United States Court of Appeals
For the First Circuit

No. 07-2626

NEW JERSEY CARPENTERS PENSION & ANNUITY FUNDS; FOLKSAM ASSET MANAGEMENT; THIRD MILLENNIUM TRADING LLP; DEERFIELD BEACH NON-UNIFORMED MUNICIPAL EMPLOYEES RETIREMENT PLAN; PLUMBERS AND PIPEFITTERS LOCAL NO. 520 PENSION FUND; HORATIO CAPITAL LLC,

Plaintiffs, Appellants,

CHARLES BROWN, Individually and on Behalf of All Others Similarly Situated; ROCHELLE LOBEL; BIOGEN INSTITUTIONAL INVESTOR GROUP; LONDON PENSIONS FUND AUTHORITY; NATIONAL ELEVATOR INDUSTRY PENSION FUND; CARY GRILL, Individually and on Behalf of All Others Similarly Situated,

Plaintiffs,

v.

BIOGEN IDEC INC.; WILLIAM RASTETTER; JAMES MULLEN; BURT ADELMAN; THOMAS BUCKNUM; PETER N. KELLOGG; WILLIAM ROHN,

Defendants, Appellees.

ON APPEAL FROM THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS

[Hon. William G. Young, U.S. District Judge]

Before

Lynch, Chief Judge,
Torruella, Circuit Judge,
Stafford,* District Judge.

* Of the Northern District of Florida, sitting by designation.

Vincent R. Cappucci with whom Stephen D. Oestreich, Robert N. Cappucci, Shannon L. Hopkins, Entwistle & Cappucci LLP, Sanford P. Dumain, Richard H. Weiss, Milberg Weiss LLP, Nancy Freeman Gans, and Moulton & Gans, PC were on brief for appellants.

James R. Carroll with whom Matthew J. Matule, Michael S. Hines, and Skadden, Arps, Slate, Meagher & Flom LLP were on brief for Biogen Idec Inc., William Rastetter, James Mullen, Burt Adelman, Peter N. Kellogg, and William Rohn.

Mark A. Berthiaume with whom Timothy E. Maguire and Greenberg Traurig LLP were on brief for Thomas Bucknum.

August 7, 2008

LYNCH, Chief Judge. In this securities case, a drug company, Biogen Idec Inc., conducted clinical trials and received accelerated FDA approval for TYSABRI, a promising new drug for multiple sclerosis and similar autoimmune diseases. The price of the company stock increased as FDA approval was sought and granted. Less than three months after the approval, on February 18, 2005, continuing clinical trials of the drug revealed that two patients had contracted a type of infection perhaps associated with the drug. One of those patients had died. Within ten days, on February 28, 2005, the company, after consultation with the FDA, voluntarily withdrew the drug from the market. The share price precipitously dropped.

This federal securities class action soon followed, alleging the company and senior executives had intentionally misrepresented the safety of and the market for the drug by omission and commission. The district court dismissed the complaint for failing to meet adequately the pleading requirements for scienter established in the Private Securities Litigation Reform Act of 1995 ("PSLRA"), Pub. L. No. 104-67, 109 Stat. 737. We affirm.

I.

On March 2, 2005, a subset of the plaintiffs in this action brought suit in federal district court against Biogen Idec

Inc. and company executives.[1] For convenience, we refer to all defendants collectively as "Biogen," except where any are specifically differentiated. The plaintiffs sued on behalf of a putative class of individuals and entities who purchased Biogen stock between February 18, 2004 and February 28, 2005, the class period. Other duplicate class actions followed, with complaints filed on March 10, 2005 and April 10, 2005. The actions were consolidated and a consolidated amended complaint was filed October 13, 2006.

We accept well-pled factual allegations in the complaint as true and draw all inferences in the plaintiffs' favor. Miss. Pub. Empl. Ret. Sys. v. Boston Scientific Corp. (Boston Scientific), 523 F.3d 75, 85 (1st Cir. 2008); see also Tellabs, Inc. v. Makor Issues & Rights, Ltd., ___ U.S. ___, 127 S. Ct. 2499, 2509 (2007); ACA Fin. Guar. Corp. v. Advest, Inc., 512 F.3d 46, 52 (1st Cir. 2008). We also consider the undisputed public documents utilized by each side in this case and considered by the district court. See Boston Scientific, 523 F.3d at 86.

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[1] The individual named defendants all were senior executives at Biogen. Specifically, at all times relevant to the complaint, William Rastetter was Biogen's Executive Chairman and a Director. James Mullen was Biogen's Chief Executive Officer and President. Peter Kellogg was Biogen's Executive Vice President of Finance and Chief Financial Officer. William Rohn was Biogen's Chief Operating Officer. Burt Adelman was Biogen's Executive Vice President of Development. Thomas Bucknum was Biogen's Executive Vice President and General Counsel from November 2003 until he resigned on March 9, 2005.

A. TYSABRI and Its Effects

TYSABRI[2] is a drug developed, manufactured, and marketed by Biogen for the purpose of treating autoimmune diseases, especially multiple sclerosis ("MS"), Crohn's disease, and rheumatoid arthritis.[3] Generally, autoimmune diseases cause the human body's immune system to attack otherwise healthy tissues in the body. TYSABRI works, in part, by preventing migration of white blood cells throughout the body.

In MS, for example, the arrival of white blood cells to the central nervous system causes inflammation, which in turn destroys nerve fiber and the fatty tissue surrounding nerve fiber, creating lesions or plaques in the nervous system. Over time, these plaques disrupt the function of the nervous system, causing the various symptoms of MS, including progressive physical disability and eventual cognitive impairment. TYSABRI prevents the

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[2] In earlier phases, TYSABRI was known by the name Antegren or by its generic name, natalizumab.

[3] MS is described in more detail in the text. Crohn's disease is a "subacute chronic [inflammation of the intestine] of unknown cause, . . . characterized by patchy deep ulcers that may cause fistulas, and narrowing and thickening of the bowel by fibrosis and lymphocytic infiltration [infiltration of white blood cells]." Stedman's Medical Dictionary 575 (26th ed. 1995) (entry on "enteritis, regional enteritis").

Rheumatoid arthritis is "a systemic disease, occuring more often in women, which affects connective tissue; . . . accompanied by thickening of articular soft tissue . . . ; the course is variable but often is chronic and progressive leading to deformities and disability." Id. at 149 (entry on "arthritis, rheumatoid arthritis").

white blood cells from migrating to the central nervous system, relieving the inflammation and mitigating the symptoms of MS.

Another effect of TYSABRI's mechanism of action is that the drug could prevent white blood cells from migrating to places in the body where they are needed. This may leave a patient vulnerable to "opportunistic infections," which occur when ordinarily benign organisms infect individuals with impaired immune systems. While a healthy immune system would prevent these organisms from causing illness, an impaired immune system may not be able to stave off infection.

One such opportunistic infection is progressive multifocal leukoencephalopathy ("PML"), a usually fatal disease of the central nervous system caused by the "JC virus." The JC virus is latent in the kidneys of almost all adults, and invades the brain and causes PML only when the immune system is severely impaired.

B. TYSABRI's Path to Market and the FDA Approval Process

The Food and Drug Administration ("FDA") requires any drug to go through a series of clinical trials before it can be approved for marketing and sales in the United States. See generally L. Sukhatme, Note, Deterring Fraud: Mandatory Disclosure and the FDA Drug Approval Process, 82 N.Y.U. L. Rev. 1210, 1219-20 (2007) (describing the FDA's drug approval process). After a drug is initially tested on animals, the developer of the drug submits

an application to the FDA for approval to test the drug on humans. Id.; see also 21 C.F.R. § 312.20. If this request is approved, human testing begins, and typically follows three phases, commonly known as clinical trials. See 21 C.F.R. § 312.21. Each phase requires the company to test the drug on a broader population and results in more stringent monitoring and evaluation. Id.

Phase I studies generally involve twenty to eighty subjects, and are designed to determine how the drug works in humans and the side effects associated with increasing doses. Id. § 312.21(a)(1). Phase II studies usually involve no more than several hundred subjects, and are designed to evaluate the effectiveness of the drug, as well as common short-term side effects and risks. Id. § 312.21(b). Phase III studies are large-scale trials, usually involving several hundred to several thousand subjects, and are intended to gather the information necessary to provide an adequate basis for labeling the drug. Id. § 312.21(c). Throughout the clinical trials, the drug company must report to the FDA and to all participating physicians any serious and unexpected adverse drug experiences that occur. Id. § 312.32(c)(1)(i)(A). After Phase III, the FDA considers the results of all of the clinical trials in determining whether to approve a drug for market. See id. §§ 314.125(b), 314.126(a).

