IN THE COURT OF APPEAL OF THE STATE OF CALIFORNIA

FOURTH APPELLATE DISTRICT, DIVISION ONE

D067839

TEAGAN HAMILTON, ET AL.,

Plaintiffs and Appellants,

v.

NOVARTIS PHARMACEUTICALS CORPORATION,

Defendant and Respondent.

Appeal from the Superior Court of San Diego County
Honorable Joan M. Lewis, Judge
No. 37-2013-00070440-CU-MM-CTL

Appellants' Opening Brief

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QUESTION PRESENTED

Under California law, tortfeasors are liable for the foreseeable consequences of their conduct. Here, Novartis knew that doctors—unaware that Brethine caused birth defects—frequently prescribed Brethine to pregnant women. Rather than warn doctors about that risk (as federal law required), Novartis sold Brethine for $26 million to a company it knew planned to market it for use with pregnant women. Is Novartis liable for birth defects caused by Brethine after it sold the drug?

STATEMENT OF FACTS

I. Novartis sweeps Brethine's danger to fetal health under the rug in order to exploit Brethine's value as a popular tocolytic drug.

The Brethine story began in 1974, when the FDA approved Brethine for the treatment of asthma. The active ingredient in Brethine, terbutaline sulfate, worked by acting as a smooth-muscle relaxant, thereby relaxing constricted airways in patients suffering from asthma. (AA 022, ¶ 27.)[1]

But trouble arose early in Brethine's life. The market for asthma drugs was crowded and, thus, fiercely competitive, with doctors favoring medications such as Volmax, Proventil, and branded and generic forms of albuterol for asthma treatment. As a consequence, Brethine had disappointing sales figures. (AA 040, ¶ 71.)

In 1976, a Swedish physician with ties to a pharmaceutical company published the results of a study involving 30 pregnant women which suggested that Brethine's active ingredient—terbutaline sulfate—had an acute "tocolytic" effect, insofar as it appeared to temporarily blunt labor contractions when given for a single 48-hour period. (AA 022 ¶ 28.)

In light of that data, Ciba-Geigy—the corporate predecessor to Novartis—acquired the exclusive right to market Brethine in the United States with the intent to boost Brethine sales by promoting Brethine as a tocolytic for the management of preterm

[1] References to the Appellants' Appendix are abbreviated as "**(AA [page]:[line].)**." References to the Reporter's Transcript are abbreviated as "**(RT [page]:[line].)**"

labor. In the mid-1980s, Ciba-Geigy thus began to promote Brethine for tocolytic use, even though a 1978 study failed to replicate the tocolytic effects of the earlier Swedish study, and even though there was no data on long-term health effects of tocolytic therapy or the fetus. (AA 022, ¶ 30.) These promotional efforts continued in the 1980s and 1990s even as data began to mount that terbutaline sulfate had dangerous consequences for fetal health, particularly for the fetal brain. (AA 022–AA033.)

In the mid-1990s, the "New Drug Application" or "NDA" for Brethine—the proverbial golden ticket on file with the FDA that gives its holder the exclusive right to market the corresponding drug in the United States—passed into Novartis's hands when Ciba-Geigy and Sandoz merged to form Novartis.

Novartis picked up where its corporate predecessor left off and actually took the promotional efforts to another level when it began promoting Brethine for so-called "maintenance tocolysis." Unlike a single, short-term administration designed to temporarily blunt labor contractions, maintenance tocolysis involved continuous consumption of Brethine over a prolonged period—weeks if not months—as a sort of blanket therapy to not just stop any preterm labor contractions that had begun (as in acute tocolytic therapy) but to prevent any such contractions from starting in the first place.

To Novartis, the pecuniary benefit of maintenance tocolysis was obvious: Whereas acute tocolytic therapy entailed only a short course of medication, the very nature of "maintenance" tocolysis required significant quantities of Brethine.

Novartis's promotional efforts paid off: Between the mid-1990s and late 2001, the use of Brethine for maintenance tocolysis had become well engrained with obstetricians throughout the United States. As a consequence, the once-fledgling asthma drug was, by 2000, posting $23 million in annual sales. (See SEC, Form 8-K/A Report for aaiPharma, Inc. (Aug. 17, 2001), at p. F-2 <http://www.sec.gov/Archives/edgar/data/1013243/000095014402002153/g74591e8-ka.txt> ("Form 8-K/A for aaiPharma".)

But while Novartis was making millions selling Brethine as a tocolytic, data throughout the 1980s, 1990s, and early 2000s, had begun to accumulate showing that beta-antagonists like Brethine cause serious fetal side effects when used for long-term, maintenance tocolysis. (AA 022–035.)

By 2001, this data was sufficiently clear that a team of doctors from the German Central Institute of Mental Health found that "motor, socio-emotional, and cognitive—especially verbal—development was impaired in a group of term children exposed to tocolytic treatment" using beta-agonist tocolytics like Brethine. (AA 034, ¶ 53.) These findings were echoed by researchers from Duke Medical Center who, by 2001, had seen enough data to conclude "that there are long-term liabilities of tocolysis with BAR agonists [*i.e.*, Brethine], including . . . impaired school performance, and subsequent cognitive impairment and psychiatric disorders." (AA 035, ¶ 54.)

These conclusions stood in stark contrast to the Brethine label used by Novartis. Not only did the label omit any mention

the data showing potential damage to the fetal brain in animal and human studies, it actually cited animal studies for the implied premise that Brethine was *safe* for tocolytic use:

> A reproduction study in Sprague-Dawley rats revealed terbutaline sulfate was not teratogenic when administered orally at doses up to 50 mg/kg (approximately 810 times the maximum recommended daily sc dose for adults on a mg/m2 basis). A reproduction study in New Zealand white rabbits revealed terbutaline sulfate was not teratogenic when administered orally at doses up to 50 mg/kg (approximately 1,600 times the maximum recommended daily sc dose for adults on a mg/m2 basis).

(FDA, Letter re: Docket No. FDA-2008-P-0358 (Feb. 17, 2011), at p. 4 <http://www.fda.gov/downloads/Drugs/DrugSafety/UCM243797.pdf> ("FDA Letter Response to Citizen's Petition").)

Federal law required Novartis, as a brand-name manufacturer, to ensure that Brethine's label warned about foreseeable risks of its drug, and the data had become increasingly clear that Brethine's was potentially dangerous to fetuses. And yet, most of Brethine's ~$20 million in annual sales were based on its popularity as a tocolytic, and nothing would threaten that value more than a warning from the manufacturer that it was dangerous to unborn children. Thus, by 2001, Novartis was faced with a difficult choice: If it did what federal law required by adding warnings to the Brethine production information regarding the potential hazards to fetal health, it would kill its "golden goose." On the other hand, if it continued marketing Brethine with an inadequate label, it would risk significant tort exposure.

Novartis, ever clever, chose a middle route. Rather than update Brethine's label *or* continue to market the drug with the existing label, Novartis sold Brethine to aaiPharma for $26.6 million in December 2001. (See SEC, Form 10-K for aaiPharma Inc. (Mar. 12, 2003), at p. 2 ("Form 10-K for aaiPharma").) In doing so, Novartis was able to eat its cake and have it too: It reaped substantial profits from Brethine's popularity as a tocolytic, but without any ongoing legal exposure for marketing a drug with a deficient label. And, because the terms of the deal called for Novartis to continue manufacturing the actual Brethine medication for aaiPharma (*id.*, at p. 5), Novartis would retain an ongoing financial interest in Brethine's popularity as a tocolytic without any tort exposure.

