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21 **UNITED STATES DISTRICT COURT**
22 **FOR THE SOUTHERN DISTRICT OF CALIFORNIA**

23 In re: INCRETIN-BASED THERAPIES
24 PRODUCTS LIABILITY LITIGATION

Case No. 13-md-2452-AJB-MDD

25 **MEMORANDUM OF POINTS**
26 **AND AUTHORITIES IN**
27 **SUPPORT OF DEFENDANTS'**
28 **JOINT MOTION FOR**
SCHEDULING ORDER
REGARDING CAUSATION

Date: February 18, 2014
Time: 9:00 a.m.

Judge: Hon. Anthony J. Battaglia
Courtroom: 3B

Magistrate: Hon. Mitchell D. Dembin

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1 proposal set *Daubert* hearings shortly before trials, starting for Byetta late next year,
2 2015, and not occurring until 2016 and 2017 for Januvia and Victoza.

3 Rather than engage in a disconnected dialogue on a variety of issues where
4 there is no alignment on the general framework for a schedule, defendants and
5 plaintiffs agreed, with the Court's concurrence, to submit their respective positions to
6 the Court on this threshold issue.

7 INTRODUCTION

8 This multidistrict litigation is quite different from the usual multidistrict
9 litigation involving a prescription medication. Typically, the Judicial Panel on
10 Multidistrict Litigation receives a request for pretrial coordination following the
11 withdrawal of a medication from the market or, at least, the publication of a major
12 study calling the medication's safety into question, with the consequent filing of
13 hundreds of cases alleging a failure to warn of the risk. Think Diet Drugs (fen-phen),
14 Vioxx, Celebrex, Bextra, Propulsid, Rezulin, Baycol, Phenylpropranolamine (PPA),
15 Prempro, Trasylol—the list goes on.

16 In the ordinary case, “general causation”—that is, whether a medication is
17 *capable* of causing the alleged harm—is often an important threshold issue in
18 pharmaceutical litigation. However, that issue is often overshadowed by issues
19 related to the warning and to “specific causation”—whether a medication caused a
20 particular plaintiff's harm. “Typical” litigations follow typical discovery schedules
21 that address general causation discovery and *Daubert* after the completion of generic
22 fact discovery.

23 But the story is different for the incretin-based therapies that are the subject of
24 this MDL. Causation is the critical issue here. None of the products has been
25 withdrawn from the market. No study in humans or animals has concluded that these
26 medicines increase the risk of pancreatic cancer. Nor has any observational study so
27 concluded.

1 What is so different about the incretin-based therapies, as compared to the
2 prescription medications in earlier MDLs, is a combination of three things: (1) there is
3 a wealth of scientific data about these medicines; (2) the scientific community has
4 reached a consensus that there is no sound scientific evidence that the medications
5 cause pancreatic cancer; and (3) that consensus is current. Indeed, there were at least
6 four expressions of that consensus in 2013:

- 7 • In July 2013, after convening a special task force to study the scientific data, the
8 European Medicines Agency (“EMA”), Europe’s equivalent to the FDA,
9 announced in a comprehensive seventeen-page report that “[c]oncerning
10 pancreatic cancer, there is currently *no support* from clinical trials that GLP-1
11 based therapies increase the risk.”¹ In a press release, the EMA announced that
12 “presently available data do not confirm recent concerns over an increased risk
13 of pancreatic adverse events with these medicines.”²
- 14 • The Food and Drug Administration said the following week that it “concur[s]”
15 with the EMA and that the EMA’s assessment reflects the FDA’s current
16 understanding of the science, as well.³
- 17 • In June 2013, the National Institute of Diabetes and Digestive and Kidney
18 Diseases (“NIDDK”) and the National Cancer Institute (“NCI”) convened a
19 first-ever joint conference of leading experts in the fields of diabetes and
20 pancreatic cancer.⁴ Afterwards, the American Diabetes Association, European
21 Association for the Study of Diabetes, and the International Diabetes Federation
22 issued a joint statement about the conference (i) explaining that the FDA

23 ¹ European Medicines Agency [EMA], *Assessment report for GLP-1 based*
24 *therapies*, at 16, EMA Doc. 474117/2013 (July 25, 2013) (“EMA Report”) (attached
25 as Ex. 17) (emphasis added).

26 ² Press Release, European Medicines Agency, *Investigation into GLP-1 based*
27 *diabetes therapies concluded: No new concerns for GLP-1 therapies identified on the*
28 *basis of available evidence* (July 26, 2013) (attached as Ex. 18).

³ Ed Silverman, *Diabetes Drugs Pancreatic Cancer Risk Not Backed By Existing*
Evidence: FDA, Pharmalot (July 31, 2013),
[https://web.archive.org/web/20130819002506/http://www.pharmalive.com/fda-
decides-no-risk-of-pancreatic-cancer-with-diabetes-drugs](https://web.archive.org/web/20130819002506/http://www.pharmalive.com/fda-decides-no-risk-of-pancreatic-cancer-with-diabetes-drugs) (attached as Ex. 37).

⁴ See NIDDK-NCI Workshop on Pancreatitis-Diabetes-Pancreatic Cancer (June
12–13, 2013), <http://www2.niddk.nih.gov/News/Calendar/PDPC2013.htm> (last visited
Feb. 4, 2014).

1 presented a thorough review of the animal data “finding *no concerns for*
2 *pancreatic disease*” and (ii) recommending the incretin-based therapies for their
3 “equivalence, if not superiority” to other antidiabetic medications.⁵

- 4 • In August 2013, the American Association of Clinical Endocrinologists and the
5 American College of Endocrinology issued a Consensus Statement concluding
6 that for incretin-based therapies there is “[*n*]o *evidence* of . . . pancreatic cancer
7 in humans.”⁶

8 Thus, the experts directly concerned with the regulation of incretin-based therapies
9 and the experts directly concerned with the treatment of diabetes and pancreatic
10 cancer have recently reviewed the body of scientific data evaluating the potential
11 relationship between the therapies and pancreatic cancer, and they have determined
12 that the data do not support the presence of an association, much less a causal
13 relationship.

14 So, on what sound scientific basis do plaintiffs rely for disagreeing with the
15 European Medicines Agency, the FDA, the American Diabetes Association (“ADA”),
16 the European Association for the Study of Diabetes (“EASD”), the International
17 Diabetes Federation (“IDF”), the American Association of Clinical Endocrinologists
18 and the American College of Endocrinology? If this litigation were to proceed on a
19 routine path, the answer to this fundamental question would not be known for years.

20 The Court has the discretion—and good cause to exercise it—to have this
21 question answered now, based on the evidence currently available. Doing so will
22 “promote[] judicial efficiency [and] prevent[] the potential waste of the parties’ and
23 the Court’s resources.” *In re Viagra Prods. Liab. Litig.*, MDL No. 1724, slip op. at 1
(D. Minn. June 30, 2006) (attached as Ex. 47). Amylin, Lilly, Merck, and Novo

24 ⁵ ADA/EASD/IDF Statement Concerning the Use of Incretin Therapy and
25 Pancreatic Disease (June 28, 2013), [http://www.diabetes.org/newsroom/press-](http://www.diabetes.org/newsroom/press-releases/2013/recommendations-for.html)
26 [releases/2013/recommendations-for.html](http://www.diabetes.org/newsroom/press-releases/2013/recommendations-for.html) (emphasis added) (“ADA/EASD/IDF
Statement”) (attached as Ex. 1).