If a proposed drug "address[es] [an] unmet medical need" for a "serious or life-threatening condition," like TYSABRI does,

the FDA provides an expedited approval process. 21 U.S.C. § 356(a)(1); see also Consolidated Am. Compl. ("CAC") ¶¶ 83-85. Through this process, which has a target for FDA action of six months, the drug maker interacts with the FDA during drug development and the FDA can begin reviewing portions of the drug application before the full application is completed. See U.S. Food and Drug Administration, Center for Drug Evaluation and Research, FDA's Drug Review and Approval Times, available at http://www.fda.gov/cder/reports/reviewtimes/default.htm. The FDA can approve drugs treating life-threatening illnesses that are significant advancements over existing treatments on the basis of preliminary evidence prior to formal demonstration of patient benefit.[4] See 21 C.F.R. §§ 314.500, 314.510.

In August 2000, Biogen and another company, Elan Pharma International Limited ("Elan"), announced that they had entered into a joint collaboration agreement to bring TYSABRI to market. The agreement required the two companies to share equally in the revenues and costs and set up a number of joint teams, so that both companies played a role in both the development of TYSABRI, including clinical trials, and the marketing of TYSABRI. The

[4] In an effort to strengthen FDA regulation of drugs already approved and on the market when problems arise, Congress enacted the Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823, which provides the FDA with enhanced authority regarding the postmarket safety of drugs, see id. §§ 901-21. The events in this case pre-date the statute.

agreement also required that any information, including adverse events, discovered by one company be reported to the other in a timely manner.

Both the pre-clinical animal trials and the first phase of clinical trials of TYSABRI as a treatment for MS had been completed in the 1990s by Elan's corporate predecessor. After the collaboration agreement, it was decided that Biogen would lead the clinical trials for MS and Elan would lead the clinical trials for Crohn's disease.

By September 2001, preliminary Phase II MS results had begun yielding promising data. Biogen then began Phase III of MS testing in December 2001 with two trials. The first trial, named AFFIRM, sought to test whether TYSABRI was effective in slowing the rate of disability in MS patients. The second, SENTINEL, sought to evaluate the safety and efficacy of TYSABRI in combination with another MS drug produced by Biogen, AVONEX.

The Phase III clinical trials for Crohn's disease began in December 2001 and consisted of two trials: ENACT-1 (designed to evaluate clinical responses to TYSABRI and its ability to induce remission of Crohn's disease) and ENACT-2 (designed to evaluate the duration and effects of TYSABRI). In July 2003, Biogen announced that it could not act on the results of ENACT-1 because of a "larger than expected placebo response rate." On January 29, 2004, Biogen announced that the ENACT-2 trial had met its primary

endpoint, and that because the ENACT-1 trial had been unsuccessful, Biogen was beginning an additional Phase III trial, ENCORE, which was designed to evaluate the safety and efficacy of TYSABRI in patients with moderate to severe Crohn's disease. Altogether, approximately 3,900 patients received TYSABRI in the three phases of the MS and Crohn's disease clinical trials.

On February 18, 2004, Biogen announced its intention to apply to the FDA for expedited approval for TYSABRI as a treatment for MS, based on data from one year of its two Phase III MS trials, AFFIRM and SENTINEL. Over the next two days, the price of Biogen stock increased from $44.26 to $58.98, an increase of 33.3%, and was traded at a daily volume of between six-and-a-half and nine times greater than the average daily trading volume during the class period. On May 25, 2004, Biogen announced that it had submitted its application to the FDA.

The FDA then conducted a detailed analysis of the safety and efficacy data available for TYSABRI, focusing on the data for the MS clinical trials but also considering any serious safety events that occurred in the Crohn's trials. For the ongoing Phase III trials, which provided the "primary evidence of safety and efficacy," the FDA's review considered "data through cut-off dates ranging from March 1st to April 30th, 2004."

On November 23, 2004, Biogen announced that the FDA had granted accelerated approval of TYSABRI and the drug was available

for sale. The following day, the stock price rose from $57.43 to $58.59, an increase of 2.0%.

The FDA placed no limitations on TYSABRI's use in combination with other drugs. The package insert label included with the drug noted only that "TYSABRI® is indicated for the treatment of patients with relapsing forms of multiple sclerosis." However, the package insert label did contain the following statement relevant to the plaintiffs' claim: "The safety and efficacy of TYSABRI in combination with other immunosuppressive agents have not been evaluated."

C. Withdrawal of TYSABRI from the Market

At approximately noon on February 18, 2005, roughly three months after TYSABRI was granted FDA approval, Biogen senior officers attended a meeting where they learned that two patients taking TYSABRI in the clinical trials had contracted PML, one of whom had died.

Ten days later, on February 28, 2005, Biogen and Elan suspended all clinical trials and withdrew TYSABRI from the market.[5] In a press release, Biogen announced to the public that two patients had contracted PML, one of the two had died, and the

[5] At this point, according to plaintiffs, Phase III of the AFFIRM MS trial was completed and Phase III of the SENTINEL MS trial was substantially completed; two of the Phase III Crohn's disease trials were completed and an additional Phase III Crohn's disease trial was in progress; and the Phase II rheumatoid arthritis trials had been underway for approximately eight months.

decision to withdraw TYSABRI was made "in consultation with [the] U.S. Food and Drug Administration (FDA)."[6] On March 30, 2005, Biogen announced that a patient in the Crohn's disease trial who died in 2003 had been misdiagnosed with brain cancer, and in fact had died from PML.[7]

The stock market reacted strongly to the withdrawal of the drug from the market. On February 28, Biogen's stock price dropped from $67.28 to $38.65, a 42.5% drop. Some 118 million shares were traded, more than thirty times the average daily trading volume during the class period.

D. Insider Trading Allegations

Plaintiffs allege that during the class period the individual insider defendants sold significant amounts of Biogen stock while they knew that the share price was artificially inflated because of the alleged misrepresentations concerning

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[6] A withdrawal of a drug from the market is not the same as a voluntary recall. "Market withdrawal means a firm's removal or correction of a distributed product which involves a minor violation that would not be subject to legal action by the Food and Drug Administration or which involves no violation." 21 C.F.R. § 7.3(j). A recall is "a firm's removal or correction of a marketed product that the [FDA] considers to be in violation of the laws it administers and against which the agency would initiate legal action." Id. § 7.3(g).

[7] According to the complaint, this announcement occurred on March 1, 2005, the day after the withdrawal. CAC ¶ 7. A press release included in the record announcing the additional PML diagnosis, the authenticity of which is not disputed, is dated March 30, 2005. Joint App'x at 309.

TYSABRI. The class period ran from February 18, 2004, the day Biogen announced it was seeking expedited FDA approval of TYSABRI, to February 28, 2005, the day that TYSABRI was withdrawn from the market. The alleged insider sales during the class period are as follows.[8]

Defendant Rastetter, Biogen's Executive Chairman, sold 582,045 shares, approximately 78% of his shares as of February 18, 2004, the beginning of the class period, for total proceeds of approximately $35 million. Defendant Mullen, the Chief Executive Officer and President, sold 192,000 shares for total proceeds of approximately $12 million, which constituted virtually all of the shares he held as of February 18, 2004. Defendant Adelman, the Executive Vice President of Development, sold 80,870 shares, virtually all of the shares he held at the beginning of the class period, for total proceeds of approximately $5 million. Defendant Rohn, the Chief Operating Officer, sold 350,000 shares, approximately 91% of the shares he held at the beginning of the class period, for total proceeds of approximately $20 million. Rohn announced his retirement on November 29, 2004, twelve days after his final alleged insider sale, and retired on January 31, 2005. Defendant Bucknum, the General Counsel, sold 188,600 shares,

[8] Each individual defendant made multiple sales on different dates in the class period. To avoid the cumbersomeness of listing each date and each corresponding amount, we describe each individual defendant's sales in aggregate.

virtually all of the shares he held at the beginning of the class period, for total proceeds of approximately $12 million.