For its part, aaiPharma was an all-too-willing partner in crime. By 2001, aaiPharma—now a defunct, bankrupt pharmaceutical company—was in the midst of a bold renaissance. Historically dedicated to research, manufacturer, and logistical support for other companies' product lines, in the early 2000s, aaiPharma decided to boost lagging revenue by acquiring and selling its own products.

To that end, aaiPharma targeted products that had large sales revenues but which might be sold a discount due to potential tort exposure. Thus, in 2001, aaiPharma purchased the rights to three highly controversial drugs: The first two were Darvocet and Darvan, the dangerous painkillers that have since spawned a flood of lawsuits throughout the United States, ultimately culminating in massive multidistrict federal litigation.

(See *In re: Darvocet, Darvan and Propoxyphene Products Liability Litigation* (E.D. Kent.) 2:11-md-02226-DCR.) The third was Brethine. By adding Brethine alone, aaiPharma boosted drug sales from $7.8 million in 2001, to nearly $30 million in 2002.

For a time, then, it seemed *both* parties would get what they wanted: aaiPharma obtained the rights to a third highly profitable drug and Novartis was able to cash in on Brethine's popularity as a maintenance tocolytic but without ongoing tort exposure.[2]

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[2] In a stipulation, the parties agreed for purposes of Novartis's demurrer that, in December 2001, Novartis sold the rights to Brethine to "NeoSan Pharmaceuticals." (See AA 098.) To clarify, NeoSan was a business division within aaiPharma. Thus, as Novartis and aaiPharma's press releases and subsequent IRS and SEC filings would confirm that, formally speaking, Novartis sold Brethine to aaiPharma. (E.g., Form 10-K for aaiPharma, *supra*, at p. 2 ["On December 13, 2001, we acquired the U.S. rights to the Brethine branded product line from Novartis Pharmaceuticals Corporation and Novartis Corporation for $26.6 million in cash."]; Form 8-K/A for aaiPharma, *supra*, at p. 2 [aaiPharma filing advising SEC of "our acquisition through NeoSan of the rights and related intangibles associated with the Brethine branded products (the 'Brethine Product Line') from Novartis Pharmaceuticals Corporation and Novartis Corporation (collectively, 'Novartis') on December 13, 2001."].) Whether it was technically aaiPharma or its wholly owned subsidiary NeoSan that acquired Brethine is academic. The Hamiltons refer to the acquiring party as "aaiPharma" throughout this brief in an effort to avoid confusion.

II. The FDA did what Novartis should have done when it mandated that increased warnings be added to Brethine's product information regarding potential hazards to fetal health.

The Brethine-as-tocolytic "gravy train" came to a halt in February 2011 when the FDA, in response to a "citizen's petition" filed in 2008, determined that the existing Brethine product information was inadequate in light of historical data showing that Brethine was neither effective *nor* safe for maintenance tocolysis. As a result, the FDA ordered manufacturers to immediately add the following "boxed warning" to the Brethine label and package insert:

> WARNING: TOCOLYSIS
>
> Oral terbutaline sulfate has not been approved for and should not be used for acute or maintenance tocolysis. In particular, terbutaline sulfate should not be used for maintenance tocolysis in the outpatient or home setting.

(FDA, Letter re: Safety Labeling Change Notification (Feb. 26, 2011), at p. 2 <http://www.fda.gov/downloads/Drugs/DrugSafety/UCM243683.pdf> ("FDA Letter re: Safety Labeling Change").)

In addition, whereas the Novartis label only cited animal studies that showed no damage to fetal brains, the FDA ordered Brethine manufacturers to add the following information to the drug label and package insert:

> Published animal studies show that rat offspring exhibit alterations in behavior and brain development, including decreased cellular proliferation and differentiation when dams were treated subcutaneously with terbutaline during the late stage of pregnancy and lactation period.

> Terbutaline exposures in rat dams were approximately 6.5 times the common human dose in adults of 15 mg/day, on a mg/m2 basis.

(*Id.*, at p. 3.)

As one would expect, Brethine's popularity as a tocolytic dropped precipitously following the FDA's decision in 2011, and it is now considered a risky and widely disfavored tocolytic therapy.

III. The long overdue changes to the Brethine label did not come in time to spare the Hamiltons brain damage from prenatal Brethine exposure.

Because aaiPharma's willingness to pay Novartis $26.6 million for the right to Brethine was predicated on Brethine's popularity—and, thus, sales potential—as a tocolytic drug, it should come as little surprise that aaiPharma continued to manufacture and market Brethine without updating Brethine's label to warn about risks to fetal health.

Without the benefit of formal warnings on the Brethine product information, Jude Hamilton's physician was apparently unaware of the mountain of data showing that Brethine's active ingredient was highly dangerous to the fetal brain. The Hamiltons are confident that discovery in this case, had it occurred, would have yielded that Jude Hamilton's physician would not have prescribed (nor would Jude Hamilton have agreed to take) Brethine as a maintenance tocolytic had the product information provided warnings regarding the potential for fetal injury.

But, thanks to Novartis's efforts to promote Brethine as the go-to drug for maintenance tocolytic, its failure to update

Brethine's label with those suitable warnings prior to selling the drug to aaiPharma, and aaiPharma's foreseeable failure to do the same, Jude Hamilton's physician did not hesitate to prescribe Brethine as a maintenance tocolytic while she was pregnant with Plaintiffs.

As researchers in the 1980s and 1990s would have predicted, the terbutaline sulfate in the Brethine that Jude Hamilton consumed passed from her bloodstream into the placenta, then leached from the placenta into the twins' bloodstream, ultimately passing through their blood–brain barriers into their undeveloped brain tissue. The result was severe and permanent cognitive defects that will drastically impact their lives for the remainder of them.

STATEMENT OF THE CASE

In December 2013, the Hamiltons filed the operative complaint—the "First Amended Complaint"—seeking redress for their physical injuries caused by their prenatal exposure to Brethine. (AA 016–054.)[3] In addition to Novartis, the operative complaint named multiple defendants, several of which have since been dismissed.[4]

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[3] Prior to serving their original complaint, the Hamiltons unilaterally elected to file an amended complaint to detail the numerous scientific studies showing that Brethine was dangerous to the fetus when used for maintenance tocolysis. (Compare AA 001–015 to AA 016–054.) Subsequently, the Hamiltons also unilaterally filed an amendment under Code of Civil Procedure section 473 to substitute "Novartis Pharmaceuticals Corporation"—the company that marketed and sold Brethine in the United States—in for "Novartis International AG," the Swiss parent of Novartis Pharmaceuticals Corporation. (See AA 055.)

[4] The Hamiltons voluntarily dismissed the pharmaceutical giant Astra-Zeneca after informally learning that Astra-Zeneca never marketed or sold Brethine in the United States.

The Hamiltons likewise voluntarily dismissed Lehigh Valley Technology ("LVT")—the company to whom aaiPharma sold the rights to Brethine in 2007—upon learning that LVT acquired the rights to Brethine from aaiPharma within days of when Jude Hamilton was prescribed Brethine, thus complicating a causal nexus between direct misconduct by LVT and the Hamiltons' injuries.