27 ⁶ See Yehuda Handelsman, et al., *Diabetes and Cancer – An AACE/ACE*
28 *Consensus Statement*, *Endocrine Practice*, 19(4):675 (2013), at 685, 687 (emphasis
added) (attached as Ex. 24).

1 Nordisk request the Court to exercise that discretion to enter a discovery schedule that
2 addresses “general causation” expert discovery and related *Daubert* issues at the
3 outset of this MDL.

4 There is nothing to lose, and everything to gain, by this approach. General
5 causation discovery is underway and can be completed quickly. Virtually all of the
6 evidence that real-world scientists rely on to make general causation determinations is
7 publicly available. To the extent that defendants are in possession of non-public data,
8 it either has been produced already or can be produced in short order. *Daubert*
9 hearings on general causation can proceed soon thereafter. At that point, if the Court
10 finds—like U.S. and European organizations—that there is no reliable basis to
11 establish causation in this case, the litigation will conclude, “sav[ing] thousands of
12 person-hours and millions of dollars [that would have been spent on] unnecessary
13 efforts.” *In re Agent Orange Prod. Liab. Litig.*, 506 F. Supp. 762, 796–97 (E.D.N.Y.
14 1980). If not, the case nevertheless will have been advanced considerably, resolving a
15 key issue common to all cases, at no extra cost to the parties or the Court.

16 By contrast, if this litigation takes the path plaintiffs prefer, the dissonance
17 between plaintiffs’ allegations and the state of the science will endure for years.
18 Under the plaintiffs’ proposals, the parties and the Court would not take up general
19 causation—concerning Byetta only—until August 2015, on the eve of the first trial.
20 Whether or not Victoza and Januvia can cause pancreatic cancer would not be
21 addressed until 2 ½ years and 3 years from now, respectively. Meanwhile, the parties
22 and the Court will embark on a long and expensive journey involving the production
23 of millions of pages of documents and the taking of scores of depositions, with legal
24 skirmishes along the way over a variety of issues. Then, only after spending untold
25 amounts of time, money, and judicial resources on discovery and procedural
26 wrangling, would the Court turn to whether there is a sound scientific basis for
27 plaintiffs’ claims and whether the litigation should proceed to bellwether trials.
28

1 This process takes a toll, and not just in time and money spent on litigation.
2 Patients who take the medications, but are subjected to litigation-driven
3 advertisements or accounts in the media about risks of the medications, may be left
4 uneasy. And doctors may be less willing to prescribe the medications, even though
5 they remain FDA-approved and despite the guidance from the ADA, EASD and IDF
6 that incretin-based therapies are “equivalen[t], if not superior[.]” to other antidiabetic
7 medications, lest they be drawn into the litigation as parties or witnesses.⁷

8 Checking speculative science at the gate “help[s] assure that the powerful
9 engine of tort liability, which can generate strong financial incentives to reduce, or to
10 eliminate, production, points toward the right substances and does not destroy the
11 wrong ones.” *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 148–49 (1997) (Breyer, J.,
12 concurring).⁸ As we explain further below, the Court is endowed with “broad
13 discretion to tailor discovery narrowly and to dictate the sequence of discovery . . . to
14 facilitate [the] prompt and efficient resolution of the lawsuit.” *Crawford-El v. Britton*,
15 523 U.S. 574, 598–99 (1998). Under the circumstances presented here, legal
16 precedent and principles of effective case management make it appropriate to exercise
17 that discretion to put the general causation question first in this case:

- 18
- 19 • First, the *Manual for Complex Litigation* encourages “sequencing and
20 limitations” on discovery, and “tak[ing] up early in the litigation” issues such as
21

22

23 ⁷ ADA/EASD/IDF Statement (Ex. 1).

24 ⁸ See also *Tamraz v. Lincoln Elec. Co.*, 620 F.3d 665, 677–78 (6th Cir. 2010)
25 (citing media reports “describing how scientists concluded, after years of litigation,
26 billions in settlements and the bankruptcy of a major manufacturer, that no evidence
27 tied breast implants to health problems”); Gina Kolata, A Case of Justice, or a Total
28 Travesty?; How the Battle Over Breast Implants Took Dow Corning to Chapter 11,
N.Y. Times (June 13, 1995), available at
<http://www.nytimes.com/1995/06/13/business/case-justice-total-travesty-battle-over-breast-implants-took-dow-corning-chapter.html>.

1 “whether the facts and expert evidence support a finding that the products . . .
2 have the capacity to cause the type of injuries alleged.”⁹

- 3 • Second, causation is an essential element of every claim. Other MDL courts
4 have structured discovery to address causation as a threshold issue. This is
5 fully consistent with plaintiffs’ obligation to have a good-faith basis for alleging
6 causation “*before* filing their claims.”¹⁰
- 7 • Third, a scientific hypothesis, as distinguished from reliable scientific evidence,
8 will not meet that obligation. As one MDL court observed, “Medical science
9 may one day determine with sufficient reliability that a causal relationship
10 exists . . . but it is not there yet and may never be. A trial court must function in
11 the present *assessing evidence that presently exists*.”¹¹
- 12 • And, finally, discovery on general causation can be accomplished quickly and
13 at little cost to the parties. Most, if not all, of the information necessary for
14 plaintiffs to make their general causation case is in the public domain or has
15 been produced to them already. There is nothing to lose, and everything to
16 gain, by taking up this threshold issue first, rather than requiring the Court and
17 the parties to delve into expensive discovery on issues that may not be
18 necessary.

14 MEDICAL BACKGROUND

15
16 Byetta, Januvia, and Victoza have all been approved by FDA for the treatment
17 of type 2 diabetes, a disease characterized by chronic high levels of blood sugar. They
18 are broadly referred to as “incretin-based therapies” because they increase levels of
19 certain incretin hormones which help lower blood sugar by stimulating production of
20 insulin. Incretin-based therapies have become an important treatment option for
21 patients with type 2 diabetes and continue to be recommended by all leading medical
22 organizations in the diabetes field.¹²

23
24 ⁹ *Manual for Complex Litigation (Fourth)* (“*Manual*”), § 11.211, at 38, § 22.634,
at 411 (2004).

25 ¹⁰ *Acuna v. Brown & Root, Inc.*, 200 F.3d 335, 340 (5th Cir. 2000) (emphasis
26 added).

27 ¹¹ *In re Propulsid Prods. Liab. Litig.*, 261 F. Supp. 2d 603, 615 (E.D. La. 2003)
(emphasis added) (citation omitted).

28 ¹² *See* ADA/EASD/IDF Statement (Ex. 1).