All but one of the alleged insider sales occurred before, often well before, February 18, 2005, the date of the meeting where plaintiffs allege that defendants first learned of the safety issues with TYSABRI. The only alleged insider trading between February 18, 2005 and the February 28, 2005 withdrawal (the end of the class period) is by defendant Bucknum, the General Counsel. On February 18, 2005, the same day as the meeting, Bucknum sold 89,700 shares for total proceeds of approximately $6 million, which constituted approximately half of all the shares he held at the beginning of the class period. The SEC filed a civil complaint against Bucknum on January 12, 2006 for his February 18 trade. He settled the action, paying $3 million in disgorgement and agreeing not to serve as an officer or director of a public company for five years. Bucknum resigned from Biogen on March 9, 2005.

E. FDA Investigation and TYSABRI's Return to Market

On March 7 and 8, 2006, the FDA's Peripheral and Central Nervous System Drugs Advisory Committee ("Advisory Committee") held public hearings to evaluate the potential reintroduction of TYSABRI. In these hearings, Biogen and the FDA shared results of further testing and analysis, and various members of the public, including physicians and patients, gave comments.

On June 5, 2006, the FDA approved TYSABRI's reintroduction into the market. The FDA's approval restricted TYSABRI to use as a monotherapy for relapsing forms of MS; it was not approved for use in combination with other drugs or for other diseases. Because of the potential risk of PML, TYSABRI was recommended only for those MS patients who do not respond to other MS treatment. Every MS patient using TYSABRI must enroll in a risk management program run by Biogen which closely monitors patients for any signs of PML. In addition, the package insert label includes a "black-box" warning, the strictest warning the FDA can require, which warns of the risk of PML. See 21 C.F.R. § 201.57(c)(1); see also CAC ¶ 17. In addition, the package insert label contains the following statement: "The safety and efficacy of TYSABRI in combination with other antineoplastic, immunosuppressant, or immunomodulating agents have not been established."[9]

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[9] The FDA in 2008 approved TYSABRI to treat "moderate-to-severe Crohn's disease in patients with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional Crohn's disease therapies." Press Release, U.S. Food and Drug Administration, FDA News: FDA Approves Tysabri To Treat Moderate-to-Severe Crohn's Disease (Jan. 14, 2008), available at http://www.fda.gov/bbs/topics/NEWS/2008/NEW01775.html. TYSABRI for Crohn's disease entails substantially the same warnings and limitations as TYSABRI for MS, and Crohn's patients must also enroll in the risk management program. Id.

On July 31, 2008, Biogen announced that two more patients had contracted PML. See Todd Wallack, Despite Risks, Many Staying with Tysabri, Boston Globe, Aug. 2, 2008, at A7. The share price

II.

Two days after the withdrawal of TYSABRI from the market following the PML diagnoses of clinical trial participants, the first group of plaintiffs brought suit against Biogen and the individual defendants.

The consolidated amended complaint alleges that during the class period, the defendants made material misstatements, including material omissions of fact concerning the safety and marketability of TYSABRI, and that this had caused the market price of Biogen to be artificially inflated, both harming investors and allowing individual insider defendants to enrich themselves in excess of $137 million. The amended complaint alleges that the acts and omissions of all of the defendants but Bucknum violated sections 10(b) and 20(a) of the Securities Exchange Act of 1934, 15 U.S.C. §§ 78j(b) and 78t(a), and Rule 10b-5, 17 C.F.R. § 240.10b-5, and that all of the defendants (including Bucknum) violated section 20A of the Securities Exchange Act of 1934, 15 U.S.C. § 78t-1.

In particular, the plaintiffs' amended complaint advances a theory of material misstatements about the safety of the drug and a related theory about material overstatements of the market for the drug and growth in the company's sales. The amended complaint alleges that during the class period, defendants made numerous unqualified statements trumpeting TYSABRI's safety and efficacy and

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of Biogen dropped approximately 28% on the news. Id. at A8.

its consequent significant positive financial impact on Biogen's profitability. When these statements were made, defendants failed to disclose in a timely manner their knowledge of at least two safety risks: that patients taking TYSABRI had developed opportunistic infections (including infections other than PML) and, in some cases, had died; and that the announced safety and efficacy of using TYSABRI in combination with other MS drugs had never been established. Given defendants' knowledge of these facts and the substantial risks posed by TYSABRI, plaintiffs allege, the defendants misrepresented the market for TYSABRI in their positive financial forecasts. These misrepresentations and omissions, in turn, harmed plaintiffs in their purchase and sale of securities.

In November 2006, all the defendants except Bucknum filed a motion to dismiss. Bucknum filed a separate motion to dismiss in January 2007. In September 2007, after oral argument, the district court dismissed all claims against all defendants. In October 2007, the district court explained its reasoning in a separate memorandum, which was unreported. In dismissing the section 10(b) and the Rule 10b-5 claims, the court found that while the plaintiffs had alleged material misrepresentations and omissions with the appropriate specificity, they had not pled facts giving rise to a strong inference of scienter. The court then dismissed the section 20(a) and 20A claims because the court had found no predicate securities violation.

III.

A. Pleading Requirements

On a Rule 12(b)(6) motion, we examine de novo whether a complaint meets the PSLRA's requirements and we "accept well-pled factual allegations in the complaint as true and make all reasonable inferences in plaintiff's favor." Boston Scientific, 523 F.3d at 85. The complaint must allege "a plausible entitlement to relief" in order to survive a motion to dismiss. Id. (quoting Bell Atl. Corp. v. Twombly, 127 S. Ct. 1955, 1967 (2007)) (internal quotation marks omitted). Here, the court also properly considered certain public documents put into the record by both plaintiffs and defendants. See id. at 86 (citing Watterson v. Page, 987 F.2d 1, 3 (1st Cir. 1993)).

The PSLRA requirements are familiar: the plaintiffs' complaint must plead adequately (1) a material[10] misrepresentation or omission; (2) scienter; (3) a connection with the purchase or

[10] Information is material if a reasonable investor would have viewed it as "having significantly altered the 'total mix' of information made available." Basic, Inc. v. Levinson, 485 U.S. 224, 232 (1988) (quoting TSC Indus. v. Northway, Inc., 426 U.S. 438, 449 (1976)) (internal quotation marks omitted); accord Boston Scientific, 523 F.3d at 85; Gross v. Summa Four, Inc., 93 F.3d 987, 992 (1st Cir. 1996). Further, "[w]hile a company need not reveal every piece of information that affects anything said before, it must disclose facts, 'if any, that are needed so that what was revealed [before] would not be so incomplete as to mislead.'" In re Cabletron Sys., Inc., 311 F.3d 11, 36 (1st Cir. 2002) (quoting Backman v. Polaroid Corp., 910 F.2d 10, 16 (1st Cir. 1990) (en banc)).

sale of a security; (4) reliance; (5) economic loss; and (6) loss causation. Id. at 85; ACA Fin., 512 F.3d at 58.

The PSLRA requires that when alleging that a defendant made a material misrepresentation or omission, a complaint must "specify each statement alleged to have been misleading [and] the reason or reasons why the statement is misleading." 15 U.S.C. § 78u-4(b)(1). If the allegation is "made on information and belief," then the complaint must "state with particularity all facts on which that belief is formed." Id.

We will assume arguendo, consistent with the district court's opinion, that plaintiffs' amended complaint satisfied the first element, that is, that plaintiffs pled material misrepresentations or omissions in a sufficiently detailed manner as to "time, place and content." Aldridge v. A.T. Cross Corp., 284 F.3d 72, 78 (1st Cir. 2002).

We turn to the question of the adequacy of the complaint's pleading scienter. We discuss materiality only insofar as it is relevant to the pleading of omissions said to be relevant to scienter.

Scienter is a "mental state embracing intent to deceive, manipulate, or defraud." Ernst & Ernst v. Hochfelder, 425 U.S. 185, 193 n.12 (1976). The plaintiff must establish that "defendants consciously intended to defraud, or that they acted with a high degree of recklessness." Aldridge, 284 F.3d at 82.

The PSLRA requires that the plaintiffs' complaint, "with respect to each act or omission . . . , state with particularity facts giving rise to a strong inference that the defendant acted with the required state of mind." 15 U.S.C. § 78u-4(b)(2).

