00030205-CU-PO-CTL, BC409306, BC415326, BC423725, BC424056, BC440822, BC463524, BC464632, BC465473, BC471562, BC475571, BC483878, BC486666, BC489119, BC505303, BC548302, and BC611229.

SUPERIOR COURT OF THE STATE OF CALIFORNIA

FOR THE COUNTY OF LOS ANGELES

IN RE BYETTA® CASES

CASE NO. JCCP 4574

RULINGS ON SUBMITTED MATTERS

Hon. William F. Highberger
Department 10
Spring Street Courthouse

I. INTRODUCTORY NOTE

Based on the parties' Stipulation and Order that they waive the opportunity for an evidentiary hearing under Evidence Code § 402 before the evidentiary motions are decided and waive court trial on the federal preemption factual issues embedded in the question of law for decision by the Court, and following oral arguments on October 20, 2020 and December 8, 2020, the Court now makes the following Rulings.

II. DEFENSE MOTION TO EXCLUDE FOUR PLAINTIFF EXPERTS (MADIGAN, PH.D.; WELLS, PH.D.; BROWN,PH.D.; AND GALE, M.D.): GRANTED

The unwillingness or inability of these experts (particularly Drs. Madigan, Wells, and Gale) to grapple with all the available epidemiological evidence is troubling. The most important expert for these purposes is medical doctor Gale since he provides the only expert opinion on the ultimate questions of general and specific causation. He does place so much reliance upon the opinions of biostatisticians Madigan and Wells that the admissibility of their conclusions is a necessary predicate for his opinion. Dr. Brown's opinion about biological possibility for the disease process is the most free-standing of the four opinions and will addressed last for this reason.

The Court notes that in the two principal cases relied upon by plaintiffs to oppose the motion—and to argue that "the absence of . . . epidemiological evidence does not preclude an expert from testifying on mechanism" (Opposition at 1:21–22)—the challenged expert HAD factored a substantial body of epidemiology evidence into the conclusion that causation was shown, a situation notably different from the record here. In *Cooper v. Takeda Pharmaceuticals America, Inc.* (2015) 239 Cal.App.4th 555, the challenged plaintiffs' expert did not discount all other possible causes of plaintiff Jack Cooper's bladder cancer to the trial court's satisfaction (i.e., specific causation opinion), but he had considered 15 epidemiology studies before reaching his general causation conclusion, and nothing in the trial court's ruling had questioned the admissibility of this portion of his testimony. *Cooper*, *supra*, 239 Cal.App.4th at 563–64, 575–76.

Similarly, in *Johnson & Johnson Talcum Powder Cases* (2019) 37 Cal.App.5th 292, the disputed expert was plaintiff's treating physician, Dr. Annie Yessaian, who had "considered numerous epidemiological studies" showing increased ovarian cancer risk for women exposed to talc. *Id.* at 309. As in *Cooper*, the erroneous trial court ruling was the ruling striking the specific causation finding, not a ruling striking the general causation opinion.

The plaintiffs here would have a much more procedurally respectable expert opinion on the essential issues of general causation if the opinions had considered all the available epidemiological evidence and not just the state of research as it existed in 2015 with limited consideration of studies done thereafter. *See Shiffer v. CBS Corp.* (2015) 240 Cal.App.4th 246, 253. Absent the circumstances of a truly rare disease such as Hepatosplenic T-cell lymphoma cancer, a disease with only 100 to 200 cases ever reported (i.e., the disease underlying the opinion in *Wendell v. GlaxoSmithKline, LLC* (9th Cir. 2019) 858 F.3d 1227, 1232), this Court finds that a medical causation opinion which not only lacks, but ignores, this essential logical support is of highly doubtful provenance.

At the outset, the Court notes that, during the December 8, 2020 hearing, plaintiffs' counsel provided a two-hour overview of the scientific evidence and documents they believe support causation (an argument that, for the first time in seven years, attempted to distinguish liraglutide from other incretin-based therapies based on its pancreatic safety). Counsel's argument included references to numerous studies, documents and analyses that, in large part, never were considered by their experts and, in some cases, were created by plaintiffs' counsel.[1] The most obvious example were the liraglutide-only risk estimates that plaintiffs' counsel

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[1] *See, e.g., Perry v. United States* (11th Cir. 1985) 755 F.2d 888, 892 ("[T]he examination of a scientific study by a cadre of lawyers is not the same as its examination by others trained in the field of science or medicine"); *Daubert v. Merrell Dow Pharmaceuticals, Inc.* (9th Cir. 1995) 43 F.3d 1311, 1318 n.8 (quoting *Perry*); *Richardson v. Richardson-Merrell, Inc.* (D.C. Cir. 1988) 857 F.2d 823, 831 n.55 (same); *Monroe v. Zimmer U.S. Inc.* (E.D. Cal. 2011) 766 F.Supp.2d 1012, 1034 ("Plaintiff's opposition to defendants' motion simply provides counsel's analysis of the literature. It does not include expert testimony regarding the scientific value of these nine reported studies. Furthermore, plaintiff's opposition does not include any expert testimony that draws any connection between the literature and a duty to warn . . . . The court cannot accept counsel's interpretation of the medical literature . . . .").

calculated themselves using a subset of data included in a number of peer-reviewed meta-analyses evaluating pancreatic cancer risk with incretin-based therapies. Not only were these risk estimates not considered by plaintiffs' experts, they do not appear anywhere in the published papers. For example, the Cao 2019 meta-analysis does not include a liraglutide-specific risk estimate; on the contrary, the authors reported that their "meta-analysis did not suggest any increased risk of cancers associated with GLP-1RAs use in T2DM" and noted that studies have suggested that liraglutide may actually inhibit the growth and spread of pancreatic cancer. See Cao et. al., Endocrine 2019, Exh. Y, Def. *Daubert/Sargon* Mot. Similarly, the authors of the El-Aziz 2019 meta-analysis conclude that "[t]he present results, which largely confirm previous analyses based on a smaller number of clinical trials, thus confirm that incretin-based glucose-lowering medications both from the GLP-1 RA and DPP-4 I classes do not expose patients to an elevated risk of pancreatic cancer." El-Aziz et. al. 2019, Exh. W, Def. *Daubert/Sargon* Mot., at 5; *see also Sargon Enterprises, Inc. v. University of Southern California* (2012) 55 Cal.4th 747, 771 (quoting *General Electric Co. v. Joiner* (1997) 522 U.S. 136, 146) ("A court may conclude there is simply too great an analytical gap between the data and the opinion proffered."); *Carnegie Mellon University v. Hoffman-LaRoche, Inc.* (N.D. Cal. 1999) 55 F.Supp.2d 1024, 1039–40 (rejecting expert's "'reinterpretation' and 'reanalysis' of data and findings in studies performed by others, all of whom reach conclusions contrary to his").

Moreover, while plaintiffs' counsel argued that the pancreatic safety of liraglutide differed from other incretin-based therapies, neither Gale nor any other plaintiffs' expert offered such an opinion or testified that liraglutide is biologically different from other incretin-based therapies in a way that would impact pancreatic cancer risk. In fact, plaintiffs' biological mechanism expert, Brown, largely dismissed any differences in the way the medications would affect GLP-1 receptors on pancreatic cells: "While the dosing and half-lives of the incretin mimetics are different, both GLP- 1R agonists and DPP4 inhibitors would be expected to have essentially continuous activation of the GLP-1 receptor." Brown 2019 Report, Williams Decl., Exh. GGG, at 4.

For these reasons, and as discussed further below, plaintiffs' counsels' vigorous arguments about the science do not and cannot fill the methodologic and foundational gaps that exist in their experts' analyses.

Dr. Madigan

Dr. Madigan is a biostatistician who offers an opinion that a statistical association exists between liraglutide use and development of pancreatic cancer. Madigan does not—and, as a statistician without medical training, cannot—offer an opinion on the ultimate issue of medical causation.

A statistical association (even if reliably arrived at) is not equivalent to causation.[2] S. Breyer et al., REFERENCE MANUAL ON SCIENTIFIC EVIDENCE (3d ed.) at 221–22 (hereinafter "Ref. Man.") ("[A]ssociation is not causation."). Accordingly, an expert who intends to offer a causation opinion must do more than simply identify evidence of an association; he must conduct some form of reliable causation analysis to assess whether the observed association is in fact causal. *In re Roundup Products Liability Litigation* (N.D. Cal. 2018) 390 F.Supp.3d 1102, 1116 ("[A]n evaluation of causation requires epidemiologists to exercise judgment about the import of those studies and to consider them in context."); *In re Lipitor (Atorvastatin Calcium) Marketing, Sales Practices & Products Liability Litigation* (D.S.C. 2017) 227 F.Supp.3d 452, 482 ("An association does not equal causation, and epidemiologists engage in a rigorous analysis of multiple factors to determine whether an association is causal."); *Henricksen v. ConocoPhillips Co.* (E.D. Wash. 2009) 605 F.Supp.2d 1142, 1175 ("[A]n association does not equal causation, and it is the duty of scientists to rigorously analyze the data to determine whether or not an association is causal.").

2015 Analysis. In 2015, Madigan performed a combined meta-analysis of clinical trial data for exenatide, liraglutide, and sitagliptin to assess whether there was a statistical association between incretin-based therapies and pancreatic cancer. That analysis found no statistically

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[2]Gale emphasized this "distinction between an association and cause and effect" in his 2016 article "Recent Progress and Concepts in Pancreatic Cancer." Exh. NNN, Def. *Daubert/Sargon* Mot.

significant association between incretin-based therapies and pancreatic cancer, and Madigan conceded that his statistical analyses did not establish that any of the medications at issue in this litigation cause pancreatic cancer.[3] (Madigan 2015 Deposition, Exh. B, 123:14–124:5; *see also id.* at 76:21–77:11, 313:20–314:6).

2019 Liraglutide Analysis. For his 2019 report, Madigan focused solely on liraglutide. Madigan elected not to update his report on sitagliptin and exenatide, and necessarily did not consider data on those drugs made available since 2015. As to those medications, Madigan only considered a "significantly incomplete universe of information[,]" leaving him "without an adequate basis to conclude" that an association—let alone causation—exists. *See Shiffer*, *supra*, 240 Cal.App.4th at 253. For this reason alone, Madigan's opinions with respect to sitagliptin and exenatide must be excluded.