Finally, the trial court sustained a demurrer in favor of Sanofi-Aventus, the brand-name manufacturer of Bricanyl, a drug that, like Brethine, also used terbutaline sulfate as its active ingredient. The Hamiltons did not appeal that order and do not challenge it in this appeal. (Cont'd on next page.)

Novartis demurred to the First Amended Complaint on the premise that its divesture of the NDA for Brethine in December 2001 insulated it from any liability for the Hamiltons' subsequent exposure to, and injuries from, Brethine in October 2007. (See AA 059–075.) In support of that premise, Novartis argued that once it divested the right to market Brethine, the federally mandated duty to ensure that Brethine's label provided sufficient warnings passed to the new brand-name manufacturer of the drug, aaiPharma.

The Hamiltons filed a timely opposition. (See AA 076–089.) In it, the Hamiltons did not deny that Novartis divested Brethine in December 2001, nor did they deny that upon divesting Brethine, the duty to police the label fell to aaiPharma.[5]

(Footnote Cont'd.) Not including Novartis, the remaining defendants consist of Jude Hamilton's treating physicians, the healthcare facility where Jude Hamilton received prenatal treatment, and the makers of the generic Brethine that Jude Hamilton consumed.

[5] The Hamiltons were confident that the fact Novartis divested Brethine in December 2001 would not negate its liability for Novartis's causal role in the Hamiltons' subsequent injuries under California law. But if the Hamiltons were wrong and Novartis's divesture would prove outcome determinative in the trial court's view, the Hamiltons agreed it would be best for all involved to find that out sooner rather than later. Because the trial court could not, in ruling on a demurrer, look to facts outside the complaint, and because the complaint did not identify the date that Novartis divested the NDA for Brethine, the Hamiltons agreed to stipulate for purposes of the demurrer that Novartis divested the NDA for Brethine in December 2001. (See AA 098–100.)

Rather, the Hamiltons pointed out that, prior to selling the Brethine rights to aaiPharma, Novartis:

- actively promoted Brethine among the obstetric profession as a tocolytic;
- knew that obstetricians were, in fact, prescribing Brethine for tocolysis;
- knew or should have known from the ample scientific data available prior to December 2001 that Brethine was dangerous to the fetal brain when used for tocolysis; *and*
- knew or should have known that—in light of unique aspects of federal drug regulations and Brethine's near singular market value as a tocolytic—subsequent manufacturers were unlikely to warn about Brethine's risks to the fetal brain.

In light of those facts, it was foreseeable to Novartis that, by failing to discharge its legal duty to warn about Brethine's risks to fetuses before it sold the drug, doctors would continue to prescribe Brethine to pregnant women indefinitely. Because California law—perhaps uniquely so—makes foreseeability the touchstone of tort liability, the Hamiltons thus insisted that Novartis bore at least a share of fault for their injuries even though they did not occur until after Novartis's control over the drug had ceased.

The trial court disagreed. In a short order notably devoid of legal citation, the court sustained Novartis's demurrer without leave to amend. (AA 101.) Without further explanation, the trial court stated that, in its view, the nearly six-year gap between

Novartis's divestiture of the right to market Brethine and the Hamiltons' exposure to Brethine, insulated Novartis from liability for any misconduct that might have occurred prior to the divesture. (*Ibid.*)

The trial court entered a judgment of dismissal in Novartis's favor (AA 103) which the Hamiltons timely appealed. (AA 113.)[6]

[6] Although the corresponding order is not formally part of the record, this Court may nonetheless be interested to learn that, on June 2, 2015, the trial court entered a stay of all trial-court proceedings on the Hamiltons' complaint during the pendency of this appeal.

STANDARD OF REVIEW

In reviewing an order sustaining a demurrer, the reviewing court's task is to determine whether the complaint "stated a cause of action under any under any possible legal theory." (*Aubry v. Tri-City Hospital Dist*. (1992) 2 Cal.4th 962, 967.)

In doing so, the reviewing court "appl[ies] a de novo standard of review" (*First Aid Services of San Diego, Inc. v. Cal. Employment Development Dept.* (2005) 133 Cal.App.4th 1470, 1476.) Moreover, the reviewing court takes as true all "material facts properly pleaded" and should "give the complaint a reasonable interpretation, reading it as a whole and its parts in their context." (*Blank v. Kirwan* (1985) 39 Cal.3d 311, 318.)

Where, as here, the demurrer was sustained without leave to amend, the reviewing court's task is to "decide whether there is a reasonable possibility that the defect can be cured by an amendment." (*Ibid.*) If so, then "the trial court abused its discretion" and the order sustaining the demurrer must be reversed with leave to amend. (*Ibid.*)

DISCUSSION

The balance of this brief will proceed in three parts:

The first part will demonstrate that Novartis had duties of care to not misrepresent Brethine's safety and efficacy as a tocolytic when promoting the drug or issuing product information.

The second part demonstrates that Novartis's breach of those duties was a substantial factor in, and thus a legal cause of, the Hamiltons' physical injuries.

The third and final part demonstrates that, because Novartis could foresee that the breach of its legal duties would result in physical harm to future children, public policy supports assigning liability to Novartis for the Hamiltons' injuries.

I. Novartis had a duty to refrain from misrepresenting Brethine's worthiness as a tocolytic.

A. Novartis had a legal duty to refrain from promoting Brethine to doctors as a safe and effective choice for tocolytic therapy when neither was true.

Under federal law, drug manufacturers must obtain FDA approval before they can introduce new drugs into the market. (21 U.S.C. § 355(a).) To do so, the manufacturer must demonstrate to the FDA's satisfaction that the drug is safe and effective for its intended use. (*Id.*, § 355(d).)

As logic would suggest, it is thus illegal for drug manufacturers to promote or market a drug for a nonapproved use. (See, e.g., 21 U.S.C. § 331(d).) This is because the non-approved therapeutic use may entail risks that the FDA would

have deemed unacceptable had they been presented for the FDA's consideration. (See *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 140 [observing that for the FDA to consider a drug safe for a particular use, the drug's "probable therapeutic benefits must outweigh its risk of harm"]; *Wyeth v. Levine* (2009) 555 U.S. 555, 566 (*Levine*) [noting that Federal Food, Drugs, and Cosmetics Act—which required premarket approval from the FDA—reflected congressional concern "about unsafe drugs and fraudulent marketing"].)

As discussed at the outset of this brief, Brethine was only FDA approved to treat asthma; it *never* received FDA approval as a tocolytic. And yet, as alleged in the Hamiltons' complaint, Novartis "actively marketed [Brethine] for tocolytic use in the United States." (AA 040–041.) Novartis did so by, among other things, employing two well-known methods through which drug manufacturers actively promote the unapproved uses of their drugs—"dissemination to physicians of independent medical and scientific publications concerning the off-label uses of their products" and "support for Continuing Medical Education (CME) programs for doctors that focus on off-label uses." (*Washington Legal Foundation v. Henney* (D.C. Cir. 2000) 202 F.3d 331, 333 (*Henney*).)

Obviously, the goal of such efforts was to expose the medical profession to an off-label use of a drug that doctors might not have otherwise considered, with the hope that such off-label use would become widespread and, ultimately, a generally accepted therapy. (E.g., *Stevens v. Parke, Davis & Co.* (1973) 9

Cal.3d 51, 55 (*Stevens*) ["Like many others of the profession, [Dr. Beland] had been exposed to the promotional tactics employed by Parke, Davis. It is reasonable to assume that the company's efforts consciously or subconsciously influenced him. In addition, plaintiff introduced expert testimony by a physician that the advertising and promotion of the drug 'played a role' in inducing physicians to prescribe it when it was not sound practice to do so."].)