Congress did not define what qualifies as a "strong inference" in the PSLRA, but in Tellabs, the Supreme Court held that in order to be "strong," an "inference of scienter must be more than merely plausible or reasonable -- it must be cogent and at least as compelling as any opposing inference of nonfraudulent intent." Tellabs, 127 S. Ct. at 2504-05.[11]

Scienter must be examined by looking at the complaint as a whole. See Boston Scientific, 523 F.3d at 86; ACA Fin., 512 F.3d at 59. A court must weigh "not only inferences urged by the plaintiff . . . but also competing inferences rationally drawn from the facts alleged." Boston Scientific, 523 F.3d at 86 (quoting Tellabs, 127 S. Ct. at 2504) (internal quotation marks omitted). "[W]here there are equally strong inferences for and against

[11] The district court misspoke when it said the Supreme Court's decision in Tellabs had "largely conform[ed] to the preexisting standard in this circuit," Dist. Ct. Mem. at 11, in adopting as adequate to show a "strong inference" of scienter the standard of whether "a reasonable person would deem the inference of scienter cogent and at least as compelling as any opposing inference one could draw from the facts alleged." Tellabs, 123 S. Ct. at 2510. In fact, Tellabs overruled our decision in In re Credit Suisse First Boston Corp., 431 F.3d 36, 49 (1st Cir. 2005), as we recognized in ACA Financial, 512 F.3d at 59. The lapse is of no consequence; the district court articulated the correct legal standard for scienter. Whether it correctly applied that standard is what is at issue in this appeal.

scienter, Tellabs now awards the draw to the plaintiff." ACA Fin., 512 F.3d at 59 (citing Tellabs, 127 S. Ct. at 2510).

Of particular import to this case is another proposition. A statement cannot be intentionally misleading if the defendant did not have sufficient information at the relevant time to form an evaluation that there was a need to disclose certain information and to form an intent not to disclose it. See id. at 62 (finding that statements were not established to be materially misleading where there was "nothing in the amended complaint to establish that the defendants were aware of facts, at the time they made their predictions, that would have made those predictions unreasonable"); see also, e.g., Crowell GST Trust v. Possis Med., Inc., 519 F.3d 778, 783 (8th Cir. 2008); Winer Family Trust v. Queen, 503 F.3d 319, 327-29 (3d Cir. 2007); Higginbotham v. Baxter Int'l Inc., 495 F.3d 753, 757-60 (7th Cir. 2007).

B. Plaintiffs' Allegations of Misleading Statements

We describe emblematic examples[12] of the alleged misleading statements and the plaintiffs' allegations that defendants knew at the time these statements were misleading.

(1) A statement in a February 18, 2004 press release attributed to the defendants that: "In previous clinical trials, the following adverse events occurred more commonly with

[12] Only seven of the over eighty statements that the plaintiffs excerpt in the complaint are included here. These statements are representative of the others.

natalizumab when compared to placebo: headache, nausea, abdominal pain, infection, urinary tract infection, pharyngitis and rash. Serious adverse events have included infrequent hypersensitivity-like reactions." CAC ¶¶ 164-165.

(2) A statement, attributed to defendant Mullen, Biogen's Chief Executive Officer and President, during a March 2, 2004 conference call with analysts that:[13]

> Now, I want to focus really on the current state of the MS market, I know a lot of people are beginning to think about that very carefully after this announcement two weeks ago. In the US, there is approximately 400 to 450,000 MS patients of which 300 to 350,000 in the relapsing forms, we consider that the eligible market, that market is slightly over half penetrated. That's about 180,000 patients in the US are on one of the interferons or Copaxone. There is more than 50,000 quitters, that number is hard to quantify but we think that's the right ballpark and there is about 10 to 15,000 new patients diagnosed annually. And when you

[13] We agree with the district court that the statements including financial projections were based on present facts relating to the safety of TYSABRI and so do not fall under the statutory safe harbor for forward-looking statements. See 15 U.S.C. § 78u-5.

In analyzing a forward-looking statement, the aspect of the statement that is based on the present fact must be distinguished from the aspect of the statement that is a future projection. See In re Stone & Webster, Inc., Sec. Litig., 414 F.3d 187, 213 (1st Cir. 2005). "The safe harbor, we believe, is intended to apply only to allegations of falsehood as to the forward-looking aspects of the statement." Id. Here, the plaintiffs' allegations of fraud, putting aside their merit, concern defendants' knowledge of the underlying facts of the safety and efficacy of TYSABRI at the time the statements were made.

> think about the EU marketplace, you can pretty much just double all those numbers except the penetration is a little bit less. So there is huge, there is still a huge unmet need out there. [W]e do believe that this innovative therapy will offer hope to a large number of patients and the market will grow significantly in the US and Europe.

CAC ¶¶ 178, 180.

(3) Defendant Adelman, the Executive Vice President of Development, made the following statement during the same March 2, 2004 conference call:

> We know that there are patients who have some degree of disease activity either as measured by relapse rate and/or MRI while they are on any of the current therapies, and that's why the clinical development program for this product includes not only a placebo-controlled trial as a standalone therapy, but includes study where we look at the efficacy of Antegren when added to patients already on interferon who still have some evidence of disease activity. So, I think it's going to be broadly applicable to the entire population of patients with MS who are or are not on therapy, who still have evidence of disease activity.

CAC ¶ 181.

(4) A statement, attributed to Mullen, in an April 30, 2004 earnings report that: "We've had an excellent start to the year. Both revenue and earnings results are up strongly. The U.S. filing of ANTEGREN by mid-year is on track. . . . With access to two large scale manufacturing facilities on both coasts, the Company is well-positioned to fulfill ANTEGREN's blockbuster potential." CAC ¶¶ 199, 208.

(5) A statement, attributed to defendant Rohn, the Chief Operating Officer, in a July 28, 2004 earnings report that: "We are convinced of Antegren's blockbuster potential. . . . We believe the potential MS market over the next few years will grow to roughly $6 billion, up from $3.6 billion today, and we believe Antegren will not only expand the market but also capture a lion's share of the market." CAC ¶¶ 234, 235.

(6) A statement, attributed to Adelman, during a July 28, 2004 conference call with analysts that: "[T]here is no evidence that Antegren is associated with accelerated disease activation or relapse as we've seen with other potential targeted therapies to lymphocyte trafficking and you know, we have a huge safety database and these issues have not come up in conversation, you know, with any regulatory authority." CAC ¶¶ 237, 238.

(7) A statement, attributed to Mullen, at a January 11, 2005 healthcare conference that AVONEX was the "ideal combination product along with Tysabri, it's the only product that has proven efficacy along side in addition to Tysabri." CAC ¶ 297.

C. Scienter

Even if plaintiffs met the standard of showing a material misrepresentation or omission, as we assume arguendo they did, they must still allege facts giving rise to a "strong inference" of scienter. "Knowingly omitting material information is probative, although not determinative, of scienter." Boston Scientific, 523

F.3d at 87; see also Aldridge, 284 F.3d at 83 ("[T]he fact that the defendants published statements when they knew facts suggesting the statements were inaccurate or misleadingly incomplete is classic evidence of scienter."). The plaintiffs allege that defendants' knowledge of the misleading nature of the statements, combined with the individual defendants' insider trading, gives rise to a strong inference of scienter.

The situation involved here is paradigmatic of securities fraud cases against drug development companies where a promising drug or medical device is approved by the FDA and then later proves to have health risks which affect the market for the drug. See, e.g., Oran v. Stafford, 226 F.3d 275 (3d Cir. 2000); In re Carter-Wallace, Inc. Sec. Litig. (Carter-Wallace I), 150 F.3d 153 (2d Cir. 1998); In re Pfizer Inc. Sec. Litig., No. 04-9866, ___ F. Supp. 2d. ___, 2008 WL 2627131 (S.D.N.Y. July 1, 2008); In re Elan Corp. Sec. Litig., 543 F. Supp. 2d 187 (S.D.N.Y. 2008); In re Bayer AG Sec. Litig., No. 03-1546, 2004 WL 2190357 (S.D.N.Y. Sept. 30, 2004); Anderson v. Abbott Labs., 140 F. Supp. 2d 894 (N.D. Ill. 2001); In re Abbott Labs. Sec. Litig., 813 F. Supp. 1315 (N.D. Ill. 1992); In re Pfizer, Inc. Sec. Litig., No. 90-1260, 1990 WL 250287 (S.D.N.Y. 1990).