As to liraglutide, Madigan conducted a separate analysis of certain clinical trial data, the majority of which came from the LEADER trial. At deposition, Madigan admitted that he had no scientific basis for limiting his 2019 analysis to liraglutide (contrary to his approach in 2015).[4] Instead, he explained that he limited his analysis in this way because that was the assignment he was given by plaintiffs' counsel. (Madigan 2020 Deposition, Williams Decl., Exh. E, at 206:1–17). In fact, Madigan agreed that it would be "perfectly legitimate" to have updated his prior combined meta-analysis of GLP-1RAs and DPP-4s, but, again, that was not what he was asked to do. Madigan 2020 Deposition, Exh. E, at 206:11–17.

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[3]Plaintiffs' epidemiology expert, Dr. Greenland, stated in his expert report that: "[I]t is sound methodology to consider results seen for other drugs or events in a class when evaluating a specific association (such usage corresponds to the "analogy" consideration in Hill, 1965) . . . Of note, the U.S. Food and Drug Administration (FDA) routinely conducts analyses of classes of drugs." *See* 2015 Greenland Report, Williams Decl. to Novo Nordisk Mot. Summ. J., Exh. 47, at 12.

[4]At oral argument on December 8, 2020, plaintiffs' counsel stated that the pancreatic safety of liraglutide was different than other GLP-1RAs, in part, because of its allegedly longer half-life. *See* Tr. at 4:2. Even if that were true (which it is not), that was neither an opinion nor explanation offered by Madigan. None of plaintiffs' experts, including Gale, testified that liraglutide is biologically different from other GLP-1RAs in a way that would impact pancreatic cancer risk. On the contrary, plaintiffs' biological mechanism expert, Brown, largely dismissed the significance of differences in half-life: "While the dosing and half-lives of the incretin mimetics are different, both GLP-1R agonists and DPP4 inhibitors would be expected to have essentially continuous activation of the GLP-1 receptor." Brown 2019 Report, Williams Decl., Exh. GGG, at 4.

On this point, the Court notes that both the FDA and numerous published peer-reviewed meta- analyses evaluated the pancreatic cancer safety of incretin-based therapies collectively, either evaluating all incretin-based therapies together or, alternately, looking at all DPP-4s and all GLP-1RAs as separate classes. Neither the FDA nor any of these researchers suggested that liraglutide should be treated separately for purposes of evaluating pancreatic cancer risk, that the findings were different for liraglutide, or that a significant association existed between liraglutide use and pancreatic cancer.

The absence of any scientific basis for Madigan's decisions to change his methodology from 2015 to 2019 raises serious concerns about the intellectual rigor he applied in performing his litigation work. *Sargon*, *supra*, 55 Cal.4th at 772 (quoting *Kumho Tire Co. v. Carmichael* (1999) 526 U.S. 137, 152 (internal quotations omitted) ("In short, the gatekeeper's role is to make certain that an expert, whether basing testimony upon professional studies or personal experience, employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field.")).

Inconsistent Exclusion and Inclusion Criteria. Also problematic is the fact that Madigan arrived at his conclusion about liraglutide by reanalyzing limited data from available studies in ways that are unreasonable and not methodically sound. For example, in his review of the LEADER trial of liraglutide, Madigan reduced the number of deaths in the placebo arm, claiming the neoplasms were adjudicated without sufficient information. *See* Williams Decl., Exh. E at 58–60, 76–79, 153–55; Exh. RR at 3. By his own admission, this significantly altered the data; had the placebo events not been removed, the resulting p-value would be one that, in Madigan's own words, would "probably not" indicate an association between use of a drug and an adverse event. Williams Decl., Exh. E at 79.

What is troubling about Madigan's decision to exclude certain pancreatic cancer cases from the placebo arm is his lack of a reasonable basis for doing so. At deposition, Madigan explained that there were two different adjudicatory bodies in LEADER (neoplasm and death), and he favored the decisions of the neoplasm adjudicatory body because it had access to

pathology. Williams Decl., Exh. E at 59-61. Based on this rationale, Madigan *excluded* four placebo events from his analysis, all of which were adjudicated as pancreatic events by the LEADER death adjudication committee, but for which pathology was not available. Madigan 2020 Deposition, Exh. E, at 58:4–59:12; *id.* at FDA June 2017 Briefing Document, Williams Decl., Exh. V, 72–73. At the same time, however, he included two events in the liraglutide arm that were adjudicated by the neoplasm committee, even though pathology evidence was "unknown." *See* FDA June 2017 Briefing Document, Williams Decl., Exh. V, at 68; Madigan 2019 Rep., Exh. KK, at 2 (Table 1).

From another study (Study '1839), Madigan included a pseudopapillary tumor of the pancreas for which pathology was available and showed that the tumor was benign, meaning "negative for malignancy." Madigan 2020 Deposition, Williams Decl., Exh. E, at 138:2–24; *see also* Madigan 2020 Deposition at Exh. 9, Exh. PP, at 425, 4111 or 23377 ("[P]athology results were negative for malignancy. Recovered."). Yet, from the same study, he excluded a "pancreatic carcinoma metastatic" for which the pathology confirmed cancer, but for which the primary organ of origin was "unknown." Madigan 2020 Deposition, Williams Decl., Exh. E, at 153:5–155:9.

And, from Study '1436, Madigan included a pancreatic cancer case that was self-reported by a patient who had been treated with liraglutide. Williams Decl., Exh. NNNN, at 35:6–21; Exh. KK, at 2 (Table 1); Exh. SS, at NNI-MDL_02223283. The event occurred five years after the study was completed and after follow-up had ended. The event was not adjudicated, no pathology was available, and, because there was no follow-up during this five-year period, there was no way to tell how many pancreatic cancer diagnoses may have occurred in the placebo group during the same time frame. *Id.*

Madigan's inconsistent method for selecting the pancreatic cancer events in his analysis is wholly unsound. He deflated the cancer events in placebo groups and effectively inflated them in liraglutide groups. Madigan's opinion on the association of liraglutide exposure with pancreatic cancer development thus is not founded on sound logic or reliable methodology. His

wholly inconsistent approach to inclusion and exclusion of events from liraglutide clinical trials is results-oriented and therefore must be excluded. *See Sargon*, *supra*, 55 Cal.4th at 772.

Failure to Consider Other Epidemiologic Data. Madigan also failed to consider a large body of epidemiologic evidence, including large observational studies involving real-world use of liraglutide, published meta-analyses of GLP-1RA clinical trial data, and analyses conducted by regulators that found no evidence of a causal effect. Indeed, one of the large observational studies Madigan ignored—Funch 2019—included more subjects treated with liraglutide and more pancreatic cancer cases than all the studies included in his analysis combined. That study found no association between liraglutide use and pancreatic cancer. Madigan's decision to ignore this evidence left him "without an adequate basis to conclude" that use of liraglutide, or any other incretin-based therapy, is associated with pancreatic cancer. *See Shiffer*, *supra*, 240 Cal.App.4th at 253.

Dr. Wells

Dr. Wells did not consider clinical trial data related to sitagliptin and expresses no opinions about sitagliptin. This means plaintiffs do not have an expert who purports to find an association between sitagliptin and pancreatic cancer.

As for exenatide and liraglutide, Dr. Wells's expert testimony suffers from defects similar to those observed in Madigan's work.[5] For exenatide, Wells admitted that, when he analyzed the clinical trial data and included EXSCEL (the largest clinical trial of exenatide, representing more than 90 percent of the data for the medication), the result was "consistent with no risk." (Wells 2020 Deposition, Exh. G, at 100:3–13; 176:4–12). This provides no basis for an association between exenatide and pancreatic cancer. He then arbitrarily changed his analysis—by excluding

[5]Like Madigan, Wells never offered a scientific basis for distinguishing liraglutide or exenatide from other incretin-based therapies based on their pancreatic safety. Instead, he limited his analysis to a subset of exenatide and liraglutide data because that is what he was asked to do by counsel. Wells 2020 Deposition, Williams Decl., Exh. G, at 95:10–96:12. Wells acknowledged that he could not say whether there were any differences between exenatide and liraglutide and any other GLP-1RA, Wells 2020 Deposition, Exh. G, at 95:10–96:12, and admitted that he did not know how the half-lives of other GLP-1RAs compared to the half-lives of liraglutide or exenatide. Wells 2020 Deposition, Williams Decl., Exh. G, at 94:19–95:20.

EXSCEL and by combining exenatide data and liraglutide data (Wells 2019 Rep., Exh. F, at 10–11), and by excluding data from the four other published GLP-1RA CVOTs that report pancreatic cancer data (*see* Fuchs Report at 20 (Exh. 51 to Laurendeau Decl.); Wells 2020 Deposition at 95:15–20 (Exh. 34 to Laurendeau Decl.))—and got a different result. There is no scientifically reliable foundation for Wells's litigation-driven decision making, and it cannot withstand scrutiny under *Sargon*, *supra*, 55 Cal.4th at 772. Indeed, there are 12 peer-reviewed, published meta-analyses of GLP-1RAs and pancreatic cancer that combine the relevant published clinical trial data, including EXSCEL, without regard to type of GLP-1RA, and none supports an increased risk of pancreatic cancer. (*See* Laurendeau Decl. Exhs. 39–51).

Further, in Dr. Wells's review of one study, (Study '1436), he *included* a pancreatic cancer case in the liraglutide group that was not adjudicated, explaining that there was no adjudication committee to adjudicate the cancer.[6] Williams Decl., Exh. G at 236–39. But he later admitted he excluded placebo cancer events that were identified by a death adjudication committee. He could not identify any scientific basis to exclude these events, other than the fact that they were not listed in the "main results table." Williams Decl., Exh. G at 257–60. Wells conceded that, had he included placebo group deaths in his analysis, the risk estimate would have gone down. He also acknowledged that the FDA had accepted inclusion of the cancer events in the placebo group in its own analysis of the LEADER pancreatic cancer data. Williams Decl., Exh. G at 259–60. He does not explain why he accepted some unadjudicated events while rejecting others, or how his liraglutide analysis fits within a consistent methodology. He also does not explain why he felt it prudent to reject certain events that the FDA and study investigators had accepted.

Wells's methodology was inconsistent in other areas. He *excluded* from his analysis some placebo cancer events that occurred in certain studies that included subjects who took both

[6]This is the event, discussed above, that was reported five years after the study was completed and for which no adjudication or pathology was available. Wells 2020 Deposition, Exh. SS (GLP-1 and the Pancreas White Paper), at Exh. 13, NNI-MDL-02223237, at NNI-MDL-02223283 (filed under seal).

liraglutide and insulin. Williams Decl., Exh. G, at 278–79. At the same time, he *included* events from the LEADER trial, which included many subjects who were taking a combination of liraglutide and insulin. Williams Decl., Exh. G, at 279–83; Williams Supp. Decl., Exh. QQ, at 64–65.