1 These medications work very differently from one another, however, having
2 different mechanisms of action, different pharmacology, different methods of
3 administration, different clinical and preclinical data profiles, and different labels.
4 Broadly speaking, Byetta and Victoza are injectable, synthetic analogs of the incretin
5 hormone GLP-1 and mimic the effects of natural GLP-1 in the body. They are known
6 as GLP-1 Receptor Agonists. Januvia, by contrast, is a DPP-4 inhibitor. It extends
7 the life of naturally occurring incretin hormones (like GLP-1) by inhibiting the DPP-4
8 enzyme, which otherwise would operate to disable or “turn off” the incretin
9 hormones.¹³

10 In this MDL, plaintiffs allege that one or more incretin-based therapies caused
11 them to develop pancreatic cancer. As the Court learned during Science Day,
12 pancreatic cancer is an insidious disease. It is the fourth leading cause of cancer death
13 in the United States and once diagnosed, patients have a one-year survival rate of
14 about 20 percent, and a five-year survival rate of less than 5 percent.¹⁴ This is because
15 pancreatic cancer develops slowly and generally lacks symptoms until it is in an
16 advanced stage. Indeed, by the time it is usually diagnosed, a person will have been
17 on the path to cancer for twenty years or more, and will have had pancreatic cancer for
18 more than ten years.¹⁵ This is a critical point given that the first incretin-based
19 therapy, Byetta, has only been on the market since 2005. In addition, diabetes and

20 ¹³ The differences between DPP-4 inhibitors and GLP-1 Receptor Agonists are
21 meaningful. In its recent report on the safety of incretin-based therapies, the EMA
22 stressed that future evaluations “should be done in a product specific manner . . .
23 considering differences in mechanism of action (i.e. GLP-1 receptor agonists [such as
24 Byetta and Victoza] versus DPP-4 inhibitors [such as Januvia]” EMA Report at

25 ¹⁴ Irene Chong & David Cunningham, *Pancreatic Cancer*, in *Harrison’s Principles*
26 *of Internal Medicine* (Dan L. Longo, et al., eds., 18th Ed. 2012) (attached as Ex. 10);
27 Jan-Bart Koorstra, et al., *Pancreatic Carcinogenesis*, *Pancreatology*, 8:110 (2008), at
28 110 (attached as Ex. 28).

¹⁵ Shinichi Yachida, et al., *Distant metastasis occurs late during the genetic*
evolution of pancreatic cancer, *Nature*, 467:1114 (2010) (attached as Ex. 44).

1 pancreatic cancer are deeply interrelated. Diabetes is a serious risk factor for
2 pancreatic cancer. Approximately 50 to 80 percent of all pancreatic cancer patients
3 have diabetes at the time they are diagnosed.¹⁶ Likewise, undiagnosed pancreatic
4 cancer can also cause diabetes—that is, diabetes can be a symptom of the cancer
5 before the cancer is known to exist.

6 ARGUMENT

7 This multidistrict litigation is different from other pharmaceutical MDLs. None
8 of the products at issue in this case has been withdrawn from the market. There is no
9 study—preclinical or clinical—that demonstrates that any of the products cause the
10 alleged harm, pancreatic cancer. Indeed, in the months leading up to the
11 establishment of this MDL, U.S. and European regulators, along with the scientific
12 community, concluded that there is no evidence that these products do what plaintiffs
13 claim. Rather, these products have been deemed safe and remain a critical part of the
14 battle against the diabetes epidemic.

15 The Federal Rules provide the Court with the discretion to meet these unique
16 circumstances with a tailored solution. And while it is rare at the outset of
17 pharmaceutical litigation for there to be a broad consensus that the medications at
18 issue are safe, it is by no means unprecedented to address general causation first to
19 promote efficiency and the conservation of resources.¹⁷ Indeed, it makes eminent
20

21 ¹⁶ YunFeng Cui & Dana Andersen, *Diabetes and pancreatic cancer*, *Endocrine-*
22 *Related Cancer*, 19:F9 (2012) (attached as Ex. 11); Feng Wang, et al., *The*
23 *relationship between diabetes and pancreatic cancer*, *Molecular Cancer*; 2:4 (2003)
(attached as Ex. 42).

24 ¹⁷ *See, e.g., In re Viagra Prods. Liab. Litig.*, MDL No. 1724, slip op. at 1 (D. Minn.
25 June 30, 2006) (limiting first phase of discovery to general causation and holding
26 early *Daubert* hearing) (attached as Ex. 47); *In re Phenylpropanolamine (PPA) Prods.*
27 *Liab. Litig.*, MDL No. 1407, slip op. at 1 (W.D. Wash. Mar. 22, 2002) (setting
28 schedule for expert discovery within first few months after MDL was formed)
(attached as Ex. 46); *In re Bextra & Celebrex Mktg. Sales Practices & Prod. Liab.*
Litig., MDL No. 1699, slip op. at 1–4 (N.D. Cal. Mar. 16, 2007) (ordering early expert
discovery and *Daubert* hearings regarding plaintiffs' experts' causation opinions)

1 sense to give priority to discovery on the potentially dispositive threshold issue of
2 general causation.¹⁸ Taking up general causation “early in the litigation” is an
3 approach recommended by the *Manual for Complex Litigation*. *Manual for Complex*
4 *Litigation* § 22.634, at 411. For the reasons described below, the Court should do so
5 here. There is no downside.

6
7 **I. The Scientific Consensus Is that There Is No Reliable Evidence that the**
8 **Incretin-Based Therapies Cause Pancreatic Cancer.**

9 In their Master Complaint, the plaintiffs point to various studies, conducted
10 largely by one group of academic researchers led by Dr. Peter Butler from UCLA. A
11 closer examination of these studies reveals, however, that they do not support the
12 plaintiffs’ contentions:

- 13
- 14 • The first publication—an editorial, not a study—by Dr. Peter Butler and his
15 team, was published in February 2010 and offers nothing more than a
16 hypothesis that GLP-1 based therapy “may” increase the risk of pancreatitis
17 (inflammation of the pancreas).¹⁹ The strongest language that the Complaint
18 can quote from the Butler article is: “We *feel* that enough *preliminary*
19 evidence has accumulated to *suggest* that there is a *plausible* risk that long-
20 term recipients of GLP-1 based therapy *may* develop asymptomatic
pancreatitis [], and worse, subsequently a minority of individuals treated by
this class of drugs *may* develop pancreatic cancer.”²⁰ This hedged
conclusion falls far short of a reasonable degree of scientific certainty.²¹

21 (attached as Ex. 45); see also *In re Bextra & Celebrex Mktg. Sales Practices & Prod.*
22 *Liab. Litig.*, 524 F. Supp. 2d 1166 (N.D. Cal. 2007).

23 ¹⁸ See *Crawford-El*, 523 U.S. at 599–600.

24 ¹⁹ See Master Compl. ¶¶ 43–44 (Dkt. No. 206); Peter C. Butler, et al., *GLP-1-*
25 *Based Therapy for Diabetes: What You Do Not Know Can Hurt You*, *Diabetes Care*;
33(2):453 (2010), at 455 (attached as Ex. 9).

26 ²⁰ See Peter C. Butler, et al., *GLP-1-Based Therapy for Diabetes: What You Do*
27 *Not Know Can Hurt You*, *Diabetes Care*, 33(2):453 (2010), at 453–54 (Ex. 9).