Within two days of the withdrawal of TYSABRI from the market, this securities fraud lawsuit was filed. The theory of the original complaints was that defendants knew much earlier than

disclosed that TYSABRI would cause PML. That theory appears to have been abandoned in favor of a theory, in the consolidated amended complaint, that defendants knew TYSABRI would cause a range of opportunistic infections other than PML and that TYSABRI used in combination with other drugs created a substantial safety risk, and yet they failed to disclose this to the investing public and the FDA. The key theme of the suit is that Biogen and the defendants were aware or at least were recklessly unaware of greater safety risks with TYSABRI for opportunistic infections, particularly in combination with other MS therapies, than had been announced to the public, and then intentionally failed to disclose this information in order to keep share prices high. Plaintiffs' claim is not only that Biogen misled the investing public, but that Biogen misled the FDA in order to achieve accelerated FDA approval.

The reports which companies make to the FDA about drug trials are not generally made public. See P. Lurie & A. Zieve, Sometimes the Silence Can Be Like the Thunder: Access to Pharmaceutical Data at the FDA, Law & Contemp. Probs., Summer 2006, at 85, 89. And so the investing public has few alternatives to double-check the accuracy of a drug company's statements to the public or to the FDA about the safety of an experimental drug. Fraud on the FDA is, to be sure, prohibited, see 21 U.S.C. § 331, and the FDA has statutory power to catch, punish, and deter such fraud, see id. § 372 (FDA empowered to conduct investigations); id.

§ 332 (FDA can seek injunctive relief); id. § 333 (FDA can pursue criminal prosecutions and civil penalties); Buckman Co. v. Plaintiffs' Legal Comm., 531 U.S. 341, 349-50 (2001). Sometimes FDA data becomes public much later, as in this case, where both sides use information from the FDA Advisory Committee hearings on March 7-8, 2006 to attempt to characterize what was known during the class period.

By the same token, the investing public is well aware that drug trials are exactly that: trials to determine the safety and efficacy of experimental drugs. And so trading in the shares of companies whose financial fortunes may turn on the outcome of such experimental drug trials inherently carries more risk than some other investments. This is true even when the FDA has given fast-track approval to a new drug.

Against this background we analyze plaintiffs' various theories.

1. PML Deaths and Other Opportunistic Infections

Plaintiffs' initial complaints alleged that defendants knew of PML deaths from the SENTINEL combination therapy trial earlier than February 18, 2005 and failed to timely disclose the information. If plaintiffs have not abandoned this claim, it fails anyway. We agree with the district court that there is no evidence of record which makes this claim of knowledge before February 18, 2005 a permissible inference.

Plaintiffs' primary theory advanced on appeal is that the defendants knew earlier of a series of opportunistic infections from use of TYSABRI including but not limited to PML, they failed to adequately disclose these risks, and they announced market projections they knew to be too optimistic in light of the risk of all opportunistic infections.[14] Plaintiffs allege the causal connection between TYSABRI's market share and a higher risk of all opportunistic infections was demonstrated by the market's reaction to the withdrawal of the drug from the market on February 28, 2005 and the limitations placed on TYSABRI when it was later reintroduced.

The plaintiffs argue that TYSABRI was withdrawn not only because of the PML deaths but also because of the other opportunistic infections. The defendants respond that they meant what they said when, in the press release announcing the withdrawal of the drug, they specified that TYSABRI was being voluntarily withdrawn from the market because of the PML deaths. Again, we agree with the district court that no plausible inference can be drawn from the allegations and documents that the reason TYSABRI was withdrawn was something other than the PML deaths.

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[14] These opportunistic infections include pulmonary aspergillosis, pneumocystis carinii pneumonia, cryptosporidial gastroenteritis, Mycobacterium avium intracellular pneumonia, and Burkholderia cepacia pneumonia.

That analysis does not itself end any claim by plaintiffs of securities fraud. It may still be true that a reduction in the market for TYSABRI based on the risk of opportunistic infections other than PML would have an effect on Biogen's share prices. But even then, defendants cannot have committed fraud if they did not know at the time that the failure to provide additional information was misleading. See ACA Fin., 512 F.3d at 62 ("There is nothing in the amended complaint to establish that the defendants were aware of facts, at the time they made their predictions, that would have made those predictions unreasonable . . . ."); Boston Scientific, 523 F.3d at 86 ("Securities actions raise questions of what corporate managers knew and when they knew it." (emphasis added)).

Plaintiffs' amended complaint fails to allege facts both (1) as to when defendants had information about non-PML opportunistic infections and (2) that the information available sufficiently suggested a causal relationship between TYSABRI and non-PML opportunistic infections.

The plaintiffs rely heavily on the information disclosed in the initial November 2004 approval of the drug, on the hearings held by the FDA Advisory Committee on March 7-8, 2006, and on the "black-box" warning labels the FDA required when TYSABRI was reintroduced on June 5, 2006 for a more limited market. They also rely on some other evidence, including confidential source allegations.

We must take it as true from plaintiffs' allegations that one of the potential risks of TYSABRI, given its mechanism of action, was the risk of resulting opportunistic infections. The FDA said as much in its November 2004 medical review recommending the drug for accelerated approval. Joint App'x at 448 ("[G]iven the mechanism of action of natalizumab, this [opportunistic infections] issue deserves continued scrutiny . . . to more fully characterize the effect of natalizumab on the immune system."). This risk was one reason for the continued scrutiny of the drug which did occur, during the remaining two years of trials and in examining post-marketing experiences.

Plaintiffs claim that the FDA gave its approval only because defendants hid data from it about opportunistic infections. This is a very serious charge and is not substantiated by the allegations in the complaint or the documents in the record. The FDA's accelerated approval was granted in November 2004. Plaintiffs allege defendants were aware by February 2004 of "all incidents of death and innumerable opportunistic infections that occurred during [prior] trials."[15] Pls.' Br. at 10.

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[15] Plaintiffs claim that this knowledge existed because the following trials had been completed and their data had been unblinded by the following dates: (1) Phase I of the MS trials by 1995; (2) Phase II of the MS trials by September 2001; (3) Phase II of the Crohn's trials by May 23, 2001; (4) Phase III of the Crohn's ENACT-1 study by July 2003; (5) Phase III of the Crohn's ENACT-2 study by January 29, 2004; (6) the first year of Phase III of the MS trials by February 18, 2004.

Biogen submitted its application to the FDA on May 25, 2004 and, on June 28, 2004, announced the FDA had designated TYSABRI for priority review. During the review process the FDA evaluated safety data primarily from the Phase III MS clinical trials and considered data from the ongoing Crohn's disease studies. The cut-off dates for data reviewed ranged from March 1 to April 30, 2004. We thus take April 30, 2004 as a cut-off date for information that the FDA would have known. If the FDA were misled, as plaintiffs assert, it was with respect to pre-April 30, 2004 data. There is no evidence which permits any inference the defendants intentionally failed to disclose relevant data to the FDA between April 30, 2004 and when the FDA gave approval on November 23, 2004, or from the approval date to the withdrawal of the drug on February 28, 2005.

The plaintiffs' claim that Biogen hid data from the FDA is not based on any FDA finding that this was true. Rather, it is based primarily on plaintiffs' reading of after-the-fact statements about earlier events made (a) by a Biogen employee at the post-withdrawal Advisory Committee hearings, (b) by an FDA employee at the same hearings, and (c) by confidential sources.

The Biogen employee, Dr. Michael Panzara, presented data at the hearings from both the MS and the Crohn's disease trials. In total, 3,900 patients received TYSABRI in both sets of trials. In the MS trials, a total of three patients developed opportunistic

infections, including the two who developed PML. During the Crohn's disease trials, five patients were diagnosed as having suffered from opportunistic infections, including one patient who had been diagnosed with PML. This results in an incidence rate of 0.2%, including the PML infections. If the PML were excluded, the incidence rate would be even lower.

There is no basis to conclude that these results, excluding the PML infections, were statistically significant. There is no plausible inference from the reports of just five patients with non-PML opportunistic infections that the defendants knew of any causal relationship between the use of TYSABRI and the separate opportunistic infections diagnosed for the five patients, and then intentionally withheld data. "[T]he receipt of an adverse report does not in and of itself show a causal relationship between [a drug] and the illness mentioned in the report." In re Carter-Wallace, Inc. Sec. Litig. (Carter-Wallace II), 220 F.3d 36, 41 (2d Cir. 2000). "Some adverse events may be expected to occur randomly, especially with a drug designed to treat people that are already ill." Id.