Further, there is evidence that at least one event included in Wells's analysis was actually a benign tumor. Williams Decl., Exh. G at 203–08. Benign tumors are not the sort of malignant cancers that plaintiffs claim they developed due to exposure to defendants' products. The inclusion of a benign pseudopapillary tumor indicates that some of the material relied on by Wells and counted against liraglutide was irrelevant to the question at hand—whether incretin-based therapies caused an increased risk of malignancies (i.e., pancreatic cancer). It was unreasonable for Wells to use this data, and it has further polluted his report.

Finally, like Madigan, Wells failed to consider a large body of other epidemiologic data, including the Funch 2019 study discussed above, as well as other observational studies and meta-analyses evaluating the relationship between incretin-based therapies such as liraglutide and pancreatic cancer.

Together, these inconsistencies and methodologic failures reflect the unsound, ramshackle methodology employed by Wells in forming his expert opinion. They speak to an undisciplined analysis suggestive of an authorial interest focused on achieving certain results rather than examining the data objectively. Accordingly, Wells's liraglutide and exenatide analyses and opinions will be excluded.

Dr. Gale

Dr. Gale is the only one of plaintiffs' experts who offers an updated medical causation opinion. Because his opinion is predicated on the statistical analyses conducted by Madigan and Wells and those analyses have been excluded, Gale's causation opinion lacks a proper foundation and must be excluded. Moreover, as discussed below, Gale's opinion suffers from numerous other methodologic problems that require exclusion under *Sargon*.

As previously noted, a statistical association (even if reliably arrived at) is not equivalent to causation.[7] Ref. Man. at 221–22. Accordingly, an expert who intends to offer a causation opinion must do more than simply identify evidence of an association; he must conduct some form of reliable causation analysis to assess whether the observed association is in fact causal. *In re Roundup Products Liability Litigation*, *supra*, 390 F.Supp.3d at 1116 ("[A]n evaluation of causation requires epidemiologists to exercise judgment about the import of those studies and to consider them in context."); *In re Lipitor (Atorvastatin Calcium) Marketing, Sales Practices & Products Liability Litigation*, *supra*, 227 F.Supp.3d at 482 ("An association does not equal causation, and epidemiologists engage in a rigorous analysis of multiple factors to determine whether an association is causal."); *Henricksen v. ConocoPhillips Co.*, *supra*, 605 F.Supp.2d at 1175 ("[A]n association does not equal causation, and it is the duty of scientists to rigorously analyze the data to determine whether or not an association is causal.").

Here, Gale claims to have performed a "weight-of-the-evidence" analysis. Gale testified: "The method I used is a weight-of-evidence approach as recommended, I would say most strongly, in the 2005 EPA guidelines for risk assessment." Gale 2015 Deposition, Exh. J, Def. *Daubert/Sargon* Mot., at 240:25–241:2. The EPA guidelines make clear that a "weight-of-the-evidence" analysis must, at a minimum, include (1) consideration of "all of the evidence in reaching conclusions about the human carcinogenic potential of agents" and (2) explanation of the "kinds of evidence available," how that evidence "fit[s] together in drawing conclusions," and of "significant issues/strengths/limitations of the data and conclusions." 2005 EPA Guidelines, Exh. HHH, Def. *Daubert/Sargon* Mot., at 1. In other words, Gale's methodology required him to review the totality of available evidence and then "supply his method for weighting the studies he has chosen to include in order to prevent a mere listing of studies and jumping to a conclusion." *Magistrini v. One Hour Martinizing Dry Cleaning* (D.N.J. 2002) 180 F.Supp.2d 584, 602. Gale failed to reliably complete either prong.

[7]Gale emphasized this "distinction between an association and cause and effect" in his 2016 article "Recent Progress and Concepts in Pancreatic Cancer." Exh. NNN, Def. *Daubert/Sargon* Mot.

Failure to Review the Totality of Relevant Evidence. Gale conceded he did not consider a number of studies in reaching his conclusion about the carcinogenic nature of incretin-based therapies. He admitted he considered no epidemiological data related to GLP-1RAs that has been published since 2015, when he submitted his prior expert report. Williams Decl., Exh. I, at 153. He directly admitted he had not considered the EXSCEL study on exenatide. Williams Decl., Exh. I, at 111. He also relied on Madigan's and Wells's reports, which entirely omitted data on sitagliptin. As to liraglutide, Gale failed to review the LEADER data or consider the results of at least six observational studies and more than a dozen peer-reviewed meta-analyses that evaluated the pancreatic safety of liraglutide in over 50,000 patients.[8] Gale's failure to consider all the available data leaves his report and testimony on an unsound basis. *Sargon* compels the exclusion of his testimony.

Failure to Weigh the Evidence. As to the evidence he did consider, Gale failed to articulate any objective methodology by which he weighed that evidence. *See, e.g., In re Mirena IUS Levonorgestrel-Related Products Liability Litigation (No. II)* (S.D.N.Y. 2018) 341 F.Supp.3d 213, 247. When questioned about his method, Gale admitted his approach could only be reproduced by his "clone." Gale 2015 Deposition, Exh. J, at 243:20–244:3. He also could not identify what weight he gave to the studies he considered, explain why he gave them that weight, or state how he compared those weights against other available data. *See* Gale 2015 Deposition, Williams Decl., Exh. J, at 242:14–244:3. As a result, Gale's causation analysis is a black box that cannot be examined, replicated, or reproduced by other scientists or physicians. For that reason also, Dr. Gale's causation opinion must be excluded. *See United States v. Hebshie* (D. Mass. 2010) 754 F.Supp.2d 89, 125 (explaining that "reproducibility is the sine qua non of science.").

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[8] *See* Marso 2016, Exh. QQ, Exh. AAA; *see also, e.g.*, Chen 2016, Exh. WWW; Evans 2016, Exh. 70, Novo Nordisk Mot. Summ. J.; Guo 2016, Exh. DDDD; Monami 2017, Exh. EEEE; Zhang 2017, Exh. SSS; Bethel 2018, Exh. BBB; Jia 2018, Exh. FFFF; Liu 2018, Exh. JJ; Wang H. 2018, Exh. QQQ; Pinto 2019, Exh. GGGG; Cao 2019, Exh. Y; Kristensen 2019, Exh. HHHH; El Aziz 2019, Exh. W; Funch 2019, Exh. VV; Knapen 2015, Exh. 41, Novo Nordisk Mot. Summ. J.; Azoulay 2016, Exh. 42, Novo Nordisk Mot. Summ. J.; Boniol 2018, Exh. 43, Novo Nordisk Mot. Summ. J.; Liang 2019, Exh. 44, Novo Nordisk Mot. Summ. J.; *see also* Reid Report at 38 (discussing additional Novo Nordisk observational studies, including CPRD study).

Inappropriate Reliance on Drs. Madigan and Wells. Gale also failed to evaluate whether Madigan's and Wells's statistical analyses are based on a reliable medical foundation and reflect a true causal effect. As discussed above, there are serious and fatal infirmities with Madigan's and Wells's epidemiological reports due to their bizarre, undefined method of counting pancreatic cancer events. Gale has assumed the facts of Madigan's and Wells's reports to be true, "without any foundation for concluding those assumed facts exist." *Wicks v. Antelope Valley Healthcare District* (2020) 49 Cal.App.5th 866, 881–82.

Unlike Madigan and Wells, Gale is a physician and oncologist. As such, Gale is uniquely able to assess whether the pancreatic events were appropriately included in (or excluded from) the analyses and assess whether the reported statistical association was sufficiently strong and free of bias and confounding to support an opinion that liraglutide or any other incretin-based therapy causes pancreatic cancer. For example, Gale could have assessed whether a benign pseudopapillary tumor is relevant to assessing the relationship between liraglutide and pancreatic cancer, or how pancreatic cancers that occurred prior to liraglutide use (two of which were included in the Madigan and Wells analyses) allegedly support an opinion that liraglutide causes pancreatic cancer. Madigan 2020 Deposition, Williams Decl., Exh. NNNN, at 37:13–38:7 (acknowledging classifications of pancreatic cancer were not "within [his] expertise"); Wells 2020 Deposition, Exh. G, at 20:5–21:11 (conceding he did not know the type of pancreatic cancer at issue in this litigation). Gale elected not to ask any of these questions or to perform any independent validation of the analyses:

> Q. I want to ask you a little bit more specific question. Did you do anything to independently valuate the pancreatic cancer event counts in Dr. Madigan's analysis?
>
> A. No.
>
> * * *
>
> Q. Did—did you actually make sure that all of the events of pancreatic cancer that he included in his report were—were, in fact, pancreatic cancer events and not some other—and not as classified by Dr. Wells?
>
> A. I don't know how I would do that.

Gale 2020 Deposition, Exh. 3, Novo Nordisk General Causation Mot., at 205:5–206:11. An expert cannot "weigh" evidence without assessing its strengths, limitations, and reliability.[9] Accordingly, his opinion based on the flawed analyses by Madigan and Wells thus "has no evidentiary value" and is "based on a matter of a type on which an expert may not reasonably rely[.]" *Id.*; *Sargon*, *supra*, 55 Cal.4th at 771.

Methods Inconsistent with Work Outside the Courtroom. Perhaps most damning of all to Gale's conclusion is that he has undermined it with his own work. Gale briefly discussed the causes of pancreatic cancer in a published, peer-reviewed article in THE ASCO POST dated November 25, 2016. Gale had the following to say about the connection between diabetes drugs and the risk of pancreatic cancer:

> Because persons with diabetes often receive therapy, there may be confounding between increased or decreased insulin levels, other antidiabetic drugs, and pancreatic cancer risk. Some data suggest that insulin therapy may further increase pancreatic cancer risk, whereas other drugs such as metformin may decrease risk. Some other antidiabetes drugs have no discernible effect on pancreatic cancer risk, while others are controversial, requiring further study.