This is precisely what transpired with Brethine. Touting studies that purported to show that Brethine's active ingredient, terbutaline sulfate, was effective when used for tocolytic therapy (AA 022), Novartis—picking up where its predecessor corporation, Ciba-Geigy, left off—began heavily promoting Brethine's off-label use as a long-term or "maintenance" tocolytic beginning in the mid-1990s. In response, obstetricians began prescribing Brethine for maintenance tocolysis with increasing frequency. (AA 040–041, ¶ 71.) By the time Novartis divested the rights to Brethine in December 2001, the obstetrics community regarded Brethine as an established treatment for the management of preterm labor.

Of course, Novartis's successful effort to market Brethine's off-label use as a tocolytic was not only illegal under federal law, it was dishonest and dangerous. Dozens of studies between 1978 and 2001 not only called into doubt Brethine's efficacy as a long-term tocolytic, but also raised legitimate concerns that Brethine was dangerous to the fetal brain. (AA 022–035.) By 2001, this data was sufficiently clear that a team of doctors from the

German Central Institute of Mental Health found that "motor, socio-emotional, and cognitive—especially verbal—development was impaired in a group of term children exposed to tocolytic treatment" using beta-agonist tocolytics like Brethine. (AA 034, ¶ 53.) These findings were echoed by researches from Duke Medical Center who, by 2001, had seen enough data to conclude "that there are long-term liabilities of tocolysis with BAR agonists [*i.e.*, Brethine], including . . . impaired school performance, and subsequent cognitive impairment and psychiatric disorders." (AA 035, ¶ 54.)

Federal law requires brand-name drug manufacturers like Novartis to periodically review scientific and medical data regarding its drugs, including adverse reactions involving nonapproved—but foreseeable—uses. (See 21 C.F.R. §§ 201.57 (c)(6)(i), 314.80(b).) Novartis, like most major pharmaceutical companies, dedicated substantial resources to this very task. (AA 041, ¶ 73.)

As a result, Novartis either knew or should have known that Brethine was not effective when used for maintenance tocolysis, and even worse, posed a risk to fetuses when used as a tocolytic. (AA 041, ¶ 74.) Thus, by continuing to promote Brethine as a tocolytic in an effort to induce obstetricians to prescribe it for maintenance tocolysis, Novartis not only violated federal law, it committed actionable misrepresentation under California law. (See, e.g., *Diediker v. Peelle Financial Corp.* (1997) 60 Cal.App.4th 288, 297 ["Where the defendant makes false statements, honestly believing that they are true, but without

reasonable ground for such belief, he may be liable for negligent misrepresentation."]; *Engalla v. Permanente Medical Group, Inc.* (1997) 15 Cal.4th 951, 974 (*Engalla*) ["[F]alse representations made recklessly and without regard for their truth in order to induce action by another are the equivalent of misrepresentations knowingly and intentionally uttered."].)

B. Novartis had a legal duty to ensure that Brethine's warning label accurately reflected the risks associated with its foreseeable use.

In addition to Novartis's promotional effort to induce obstetricians to regard Brethine as the drug of choice for maintenance tocolysis, Novartis misrepresented the safety of Brethine as a tocolytic by failing to warn that Brethine posed hazards to the fetus when used as a tocolytic on the drug's label.[7]

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[7] Under federal law, a "label" includes not only the print material on the actual bottle or box, but any printed material *inside* the package (the so-called "package insert"), as well as any writings by the manufacturers regarding the drug, such as the manufacturer-supplied drug information published in the *Physician's Desk Reference* (an encyclopedia of drugs upon which physicians universally rely in their practices) and any promotional materials or letters issued to physicians. (See, e.g., 21 U.S.C. § 321(m); 21 C.F.R. § 202.1(*l*)(2); *PLIVA v. Mensing* (2011) 131 S.Ct. 2567, 2576.) Federal law requires that all such materials mirror the approved "label" on file with the FDA. (E.g., 21 C.F.R. § 201.100(d).) All references to the Brethine "label" and/or "product information" in this brief are thus intended to include not only the printed material on the Brethine package, but also the package insert, the passage in the *Physician's Desk Reference* regarding Brethine, and any correspondence issued by a Brethine manufacturer to physicians about Brethine.

Under California law, a duty to affirmatively disclose information can arise in some limited circumstances. One is when the duty to relate particular information is "directly imposed by statute or other prescriptive law." (*SCC Acquisitions, Inc. v. Central Pacific Bank* (2012) 207 Cal.App.4th 859, 860). Another arises when the defendant "makes representations but does not disclose facts which . . . render his disclosure likely to mislead." (*Warner Construction Corp. v. City of Los Angeles* (1970) 2 Cal.3d 285, 294 (*Warner*).) Here, Novartis had a duty to speak under both scenarios.

Two aspects of federal drug regulations combine to establish that Novartis had the statutory duty to disclose foreseeable risks associated with Brethine use by disclosing such risks on the warning label.

First, as noted above, federal law requires brand-name drug manufacturers like Novartis to periodically review scientific and medical data regarding potential adverse effects of its drugs, including adverse reactions involving nonapproved—but foreseeable—uses. (See 21 C.F.R. §§ 201.57(c)(6)(i), 314.80(b).)

Second, federal law charges brand-name manufacturers with the responsibility to "ensur[e] that its warnings remain adequate as long as the drug is on the market" (*Levine*, *supra*, 555 U.S. at p. 572), and thus specifically require manufacturers "to include a warning as soon as there is a reasonable evidence of an association of a serious hazard with a drug." (21 C.F.R. § 201.80(e); see also 73 Fed. Reg. 49605 ["Manufacturers continue to have a responsibility under Federal law . . . to maintain their

labeling and update the labeling with new safety information."]; 21 U.S.C. § 352(f) [prohibiting distribution of drugs without "adequate warnings"].)

To that end, federal law gives brand-name drug manufactures like Novartis unilateral authority to immediately "add or strengthen a contradiction, warning, precaution" that "is intended to increase the safe use of the drug product" without waiting for FDA approval of the label change. (See 21 C.F.R. § 314.70(c)(6)(iii)(A)–(C); see also *Levine*, *supra*, 555 U.S. at p. 568.)

Taken together, these aspects of federal drug regulation confirm that, until it divested Brethine in December 2001, Novartis had the obligation to continuously assess the adequacy of Brethine's label and to immediately update the label with appropriate warnings upon sensing "reasonable evidence" of a hazard that was not addressed by the existing label.

Federal law aside, Novartis also had an affirmative duty to disclose the risks to fetal health associated with Brethine's use as a tocolytic by virtue of having made certain representations that were misleading in the absence of a disclosure that Brethine was dangerous to fetal health. (*Warner*, *supra*, 2 Cal.3d at p. 294).

Here it is notable that, beginning in the early 1990s, Brethine's warning label actually was updated to include a warning against tocolytic use. (AA 042, ¶ 75.) But the problem was that it only discussed the potential for minor conditions to the mother and was *completely silent as to any risk of injury to the fetus*. Indeed, the only time the subject of potential fetal

injury arose was when the label cited animal studies that purported to show it was *safe* for the fetus.