Plaintiffs also cite the testimony of the FDA's Dr. Alice Hughes at the post-withdrawal Advisory Committee hearings, who stated that there were seventeen deaths during the clinical trials, thirteen of which involved patients taking TYSABRI. But plaintiffs allege that only four of those were a result of an opportunistic

infection (two being PML), and have not pled there was any causal significance evident from the data. Moreover, there is contrary evidence. During these same hearings, the FDA's Deputy Director of Neurology Products, Dr. Marc Walton, stated: "We were not impressed that the overall mortality rate was markedly different than we might expect in MS studies." And before the drug was approved, the FDA's Deputy Director of the Office of Drug Evaluation, Dr. David Ross, wrote to his superior that the deaths to date in the clinical studies "d[id] not represent a clear safety signal."

Further, the plaintiffs also have failed to allege when the information on the non-fatal opportunistic infections became known. Many of the infections occurred in the Crohn's disease trials, but at least three of these trials were ongoing after January 29, 2004, and so the infections may have occurred or become known after the relevant time periods.

Plaintiffs advance the proposition that the fact "that even one opportunistic infection occurred is significant enough to put TYSABRI's safety and marketability in question." Pls.' Br. at 30 n.16. In the absence of an allegation or inference of proof of any statistical significance of the occurrence of one or more non-PML opportunistic infections, the statement is simply not true and is also incorrect as a matter of law.

Indeed, there are no allegations by plaintiffs that defendants knew of a significant risk of non-PML opportunistic

infections while the FDA was reviewing TYSABRI. No strong inference can be drawn that defendants knowingly or recklessly withheld material information from the FDA in order to get fast-track review and accelerated approval.

Nor do any statements by FDA officials support such an inference. Plaintiffs argue that the November 23, 2004 memo from the FDA's Dr. David Ross, discussed above, which recommended the approval of TYSABRI, establishes that Biogen withheld data. Dr. Ross stated: "The events reported do not appear to represent infections due to opportunistic pathogens . . . ." It is not plausible to read this as evidence of wrongdoing by Biogen; plaintiffs have not even presented a viable theory that the statement means that data was withheld, as opposed to what it says.[16]

This leaves only the allegations based on confidential sources. Our standard for evaluating whether confidential source material is sufficient under the PSLRA is as follows:

> [W]here plaintiffs rely on confidential personal sources but also on other facts, they

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[16] Plaintiffs also advance a theory that defendants knew or recklessly disregarded information that TYSABRI "turn[ed] off" the immune system. CAC ¶ 382. At most this is a hypothesis and would hardly support a plausible inference of scienter when the data from the clinical trials do not. The plaintiff overstates a 2004 hypothesis by Dr. Lawrence Steinman in a journal article that there is "at least a theoretical concern that recipients of the therapy would become generally compromised in their ability to fight infection."

> need not name their sources as long as the latter facts provide an adequate basis for believing that the defendants' statements were false. Moreover, even if personal sources must be identified, there is no requirement that they be named, provided they are described in the complaint with sufficient particularity to support the probability that a person in the position occupied by the source would possess the information alleged. In both of these situations, the plaintiffs will have pleaded enough facts to support their belief, even though some arguably relevant facts have been left out.

Cabletron, 311 F.3d at 29 (quoting Novak v. Kasaks, 216 F.3d 300, 314 (2d Cir. 2000)) (block quotation). Consequently, we "look at all of the facts alleged to see if they 'provide an adequate basis for believing that the defendants' statements were false.'" Id. (quoting Novak, 216 F.3d at 314). "This involves an evaluation, inter alia, of the level of detail provided by the confidential sources, the corroborative nature of the other facts alleged (including from other sources), the coherence and plausibility of the allegations, the number of sources, the reliability of the sources, and similar indicia." Id. at 29-30.

Defendants argue that Tellabs requires us to revise our law on confidential sources, but we believe our law on this point is unchanged. They cite to the Seventh Circuit's decision in Higginbotham, 495 F.3d at 756 (because of Tellabs, court must "discount" confidential source allegations). But plaintiffs overstate their position, even as to Seventh Circuit law. See Makor Issues & Rights, Ltd. v. Tellabs Inc., 513 F.3d 702, 712 (7th

Cir. 2008) (finding confidential source allegations sufficient where they are "numerous and consist of persons who from the description of their jobs were in a position to know at first hand the facts to which they are prepared to testify"); id. ("[T]he absence of proper names does not invalidate the drawing of a strong inference from informants' assertions.").

Tellabs requires that all information in plaintiffs' complaint be evaluated. 127 S. Ct. at 2509. We think that includes confidential source information, subject to the restrictions stated in our case law. We have never said a complaint would survive if it were based only on confidential source allegations. Indeed, we have said there must be a hard look at such allegations to evaluate their worth. See Cabletron, 311 F.3d at 30 ("[C]ourts can competently make a careful evaluation of securities fraud pleadings based on anonymous sources, and separate frivolous complaints from those with potential merit.").

Scienter involves wrongdoing by high-level company officials; low-level employees or consultants may well know of the wrongdoing and wish to disclose it but fear retaliation if their names appear among the accusers. Legislatures, both federal and state, have recognized similar fears in enacting anti-retaliation statutes and in encouraging whistle-blowers. Some allowance at the motion to dismiss stage for consideration of confidential sources in litigation is consistent with those policies. See

id. ("Employees or others in possession of important information about corporate malfeasance may be discouraged from stepping forward if they must be identified at the earliest stage of a lawsuit."); Novak, 216 F.3d at 314 ("Imposing a general requirement of disclosure of confidential sources . . . could deter informants from providing critical information to investigators in meritorious cases or invite retaliation against them.").

Before discovery, a confidential source would wish to remain unnamed, as "a suit might never be brought or if brought might be settled before any discovery [i]s conducted." Makor Issues & Rights, 513 F.3d at 711. We decline to adopt a rule which would exclude confidential source allegations which have every indication both that the source had access to information and that the information has the earmarks of credibility, simply because the identity of the source is not initially revealed.[17] And we see no reason to exclude consideration of such information from the evaluation of whether plaintiffs' strong inferences of scienter are at least as plausible as defendants' inferences.

[17] Indeed, Higginbotham presented a different problem: the identities of the confidential sources in that case would never have been revealed, 495 F.3d at 757, so the reliance on confidential sources in the complaint was apparently solely a device by plaintiffs to get past a motion to dismiss and into discovery.

Here, however, the allegations made by the confidential sources, even if we assume them to be true, still do not create a strong inference of scienter.

Plaintiffs allege that one confidential source, "CS 3," a neurologist who was involved in the clinical trials for MS, confirmed the existence of several serious opportunistic infections during the MS and Crohn's disease trials, and the source specifically cited one opportunistic infection that occurred during the MS trials and two from the Crohn's disease trials. CAC ¶ 144. However, this allegation does not indicate when during the trials these infections became known. Moreover, the allegation does not contribute anything additional to plaintiffs' case. Dr. Panzara said during the FDA hearings that three patients in the MS trials and five patients in the Crohn's disease trials developed opportunistic diseases, and Dr. Hughes stated that there were two deaths during the clinical trials attributable to non-PML opportunistic diseases. We discussed earlier the shortcomings of these allegations in establishing the requisite scienter. Nothing is added by the existence of a confidential source who states that there were "several" opportunistic infections during the trials and cites three.[18] Similarly, nothing is added by the allegation, even

[18] Plaintiffs also allege that "in CS 3's opinion," many of the problems with TYSABRI "were the result of executives at Biogen being excessively aggressive in getting" the drug to the market. CAC ¶ 146. As with any bald assertion, this gets plaintiffs nowhere.

if true, that another confidential source, "CS 4," was aware of "serious opportunistic infections" during the Crohn's disease trials. CAC ¶ 145.

Plaintiffs also point to statements by two other confidential sources. "CS 5," a neurologist involved with the SENTINEL Phase II trial, stated that five participants in the Crohn's disease trials developed cancer, as opposed to one patient in the placebo group, and he was concerned about the types of cancer the patients had contracted, which included malignant melanoma and cervical cancer. CAC ¶ 147. Again, there is no indication as to when during the trials these occurrences became known. Regardless, assuming it to be true, the allegation that five people developed cancer in clinical trials involving hundreds of people does not itself support a plausible inference that defendants knew that TYSABRI increased the risk of patients developing cancer, let alone an inference that TYSABRI increased the risk of opportunistic infections, which are distinct from cancer.