Williams Decl., Exh. NNN, at 7–8. Gale's article is telling. He stated that "[s]ome data *suggest*" insulin therapies "*may* further increase pancreatic risk," although some drugs "may decrease risk." Some other unspecified diabetes drugs "have no discernible effect on pancreatic cancer risk, *while others are controversial, requiring further study.*" Gale could not bring himself to repeat in a peer-reviewed article in 2016 his prior, purely forensic conclusion in 2015 that incretin-based therapies cause or contribute to the development of pancreatic cancer. But now he renews that forensic opinion apparently oblivious to his intervening attempt to present research results which his peers would respect. Plaintiffs' explanation that this flip-flop is because the

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[9]The Court notes that the FDA's oncologists were far more cautious than Gale. When the FDA evaluated the pancreatic findings in LEADER, they found a "slight imbalance" in the event counts but noted that the "number of cases [was] too small to permit conclusions regarding whether this imbalance is due to chance alone." FDA June 2017 Briefing Document, Williams Decl., Exh. V, at 132–33. Ultimately, they concluded that the LEADER data did not alter the conclusions reported in the FDA's 2014 NEJM Assessment. FDA June 2017 Briefing Document, Williams Decl., Exh. V, at 133.

conclusion he reached for this litigation is based in part on confidential material is unpersuasive. Plaintiffs provide no explanation of which confidential data shielded by a protective order led Gale to conclude for this action that defendants' drugs increase the risk of cancer while simultaneously suggesting the opposite to the medical community at large. Plaintiffs did not even bother to secure a sworn declaration from Gale simply stating that the non-public information he received in his work on this case led him to the firm causation conclusion he could not publicly express in his 2016 piece. Plaintiffs have stipulated that no further evidence need be received by the Court to rule on the admissibility of this expert witness's testimony. The caution Gale exhibited in THE ASCO POST article—noting the need for "further study" of "controversial" indications of increased pancreatic cancer risk—belies the premise that his conclusion reached in support of plaintiffs' case employed "the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." *Sargon*, *supra*, 55 Cal.4th at 772 (quoting *Kumho Tire Co. v. Carmichael* (1999) 526 U.S. 137, 152). For the reasons discussed above, the Court excludes Gale's expert opinion.

Dr. Brown

The core problem with Dr. Brown's opinion is different in nature: He plausibly explains how exposure to incretin mimetics can stimulate GLP-1 receptors, stimulating cell growth, but his necessary logical next step that this condition increased the risk of pancreatic cancer was based on nothing more than hope or supposition, which is not enough. *Sargon*, 55 Cal. 4th at 771–72.

Brown testified that GLP-1 receptors would be associated with carcinogenesis if there was either (1) overexpression of certain genes related to carcinogenesis or (2) the GLP-1 receptors had increased affinity for the ligand. Williams Decl., Exh. H, at 76–79, 88–90. Brown conceded no studies had been conducted to show increased affinity. *Id.* He also admitted that only one study addressed overexpression, but did not show GLP-1 overexpression in pancreatic cancer cells. Williams Decl., Exh. H, at 90–91. He agreed that an absence of evidence for an increase in affinity or an increase in overexpression would leave no basis to conclude GLP-1

played a role in carcinogenesis. Williams Decl., Exh. H, at 79. He then conceded there was no evidence showing overexpression or increased affinity of GLP-1 receptors. Williams Decl., Exh. H, at 91. Furthermore, Brown acknowledged that his biological plausibility opinion was an unproven hypothesis, *see* Brown 2020 Deposition, Exh. H, Def. *Daubert/Sargon* Mot., at 192:6–16, and that it was a mere hypothetical possibility that incretin-based therapies could cause pancreatic cancer. *Id.* at 96:21–97:12.

When an expert presents a theory of medical causation explaining an injury, he or she is not required to support every aspect of the theory with research on the identical point. *See Domingo ex rel. Domingo v. T.K.* (9th Cir. 2002) 289 F.3d 600, 607. But the reasoning between steps must be "based on objective, verifiable evidence and scientific methodology of the kind traditionally used by experts in the field." *Id.* While there may be evidence that incretin-based therapies increase cell division through GLP-1 receptors, there is, by Brown's own admission, no evidence that GLP-1 receptors are themselves associated with carcinogenesis because there is no data linking GLP-1 receptors to overexpression of genes linked to carcinogenesis or an increased affinity, which Brown testified were the two ways one could conclude GLP-1 receptors play a role in development and promotion of pancreatic cancer. Accordingly, there is insufficient scientific data to support the next link in Brown's theory—connecting GLP-1 to carcinogenesis. *See Domingo,* 289 F.3d at 606–07. There is thus insufficient data to raise Brown's theory beyond inadmissible speculation. *Sargon*, *supra*, 55 Cal.4th at 771–72. The Court will therefore exclude Brown's expert testimony.

III. DEFENSE MOTION TO EXCLUDE FOUR OTHER PLAINTIFF EXPERTS (BETENSKY, PH.D. (WITHDRAWN); LANDOLPH, PH.D.; WOOLF, M.D.; AND TAYLOR, M.D.): MOOT AS TO BETENSKY, GRANTED AS TO THE OTHER THREE

Dr. Landolph

As to Landolph, his testimony five years ago in deposition was that he ran out of time to do a thorough analysis, but he has not fixed this in the intervening period.

Landolph described his method as "look[ing] at the totality of the evidence that you have, because sometimes you're missing something you would like to have, and that's a problem." Laurendeau Decl., Exh. B, at 131–32. In evaluating liraglutide, Landolph stated he "did not go through all the clinical trials" because he did not have access to that kind of data and did not search for it, having confined his search to "carcinogenesis, carcinogenicity and cancer in liraglutide." *Id.* at 279. He also said it was not his assignment to review clinical trial or epidemiological data; that was put before other experts. His role was to review preclinical studies and animal carcinogenesis studies. *Id.* at 293, 295. He conceded he had not received any data on animal studies of the effects of incretin-based therapies. *Id.* at 304–06. At other points Landolph indicated he had not received or reviewed certain data. *See id.* at 181, 280. When pressed by defense counsel, Landolph admitted there were several animal studies he had not reviewed. *Id.* at 296–99. Finally, Landolph admitted he would like to supplement the report he provided to plaintiffs' counsel in 2015 with new literature and information. *Id.* at 83.

Since Landolph did not, by his own admission, consider all the relevant data, his conclusion is not worthy of consideration by a jury. *See Shiffer v. CBS Corp.* (2015) 240 Cal.App.4th 246, 253.

Dr. Woolf

Woolf is a gastroenterologist and for the task of providing this expert opinion he was self-taught for purposes of assessing PanIN lesions (i.e., "on-the-job" training, to quote his deposition (Laurendeau Decl., Exh. C, at 17–18)). Equally important, when deposed five years ago Woolf acknowledged there was additional research he would have liked to have done if he had more time and access to cited articles (which apparently cost too much to access on the web given his retainer fee). *See id.* at 42–45, 58-59, 94, 150). Even with the benefit of a five-year hiatus, no such update has been provided. Since he did not, by his own admission, consider all the relevant data, his conclusion is not worthy of consideration by a jury. *See Shiffer*, *supra*, 240 Cal.App.4th at 253.

Dr. Taylor

Dr. Taylor undertook to study images of PanIN lesions in baboons exposed to exenatide, but no prior standard for assessing such lesions in baboons had been established so he simply did an ad hoc analysis applying human specimen standards. While he noted the genetic overlap of humans and baboons, he did not show how baboon pancreas etiology corresponded to disease processes in humans. *See generally* Laurendeau Decl., Exh. L. Equally important to the relevance of his conclusion that the presence of certain PanIN lesions in baboons was presumptively predictive of future pancreatic cancer, Taylor provided no response to the unchallenged report of defendants' expert David Klimstra, who concluded no literature validates any association of PanIN lesions in non-human primates with the development of pancreatic cancer, and who opined that "the use of the PanIN system in non-human primates to draw any conclusions about the risk to non-human primates to develop pancreatic cancer would be scientifically unreliable." *See generally* Laurendeau Decl., Exh. M. In the face of this report, some reasoned response from Dr. Taylor would be needed before his opinions could be considered worthy of consideration by a jury. Because Taylor's methodology cannot reliably be applied to humans, his testimony must be excluded. *See, e.g.*, *General Electric Co.*, *supra*, 522 U.S. at 146 (upholding exclusion of expert testimony because animal studies involving mice were an unreliable basis for the expert's opinion on causation of cancer in humans); *Domingo ex. rel. Domingo*, *supra*, 289 F.3d at 606–07 (upholding exclusion of expert testimony in part because the expert did not provide "analytical support" for his extrapolation of animal studies to humans).

IV. DEFENDANTS' INDIVIDUAL MOTIONS FOR SUMMARY JUDGMENT BASED ON ABSENCE OF EVIDENCE OF GENERAL CAUSATION: GRANTED

Each defendant brought a motion for summary judgment based on the absence of evidence of general causation. Because plaintiffs have no experts who can opine on causation., plaintiffs cannot show that the various incretin-based therapies are responsible for their injuries.

See Jones v. Ortho Pharmaceutical Corp. (1985) 163 Cal.App.3d 396, 403 (etiology of cancer beyond the experience of a layman and must be explained through expert testimony). For this reason, all three motions are granted.

Motions for summary judgment by Merck (sitagliptin) and by Amylin and Eli Lilly (exenatide) are granted on the additional grounds that plaintiffs cannot establish a causal association between sitagliptin or exenatide and pancreatic cancer. *See, e.g.*, *In re Viagra (Sildenafil Citrate) & Cialis(Tadalafil) Products Liability Litigation* (N.D. Cal. 2020) 424 F.Supp.3d 781, 795 (it is plaintiffs' burden to establish a causal association between the products at issue and pancreatic cancer); *In re Mirena IUS Levonorgestrel-Related Products Liability Litigation (No. II)*, *supra*, 387 F.Supp.3d at 336–41, 347 (same).

Plaintiffs concede they are not arguing that there is epidemiological evidence to support general causation as to Merck (sitagliptin) and Amylin and Eli Lilly (exenatide), and instead hope to "get over the line, vis-à-vis, the biological plausibility argument." Dec. 8, 2020 Tr. of Oral Argumentat 56:22–57:16. Biological plausibility, however, is insufficient to establish causation. *In re Viagra*, *supra*, 424 F.Supp.3d at 791 (explaining biological plausibility is "only a subsidiary consideration in the larger question of general causation"). Therefore, even if admissible, opinions from plaintiffs' experts relating to biological plausibility are not sufficient to establish general causation as to Merck or Amylin and Eli Lilly.

Plaintiffs cannot get around their burden by advancing theories their experts do not endorse—and in some instances affirmatively contradict. *See, e.g.*, *Bockrath v. Aldrich Chemical Co.* (1999) 21 Cal.4th 71, 79 (in cases "presenting complicated and possibly esoteric medical causation issues," a plaintiff must prove causation based on "competent expert testimony"). Counsel's assertions and citations of medical literature are argument, not evidence sufficient to create a triable issue of material fact. *York v. City of Los Angeles* (2019) 33 Cal.App.5th 1178, 1191.