28 ²¹ See *Kilpatrick v. Breg, Inc.*, No. 08-10052-CIV, 2009 WL 2058384, at *7 (S.D.
Fla. June 25, 2009) (finding editorial written by expert was “to say the least,

1 And, indeed, Butler and his colleagues did not purport to claim that their
2 work established causation.²²

- 3 • The second²³ and third reports²⁴ cited in the Master Complaint²⁵ are based
4 on materially limited analyses of spontaneous adverse event reports. Both
5 reports acknowledge that they are fundamentally limited due to their reliance
6 on spontaneous adverse event reports (“AERS”) collected by the regulators.
7 Although important to the FDA’s monitoring of drug safety, the FDA
8 expressly cautions that AERS data cannot support statistical conclusions of
9 causation:²⁶ the data is inherently unreliable and incomplete and the
10 databases are subject to proven bias arising from, among other things,
11 attorney advertising and case filings. The courts have held repeatedly that
12 adverse-event data cannot support a conclusion about causation.²⁷

11 inadequate as a basis for a scientific judgment about the general causation”), *aff’d*,
12 613 F.3d 1329 (11th Cir. 2010).

13 ²² See *Perry v. Novartis Pharm. Corp.*, 564 F. Supp. 2d 452, 468 (E.D. Pa. 2008)
14 (“In cases where no adequate study shows the link between a substance and a disease,
15 expert testimony will generally be inadmissible, even if there are hints in the data that
16 some link might exist.”); *Bickel v. Pfizer, Inc.*, 431 F. Supp. 2d 918, 924 (N.D. Ind.
2006) (rejecting causation theory purportedly based on published medical literature
17 where the literature merely “‘proposed’ a connection”).

18 ²³ Michael Elashoff, et al., *Pancreatitis, Pancreatic, and Thyroid Cancer With
19 Glucagon-Like Peptide-1–Based Therapies*, *Gastroenterology*, 141:150 (2011)
20 (attached as Ex. 13).

21 ²⁴ Arzneimittelkommission der deutschen Ärzteschaft (Drug Commission of the
22 German Medical Association - AkdÄ), *Pancreatic cancers associated with exenatide
23 (Byetta®)*, *German Medical Journal*; 108(19):1080 (2011) (attached as Ex. 4).

24 ²⁵ See Master Compl. ¶¶ 45–54.

25 ²⁶ See FDA Adverse Event Reporting System (FAERS) (formerly AERS),
26 [http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/
27 AdverseDrugEffects/default.htm](http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm).

28 ²⁷ See, e.g., *McClain v. Metabolife Int’l, Inc.*, 401 F.3d 1233, 1250 (11th Cir.
2005); *In re Zicam Cold Remedy Mktg., Sales Practices, & Prods. Liab. Litig.*, No.
09-md-2096-PHK-FJM, 2011 WL 798898, at *10–11 (D. Ariz. Feb. 24, 2011); *In re
Baycol Prods. Litig.*, 532 F. Supp. 2d 1029, 1041 (D. Minn. 2007); *DeLuca ex rel.
DeLuca v. Merrell Dow Pharms., Inc.*, 791 F. Supp. 1042, 1051 (D.N.J.
1992) (adverse event reports “are not of a type of data that are reasonably relied upon
by experts in the fields of epidemiology and public health to make a determination of

- 1 • The Master Complaint also cites hypothesis-generating studies in animals
2 that are rebutted by the majority of the science and, critically, that scientists
3 have been unable to reproduce.²⁸ The consensus in the scientific community
4 is that these studies do not create a safety concern. In these studies—one
5 that treated just 16 rats with Januvia,²⁹ and two others that treated just 10
6 and 15 rats with Byetta^{30, 31}—researchers reported that incretin-based
7 therapies were associated with an increased incidence of pancreatitis and
8 histomorphological changes to the exocrine pancreas. None of these animals
9 developed pancreatic cancer. Moreover, these findings conflict with studies
10 performed on thousands of animals to support the approval of these
11 medicines,³² as well as recent studies that were unable to replicate the
12 findings using larger numbers of animals and longer exposures to Januvia,³³
13 Victoza,³⁴ and Byetta.³⁵

12 the causal relationship between a given substance and human birth defects”); *Nelson*
13 *v. Am. Home Prods. Corp.*, 92 F. Supp. 2d 954, 969 (W.D.Mo.2000) (adverse event
14 reports are not proof of causation).

15 ²⁸ See Master Compl. ¶¶ 56–60.

16 ²⁹ Aleksey Matveyenko, et al., *Beneficial endocrine but adverse exocrine effects of*
17 *sitagliptin in the human islet amyloid polypeptide transgenic rat model of type 2*
18 *diabetes: interactions with metformin*; *Diabetes* 58:1604–1615 (2009) (attached as Ex.
19 30).

20 ³⁰ J.S. Nachnani, et al., *Biochemical and histological effects of exendin-4 (exenatide)*
21 *on the rat pancreas*, *Diabetologia* 58:1604–1615 (2009) (attached as Ex. 33).

22 ³¹ Belinda Gier, et al, *Chronic GLP-1 receptor activation by exendin-4 induces*
23 *expansion of pancreatic duct glands in rats and accelerates formation of dysplastic*
24 *lesions and chronic pancreatitis in the Kras^{G12D} mouse model*, *Diabetes*, 61(5): 1250-
25 1262 (2012) (attached as Ex. 22).

26 ³² Tim Hummer, Acting Supervisory Toxicologist, Division of Metabolism and
27 Endocrinology Products, U.S. Food & Drug Administration, Presentation on FDA
28 Surveillance of Adverse Drug Effects (June 13, 2013) (attached as Ex. 27) (reviewing
data from over 250 studies involving more than 18,000 animals).

29 ³³ See, e.g., Katheryn Aston-Mourney K, et al., *One year sitagliptin treatment*
30 *protects against islet amyloid-associated β -cell loss and does not induce pancreatitis*
31 *or pancreatic neoplasia in mice*, *Am. J. Physiol. Endocrinol. Metab* 305:E475–E484
32 (2013) (attached as Ex. 5); Thomas Forest, et al., *Characterization of the Exocrine*
33 *Pancreas in the Male Zucker Diabetic Fatty Rat Model of Type 2 Diabetes Mellitus*

- 1 • Finally, the Master Complaint³⁶ relies on a study in which the Butler group
2 examined the pancreases of eight brain dead organ donors who had been
3 treated with incretin-based therapies and purported to find that those subjects
4 had increased pancreatic mass and pancreatic α -cell hyperplasia.³⁷
5 Independent experts have rejected this study for its serious methodological
6 flaws, including the failure to properly match treated and untreated subjects
7 and omission of important confounding data on the subjects that was readily
8 available.³⁸ As described below, the European Medicines Agency expressly
9 rejected Dr. Butler’s study for its unsound scientific basis.

10 Significantly, what the Master Complaint does not cite is the most recent analysis of
11 the evidence by the same group of researchers which concluded that, while there is a
12 “plausible mechanism” based on animal data to infer “a potential risk of pancreatic

13 *Following 3 Months of Treatment with Sitagliptin*, *Endocrinology* (2014) (attached as
14 Ex. 20).