Finally, "CS 6," a data entry clerk who worked for Biogen from May to December of 2004, alleged that the number of adverse events being reported to the company concerning TYSABRI was on average between fifty and sixty per day; that in June 2004 and just prior to TYSABRI's approval in November 2004, this volume was "extremely high, particularly when compared to other clinical

trials" in which this confidential source was involved; and that "many" of these adverse reports were "serious," such as an increase in the size of tumors and "complaints suggesting symptoms of PML." CAC ¶¶ 148-149.

With the exception of this last assertion, these allegations say nothing about the nature of the adverse event reports and therefore, even if true, cannot support an inference that it was known that TYSABRI causes opportunistic infections. As for the claim that there were a number of "serious" adverse event reports, even assuming this to be true, the source provides no information regarding whether these reports were confirmed, whether the symptoms being reported were shown to have any connections to opportunistic infections, or even whether any connections were made between the symptoms being reported and a patient's use of TYSABRI.[19] Again, "the receipt of an adverse report does not in and of itself show a causal relationship between [a drug] and the illness mentioned in the report." Carter-Wallace II, 220 F.3d at 41.

Plaintiffs' claims as to non-PML opportunistic infections fail to meet the scienter standards of the PSLRA.

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[19] At one point in their complaint, when discussing an FDA adverse event report, plaintiffs appear to count each reported adverse event as a new adverse event, even if some of the reports were follow-up reports to already-reported adverse events. See CAC ¶ 153. This resulted in higher counts of adverse events, since one adverse event involving one patient was counted multiple times.

2. Combination Therapy Claims

In a related but distinct set of claims, plaintiffs allege that defendants affirmatively stated that TYSABRI was safe when used in combination with other drugs when in fact they had no reasonable basis to believe so. This is different from the allegations that defendants knew of the risk of opportunistic infections but did not disclose the risk.

Plaintiffs point out the two PML diagnoses which led to withdrawal of the drug occurred during the clinical trials of TYSABRI in combination with AVONEX, Biogen's other MS drug. And when the FDA approved the reentry of TYSABRI into the market, the package insert contained the following warning about the use of TYSABRI with other MS therapies: "Concurrent use of antineoplastic, immunosuppressant, or immunomodulating agents may further increase the risk of infections, including PML and other opportunistic infections, over the risk observed with use of TYSABRI alone."

The plaintiffs allege that the use of TYSABRI in combination therapy was highly material to TYSABRI's future market share because approximately 180,000 patients or "slightly over half" of the potential MS market was on other MS drugs. CAC ¶ 180.

a. Waiver

Before addressing the merits of the argument, we look to whether it has been waived. The defendants argue that this combination therapy theory has been waived because plaintiffs did

not brief it in their opposition to the motion to dismiss. Further, the district court did not comment on the theory at all.

The theory is, however, plainly stated in the amended complaint. See CAC ¶¶ 402-404. It was the defendants' motion to dismiss which failed to mention or brief the theory, thus failing to call the court's attention to it. Plaintiffs may have been unwise not to brief the theory in their opposition and thus be sure the district court was aware of it. However, plaintiffs did refer to the theory, albeit briefly, at oral argument in the district court. Defendants' failure to brief in their motion to dismiss a theory raised by the complaint should not be rewarded by finding waiver by plaintiffs. Cf. Peterson v. Highland Music, Inc., 140 F.3d 1313, 1318 (9th Cir. 1998) (finding that defendants did not waive on appeal its defense of lack of personal jurisdiction when, in the absence of any allegations of "deliberate, strategic behavior," defendants contested jurisdiction only in their initial pleading and did not raise the issue again until appeal). Neither side advances the cause by hiding the ball from the district court. Cf. Adden v. Middlebrooks, 688 F.2d 1147, 1156-57 (7th Cir. 1982) (finding no waiver by defendants even though defendants never raised issue after initial pleading until supplemental briefing was ordered by the appellate court, but warning that "[defendants] are well advised to brief fully all grounds . . . in their favor").

b. Merits

On the merits, the plaintiffs' theory -- that defendants had no reasonable basis to say at the time they made their statements that TYSABRI was safe in combination with AVONEX -- is not nearly as compelling as opposing inferences from the undisputed facts in the record. First, and most importantly, at the time these statements were made, the FDA had approved TYSABRI for use with AVONEX after contemplating any safety risks. In the FDA's medical review of the drug before approval, the FDA analyzed data from the first year of the SENTINEL trial, which tested TYSABRI in combination with AVONEX. In the "Safety" section of the review, the FDA noted that "[n]atalizumab's overall safety profile was similar in Studies 1801 [TYSABRI as a monotherapy] and 1802 [TYSABRI in combination with AVONEX]," suggesting that "co-administration of [AVONEX] does not necessitate a change in that natalizumab dose to maintain safety." Biogen included similar language as part of the original package insert label accompanying TYSABRI. Addendum to Defs.' Br. at 5.

Plaintiffs point to this language in the original label as evidence that defendants falsely implied that TYSABRI was safe when used in combination with AVONEX. When viewed along with the FDA review described above and the new package insert label after TYSABRI's re-introduction, the inference of scienter is less than compelling. The original label's "Indications and Usage" section, which described the FDA-approved uses of the drug, noted that:

"TYSABRI® is indicated for the treatment of patients with relapsing forms of multiple sclerosis." Addendum to Defs.' Br at 4. The new package insert label specifically states that TYSABRI should be used on its own: "TYSABRI® is indicated as monotherapy for the treatment of patients with relapsing forms of multiple sclerosis . . . ." Joint App'x at 538 (emphasis added). Also, as discussed above, the label comes with a warning of the risk of TYSABRI when used in combination with other MS therapies.

Based on these undisputed facts, we find the defendants' inference more compelling: up until the first diagnosis of PML, no significant safety risk had been associated with use of TYSABRI as a combination therapy. To the contrary, one of the clinical trials (SENTINEL) was focused on the safety and efficacy of TYSABRI in combination with AVONEX. Once the diagnoses of PML occurred and the drug was withdrawn, Biogen recognized that a safety risk may exist when TYSABRI is used as a combination therapy because the two instances of PML had occurred in the SENTINEL trial. This was reported to the FDA and discussed in the Advisory Committee hearings. When the FDA re-approved the drug for use in June 2006, it was only as a monotherapy, and Biogen disclosed this in the label accordingly.

Defendants may have based their optimistic financial projections on a broader market that includes TYSABRI being used with AVONEX. But plaintiffs have not raised a plausible inference

that defendants knew at the time these projections were made that TYSABRI used with AVONEX was unsafe. As a result, we cannot say that either defendants' representations about TYSABRI as a combination therapy or the ensuing forecasts about market share were misleading at the time they were made. There is no strong inference of scienter.

3. Insider Trading Allegations

If there is reason to be concerned about material omissions or misrepresentations, the presence of insider trading can be used, in combination with the other evidence, to establish scienter. Boston Scientific, 523 F.3d at 92; Greebel v. FTP Software, Inc., 194 F.3d 185, 197-98 (1st Cir. 1999); Shaw v. Digital Equip. Corp., 82 F.3d 1194, 1204 (1st Cir. 1996).

Here, we have already discounted the inferences of scienter from claims about failure to disclose the risk of non-PML opportunistic infections and of safety concerns with combination therapy. Even if defendants' statements were arguably misleading, plaintiffs have not sufficiently alleged that the statements were intentionally so; that is, that defendants had any reason to know their statements were misleading before February 18, 2005, the day of the meeting where the defendants first learned of the PML diagnoses. Thus, any insider trading which occurred during the class period until February 18, 2005 cannot be used to support a strong inference of scienter, since "[i]nsider trading cannot

establish scienter on its own."[20] Boston Scientific, 523 F.3d at 92.