Finally, in response to each of defendants' motions for summary judgment, Plaintiffs argued that they can still establish causation through a differential diagnosis, citing to *Wendell v. GlaxoSmithKline LLC* (9th Cir. 2017) 858 F.3d 1227 and *Roberti v. Andy's Termite & Pest*

Control, Inc. (2003) 113 Cal.App.4th 893. But *Wendell* involved a "rare cancer" that had only occurred a few hundred times in medical history. 858 F.3d at 1236. There was an accordant lack of epidemiological data, leading the court to find good cause to permit experts to opine as to specific causation without establishing general causation. *See id.* Here, there is no showing pancreatic cancer is a rare cancer. One of plaintiffs' experts described pancreatic cancer as the eighth most common cancer. And there is plentiful epidemiological data not just on pancreatic cancer, but on its relation to the incretin-based therapies at issue in this suit—TECOS, which studied sitagliptin; EXSCEL, which concerned exenatide; and LEADER, which reviewed the effects of a liraglutide. *See generally* Williams Decl., Exhs. BB, AAA, ZZ. The data available here does not permit plaintiffs to skip the general causation question. And their citation to *Roberti* is unpersuasive because that case did not expressly permit a litigant to leapfrog over general causation and was decided nine years before *Sargon*, leaving its continued applicability questionable.

V. PLAINTIFFS' MOTION TO EXCLUDE THREE NOVO NORDISK EXPERTS (THAYER, M.D., PH.D.; WANG, M.D.; AND SCHARFSTEIN, SC.D.): MOOT

Plaintiffs moved to exclude three Novo Nordisk experts. Because the Court excludes the plaintiffs' experts and grants the motions for summary judgment based on absence of general causation evidence, this motion is moot. The Court did not consider the expert testimony offered by Thayer, Wang, or Scharfstein in reaching its conclusions here. To the extent some of the Thayer testimony (concerning an abortive post-hoc analysis of rat tissue) was considered in deciding the concurrent defense motion for summary judgment based on FDA preemption, such testimony was not specifically challenged by plaintiffs' motion, nor was it essential to the ruling on the preemption issue.

VI. DEFENSE MOTION FOR SUMMARY JUDGMENT BASED ON FDA PREEMPTION: GRANTED

Given the above rulings, there is no need to revisit the alternative defense argument that all these claims must be dismissed based on federal preemption. Nevertheless, for the completeness of the record and in case a reviewing court disagrees with this Court's conclusion

about the admissibility of plaintiffs' current experts and the resulting impact on the plaintiffs' ability to avoid summary judgment, the Court will turn to this issue.

Introductory Note

As noted at the start of this Order, the parties waived the opportunity for a court trial before the FDA preemption issue was decided pursuant to a Stipulation and Order to Waive Court Trial Before Preemption Question Is Decided, filed October 30, 2020.

Evidentiary Objections

Plaintiffs' Objections to Exhibits to Boehm Declaration:

All overruled for reasons noted in Defendants' Response to Plaintiffs' Objections, dated September 4, 2020.

Defendants' Objections to Exhibits to Crooke Declaration:

Whether or not these items are admitted in full, in part, or not at all does not have an impact onthe Court's ultimate ruling on the merits. Therefore, the objections are overruled.

Plaintiffs' Notice of Additional Authority and Request for Additional Briefing

Plaintiffs submitted a request for additional briefing on supplemental authority: *In re Taxotere (Docetaxel) Products Liability Litigation* (E.D. La. 2020) ___ F.Supp.3d ___, 2020 WL 7480623. The request is denied. In *Taxotere* the court found the FDA was not "fully informed" because it had limited knowledge of the risk of an adverse event and made repeated requests to the drug manufacturer to provide additional information. 2020 WL 7480623 at *11. There is no evidence here that the FDA made requests to defendants for more information about the pancreatic cancer risk and, as discussed below, the FDA did not have limited knowledge of the risk, demonstrated in part by the participation of its personnel in the authorship of a published medical journal article on the topic. Further briefing on the *Taxotere* holding would not persuade the Court to change its preemption analysis in this matter.

Merits:

The ultimate question is whether or not the several defendants' labels for incretin-mimetic products could have been amended by the unilateral action of one or all of the manufacturers by implementation of a Changes Being Effected ("CBE") label change to add disclosure of a risk of pancreatic cancer without being stopped by the federal Food and Drug Administration ("FDA") from doing so under its supervisory authority over prescription drug labels. *Wyeth v. Levine* (2009) 555 U.S. 555. Defendants say they would have been prevented had they tried to do so, and, as such, that they are entitled to a finding of "impossibility preemption" such that any attempt by plaintiffs to advance a state law negligence claim (or other claim) assuming that such a label change should have occurred is preempted under the Supremacy Clause of the U.S. Constitution.

Why No Court Trial at This Time?

The trial court is mindful of the "law of the case" based on the prior ruling of the Court of Appeal in B275314 *Rotondo v. Amylin Pharmaceuticals, Inc.* (Nov. 16, 2018) which expressly held:

> We also agree with the Ninth Circuit's conclusion that the trial court's refusal to consider plaintiffs' new safety evidence requires reversal of the judgment. Judge Highberger's decision incorporated Judge Battaglia's findings that the parties' evidence did not show whether the FDA had actually considered plaintiffs' new evidence, or whether "this data would have altered the FDA's conclusion." The court additionally found that the parties' experts had presented conflicting opinions whether the new information was material to the FDA's analysis. As explained by the Ninth Circuit, **this uncertainty regarding what effect (if any) the plaintiffs' new evidence might have had on the FDA's conclusions demonstrates the existence of a disputed issue of material fact that "should have prevented entry of summary judgment."** [9] (*Incretin-Based Therapies Litigation II, supra*, 721 Fed.Appx. at p. 584; see *Teselle v. McLoughlin* (2009) 173 Cal.App.4th 156, 163, fn. 7 ["'A defendant is entitled to summary judgment [only] if the record establishes as matter of law that . . . plaintiff's asserted causes of action [cannot succeed]'"].)

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[9] **At the summary judgment stage of the proceedings, the existence of a disputed issue of material fact prevents entry of judgment regardless of whether**

> ***Wyeth* preemption presents a question of law that the court must decide, or a question of fact to which the right to jury attaches.** The key inquiry at summary judgment is whether a triable issue of material fact exists, meaning "evidence that would allow a reasonable trier of fact to find the underlying fact in favor of the party opposing the motion. . . ." (*Aguilar v. Atlantic Richfield Co.* (2001) 25 Cal.4th 826, 850.) **For purposes of this standard, it is immaterial whether the trier of fact will be the court or a jury. Because the trial court found there was conflicting evidence regarding what effect the excluded data might have had on the FDA's conclusions about the propriety of a pancreatic cancer warning, the motion must be denied even if that factual question will ultimately be resolved through a bench trial, rather than a jury trial.**

Rotondo v. Amylin Pharmaceuticals, Inc., 2018 WL 5800780 at *12 & n.9 (bold emphasis added).

Subsequent to the issuance of the decision in *Rotondo*, the U.S. Supreme Court shed light on the process question by clearly holding that the issue of FDA preemption presents a question of law for decision by the Court and that in the course of doing so, the Court is authorized to decide all predicate factual questions necessary to the resolution of the ultimate legal question of whether or not "impossibility" preemption applies in a given case. The Supreme Court held in *Merck Sharp & Dohme Corp. v. Albrecht* (2019) 139 S.Ct. 1668, 1680, that a trial court is authorized toresolve the "brute facts . . . relevant to a court's legal determination about the meaning and effect of [the FDA's] decision" regarding whether a label change to add a warning for pancreatic cancer would have been accepted. Given an express offer by this Court to conduct a court trial before the FDA preemption question is decided (to satisfy the language in *Rotondo*), the parties have stipulated that all evidence necessary to decide the preemption issue is before the Court, and no bench trial is necessary. Therefore, the parties have waived any obligation this Court might still have (post-*Albrecht*) to conduct a court trial before the legal question is resolved.[10]

[10]Note, too, that by the elimination of Dr. Fleming's declaration and deposition testimony from this record opposing summary judgment, plaintiffs have removed the factual basis on which each of the appellate courts previously found the existence of a triable issue of material fact. See n.11, *infra*, for more details on this point.

Resolution of Predicate Factual Disputes:

1. ***Would missing "new safety evidence" impact the FDA's decisions?***

Working with the current evidentiary record to resolve the predicate factual questions, the first issue is what "new safety evidence," if any, should have been considered by the FDA before it decided (to the extent it decided anything) that the current labels were correct with no warning of a risk of pancreatic cancer.

On this issue, plaintiffs—as the parties urging that the FDA should have been presented with additional information by the manufacturers—have the burden of persuasion. As a practical matter, since plaintiffs are urging that some additional information would have prompted a change in the FDA's regulatory action (or inaction), it is plaintiffs who have to identify the missing information, confirm it was not available to the FDA from public sources or otherwise, and, most importantly, then show why this extra information would have foreseeably made a difference in the FDA's actions (or inaction). This Court, like virtually every other judge in the country, is a not a graduate of medical school or the holder of an advanced degree in biological science, so it is incumbent on plaintiffs and their advocates to show not just that some information was missing but HOW and WHY such information would have made a difference in the FDA's deliberative processes.

When the previous iteration of this motion was heard and decided in 2015, plaintiffs placed great reliance on the opinion testimony of their FDA regulatory expert, Dr. G. Alexander Fleming, a former senior medical officer on the FDA's staff, but there is no reference to Dr. Fleming in any of the current opposition papers.[11] No other medical expert is offered at this time

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[11]It was only by reference to Dr. Fleming's previously offered testimony that the Ninth Circuit determined that six years ago on a different factual record there was "a disputed issue of material fact [that] should have prevented entry of summary judgment on the defendants' preemption claim." *In re Incretin-Based Therapies Products Liability Litigation* (9th Cir. 2017) 721 Fed.Appx. 580, 584. Reference to that legal conclusion was the basis for the Second District Court of Appeal's previously cited conclusion in *Rotondo*, *supra*, that "[b]ecause the trial court found there was conflicting evidence regarding what effect the excluded data might have had on the FDA's conclusions about the propriety of a pancreatic cancer warning, the motion must be denied even if that factual question will ultimately be resolved through a bench trial, rather than a jury trial." 2018 WL 5800780 at *12 n.9 This evidence is not part of this record, for which reason there is no triable issue of material fact on this point at this time, even if the parties here (i.e., plaintiffs) had not waived their right to a court trial before this question of law was decided.

by plaintiffs in his stead. This forces the Court, as a medical layman, to try to divine why this or that allegedly missing piece of "new safety evidence" might have made a material impact on the FDA's decision-making process.