15 ³⁴ N. Vrang, et al., *The effects of 13 wk of liraglutide treatment on endocrine and*
16 *exocrine pancreas in male and female ZDF rats: a quantitative and qualitative*
17 *analysis revealing no evidence of drug-induced pancreatitis*, *Am. J. Physiol.*
18 *Endocrinol. Metab.*; 303:E253-E264 (2012) (attached as Ex. 41).

19 ³⁵ K. Tatarkiewicz, et al., *No evidence of drug-induced pancreatitis in rats treated*
20 *with exenatide for 13 weeks*, *Diabetes, Obesity & Metabolism* (2012) (attached as Ex.
21 38).

22 ³⁶ See Master Compl. ¶¶ 72–75.

23 ³⁷ Alexandra Butler, et al., *Marked Expansion of Exocrine and Endocrine Pancreas*
24 *With Incretin Therapy in Humans With Increased Exocrine Pancreas Dysplasia and*
25 *the Potential for Glucagon-Producing Neuroendocrine Tumors*, *Diabetes* 62:2595–
26 2604 (2013) (attached as Ex. 7).

27 ³⁸ Evis Harja, et al., *An Analysis of Characteristics of Subjects Examined for*
28 *Incretin Effects on Pancreatic Pathology*, *Diabetes Technology & Therapeutics*
15:609 (2013) (concluding “that the data and the implications of the data . . . are
vastly overstated and seemingly irresponsibly articulated” and that the “irresponsible
indictment of two classes of drugs that are used by millions of people . . . is
reprehensible”) (attached as Ex. 25); Susan Bonner-Weir, et al., *Re-analysis of study*
of pancreatic effects of incretin therapy: Methodological deficiencies, *Diabetes,*
Obesity & Metabolism (2014) (“the data presented in the Butler paper have serious
methodological deficiencies that preclude any meaningful conclusions”) (attached as
Ex. 6).

1 cancer,” the “case presented here does not prove that these agents are unsafe.” Peter
2 C. Butler, et al., *A Critical Analysis of the Clinical Use of Incretin-Based Therapies:
3 Are GLP-1 therapies safe?*, *Diabetes Care* (published online ahead of print May 6,
4 2013) (attached as Ex. 8).

5 Arrayed against the reports cited in the Master Complaint are the conclusions
6 reached by the principal scientific bodies concerned with incretin-based therapies,
7 diabetes, and pancreatic cancer. Within the past year, these independent scientific
8 bodies have evaluated the possible association between the therapies and pancreatic
9 cancer. This includes all of the data that plaintiffs purport to rely on to allege
10 causation. And these independent bodies have concluded, overwhelmingly, that the
11 evidence does not support a causal link between incretin-based therapies and
12 pancreatic cancer.

13 *The EMA Report (July 2013)*. In 2013, the European Medicines Agency
14 reviewed all of the preclinical (animal) and clinical (human) data on incretin-based
15 therapies, and convened a group of distinguished experts to consider the safety of the
16 incretin-based therapies “further to the findings by a group of academic researchers
17 [the Butler group] suggesting an increased risk of pancreatitis and cellular changes in
18 patients treated for [Type-2 diabetes] with GLP-1 based therapies.”³⁹ The EMA
19 specifically evaluated Dr. Butler’s organ donor study,⁴⁰ then thoroughly reviewed and
20 summarized the preclinical and clinical data for each incretin-based therapy “with a
21 focus on pancreatitis and/or pancreatic cancer.”

22 The EMA reached and published the following conclusions:

- 23
- 24 • “With respect to nonclinical data, *available studies previously submitted for
25 the approved products have not raised concern with respect to pancreatic*

25 ³⁹ EMA Report at 13.

26 ⁴⁰ Alexandra Butler, et al., *Marked Expansion of Exocrine and Endocrine Pancreas
27 With Incretin Therapy in Humans With Increased Exocrine Pancreas Dysplasia and
28 the Potential for Glucagon-Producing Neuroendocrine Tumors*, *Diabetes* 62:2595–
2604 (2013) (Ex. 7).

1 *safety*. Further, published studies have not shown any evidence for treatment-
2 related pancreatitis or preneoplastic [i.e., pre-cancerous] lesions”

- 3 • “Concerning pancreatic cancer, *there is currently no evidence from clinical*
4 *trials that GLP-1 based therapies increase the risk.*”
- 5 • “[T]he randomized, controlled nature of the clinical studies gives a robust
6 estimate of risk in relation to placebo and other treatments. *The data currently*
7 *available from clinical trials do not indicate an increased risk for pancreatic*
8 *cancer with these medicines.*”⁴¹

9 The EMA also found that the Butler organ donor study was not well-designed
10 or conducted, and that the data did not support even its tentative conclusions.⁴² In its
11 assessment report, the EMA explained in detail the Butler study’s flaws and said by
12 way of summary:

- 13 • “Overall the experts considered that *there was a high number of*
14 *methodological issues, confounding factors and potential sources of bias in*
15 *the Butler et al 2013 publication* and that *these precluded any meaningful*
16 *conclusions* to establish a link between GLP-1 based therapies and
17 morphological changes of the pancreas indicating an increased risk of
18 pancreatic malignancies.”
- 19 • “Overall, the experts considered that the presented evidence did *not* support the
20 view that GLP-1 based therapies resulted in histological changes of the
21 pancreas in these individuals indicating an increased risk of pancreatic
22 adenocarcinoma.”⁴³

23 The EMA Report is the most current and comprehensive review of the scientific data
24 concerning incretin-based therapies and pancreatic cancer.⁴⁴

25 ⁴¹ EMA Report at 15, 16.

26 ⁴² As noted above, Dr. Butler does not assert that the incretin medicines increase
27 the risk of pancreatic cancer. Peter C. Butler, et al., *A Critical Analysis of the Clinical*
28 *Use of Incretin-Based Therapies: Are GLP-1 therapies safe?*, *Diabetes Care*
(published online ahead of print May 6, 2013) (Ex. 8).

⁴³ EMA Report at 11, 17.