The fact that the label went out of its way to note minor risks to the mother from the tocolytic use of Brethine—but neglected to mention potential hazards to fetuses—would suggest to a reasonable reader that there *were* no risks to fetal health associated with Brethine's use as a tocolytic. Indeed, it would be entirely *unreasonable* to assume that a drug manufacturer would list minor risks to the mother, but would omit the far more serious risks to the fetus if they in fact existed.

This effect was amplified when the only data regarding fetal health cited in the label consisted of animal studies in which no adverse fetal effect was found. Including such studies while ignoring the contrary data was thus a misrepresentation by omission.

Nor could Novartis have expected this warning to dampen Brethine's use as a tocolytic. It is perhaps too obvious to state that reasonable mothers would willingly encounter a minor risk of injury to themselves if it meant avoiding the more serious consequences for their children associated with a premature birth.

Moreover, as discussed above, any chilling effect that this warning might have had on the tocolytic use of Brethine was more than overridden by Novartis's promotional efforts to induce doctors to use Brethine for tocolysis. (See *Stevens*, *supra*, 9 Cal.3d at p. 53 ["[A]n adequate warning to the profession may be eroded or even nullified by overpromotion of the drug through a vigorous

sales program which may have the effect of persuading the prescribing doctor to disregard the warnings given."]; see also AA 042, ¶ 76.)

Of course, there is no doubt that the information Novartis failed to disclose—that Brethine posed a risk of damage to the fetal brain—was material. "A misrepresentation is judged to be 'material' if 'a reasonable [person] would attach importance to its existence or nonexistence in determining his choice of action in the transaction in question'...." (*Engalla*, *supra*, 15 Cal.4th at p. 977, quoting Rest.2d Torts, § 538, subd. (2)(a).)

As a threshold matter, materiality is a question that can rarely, if ever, be determined at the demurrer stage. (*Engalla*, *supra*, 15 Cal.4th at p. 977; see also *Gervase v. Superior Court* (1995) 31 Cal.App.4th 1218, 1244 (*Gervase*) ["The types of representations set forth by plaintiffs give rise to factual questions concerning such things as materiality, plaintiffs' reliance, and whether reliance was justified, but these questions are factual in nature and cannot support an order sustaining a demurrer."].)

Moreover, under California law, a presumption that undisclosed information was material arises where, as here, the defendant was under a statutory obligation to disclose the information. (See *Kwikset Corp. v. Superior Court* (2011) 51 Cal.4th 310, 333 [holding that California Legislature's enactment of a specific statute compelling retailers to truthfully state the geographic origin of goods confirms that this "is precisely the sort of consideration reasonable people can and do attach importance

to in their purchasing decisions"].) Thus, the fact that federal drug regulations required Novartis to disclose risks of its drugs when "reasonable evidence" suggests that such a hazard exists, gives rise to a presumption that the risk to fetal health associated with Brethine's tocolytic use was material information.

And, of course, that premise makes sense: Just as any reasonable mother would willingly risk of injury if it meant sparing their child a more serious one, *no* reasonable mother would take a drug for the purpose of avoiding serious injury to their child if the drug was just as—if not *more*—likely to cause those same results. Put simply, a reasonable person would not embrace a cure that is worse than the disease.

II. Novartis's misrepresentations regarding Brethine's worthiness as a tocolytic were the legal cause of the Hamiltons' injuries.

The preceding section established that, until December 2001, Novartis had at least two duties of care as a Brethine manufacturer: First, Novartis had a duty to refrain from promoting Brethine's virtues as a tocolytic among the medical profession, and thus inducing the profession to employ Brethine for tocolytic therapy, when it knew or should have known that Brethine was in fact dangerous to fetal health. Second, Novartis had a duty—both under federal law and under California tort law—to detect and affirmatively disclose foreseeable risks associated with Brethine use by, at a minimum, updating its label.

Regarding whether Novartis breached those duties by

promoting Brethine off-label and failing to update Brethine's label, the Hamiltons alleged that there were dozens of studies sufficient to put Novartis on notice that Brethine was dangerous to the fetal brain prior to December 2001 (AA 022–035), and that Novartis, through a sophisticated and complex system to precisely track which doctors are prescribing their drugs and for what purpose, was acutely aware that obstetricians were frequently prescribing Brethine for tocolysis. (AA 041, ¶ 72.) If these allegations are true—and they must be regarded as such at this stage—(e.g., *Kiseskey v. Carpenters' Trust for So. California* (1983) 144 Cal.App.3d 222, 228 (*Kiseskey*)—then they certainly support a presumption that Novartis breached its duties of care by misrepresenting the safety and efficacy of Brethine as a tocolytic. (*Lawrence v. La Jolla Beach & Tennis Club* (2014) 231 Cal.App.4th 11, 32 (*Lawrence*).)

Thus, the next question at *this* juncture is whether there is a causal role between Novartis's wrongful conduct prior to December 2001 and the Hamiltons' prenatal exposure to Brethine in October 2007. The Hamiltons address that issue in the sections that follow.

A. Novartis's misconduct was a substantial factor in the Hamiltons' injuries.

An actor's acts or omissions constitute a legal cause of injury if they played a "substantial factor" in causing the injuries to occur. (*Rutherford v. Owens-Illinois, Inc.* (1997) 16 Cal.4th 953, 977.) Logically, an omission is the legal cause of injuries if the injuries would not have occurred had the omission been replaced

by conduct consistent with due care. (See *Saelzler v. Advanced Group 400* (2001) 25 Cal.4th 763, 778–779.)

The Hamiltons alleged that they were physically injured when their mother, Jude Hamilton, was given Brethine while they were gestating, which crossed "through the placenta . . . , passed through the unborn twins' blood–brain barriers and caused both twins to suffer severe, catastrophic, and permanent neurological injuries." (AA 043, ¶ 85.)

The Hamiltons further alleged that their mother and their mother's physician relied on Brethine's warning label in deciding to use Brethine for tocolytic purposes. (E.g., AA 049, ¶ 116.) They further alleged that their mother's physician would not have prescribed—and their mother would not have agreed to take—Brethine had they been advised of the risks to fetal health associated with its tocolytic use. (E.g., AA 049, ¶ 118.)

These allegations must be taken as true at this stage. (See *Randi W. v. Muroc Joint Unified School. Dist.* (1997) 14 Cal.4th 1066, 1078 (*Randi W.*) ["We must assume, for purposes of demurrer, that the plaintiff was indeed injured in the manner she alleges, and that a causal connection exists between defendants' conduct and the injury suffered."]; *Gervase*, *supra*, 31 Cal.App.4th at p. 1244.

The only remaining question, then, is whether the Brethine labeling that Jude Hamilton's physician encountered in 2007 would, more likely than not, have contained a warning regarding risks to fetal health had Novartis fulfilled its duty to update

Brethine's warning label with that information prior to selling the drug to aaiPharma in December 2001.

There is little doubt that it would have: Although a brand-name manufacturer does not need prior FDA approval to *strengthen* a drug label by, for example, *adding* a warning, a brand-name manufacturer cannot *remove* (or water-down) warnings without the FDA's prior approval. (See 21 C.F.R. § 314.70(c)(6)(iii)(A)–(C); see also *Levine*, *supra*, 555 U.S. at p. 568.)