When this Court dealt with the question previously (on a different record from the one now before this Court, as noted above), it committed reversible error by disregarding plaintiffs' "new safety evidence" under the erroneous theory that *Buckman Co. v. Plaintiffs' Legal Committee* (2001) 531 U.S. 341, prohibited its consideration. For the very reason that this Court had decided the ultimate legal question on an incomplete record, the appellate court itself did not reach the ultimate question and simply "remanded for further proceedings," leaving open the possibility that defendants might still prevail on the ultimate question once a properly complete record was received by the trial court.

As summarized by the appellate court, the "new safety evidence" which plaintiffs wished this Court to consider in 2015 was as follows:

> Plaintiffs also argued that they had identified several categories of "'new safety information'" that the FDA had not "considered . . . in any of its reviews." **First**, plaintiffs cited a 100-page report from **Health Canada** (the FDA's Canadian counterpart) finding that sitagliptin (the active ingredient in Januvia and Janumet) may increase the risk of pancreatic cancer. **Second**, plaintiffs contended that evidence obtained during discovery showed that the **"pooled data analysis"** defendants had submitted to the FDA **omitted "a number of studies that reported cancer,"** resulting in a statistical imbalance that was unknown to the FDA. **Third**, plaintiffs asserted that **their expert witnesses had reviewed tissue slides** from some of the defendants' nonclinical studies, and found evidence of precancerous lesions that defendants had not identified or reported to the FDA. **Fourth**, plaintiffs cited a **nonclinical study that a UCLA research team** had performed using the "Kras mouse," a rodent engineered to have susceptibilities to pancreatic cancer common in aging persons with diabetes. The study **concluded that incretin-based drugs "advance[d] the rate" of formation of precancerous lesions** in pancreas cells. **[Fifth]**, plaintiffs cited a **"pooled analysis" that David Madigan**, a statistics professor at Columbia University, **had performed** on data from numerous clinical trials. Madigan's analysis showed that the rate of pancreatic cancer among diabetics who had been treated with incretin-based drugs greatly exceeded the background rate of pancreatic cancer among diabetics.

Rotondo, *supra*, 2018 WL 5800780 at *4 (bold emphasis added).

Respectful of law of the case, it is this Court's duty now to consider the evidence previously disregarded based on misplaced reliance on *Buckman* insofar as plaintiffs are again relying on such evidence. To what extent is the previously rejected "new safety evidence" reoffered at this time by plaintiffs and, insofar as it is re-offered, what is its significance?

a. ***Health Canada:*** While plaintiffs still cite to this (Pl. Add'l Disputed Facts ["PLADF"] No. 8), defendants have persuasively shown that Health Canada, the Canadian counterpart to the FDA, has swung around to express the view that no association of these drugs with pancreatic cancer is shown. *See* Defendants' Response to PLADF No. 8. Specifically, Health Canada later stated in 2014 that "existing data do not suggest a causal relationship between incretin-based therapies and" pancreatic cancer, and in 2016 wrote that there was "not enough evidence at this time to confirm a link between incretin-based therapies and pancreatic cancer." Boehm Decl., Exhs. AI, AJ.

b. ***Pooled Data Analysis:*** The appellate court determined that the pooled data analysis submitted to the FDA by defendants contained a statistical imbalance unknown to the FDA. Since 2015 there have been a number of new studies of the connection between pancreatic cancer and incretin-based therapies—to name just a few, the TECOS, LEADER, and EXSCEL studies contained thousands of patients who received defendants' drugs. The presence of a mountain of new data at the present indicates that the prior pooled data analysis—standing alone—is now out of date and unreliable, and thus its supposed effect on the FDA would be irrelevant in light of the new data.

c. ***Plaintiffs' experts review of certain tissue slides:*** Plaintiffs retained Dr. Clive R. Taylor to conduct a review of baboon pancreas tissue slides using the PanIN lesion scoring system. Defendants have brought a motion to exclude Taylor's testimony, which is well taken. The PanIN classification system has never been validated for use in non-human primates. Any

conclusion reached via an analysis of PanIN lesions in non-human primates would be wholly speculative and therefore both inadmissible in this Court and of no value to the FDA.

d. ***UCLA Kras mouse study:*** A study explicitly identified as the "UCLA Kras mouse study" was not discussed in the 2020 moving papers. However, the 2008 Drucker study of desfluorositagliptin in rodents was discussed, but defendants made clear it was published (and therefore available to the FDA) and revealed no pancreatic cancer safety concerns. Boehm Supp. Decl., Exh. BC, at 191–97. Further, a study of desfluorositagliptin is of questionable relevance because that compound is not at issue in this case and its suitability as a substitute for sitagliptin has not been established by competent testimony.

e. ***Dr. Madigan's "pooled data analysis":*** Dr. Madigan's testimony has been stricken based on the ruling set forth above in some detail. Since his conclusions are not worthy of admission in this Court of law, they rationally have no greater relevance as a potentially persuasive submission to the FDA in favor of a permissible label change to add a pancreatic cancer warning.

Five years have elapsed and with it more clinical trials, the publication of various papers and studies potentially relevant to this action, the hiring of new plaintiff experts, and the preparationof various unpublished research papers. What new material is offered by plaintiffs in the way of "new safety evidence" which should have been considered by the FDA and which would have modified its regulatory actions? According to plaintiffs' Response to Defendants' Separate Statement of Undisputed Facts, the following additional matters should have been considered:

f. ***Alleged late submission by Novo Nordisk of pseudopapillary tumor during weight management trial.*** PLADF No. 7. The exhibit supporting this fact describes this tumor as non-malignant (i.e., not pancreatic cancer), as does additional information submitted by Defendants. Crooke Decl.,

Exh. 4 at 8 ("Pathology slide results were negative for malignancy of the tumor."); *see also* Boehm Supp. Decl., Exh. BK. Plaintiffs have not established how this non-malignant event would contribute to an FDA decision to mandate a pancreatic cancer warning.

g. ***Alleged omission by Merck of half of pancreatic cancers in sitagliptin study.*** PLADF No. 9. Plaintiffs argue that information submitted to the FDA about Merck's clinical trials omitted half of the pancreatic cancer incidents. They reference defendants' expert, Dr. Goldkind, who they argue testified that the imbalance could have affected FDA's assessment. PLADF No. 10. Goldkind's cited testimony is not so clear; he was answering a hypothetical and was not directly presented with the study and omissions plaintiffs argue would have altered the FDA's decision. *See* Crooke Decl., Exh. 6, at 80–81, 154–60. And the only exhibit cited in support of the conclusion that Merck manipulated data is a list of materials relied on by an expert witness. *See* Crooke Decl., Exhs. 5, 39. There is no evidence showing Merck manipulated data collected in its clinical trials by omitting three pancreatic cancer incidents. Notably, Merck disclosed that some studies were excluded from a pooled analysis and explained that these studies were omitted because they included patients with renal failure receiving lower doses of sitagliptin, or because data was otherwise lacking. *See* Boehm Supp. Decl., Exh. BV at 111.

h. ***Alleged erroneous citation in 2014 New England Journal of Medicine ("NEJM") to Merck-sponsored study.*** PLADF No. 11. Plaintiffs complain that the NEJM article includes a citation to a Merck-sponsored analysis "that was wrong at the time it was published[.]" Plaintiffs' supporting evidence is that footnote 3 of the article cites a pooled analysis of 25 clinical studies that excluded three trials that had sitagliptin pancreatic cancer cases. However, the pooled analysis report clearly states that the subjects reviewed from the 25 studies were those receiving 100 milligrams per day of sitagliptin for at least

twelve weeks (and up to two years) and for which results were available by December 1, 2011. Boehm Supp. Decl., Exh. AV, at AV-10. Plaintiffs provide no expert testimony to establish that the analysis "was wrong at the time it was published" or that the omission of certain subjects outside the stated parameters of the analysis renders its conclusions infirm or irrelevant to the question of an association of pancreatic cancer with sitagliptin exposure. Nothing suggests the FDA personnel who cited the report were misled. Plaintiffs, in deprecating this one citation in the NEJM article, are really trying to get the Court to decide the science. That is something this lay Court is completely incapable of doing, especially in the absence of competent expert testimony.

i. ***Scoring of PanINs in primates by Dr. Owston and Dr. Dick for Amylin inferentially not supplied to FDA (not expressly stated).*** PLADF Nos. 12–13. Plaintiffs concede this study was available to the FDA but argue internal analyses by Amylin scientists and an expert retained by plaintiffs should have been disclosed. First, the evidence suggesting Amylin's scientists made such a finding is merely a one-page chart that is lacking context. *See* Crooke Decl., Exh. 8. It has columns for "Exenatide" and "No exenatide" and rows for "PanIN" (i.e., pancreatic lesions) and "no PanIN" which display data that might suggest there were more cases of lesions in subjects exposed to exenatide. But there is nothing to explain what the data refers to. It would not be reasonable to demand a warning label based on this single sheet of paper. Second, the other evidence cited by plaintiffs is a report by their own expert, which was prepared in anticipation of litigation and is neither peer-reviewed nor published, and thus cannot be reasonable evidence of an association. For reasons noted above in considerable detail, the testimony of Dr. Taylor has been stricken. Therefore, the baboon PanIN study does not supply a reasonable causal link between exenatide use and

pancreatic cancer, and thus could not have been an impetus for the FDA to seek a label change.

j. ***Amylin allegedly withheld comparative analysis of primate tissue from FDA.*** PLADF No. 14. See above; this references Taylor's report.

k. ***Novo alleged withholding of secondary analysis of 13-week ZDF rat study.*** PLADF Nos. 15–18. Plaintiffs focus on an internal statement relating to the study in which it was noted that "liraglutide has some effect on [pancreatic ductal gland] mass/proliferation." Crooke Decl., Exh. 9. But plaintiffs do not put forward evidence showing how this would provide "reasonable evidence of a causal association" between liraglutide and pancreatic cancer. And plaintiffs do not point to anything in the study indicating the rodent subjects developed pancreatic cancer. They focus on data about regeneration and acinar hyperplasia, but again fail to explain how this would be reasonable evidence of association with pancreatic cancer. Indeed, defendants explain in their Reply that acinarhyperplasia is a benign increase in the size of acinar cells that is not a cancerous or pre-cancerous condition. *See* Boehm Supp. Decl., Exh. BT ("No evidence of progression to carcinoma").

l. ***Various other undisclosed rat/rodent studies and alleged attempt to "write over" bad results.*** PLADF Nos. 19–29. Plaintiffs reference a post-hoc analysis of rat tissue that attempted to look at the effect of liraglutide treatment on the pancreatic duct glands, which apparently was labeled "Project: NNxxxx." *See* Crooke Decl., Exh. 18. Defendants concede this was not provided to the FDA. However, one of the team members, Lotte Knudsen, M.D., testified that the post-hoc analysis did not have any valid results, and thus could not be reported, and it was a team decision to determine there were no valid results. Boehm Decl., Exh. AR, at 172. Defendants' expert, Sarah Thayer, agrees and describes the shortcomings of the study, such as lack of adequate data and mistaken means of identifying pancreatic duct glands.