We are, however, concerned by the only allegations of a sale on or after February 18, 2005: the allegations that Bucknum, the General Counsel, sold 89,700 shares for total proceeds of approximately $6 million on February 18, 2005. The SEC investigated this sale and an agreement was reached under which Bucknum disgorged profits of $3 million. As best as can be inferred from the documents in evidence, Bucknum proposed his sale to his broker at 8:45am, Biogen's legal department approved the sale at 10:00am, the meeting at which PML was discussed was at 12:00pm, and Bucknum instructed his broker to sell the shares at 1:30pm. Plaintiffs do not allege that any individual defendant knew before the noon meeting of the patient death from PML, that an agenda containing that information was circulated in the morning, or even who first learned the information and when. There is no

[20] We need not address the defendants' arguments that defendant Rohn's trading was immunized because of its proximity to his retirement and that much of the individual defendants' trading occurred pursuant to Rule 10b5-1 plans. An examination of publicly available SEC filings shows that at least two defendants, Rastetter and Adelman, entered into Rule 10b5-1 plans during the class period. See, e.g., Biogen Idec Inc., Form 8-K: Current Report Pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934 (SEC File No. 0-19311, Dec. 13, 2004), Item 8.01 (Rastetter entered into two plans on December 13, 2004); Biogen Idec Inc., Form 8-K: Current Report Pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934 (SEC File No. 0-19311, Oct. 18, 2004), Item 8.01 (Adelman entered into a plan on October 18, 2004).

allegation that Bucknum knew of the information before he sought permission to sell the stock. Perhaps Bucknum acted on insider information in the sense of failing to refrain from trading once he learned of the PML death. It is notable that plaintiffs excluded Bucknum from their section 10(b) claim; the claim is against Biogen and the other individual defendants. But no one else among the defendants traded that day.

Based solely on Bucknum's trading, a strong inference of scienter on the part of Biogen and the other individual defendants cannot be drawn.[21] See Abrams v. Baker Hughes Inc., 292 F.3d 424, 435 (5th Cir. 2002) (noting that "even unusual sales by one insider do not give rise to a strong inference of scienter" when other insiders had not engaged in suspicious trading during the class period); see also, e.g., Southland Sec. Corp. v. INSpire Ins.

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[21] Plaintiffs may be arguing that Bucknum himself violated an independent duty to disclose under section 10(b) because he did not abstain from trading after learning of the incidences of PML. See Shaw, 82 F.3d at 1203 ("There is no doubt that an individual corporate insider in possession of material nonpublic information is prohibited by the federal securities laws from trading on that information unless he makes public disclosure."). We need not decide this issue, however, because plaintiffs elected not to pursue a section 10(b) claim against Bucknum as an individual.

If the plaintiffs are arguing that Biogen itself had a duty to disclose because of Bucknum's trading, that proposition is unsupported by the law. The duty to "disclose or abstain" carries over to the corporation when the corporation itself trades in its own stock, and there is no such allegation here. See, e.g., id. at 1203-04; San Leandro Emergency Med. Group Profit Sharing Plan v. Philip Morris Cos., 75 F.3d 801, 814-15 (2d Cir. 1996).

Solutions, Inc., 365 F.3d 353, 369 (5th Cir. 2004); San Leandro Emergency Med. Group Profit Sharing Plan v. Philip Morris Cos., 75 F.3d 801, 814 (2d Cir. 1996); Acito v. IMCERA Group, 47 F.3d 47, 54 (2d Cir. 1995). Moreover, Bucknum made none of the statements alleged to be misleading, and there is no specific allegation that Bucknum was any more knowledgeable than any of the other individual defendants. See Ronconi v. Larkin, 253 F.3d 423, 436 (9th Cir. 2001) ("One insider's well timed sales do not support the 'strong inference' required by the statute where the rest of the equally knowledgeable insiders act in a way inconsistent with the inference that the favorable characterizations of the company's affairs were known to be false when made." (footnote omitted)).

What is clear is that neither Biogen nor any other individual defendant sold any shares during the class period after they learned of the PML death on February 18. No strong inference of scienter in plaintiffs' favor arises in an absence of insider sales by these defendants.

D. New Claims About Shortened Class Period on Motion To Dismiss

1. Lateness of Assertion of Claim

The plaintiffs filed four successive complaints in this matter over a period of twenty months before oral argument on the motions to dismiss on September 11, 2007.[22] Despite ample

[22] They also sought to file yet another complaint after the court entered a dismissal order.

opportunity to assert their claims earlier, plaintiffs came up with a new theory, the shortened class period theory, in their memorandum in opposition to the motion to dismiss. The district court permitted argument on the theory but was not persuaded. Indeed, the court does not discuss the theory at all in its memorandum supporting its ruling on the motion to dismiss.

Defendants argue the theory was waived. Our concern about theories raised for the first time by plaintiffs in response to defendants' motions to dismiss in securities cases is based in part on traditional notions of waiver and in part on the unusual requirements of the PSLRA. In enacting the PSLRA, Congress intended to raise the standards plaintiffs must meet to survive a motion to dismiss, for defendants to have a fair chance to test the viability of a complaint, and for courts to carefully scrutinize complaints. See Tellabs, 127 S. Ct. at 2509. That deliberate scheme is thrown into disarray when new theories are first produced in response to a motion to dismiss. The need for clarity and specificity about what plaintiffs' theories actually are is undercut. The PSLRA did not impose special burdens on Fed. R. Civ. P. 15(a), regarding amendments of complaints. See ACA Fin., 512 F.3d at 56. But plaintiffs here did not attempt to present this new theory in any of their amended complaints. That meant neither the court nor defendants had prior notice of the theory, much less prior opportunity to consider whether the theory met the PSLRA

standards. The district court would have acted well within its discretion in declining to permit advancement of the new theory. And in future cases, honoring the purposes of the PSLRA, we may decline to hear arguments challenging dismissal based on belatedly advanced theories not contained clearly in amended complaints.

2. Merits of Shortened Class Period Claim

Here, even considering the theory, it fails.

There was a ten-day period between the earliest knowledge on February 18, 2005 of one PML death and the potential PML diagnosis of a second patient, and the announcement on February 28, 2005 that TYSABRI was being withdrawn due to the PML diagnoses. That was a reasonable period of time for defendants to make their disclosures.[23] See Higginbotham, 495 F.3d at 761 ("Managers cannot tell lies but are entitled to investigate for a reasonable time, until they have a full story to reveal.").

At a minimum, Biogen needed to understand whether PML was caused by TYSABRI. This entailed understanding whether both patients with PML had any medical history showing they were susceptible to PML and sorting through whether, if there were a

[23] The district court reasoned at oral argument that the theory must fail because defendants had no duty to disclose in that period because they made no public statements. However, because there had been prior statements about the drug's risks which would have been material to Biogen's financial health, there was a duty to disclose within a reasonable time. See Cabletron, 311 F.3d at 36 (noting a duty to correct prior statements in light of subsequent developments). There is no need to discuss whether there were other sources of an obligation to disclose.

causal connection, it involved TYSABRI alone or an interaction between TYSABRI and AVONEX, since both patients were participating in the combination trial. During the ten-day period, the company was also cooperating with the FDA.

The company would have behaved irresponsibly (and possibly in violation of the securities laws) if it had made a public announcement which was possibly inaccurate because the situation of the PML incidences had not yet been adequately investigated. This obligation on drug companies to investigate and to be accurate in their material public statements holds even when the adverse information comes from clinical trials on drugs to treat very ill patients. See id. at 758 ("Knowing enough to launch an investigation ([the defendants] could not simply assume that the initial report of bad news was accurate) is a very great distance from convincing proof of intent to deceive."); id. at 760-61 ("Prudent managers conduct inquiries rather than jump the gun with half-formed stories as soon as a problem comes to their attention."); cf. Carter-Wallace I, 150 F.3d at 157 ("Drug companies need not disclose isolated reports of illnesses . . . until those reports provide statistically significant evidence that the ill effects may be caused by -- rather than randomly associated with -- use of the drugs and are sufficiently serious and frequent to affect future earnings.").

IV.

Because the complaint has not pled a strong inference of scienter against either Biogen or any of the individual defendants, we do not reach the question of whether it is possible to raise a strong inference of scienter against the company without doing so against any individual defendants. See Teamsters Local 445 Freight Div. Pension Fund v. Dynex Capital Inc., No. 06-2902, ___ F.3d ___, 2008 WL 2521676, at *4 (2d Cir. June 26, 2008); Makor Issues & Rights, 513 F.3d at 710.

In addition to their claims under section 10(b) and Rule 10b-5, the plaintiffs pled claims under sections 20(a) and 20A of the Securities Exchange Act of 1934, 15 U.S.C. §§ 78t(a) and 78t-1. Because we have found that plaintiffs have not adequately alleged an underlying 10b-5 violation, those claims must fail. See ACA Fin., 512 F.3d at 67-68; In re Stone & Webster, Inc., Sec. Litig., 424 F.3d 24, 27 (1st Cir. 2005); In re Advanta Corp. Sec. Litig., 180 F.3d 525, 541 (3d Cir. 1999).

The decision of the district court is affirmed.