Although a definitive answer to this question will have to wait for a later date, it seems quite unlikely that the FDA would have granted a subsequent brand-name manufacturer's request to drop the warning regarding potential fetal injury. Indeed, in 1993, the then manufacturer of Brethine—Novartis's predecessor-in-interest, Ciba-Geigy—voluntarily withdrew an application to seek FDA approval of Brethine as a tocolytic, ostensibly because it knew that FDA approval was unlikely even in light of the scientific data in existence at the time. (AA 042, ¶ 75.) Moreover, the FDA's unilateral decision to order Brethine manufacturers to add warnings regarding potential fetal injury in 2011 was based in large part on data that existed before, or shortly after, 2001.

At this juncture, Novartis may be tempted to point out that the Hamiltons' mother was prescribed *generic* Brethine, and therefore that there is no causal nexus between its failure to update the brand-name label and the Hamiltons' exposure.

As a factual matter, this is not completely true: The Hamiltons' mother was given *both* brand name and generic forms of Brethine.[8]

Regardless, this fact would not alter the cause-and-effect relationship between Novartis's misconduct and the Hamiltons' exposure to Brethine. This is because federal regulations require generic manufacturers to adopt, *verbatim*, the operative warning label on the brand-name form of the drug. (*See* 21 U.S.C. § 355(j)(2)(A)(v) [in order to market a generic form of a drug, the drug manufacturer must show that "the labeling proposed for the [generic] drug is the same as the labeling approved for the [approved brand-name] drug"]; *PLIVA, Inc. v. Mensing* (2011) 131 S.Ct. 2567, 2574–2575 (*Mensing*) ["[T]he warning labels of a brand-name drug and its generic copy must always be the same—thus, generic drug manufacturers have an ongoing federal duty of 'sameness.'"].)

Moreover, unlike brand-name manufacturers, which have the ability to unilaterally add warnings to a drug label without FDA approval, "[g]eneric manufacturers are . . . prohibited from making any unilateral changes to a drug's label." (*Mutual Pharmaceutical Co. v. Bartlett* (2013) 133 S.Ct. 2466, 2471, quoting 21 C.F.R. §§ 314.94(a)(8)(iii), 314.150(b)(10).) As such, generic manufacturers cannot add a warning to a drug label even

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[8] Admittedly, this fact is difficult to discern from the Hamiltons' operative complaint. The Hamiltons do not believe this fact is outcome determinative with respect to Novartis's liability, but if this Court finds it significant, the Hamiltons pray for leave to amend to clarify that they were given both generic *and* brand-name Brethine.

if they believe it is necessary. (See *Mensing*, *supra*, 131 S.Ct. at p. 2575 [adopting the FDA's view that generic manufacturers cannot "unilaterally strengthen their warning labels" because "changes unilaterally made to strengthen a generic drug's warning label would violate the statutes and regulations that require a generic drug's label to match its brand-name counterpart's"].)

Thus, had Novartis unilaterally included a warning on the Brethine label regarding risks to fetal health prior to divesting control over the drug in December 2001, every subsequent Brethine manufacturer—brand-name or generic—would almost certainly have included that same warning on their labels.

While perhaps not as easy to isolate as the causal connection between the Hamiltons' injuries and Novartis's failure to warn that Brethine poses risks to fetal health, one cannot ignore the causal role that Novartis's promotional efforts played in the Hamiltons' eventual prenatal exposure to Brethine.

Indeed, the cause-and-effect role between a drug company's promotional efforts and the medical profession's resulting reliance on a particular drug as a standard treatment is well established. (E.g., *Henney*, *supra*, 202 F.3d at p. 333 ["While a manufacturer's direct advertising or explicit promotion of a product's off-label uses is likely to provoke an FDA misbranding or 'intended use' enforcement action, manufacturers have sought to employ more indirect methods of informing physicians about their products' off-label uses."]; *Stevens*, *supra*, 9 Cal.3d at p. 54 [finding that drug company's promotional efforts regarding a

particular drug caused "members of the medical profession . . . to prescribe it when it was not justified"].)

This case was no different. Were it not for Novartis's promotional efforts, Brethine likely would have never gained traction among obstetricians as a maintenance tocolytic in the first place. Thus, there is little doubt that Novartis's promotional efforts played a substantial, if not predominant, role in the fact that, by 2007, the obstetrics community—including, obviously, Jude Hamilton's physician—had come to regard Brethine as the established choice for maintenance tocolysis. (E.g., AA 048–049, ¶¶ 114–116.)

Without the benefit of discovery, it is difficult to quantify the exact ratio that Novartis's promotional efforts played in the decision by Jude Hamilton's physician to prescribe her Brethine. But, to borrow a famous description of the interrelation of ground water to surface water, it perhaps suffices to say at this juncture, that if Novartis's promotional efforts regarding Brethine were red dye, then the obstetric profession's perception of Brethine remained at least a deep shade of pink in 2007. (See Richard S. Harnsberger et al., *Groundwater: From Windmills to Comprehensive Public Management* (1973) 52 Neb. L. Rev. 179, 186.)

Ultimately, whether due to Novartis's promotional efforts, its failure to adequately warn the public regarding the risks of using Brethine as a tocolytic, or both, an untold number of children—including the Hamiltons—were exposed to Brethine in utero between 2001 and 2011, a significant subset of which, like

the Hamiltons, developed cognitive/behavioral disorders as a result.

B. Because Novartis had reason to expect that aaiPharma would *not* warn about Brethine's risks to fetal health, the fact that Novartis divested Brethine to aaiPharma does not constitute a "superseding cause" of the Hamiltons' injuries.

If past is prelude, Novartis will inevitably point out that once Novartis sold Brethine to aaiPharma, the federally mandated obligation to ensure the adequacy of Brethine's label passed from Novartis to aaiPharma. Because aaiPharma could have, but did not, prevent the Hamiltons' exposure to Brethine by updating its label, Novartis will insist aaiPharma's failure to do so is a "superseding cause" that breaks the causal chain between Novartis's misconduct and the Hamiltons' injuries.

The Hamiltons do not dispute that Novartis divested Brethine to aaiPharma in December 2001. Nor do the Hamiltons dispute that, in doing so, the obligation to monitor and update Brethine's label after December 2001, passed from Novartis to aaiPharma.

But Novartis is wrong in its conclusion that this cut off its liability for failing to update the label while it still had control over the drug. California law is clear that the doctrine of "superseding cause" only applies if the original tortfeasor "had no reason to expect" that the third party "would act in a [wrongful] manner." (CACI No. 432.) But an "originally negligent actor remains liable although a third [party] negligently fails to discharge a duty to take affirmative action which would have

prevented the harm, if the third [party]'s conduct is reasonably foreseeable." (*Cline v. Watkins* (1977) 66 Cal.App.3d 174, 179–180 (*Cline*), citing Rest.2d Torts, § 452.)

Thus, aaiPharma's failure to update Brethine's warning label does *not* relieve Novartis of liability for its *own* unreasonable failure to do so if Novartis had reason to expect that aaiPharma might not update the Brethine label either.

In answering that question, the Hamiltons would remind the reader that by the time Novartis began marketing Brethine in the mid-1990s, Brethine was no longer a popular asthma treatment. (AA 040, ¶ 71.) Rather, thanks to Novartis's promotional efforts to establish Brethine as *the* maintenance tocolytic in the United States, the overwhelming majority of Brethine's approximate $20 million in annual sales by 2001—and, thus, most of its market value—resulted from its use as a tocolytic, not an asthma drug. (AA 040–040, ¶¶ 70–72.) Thus, when aaiPharma agreed to buy the Brethine product line from Novartis for **$26.6 million** in 2001, it did so *not* because of its potential as an asthma drug, but because aaiPharma, like Novartis, recognized Brethine's future profitability as a tocolytic.