Boehm Decl., Exh. AT at 21 (Thayer Expert Report). Although plaintiffs seek to exclude Thayer's testimony, their motion does not attack her review of the post-hoc analysis of rat tissue. Defendants have put forth persuasive evidence that the FDA would not have treated the incomplete post-hoc analysis as "reasonable evidence" of an association between liraglutide and pancreatic cancer. Further, a review of the report's conclusions indicates it was noncommittal as to whether liraglutide was responsible for any of the effects on pancreatic tissue observed in the animal subjects. Crooke Decl., Exh. 18, at 11, 49–50. Novo Nordisk conducted two studies, JYNR130201 and KLyk131001, where one animal in each was observed to have an inflamed pancreas. The studies were not designed to evaluate pancreatic tissue. The former sought to evaluate liraglutide's effect in the prevention of diabetic nephropathy. Boehm Supp. Decl., Exh. BN at 10. The latter's aim was to evaluate the combined effect of liraglutide and another compound on mice body weight, body composition, and bone mineralization. Boehm Supp. Decl., Exh. BP at 12. While there is no indication the FDA received this information, it is not clear that the FDA would consider it meaningful, since each study was meant to evaluate something other than pancreatic cancer risk. And the results only showed an inflamed pancreas, not cancer. Plaintiffs have not directed the Court to any expert testimony explaining how the results of JYNR130201 and KLyk131001 would persuade the FDA that a pancreatic cancer warning was necessary. Finally, plaintiffs reference Study ADPC140901, referring to a portion of the test where an L-arginine challenge was conducted, causing four rats to die in less than twenty-four hours and four more to become ill. Crooke Decl., Exh. 15. But none of the rats were recorded to have pancreatic *cancer*, just inflammation and bleeding of the pancreas. *Id.* Plaintiffs do not explain how this is establishes a reasonable causal link to pancreatic *cancer* in *humans* using liraglutide.

m. ***Alleged distortions by Novo Nordisk of data contained in LEADER study.*** PLADF Nos. 30–41. LEADER was the chief clinical trial of liraglutide. Plaintiffs argue that Novo Nordisk failed to fully inform the FDA about LEADER and actively misled the agency. During the LEADER study, Novo Nordisk used the Humedica database to assess the background rate of pancreatic cancer in diabetes patients. Plaintiffs argue the results show that the placebo rate of pancreatic cancer in the LEADER trial was similar to the "background rate" from the Humedica study, which indicated the LEADER trial's elevated rates of pancreatic cancer among subjects exposed to liraglutide was significant. Plaintiffs accuse Novo Nordisk of never publishing the comparative Humedica data and never informing the FDA. For one, the object of the study was to provide contextual data about expected rates of cancer development if certain subjects had not taken liraglutide. Crooke Decl., Exh. 20, at 3–4, 26. And more importantly, the information is publicly available on the clinicaltrials.gov website, which indicates it was published and made available to the FDA. Although the reference is only provided in footnote 88 to the Reply, and not as additional evidence, it stills serves as clear evidence the FDA received this information, or at least had access to it, because it is on a website maintained by the NIH and FDA. *See* https://clinicaltrials.gov/ct2/about-site/background. The Court is thus inclined to conclude the FDA received the Humedica database study and was fully informed about cancer event rates found in the LEADER study.

n. ***Alleged conscious choice by Merck to perform studies with desfluorositagliptin as opposed to sitagliptin.*** PLADF Nos. 43–56. Plaintiffs argue that Merck should have disclosed the results of its "secret nonclinical research projects" with desfluorositagliptin,which is a chemical analogue to sitagliptin. Apparently, desfluorositagliptin has been described as having "virtually identical" properties to sitagliptin and only differs from sitagliptin

by one atom. PLADF Nos. 44, 49. Merck did not provide its desfluorositagliptin animal studies to the FDA when the agency sought information about pancreatic toxicity. PLADF No. 48. Plaintiffs' argument suggests that Merck used the desfluorositagliptin studies to ensure it had favorable results with sitagliptin, and it should have also disclosed the results of a 2008 desfluorositagliptin study to the FDA. This argument falls flat. Desfluorositagliptin has never been marketed by Merck and no plaintiff alleges it caused injury. This should end the analysis. Plaintiffs cite no authority that requires a drug manufacturer to disclose the results of studies that involve *similar* compounds to those the manufacturer sells. There is no evidence that a study of desfluorositagliptin would provide reasonable evidence of a causal relationship between sitagliptin exposure and pancreatic cancer. Plaintiffs' witness called desfluorositagliptin and sitagliptin similar molecules with some identical properties, but conceded they were still "by nature two different molecules." Boehm Supp. Decl., Exh. BA, at 147–48; *see also* Exh. BB, at 99. No expert opines that desfluorositagliptin and sitagliptin are so similar that the former is a suitable substitute for the latter in a clinical setting. And the 2008 Drucker study of desfluorositagliptin in rodents was published—therefore available to, and not hidden from, the FDA—and did not reveal any pancreatic safety concerns. Boehm Supp. Decl., Exh. BC, at 191–97. This study would not be new or material information to the FDA.

o. ***Alleged process failures by Merck in management of TECOS trial, results of which were shared with FDA.*** PLADF Nos. 57–63. Plaintiffs argue the TECOS study protocol was misleading because it did not collect information about events (i.e., pancreatic cancer events) that occurred more than 28 days after a subject's last treatment with the study drug. But the FDA was informed of this data collection limitation, as evidenced by a 2014 letter from Merck informing the FDA of a change in the protocol allowing collection of

data for events occurring more than 28 days after discontinuation of treatment. Boehm Supp. Decl., Exh. AY. Plaintiffs' contention that Merck "never flagged any of these issues for the FDA" (Opposition at 37) is simply untrue. The FDA was well aware of the parameters of the TECOS study and any possible shortcomings it had with respect to the limitation of reporting only events that occurred within 28 days of cessation of treatment. This is not newly acquired information that would alter the FDA's labeling decision; the agency had already been fully informed of the TECOS study's methodology.

p. ***Alleged process and record-keeping failures with Amylin's EXSCEL study, results of which were shared with FDA.*** PLADF Nos. 64–79. Plaintiffs attack the EXSCEL study and complain of its deficient protocol for reporting pancreatic cancer incidents. Plaintiffs also complain that some subjects reported as being on placebos had received other incretin-based treatment. The first argument is quickly disposed of: the FDA was aware of the protocols governing the EXSCEL study and any amendments to the protocols. Boehm Supp. Decl., Exh. BE. Plaintiffs' complaints about inclusion of patients who were taking other incretin-based therapies are meritless; users of DPP-4 inhibitors (i.e., sitagliptin) were permitted in the study and this was expressly stated. *See* Boehm Supp. Decl., Exh. BF, at BF-100. Even if a placebo subject took liraglutide, it has not been demonstrated that this was outside the information received by the FDA. Other data sets Plaintiffs complain of, such as placebo case diagnoses or the "buried" figure of 12 exenatide pancreatic cancer cases versus nine placebo cases, were apparently submitted to the FDA. *See, e.g.*, Crooke Decl., Exh. 59. Despite Plaintiffs' argument that they "cannot be found in the FDA submissions or even in the body of the clinical study report," nothing establishes that this data was found outside FDA-submitted materials. Indeed, its formatting and appearance are identical to other materials plaintiffs concede were submitted to the FDA. *Compare*

Crooke Decl., Exh. 46 *with* Exh. 59. Plaintiffs' argument that the information was not submitted to the FDA is misleading. All indications are that the FDA received full disclosure of the EXSCEL study and supporting data.

q. ***Alleged data manipulation by Amylin of non-EXSCEL study submitted to the FDA.*** *See* Opposition at 37-38, not expressly stated in Plaintiffs' Additional Disputed Facts. Plaintiffs argue that internal Amylin data suggested exenatide users had double the rates of pancreatic cancer compared to subjects not exposed to exenatide, but Amylin scrubbed this data from its submission to the FDA. What is significant here is that there is internal data from Amylin indicating different rates of pancreatic cancer events in patients exposed to exenatide and not exposed to exenatide. Crooke Decl., Exh. 45 at 330. There is a subsequent report submitted to the FDA which only includes data on those exposed to exenatide. Crooke Decl., Exh. 46. The FDA did not have the control data to compare to the data regarding those exposed to exenatide. The controlling regulation, 21 U.S.C. § 314.3(b), defines newly acquired information as, *inter alia*, "data, analyses, or other information not previously submitted to the Agency, . . . if the studies, events, or analyses reveal risks of a different type or greater severity or frequency than previously included in submissions to FDA." The internal analysis appears to indicate exposure to exenatide had double the incidence rate. Exhibit 46 is stripped of this comparative data, suggesting the FDA was deprived of reasonable evidence of a causal link. But again, plaintiffs provide no citation to expert testimony to explain how the FDA would have used this information if it had been received.

For the reasons cited in much more detail in defendants' Reply in Support of Separate Statement of Undisputed Fact, etc., filed September 4, 2020, the Court finds that defendants have shown that these alleged errors and omissions are variously unsubstantiated by plaintiffs in their

papers, misstated, or of no material consequence.[12] Even more importantly, plaintiffs have not offered at this time an expert competent in the management of clinical drug trials and the submission of reports to the FDA to demonstrate in terms comprehensible to the Court, as a layman to medical research, why the various alleged sins recounted in PLADF Nos. 7–70 would have made a difference to the FDA's evaluation of the safety of incretin-based mimetics and, more particularly, their tendency to cause pancreatic cancer. To the extent that plaintiffs would offer Madigan or Taylor as experts to fulfill such a role, the Court has found their testimony inadmissible. To the extent plaintiffs expect the Court to reply on defense expert Goldkind, the citations to his deposition testimony do not squarely support the conclusions plaintiffs make.