⁴⁴ The EMA report acknowledges that pancreatic cancer is rare and may not be
detected in clinical or even observational studies and, therefore, further study is

1 *The FDA.* The FDA recently stated that it concurs with the EMA’s findings,
2 has completed its own review of the data (including for over 18,000 animals studied
3 during the preclinical development and postmarketing analysis of incretin-based
4 therapies), has conducted its own animal studies, and is drafting its own report. An
5 FDA spokeswoman said that “the agency believes that the current labeling for
6 approved GLP-1 based therapies reflects the extent of our understanding of the safety
7 signals at this point in time.”⁴⁵

8 *The American Diabetes Association, the European Association for the Study of*
9 *Diabetes, and the International Diabetes Federation, NCI, and NIDDK.* In June
10 2013, the National Cancer Institute and the National Institute of Diabetes and
11 Digestive and Kidney Diseases convened a joint conference of leaders in the fields of
12 diabetes and pancreatic cancer.⁴⁶ The conference addressed whether there is evidence
13 that incretin-based therapies cause pancreatic cancer. The FDA made a presentation.
14 Following the NCI/NIDDK conference, the American Diabetes Association, the
15 European Association for the Study of Diabetes, and the International Diabetes
16 Federation issued a joint statement:

17 A June 2013 NIH workshop reviewed the epidemiologic
18 associations between diabetes and pancreatic carcinoma
19 The FDA presented a thorough review of the pre-clinical
20 pathology from submissions of all [incretin-based therapies]

21 warranted. But, as the EMA recognizes, scientific conclusions must be drawn from
22 current data and the current data does not support a causal link between incretin-based
23 therapies and pancreatic cancer. Similarly, the law mirrors good science. As
24 explained in Part II, the law is clear that a litigant must rely on the science as it is, and
25 not how it might—or might not—be. Allegations about causation must be based on
data and not simply act as a placeholder in the hope that other scientific evidence

26 ⁴⁵ Ed Silverman, *Diabetes Drugs Pancreatic Cancer Risk Not Backed By Existing*
27 *Evidence: FDA*, Pharmalot (July 31, 2013) (Ex. 37).

28 ⁴⁶ See NIDDK-NCI Workshop on Pancreatitis-Diabetes-Pancreatic Cancer (June
12–13, 2013), <http://www2.niddk.nih.gov/News/Calendar/PDPC2013.htm>.

1 on the market and under development, and three additional
2 submissions requested, *finding no concerns for pancreatic*
3 *disease*.⁴⁷

4 The ADA, EASD, and IDF all affirmed their recommendation of incretin-based
5 therapies as an important option for treating diabetes.

6 *Endocrinologists*. On August 20, 2013, the American Association of Clinical
7 Endocrinologists and the American College of Endocrinology issued a Consensus
8 Statement on the relationship between diabetes and cancer. The organizations
9 acknowledged Dr. Butler’s “speculations about the theoretical possibility of increased
10 incidence of pancreatic cancer” arising from incretin-based therapies, but concluded
11 that the risk has not been proven. “[N]o randomized controlled prospective human
12 study of [incretin-based therapies] has conclusively shown that these drug classes play
13 a role in the genesis of pancreatic cancer,” the statement noted, and it summarized the
14 data in these words: “No evidence of . . . pancreatic cancer in humans.”⁴⁸

15 *Randomized Clinical Trial Data*. The “gold standard” for assessing general
16 causation is randomized clinical trial data. *Reference Manual on Scientific Evidence*
17 555 (Fed. Judicial Ctr. 3rd ed. 2011); *see also id.* at 729 (“Well-performed
18 randomized [clinical] trials provide the least biased estimates of treatment benefit and
19 harm by creating groups with equivalent progress.”).⁴⁹ The randomized clinical trial
20 data for Januvia, Byetta, and Victoza do not show an increased risk of pancreatic
21 cancer in patients taking incretin-based therapies.⁵⁰ Indeed, currently there are more
22 than 80,000 patients enrolled in large-scale clinical trials of cardiovascular safety of

23 ⁴⁷ ADA/EASD/IDF Statement (Ex. 1).

24 ⁴⁸ Yehuda Handelsman, et al., *Diabetes and Cancer – An AACE/ACE Consensus*
25 *Statement*, *Endocrine Practice*; 19(4):675 (2013), at 686, 687 (Ex. 24).

26 ⁴⁹ *See also In re Bextra & Celebrex Mktg. Sales Practices & Prod. Liab. Litig.*,
27 524 F. Supp. 2d 1166, 1172–73 (N.D. Cal. 2007).

28 ⁵⁰ Summaries of the clinical, observational, and animal data for Januvia, Victoza, and
Byetta are set forth in detail in Exhibits B, C, and D, respectively.

1 incretin-based therapies. These studies are evaluated by independent Data Safety
2 Monitoring Boards, which have the ethical responsibility to terminate the trial if there
3 are safety concerns. The trials for Byetta, Victoza, and Januvia are monitoring
4 pancreatic cancer events and none has been terminated for a safety concern. Two
5 trials for other incretin-based therapies were completed in late 2013. Their results
6 were published in the *New England Journal of Medicine*.⁵¹ Neither trial found
7 evidence of an increased pancreatic cancer risk. Indeed, for the DPP-4 inhibitor
8 saxagliptin, there were five incidences of pancreatic cancer in the treatment group and
9 twelve in the group that received a placebo. For alogliptin, no pancreatic cancer was
10 reported.

11 *Observational Studies.* Observational studies using healthcare databases and
12 similar sources can provide important information regarding the safety of medications
13 under real world conditions. Although less favored than randomized clinical trial data
14 because they have fewer controls, observational studies can also provide insights into
15 causation.⁵² Observational studies of Januvia, Byetta, and Victoza currently canvass
16 more than 75,000 patient-years of exposure to these medications. None of these
17 studies found evidence that these products increase the risk of pancreatic cancer.

18 *Studies in Animals.* Animal studies generally cannot prove causation in and of
19 themselves.⁵³ Here, however, the animal studies align with the observational and
20 randomized clinical data. The defendants all conducted extensive animal toxicity and
21 carcinogenicity studies as part of the approval process and as part of their

22 ⁵¹ See Scirica, et al., *Saxagliptin and Cardiovascular Outcomes in Patients with Type*
23 *2 Diabetes Mellitus*, *New England J. of Medicine* 369:14;1317 (2013) (attached as Ex.
24 36); White, et al., *Alogliptin after Acute Coronary Syndrome in Patients with Type 2*
25 *Diabetes*, 369:14;1327 (2013) (attached as Ex. 43).

26 ⁵² See *Reference Manual on Scientific Evidence* 555.

27 ⁵³ See *Reference Manual on Scientific Evidence* 23; see also *Domingo ex rel.*
28 *Domingo v. T.K.*, 289 F.3d 600, 606 (9th Cir. 2002); *Daubert v. Merrell Dow Pharm.,*
Inc. (Daubert II), 43 F.3d 1311, 1315 (9th Cir. 1995); *In re Silicone Gel Breast*
Implants Prods. Liab. Litig., 318 F. Supp. 2d 879, 890 (C.D. Cal. 2004).

1 postmarketing obligations; none demonstrated that the incretin-based therapies
2 increase the incidence of pancreatic cancer. In addition, at the request of the FDA, the
3 manufacturers conducted studies to evaluate the pancreatic effects of their incretin-
4 based therapies in diabetic rats. None of these studies found evidence of adverse
5 pancreatic effects, negating the outlying rat studies performed by the Butler group,
6 described above.

7
8 **II. The Federal Rules and Principles of Sound Judicial Management Favor**
9 **Ordering Structured Discovery Addressing General Causation First.**

10 This litigation is the quintessential case for the consideration of causation early
11 in the litigation—before millions of dollars and substantial resources are spent on
12 other issues. Recent, systematic, and consensus-setting reviews of the available
13 science by neutral experts have produced a near-unanimous view that there is no
14 sound scientific basis on which to conclude that there is a causal link between
15 incretin-based therapies and pancreatic cancer.⁵⁴ General causation is a “pivotal”
16 issue that may “provide the foundation for a dispositive motion.” *Manual for*
17 *Complex Litigation*, § 11.422, at 54–55 (2004). Addressing it first has the potential to
18 “preempt[] the need for almost all of the discovery” that would otherwise be
19 undertaken. *In re Agent Orange Prod. Liab. Litig.*, 506 F. Supp. 762, 796–97
20 (E.D.N.Y. 1980).