Of course, nothing would have threatened Brethine's value as a tocolytic more than including language on Brethine's warning label that it may be hazardous to the fetal brain.

In short, because Brethine's market value depended heavily on its popularity as a tocolytic, Novartis had every reason to foresee that any companies looking to buy or sell Brethine would have a strong disincentive to warn the public that it was

dangerous to fetal health and thus would be unlikely to do so. This, of course, is *exactly* what happened—and likely would have continued to happen—had the FDA not intervened in 2011.

Again, the analysis does not change even if the Hamiltons were exclusively prescribed generic Brethine. Because federal law requires *generic* manufacturers to copy the operative brand-name label for Brethine (see 21 U.S.C. § 355(j)(2)(A)(v); *Mensing*, *supra*, 131 S.Ct. at pp. 2574–2575), Novartis knew or should have known that whatever label aaiPharma was using would inevitably be used by generic manufacturers as well. Because Novartis knew that aaiPharma had a strong financial disincentive to update Brethine's label and was thus quite unlikely to add a warning regarding Brethine's dangers to fetal health, Novartis should have foreseen that future generic Brethine manufacturers would continue to use the same insufficient warning label in place when Novartis sold Brethine to aaiPharma.

III. Public policy supports assigning liability to Novartis for its causal role in the Hamiltons' injuries.

The preceding sections have established, first, that Novartis had a general duty of care to avoid misrepresenting Brethine's fitness as a tocolytic, and second, that Novartis's failure to do so was the legal cause of injury to the Hamiltons.

Because the default rule in California is that "all persons have a duty to use ordinary care to prevent others from being injured as the result of their conduct" (*Randi W.*, *supra*, 14 Cal.4th at p. 1077, citing Civ. Code, § 1714), the causal link

between Novartis's failure to exercise due care and the Hamiltons' injuries should be sufficient to impose liability on Novartis.

Nevertheless, Novartis will likely argue that the nexus between Novartis's misconduct and the Hamiltons injuries is too attenuated to justify imposing liability on Novartis, and thus that an exception to the general rule of tort liability is warranted in this case under the now familiar multifactor test set forth in *Rowland v. Christian* (1968) 69 Cal.2d 108.

But as discussed below, application of the *Rowland* factors to this case militates strongly in favor of finding that Novartis's duty of care to refrain from misrepresenting the safety of Brethine extended to future victims of Brethine, including the Hamiltons.

A. Novartis should have foreseen that its failure to update Brethine's warning label would cause doctors to continue to prescribe Brethine to pregnant women in the future.

The chief element in analyzing whether to assign liability to a tortfeasor for its causal role in the plaintiff's injuries is the foreseeability of the plaintiff's injuries. (See *Wright v. City of Los Angeles* (1990) 219 Cal.App.3d 318, 345 "The chief element in determining whether a duty should be imposed is the foreseeability of the risk."]; see also *Ballard v. Uribe* (1986) 41 Cal.3d 564, 572–573, fn. 6 ["The foreseeability of a particular kind of harm plays a very significant role in this calculus."].)

This is particularly true where, as here, the defendant's alleged misrepresentations were not conveyed to the plaintiff

directly, but were instead conveyed to an intermediary, who then relied upon the accuracy of that information in undertaking action to the plaintiff's physical detriment. In such cases, the question is whether the defendant could foresee that the intermediary would rely on the accuracy of that information in choosing actions that would cause harm to such third parties as the plaintiff. (See *Randi W.*, *supra*, 14 Cal.4th at pp. 1077–1078; Rest.2d Torts, § 310 ["An actor who makes a representation is subject to liability to another for physical harm which results from an act done by the other or a third person in reliance upon the truth of the representation, if the actor . . . should realize that it is likely to induce action by the other, or a third person."]; Rest.2d Torts, § 311 ["One who negligently gives false information to another is subject to liability for physical harm caused by action taken by the other in reasonable reliance upon such information, where such harm results . . . to such third persons as the actor should expect to be put in peril by the action taken."].)

Notably, in conducting the foreseeability analysis, the court's task "is not to decide whether a particular plaintiff's injury was reasonably foreseeable in light of a particular defendant's conduct, but rather to evaluate more generally whether the category of negligent conduct at issue is sufficiently likely to result in the kind of harm experienced that liability may appropriately be imposed on the negligent party." (*Ballard*, *supra*, 41 Cal.3d at pp. 572–573, fn. 6.) Put simply, the question is whether Novartis's wrongful acts and omissions prior to

December 2001 created a "foreseeable risk to a foreseeable plaintiff" in the future. (Martin A. Ramey, Conte v. Wyeth*: Caveat Innovator and the Case for Perpetual Liability in Drug Labeling* (2010) 4 Pitt. J. Envtl Pub. Health L. 73, 102.)

Regarding Novartis's failure to update Brethine's warning label, foreseeability turns on two underlying questions:

First, was it foreseeable to Novartis that physicians would rely, at least in part, on a drug's warning label in deciding whether to prescribing a drug to their patient?

Second, was it foreseeable to Novartis that, by failing to update Brethine's warning label prior to divesting control over the drug in December 2001, obstetricians would continue to prescribe Brethine to their pregnant patients in the future?

Regarding the first question, Novartis cannot credibly deny that it knew doctors would rely on the risks set forth in a manufacturer's warning label in choosing whether to prescribe a drug to their patients. Indeed, this is the entire purpose of federal labeling requirements. As discussed previously, nor can Novartis deny that Brethine's potential risk to fetal health is material information that would have impacted an obstetrician's decision to prescribe Brethine to his or her pregnant patient (and those pregnant patients' willingness to take Brethine).

The second question—whether it was foreseeable to Novartis that, by failing to update Brethine's warning, obstetricians would continue to prescribe Brethine to their pregnant patients in the future—was already answered in the

affirmative in response to Novartis's anticipated argument regarding superseding causation.

Again, brand-name manufacturers are required to use, verbatim, the warning label on file with, and approved by, the FDA. (See 21 U.S.C. § 355; 21 C.F.R. § 314.105(b).) Moreover, federal regulations require *generic* manufacturers to adopt, verbatim, the operative warning label on the brand-name form of the drug. (See 21 U.S.C. § 355(j)(2)(A)(v) [label on generic drug must match label on brand-name form of the same drug]; *Mensing*, *supra*, 131 S.Ct. at pp. 2574–2575 [generic drug manufacturers have ongoing federal duty of "sameness" to ensure their label mirrors the label in use by brand-name manufacturers of the same drug].)

Of course, because Brethine's market value was, by 2001, largely dependent on its popularity as a tocolytic, Novartis knew or should have known that neither aaiPharma (nor any other companies interested in purchasing the Brethine brand rights) would be likely to warn the public that Brethine was dangerous to fetal health.

Thus, Novartis knew or should have known that its failure to update Brethine's warning label prior to December 2001 would likely result in a situation in which manufacturers—brand-name *and* generic—would continue to supply Brethine without a warning to reflect the mounting evidence that Brethine was dangerous to fetal health.