So, while the Court has seriously considered each piece of plaintiffs' proposed "new safety evidence," the Court makes the predicate finding of one of the "brute facts" needed to resolve this legal question: plaintiffs have failed to show that defendants failed to provide the FDA in a timely fashion with one or more piece of additional safety evidence which might have a tendency to change the FDA's behavior.

2. What constitutes "agency action carrying the force of law"?

With the "new safety evidence" question decided, the next predicate fact which needs to be decided on remand is whether the defendants have met their burden to produce "clear evidence" (to quote *Wyeth v. Levine*, *supra*) that a CBE label change adding a warning for pancreatic cancer would have been rejected by the FDA. Bound up with this functionally factual question is the threshold legal question of what is or is not cognizable "agency action" under *Albrecht* such that it can be considered the act of this federal agency pursuant to properly delegated congressional authority such that Supremacy Clause preemption can flow from the act or failure to act. *Albrecht*, *supra*, 139 S.Ct. at 1679.

[12]This Court concurs with Judge Battaglia's analysis of essentially the same proffered plaintiffs' evidence in his March 9, 2021 MDL Omnibus Order at pp. 14–26 wherein he concluded that "as previously analyzed, none of the purported new safety information reflects well-grounded scientific evidence of causal association that would have made the risk of pancreatic cancer apparent to Defendants," for which reason none of this alleged "newly acquired information" was a sufficient basis for a CBE label change under the controlling definition at 21 C.F.R. § 314.70(c)(6)(iii)(A).

The *Albrecht* court noted that disapproval of a warning can be expressed through official action by notice-and-comment rulemaking setting forth labeling standards, formally rejecting a warning label that would have been adequate under state law, or with "other agency action carrying the force of law[.]" *Id.* However, the *Albrecht* court did not have the "question of disapproval 'method'" before it. *Id.* Justice Alito, in a concurring opinion joined by two other members of the Court, remarked that the FDA's failure to act pursuant to 21 U.S.C. § 355(*o*)(4)(A) may constitute official action informing the preemption analysis. *See id.* at 1684–85. The FDA's refusal "to require a label change despite having received and considered information regarding a new risk" under section 355(*o*)(4)(A) supplies a "logical conclusion" "that the FDA determined that a label change was unjustified." *Id.* at 1684. The FDA's duty does not depend on whether the relevant drug manufacturer brought the new information to the agency's attention, and the FDA is not required to communicate that a label change is unwarranted. *Id.*

The "elephant in the room" for purposes of FDA preemption analysis in the context of this specific group of cases is the FDA's active participation in the publication of a peer-reviewed article in the highly respected NEW ENGLAND JOURNAL OF MEDICINE in February 2014: A. Egan et al."Pancreatic Safety of Incretion-Based Drugs—FDA and EMA Assessment" (hereafter "NEJM article"). It was co-authored by professional staff at the FDA and the European Medicines Agency and described as "From the Office of New Drugs, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD [referencing four FDA co-authors]; the European Medicines Agency, London [citing one co-author]; Läkemedelsverket, Uppsala, Sweden [citing one co-author]; and the Dutch Medicines Evaluation Board, Utrecht, the Netherlands [citing the final co-author]." The authors have never thereafter retracted or publicly hedged about their authorship of the article and its factual correctness. The NEJM article concluded, in relevant part, as follows:

> Thus, the FDA and EMA have explored multiple streams of data pertaining to a pancreatic safety signal associated with incretin-based drugs. Both agencies agree that assertions concerning a causal association between incretin-based drugs and pancreatitis or pancreatic cancer, as expressed

> recently in the scientific literature and in the media, are inconsistent with the current data. *** The FDA and the EMA believe that the current knowledge is adequately reflected in the product information or labeling, and further harmonization among products is planned in Europe . . . .

The subject of pre-publication article review and the use of disclaimers is addressed in the FDA STAFF MANUAL GUIDE at 2126.3, "Review of FDA-Related Articles and Speeches" § 6.A, effective Feb. 2, 2011 (available at https://www.fda.gov/media/80061/download). The STAFF MANUAL says the following on the subject of disclaimers:

> **A. FDA-Assigned Articles or Speeches**
>
> Articles or speeches that are assigned work will be reviewed and cleared through the standard supervisory channels established by the Center or the agency and on a schedule to be determined by the employee and the supervisor. The time limits given below (in section 7.B.) do not apply to assigned work.
>
> **If,** during the review and clearance process of an FDA-assigned article or speech, an employee and his or her Center do not agree about the findings, conclusions, or policy implications set forth in the FDA-assigned article or speech, or **if the Center determines that the article or speech is not appropriate as an official communication by FDA, the employee may still opt to pursue publishing the article** or presenting the speech as a non-assigned FDA-related article or speech **providing that he or she follows the procedures in section 7.B below (including use of a disclaimer as required in section 7.B.11).**
>
> **Even in the case of an FDA-related article or speech that is assigned work, the supervisor and/or the employee may decide to use a disclaimer to emphasize that the views expressed in the article or speech do not necessarily represent the official views or policies of the agency** (see 21 CFR 10.85(k)).

(bold emphasis added)

While the lack of a disclaimer in the NEJM article is notable given the general preference for including such language, that alone is not enough to elevate the article into an official communication since the Code of Federal Regulations controls over any implications created by the FDA Staff Manual. The process for obtaining a binding advisory opinion from the FDA is set forth in formal regulations at 21 C.F.R. § 10.85. The Court agrees with plaintiffs that the NEJM

article, as such, was not generated in the process required before an Advisory Opinion can issue and thus it is, of necessity, merely "an informal communication that represents the best judgment of that employee at that time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed." So, the article itself, published though it was in one of the most influential and well-regarded peer-reviewed medical journals in the world and published without disclaimer of agency endorsement, is an "informal communication" only and, as such, not "agency action."[13]

The article is nevertheless highly relevant since it explains the bases for the FDA's clear and consistent behavior when exercising its labeling authority, conduct which does constitute official "agency action." *See Albrecht*, *supra*, 139 S.Ct. at 1679 ("the only agency actions that can determine the answer to the pre-emption question, of course, are agency actions taken pursuant to the FDA's congressionally delegated authority"). The FDA has clear authority to evaluate, approve, and disapprove prescription drug labels. *See* 21 U.S.C. § 355(d), (*o*). Under section 355(*o*)(4)(A) the FDA "shall promptly notify" a drug manufacturer when it "becomes aware of new information, including any new safety information or information related to reduced effectiveness, that the [FDA] determines should be included in the labeling of the drug[.]" The FDA may then order a change in the drug label if deemed appropriate. 21 U.S.C. § 355(*o*)(4)(E). The FDA's consistent evaluation and reevaluation of a product, coupled with its obligation to raise new safety information with the manufacturer when such information independently comes to the agency's attention, constitute "official action" for the purpose of preemption. The FDA has treated with the subject of suitable labels for incretin-based mimetic products repeatedly over the last five-plus years. Its consistent declination of addition of a pancreatic cancer warning when it is otherwise officially approving such label changes does

[13]For the above stated reasons, this Court diverges from Judge Battaglia's contrary conclusion in his recent decision that the article itself can be seen as "other agency action carrying the force of law." March 9, 2021 MDL Omnibus Order at pg. 29. The article's existence does, however, powerfully explain the reasons behind formal actions taken later by the FDA in rejecting the citizen petition and in approving various incretin mimetic label changes without inclusion of a pancreatic cancer warning.

show "agency action" under its delegated authority sufficient to support application of the Supremacy Clause.

3. Have defendants shown "clear evidence" that a CBE label change would have beenrejected?

The foregoing discussion of what is and is not "agency action" provides dramatic foreshadowing of how the inherently factual question of "impossibility" preemption is to be resolved. The labeling decisions are relevant evidence of agency action, the decisions have uniformly omitted any requirement to add a pancreatic cancer risk warning, and all such actions (arguably inaction) by the FDA have followed its volitional act in allowing the publication of the very detailed NEJM article which addressed this exact issue in great detail and without a disclaimer. No recall, recanting, or questioning of the NEJM article by its authors, the FDA, or any other medical professional has been shown by plaintiffs.

Defendants have thus shown that it was impossible for them to comply with both federal and state requirements. *See Wyeth, supra*, 555 U.S. at 573; *see also Albrecht, supra*, 139 S.Ct. at 1678. There is "clear evidence" the FDA would not have approved a label for incretin drugs warning of a heightened risk of pancreatic cancer. *See Wyeth, supra*, 555 U.S. at 571; *see also Albrecht, supra*, 139 S.Ct. at 1672. This undisputed record resoundingly requires a finding that a CBE to add a pancreatic cancer risk warning would have been rejected by the FDA such that these defendants are fully entitled to the benefit of Supremacy Clause "impossibility defense" preemption of these several plaintiffs' state law tort claims.

The motion is granted for this reason as well as for the no-proof-of-causation reasons previously discussed. The ruling as to FDA preemption covers the period up to the date of submission of this matter for decision; i.e., March 1, 2021.

VII. NEXT STEPS

Counsel are now to prepare a complete list of all the still-pending plaintiffs in these several coordinated cases who are suing for pancreatic cancer such that their names and docket numbers can be included in the needed Judgment (which should be separately filed in each of the

dockets in which a given plaintiff's Complaint was actually filed). All such plaintiffs will have the opportunity to test the correctness of this legal ruling via an appeal absent compromise.

The parties need to separately address how this Court should proceed to address the remaining claims in this JCCP which relate to other diseases such as thyroid cancer. Are they stayed pending an anticipated appeal? Should discovery on the general causation merits of those claims now proceed? Are they amenable to compromise? Also, how do we deal with the relatively large number of cases where Girardi Keese is a plaintiff's counsel of record given that firm's recent bankruptcy filing.

To address all these loose ends, the Court now sets a Further Status Conference on April 22, 2021 at 1:30 p.m. with (a) proposed Judgements to be lodged by defendants by April 15, 2021 and (b) Joint Report re next steps re other-disease cases and other loose ends (e.g., how to deal with cases filed by Girardi Keese, given its bankruptcy filing, and any unfunded pancreatitis cases) to be served and filed by April 15, 2021.

IT IS SO ORDERED.

Dated: April 6, 2021

HON. WILLIAM F. HIGHBERGER
JUDGE OF THE SUPERIOR COURT