21
22
23
24
25
26 ⁵⁴ See *Allen v. Pennsylvania Eng’g Corp.*, 102 F.3d 194, 197 (5th Cir. 1996)
27 (affirming judgment as a matter of law where “not a single scientific study has
28 revealed a link between human brain cancer and EtO exposure” and “numerous
reputable epidemiological studies covering in total thousands of workers indicate there
is not a correlation between EtO exposure and cancer of the human brain”).

1 **A. Principles of Sound Judicial Management**

2 Rule 16 authorizes the Court to exercise “early and continuing control” to
3 discourage wasteful pretrial activities and to expedite disposition of the case.⁵⁵ Rule
4 26 gives the Court “broad discretion to tailor discovery . . . to facilitate prompt and
5 efficient resolution of the lawsuit.”⁵⁶ The Ninth Circuit recognizes that
6 “administering cases in multidistrict litigation is different” from administering cases
7 on a routine docket.⁵⁷ This is “a special breed of complex litigation where the whole
8 is bigger than the sum of its parts.”⁵⁸ In such cases, the case management order
9 governing the schedule for the litigation takes on even greater importance.

10 As the Court knows, the *Manual for Complex Litigation* is replete with advice
11 about steps that the Court can take early in the case to narrow the issues, avoid
12 unnecessary expense, and speed resolution. *The Manual* advises the Court to:

- 13 • “[A]nticipate[] problems before they arise” and “become[] familiar at an early
14 stage with the substantive issues in order to make informed rulings on issue
15 definition and narrowing”;⁵⁹
- 16 • “[P]ress the parties to identify, define and narrow the issues,” starting at the
17 initial conference;⁶⁰
- 18 • “[R]equir[e], with respect to one or more issues, that the parties present a
detailed statement of their contentions, with supporting facts and evidence”;⁶¹

19 ⁵⁵ *In re Phenylpropanolamine (PPA) Prods. Liab. Litig.*, 460 F.3d 1217, 1227 (9th
20 Cir. 2006) (“Rule 16, the central pretrial rule, authorizes a court to manage cases so
21 that disposition is expedited, wasteful pretrial activities are discouraged, the quality of
22 the trial is improved, and settlement is facilitated. It recognizes the need for adopting
23 special procedures for managing potentially difficult or protracted actions that may
24 involve complex issues, multiple parties, difficult legal questions, or unusual proof
problems. The goal is to get cases decided on the merits of issues that are truly
meritorious and in dispute” (internal quotation marks and citation omitted.)).

25 ⁵⁶ *Crawford-El*, 523 U.S. at 598–99.

26 ⁵⁷ *In re Phenylpropanolamine (PPA) Prods. Liab. Litig.*, 460 F.3d at 1229.

27 ⁵⁸ *Id.* at 1232.

28 ⁵⁹ *Manual* § 10.13, at 12.

⁶⁰ *Id.* § 11.31, at 42.

- 1 • Recognize that “[e]arly and full disclosure of expert evidence can help define
2 and narrow issues”;⁶² and
- 3 • Include within the “[i]ssues to be taken up early in the litigation . . . whether the
4 facts and expert evidence support a finding that the products . . . in question
5 have the capacity to cause the type of injuries alleged.”⁶³

6 The circumstances here warrant the early exploration of whether there is a
7 scientific basis to proceed, or whether the law should follow the scientific consensus
8 that there is not. The Court should follow the example of other MDL courts that have
9 structured discovery to put general causation and *Daubert* first.⁶⁴

10 There is no cost to addressing general causation first. Most of the information
11 that plaintiffs require to make their general causation case to the Court—studies and
12 other scientific data—is published and is publicly available.⁶⁵ This is the same

13 ⁶¹ *Id.* § 11.33, at 46.

14 ⁶² *Id.* § 11.481, at 99.

15 ⁶³ *Id.* § 22.634, at 411.

16 ⁶⁴ *See, e.g., In re Viagra Prods. Liab. Litig.*, MDL No. 1724, slip op. at 1 (D. Minn.
17 June 30, 2006) (limiting first phase of discovery to general causation and holding
18 early *Daubert* hearing); *In re Phenylpropanolamine (PPA) Prods. Liab. Litig.*, MDL
19 No. 1407, slip op. at 1 (W.D. Wash. Mar. 22, 2002) (setting schedule for expert
20 discovery within first few months after MDL was formed); *In re Bextra & Celebrex*
21 *Mktg. Sales Practices & Prod. Liab. Litig.*, MDL No. 1699, slip op. at 1–4 (N.D. Cal.
22 Mar. 16, 2007) (ordering early expert discovery and *Daubert* hearings regarding
23 plaintiffs’ experts’ causation opinions); *see also In re Bextra & Celebrex Mktg. Sales*
24 *Practices & Prod. Liab. Litig.*, 524 F. Supp. 2d 1166 (N.D. Cal. 2007); *Avila v. Willits*
25 *Envl. Remediation Trust*, 633 F.3d 828, 836 (9th Cir. 2011) (requiring plaintiffs to
26 make a *prima facie* showing of general causation before commencing full blown
27 discovery); *Claar v. Burlington Northern R.R.*, 29 F.3d 499, 500 (9th Cir. 1994)
28 (Where there is “concern that plaintiffs might not be able to demonstrate a causal
connection,” case management orders should be used to require plaintiffs to “explain
the scientific basis” for their claims).

⁶⁵ *See e.g., Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 143–47 (1997) (evaluating
admissibility of general causation testimony based on epidemiologic and animal
studies); *Daubert v. Merrell Dow Pharms., Inc.*, 43 F.3d 1311 (9th Cir. 1995)
(evaluating admissibility of expert testimony based on epidemiologic studies, animal

1 information that the scientific community relies on to make its determinations.
2 Further, defendants have already produced to plaintiffs all of their correspondence and
3 submissions to FDA through late 2013. These include data from internal preclinical
4 and clinical studies, investigator statements, responses to requests for information
5 from FDA, study protocols, adverse event reports, other safety reports, and annual
6 reports. If plaintiffs lack something they genuinely need to establish their general
7 causation case, defendants can produce it without undue delay. *Daubert* can follow
8 soon after.

9 No matter the outcome, early resolution of the general causation question will
10 advance the ultimate objective of the MDL process—the resolution of issues common
11 to all cases. If plaintiffs cannot produce reliable expert testimony to support their
12 general causation claims, defendants will have grounds for summary judgment. If, on
13 the other hand, the Court finds that plaintiffs’ experts’ opinions on general causation
14 are based on reliable science, the issue will have been resolved, the parties will have
15 gained valuable information about the cases, and both the Court and the parties can
16 move on to other issues.

17 **B. Early General Causation Discovery Does Not Alter Plaintiffs’ Burden**

18 A discovery plan that takes up general causation first would shift the default
19 order of discovery but would not alter the burden that plaintiffs undertook when they
20 commenced this litigation in spite of the broad consensus that the products at issue do
21 not cause pancreatic cancer. The Federal Rules of Civil Procedure require a plaintiff
22 “to ‘stop and think’ before initially making . . . factual contentions,” because a
23 complaint constitutes a certification that the “factual contentions have evidentiary
24

25 studies, and chemical analogy); *Lopez v. Wyeth-Ayerst Labs., Inc.*, 139 F.3d 905, 905
26 (9th Cir. 1998) (unpublished table decision) (evaluating admissibility of expert
27 testimony based on epidemiologic studies, animal studies, and adverse event reports);
28 *In re Bextra & Celebrex*, 524 F. Supp. 2d at 1176–83 (evaluating admissibility of
general causation testimony based on observational studies, clinical trial data, and a
biological plausibility theory).

1 support.”⁶⁶ What is true for all factual contentions is arguably true *a fortiori* for
2 contentions as to scientific causation. The law is clear that a plaintiff who has only a
3 scientific hypothesis and lacks reliable scientific evidence of causation cannot put his
4 case to the jury. *Henricksen v. ConocoPhillips Co.*, 605 F. Supp. 2d 1142, 1178 (E.D.
5 Wash. 2009) (“Evidence that is an insightful hypothesis is not admissible in court if it
6 lacks scientific rigor.”); *Rosen v. Ciba-Geigy Corp.*, 78 F.3d 316, 319 (7th Cir. 1996)
7 (“[T]he courtroom is not the place for scientific guesswork, even of the inspired sort.
8 Law lags science; it does not lead it.”). Thus, a plaintiff who has not identified
9 reliable scientific evidence of causation before filing suit has not made the reasonable
10 inquiry required by the Rules. *Acuna*, 200 F.3d at 340 (plaintiffs must have had *prima*
11 *facie* valid basis for asserting causation before filing claims).⁶⁷

12 Put differently, both the Rules of Civil Procedure and the Rules of Evidence are
13 concerned with what is true *now*. Speculation about scientific studies as yet
14 uncompleted and scientific data as yet uncollected and unreported cannot satisfy the
15 duty to base allegations on a reasonable inquiry into the facts. Nor can such
16 speculation constitute the substance of expert testimony. “Though Plaintiffs’ theory
17 may one day be validated through scientific research and experiment, the law *today*
18 cannot apply that conjecture.” *Henricksen*, 605 F. Supp. 2d at 1178 (emphasis added).
19

20
21 ⁶⁶ Fed. R. Civ. P. 11(b) & advisory committee notes, 1993 amendments.

22 ⁶⁷ See also *In re Vioxx Prods. Liab. Litig.*, 557 F. Supp. 2d 741, 744 (E.D. La.
23 2008) (same); *In re Silica Prods. Liab. Litig.*, 398 F. Supp. 2d 563, 675 (S.D. Tex.
24 2005) (awarding sanctions where law firm brought cases without basis for causation);
25 *Lore v. Lone Pine*, 1986 WL 637507, at *3 (N.J. Super. Ct. Law Div. Nov. 18, 1986)
26 (“preliminary expert reports should have been obtained prior to filing suit”); *Martinez*
27 *v. City of San Antonio*, 40 S.W.3d 587, 591 (Tex. App. 2001) (upholding causation
28 order, remarking that “[plaintiffs] are presumed to have duly investigated their case
before filing suit”); *In re Love Canal Actions*, 547 N.Y.S.2d 174, 177 (N.Y. Sup. Ct.
1989) (requiring showing of causation, noting that “New York requires attorneys in all
actions to investigate the legal and factual basis for an action before commencing
litigation”).

1 In short, lawsuits are not fishing expeditions, and, more specifically, a plaintiff
2 may not allege causation as a placeholder for supporting scientific evidence that the
3 plaintiff only hopes will materialize in the future. The Rules permit discovery—
4 sometimes wide-ranging, voluminous, and very expensive discovery—but only when
5 the initial allegations have demonstrable current “evidentiary support.” The law asks
6 whether such evidence exists *now*.⁶⁸

7 * * *

8 This litigation presents circumstances that warrant early inquiry by the Court
9 into whether plaintiffs can prove causation. There is no reason to proceed with years
10 of expensive, full-scale document and deposition discovery if there is no *Daubert*-
11 worthy scientific data that support the allegation that incretin-based medicines cause
12 pancreatic cancer. That plaintiffs may have a hypothesis about causation will not
13 suffice. Nor will it suffice that plaintiffs may hope that future studies will reach
14 different conclusions.⁶⁹ MDL coordination is meant to expedite the resolution of
15 complex litigation, not serve as a holding pen. “[T]he law cannot wait for future
16 scientific investigation and research. We must resolve cases in our courts on the basis
17 of scientific knowledge that is currently available.” *Moore v. Ashland Chem. Inc.*, 151

18 _____
19 ⁶⁸ See *Rider v. Sandoz Pharm. Corp.*, 295 F.3d 1194, 1202 (11th Cir. 2002)
20 (“courts may only admit the state of science as it is . . . not . . . speculation, conjecture,
21 or inference that cannot be supported by sound scientific principles”); *In re Human*
22 *Tissue Prods. Liab. Litig.*, 582 F. Supp. 2d 644, 690 (D.N.J. 2008) (“The Rules of
23 Evidence, however, cannot be disregarded even if at a future date, medical and
24 scientific literature proves the contrary.”); *In re Propulsid Prods. Liab. Litig.*, 261 F.
25 Supp. 2d 603, 615 (E.D. La. 2003) (“The Court is aware that the future may shed
26 more light on this matter. Medical science may one day determine with sufficient
27 reliability that a causal relationship exists between a sustained prolonged QT interval
28 and Propulsid but it is not there yet and may never be. A trial court must function in
the present assessing evidence that presently exists.” (citation omitted)).

⁶⁹ See, e.g., *Wells v. SmithKline Beecham Corp.*, 601 F.3d 375, 381 (5th Cir.
2010); *Moore v. Ashland Chem. Inc.*, 151 F.3d 269, 276 (5th Cir. 1998); *In re Human*
Tissue Prods. Liab. Litig., 582 F. Supp. 2d 644, 690 (D.N.J. 2008); *In re Propulsid*
Prods. Liab. Litig., 261 F. Supp. 2d 603, 615 (E.D. La. 2003).

1 F.3d 269, 276 (5th Cir. 1998). Therefore, the Court should adopt a scheduling order
2 that addresses “general causation” expert discovery at the outset, requires plaintiffs to
3 produce general causation expert reports, in compliance with Rule 26, and sets dates
4 for *Daubert* briefing on causation in this litigation. The schedule defendants proposed
5 does just that.

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22 **SIGNATURE ATTESTATION**

23 Pursuant to Section 2.f.4 of the Court’s CM/ECF Administrative Policies, I
24 hereby certify that authorization for the filing of this document has been obtained
25 from each of the other signatories shown above and that all signatories have
26 authorized placement of their electronic signature on this document.

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