A similar analysis applies to Novartis's illegal and deceptive efforts to promote Brethine off-label as a safe and

effective tocolytic. By promoting Brethine as a maintenance tocolytic to obstetricians, it was obviously foreseeable to Novartis that many in the obstetrical profession would come to rely on the drug for that purpose; indeed, that was Novartis's very goal. (E.g., *Stevens*, *supra*, 9 Cal.3d at p. 69 ["It cannot be said, therefore, that Dr. Beland's prescription of the drug . . . was anything other than the foreseeable consequence—indeed, the desired result—of Parke, Davis' overpromotion[.]"].)

Nor, again, did Novartis have a reasonable basis to assume that any subsequent manufacturer would undertake any efforts to change the medical profession's mind about Brethine. Again, *generic* Brethine manufacturers were powerless to alter the drug's warning label, even if they wanted to. And, in light of the fact that most of Brethine's sales revenue was based on its popularity as a tocolytic, aaiPharma—the company to whom Novartis sold the Brethine brand rights—had just as strong a financial incentive as Novartis to stay tight lipped about the fact it was neither safe nor effective for maintenance tocolysis.

Thus, by falsely promoting Brethine as a safe and effective tocolytic agent from the mid-1990s to December 2001, Novartis should have foreseen that doctors would continue to prescribe it for maintenance tocolysis for the foreseeable future, with the inevitable result that countless children would suffer the damaging effects from prenatal exposure to the drug.

B. The other *Rowland* factors militate in favor of assigning liability to Novartis.

While foreseeability is by far the most significant factor in determining whether a tortfeasor's duty of care should extend to a particular plaintiff, the California Supreme Court has consistently identified additional factors that are also relevant to the analysis. These factors are (1) "the degree of certainty that the plaintiff suffered injury," (2) "the closeness of the connection between the defendant's conduct and the injury suffered," (3) "the moral blame attached to the defendant's conduct," (4) "the policy of preventing future harm," (5) "the extent of the burden to the defendant and consequences to the community of imposing a duty to exercise care with resulting liability for breach," and (6) the availability to the defendant of ways to mitigate its liability such as through insurance or alternative courses of conduct. (*Randi W.*, *supra*, 14 Cal.4th at p. 1077.)

A definitive analysis of those factors is made difficult if not impossible at this stage by the lack of a factual record, and thus an ultimate determination may have to wait until trial. (*Conte v. Wyeth, Inc.*, (2008) 168 Cal.App.4th 89, 106–107 (*Conte*).) Nevertheless, as discussed below, the information available at this juncture shows that these factors also weigh in favor of assigning liability to Novartis for the Hamiltons' injuries.

Regarding the first of these factors—the degree of certainty that the plaintiff suffered injury—the Hamiltons have alleged that they were physically injured when their mother, Jude Hamilton, was given Brethine while they were gestating, which

crossed "through the placenta . . . , passed through the unborn twins' blood–brain barriers and caused both twins to suffer severe, catastrophic, and permanent neurological injuries." (AA 043, ¶ 85.) These allegations must be taken as true at this stage. (*Randi W.*, *supra*, 14 Cal.4th at p.1078 ["We must assume, for purposes of demurrer, that the plaintiff was indeed injured in the manner she alleges, and that a causal connection exists between defendants' conduct and the injury suffered."].)

The next *Rowland* factor—the closeness of the connection between the defendant's conduct and the injury suffered—is generally regarded as largely duplicative of foreseeability. (See, e.g., *Bryant v. Glastetter* (1995) 32 Cal.App.4th 770, 782 ["[T]he foreseeability of the harm and the closeness of the connection between the negligence and the harm are two sides of the same coin."]; see also *Cabral v. Ralphs Grocery Co.* (2011) 51 Cal.4th 764, 779 ["[T]he question of 'the closeness of the connection between the defendant's conduct and the injury suffered' . . . is strongly related to the question of foreseeability itself."]; accord *Jackson v. Ryder Truck Rental, Inc.* (1993) 16 Cal.App.4th 1840, 1844.)

It is true that there are several links in the causal chain between Novartis's wrongful act and the Hamiltons' ultimate exposure to Brethine: Novartis passed an inadequate label to aaiPharma, which issued the labels that Jude Hamilton's physician saw and relied upon in prescribing Brethine to the Hamiltons.

But as a combined consequence of both federal drug law *and* the particular facts of this case, what might at first blush appear to be an attenuated game of telephone was, in reality, a tightly related—and highly foreseeable—domino effect that was set into motion the moment Novartis divested Brethine without updating its warning label regarding the risks to fetal health. This fact becomes manifest when one begins by working backward in the causal chain from Jude Hamilton to Novartis.

First, it is imminently foreseeable to drug manufacturers that physicians will rely on, among other things, the drug's label in choosing to prescribe drugs. Again, this is the very purpose behind the federal laws regulating drug labels.

Second, federal regulations require generic manufacturers to adopt, verbatim, the operative warning label on the brand-name form of the drug. (See 21 U.S.C. § 355(j)(2)(A)(v) [label on generic drug must match label on brand-name form of the same drug]; *Mensing*, *supra*, 131 S.Ct. at pp. 2574–2575 [generic drug manufacturers have ongoing federal duty of "sameness" to ensure their label mirrors the label in use by brand-name manufacturers of the same drug].) Thus, it was foreseeable to Novartis that a doctor prescribing even a generic form of Brethine would rely upon the label information issued by the brand-name manufacturer. (*Conte*, *supra*, 168 Cal.App.4th at p. 105 [holding that "it is . . . imminently foreseeable that a physician might prescribe generic [drugs] in reliance on [a brand-name manufacturer]'s representations" about the brand-name form of the drug in light of the fact that generic drugs must be

biologically identical to, and must bear the exact same warning label as, their brand-name equivalents].)

Third, and finally, Novartis knew or should have known that aaiPharma was only interested in Brethine for its market value as a tocolytic. As such, Novartis had reason to anticipate that aaiPharma would also neglect to discharge its obligations to add a warning regarding Brethine's risks to fetal health.

Thus, the mere fact that there were intervening actors between Novartis and the Hamiltons—aaiPharma and their mother's physician—does *not* render Novartis's misconduct too attenuated to support liability for the Hamiltons' eventual injuries because Novartis could easily foresee that its failure to update the label would cause members of the medical profession to continue to prescribe (and their patients to take) Brethine for maintenance tocolysis for the foreseeable future. (See, e.g., *Schrimscher v. Bryson* (1976) 58 Cal.App.3d 660, 664 ["The general test of whether an independent intervening act, which operates to produce an injury, breaks the chain of causation is the foreseeability of that act."]; see also *Cline*, *supra*, 66 Cal.App.3d at pp. 179–180 ["[An] originally negligent actor remains liable although a third [party] negligently fails to discharge a duty to take affirmative action which would have prevented the harm, if the third [party]'s conduct is reasonably foreseeable."].)

The next factor—the moral blame attached to the defendant's conduct—certainly militates in favor of assigning liability. Taken as true, the Hamiltons' complaint stands for the

proposition that Novartis, although well aware that Brethine was dangerous to fetal health *and* that it was being prescribed to pregnant women in droves, declined to update Brethine's warning label in violation of federal law solely to drive sales of Brethine and, ultimately, to maximize the proceeds from a sale of the manufacturing rights to Brethine. (AA 040—042, ¶¶ 70–76.) As a result, an untold number of children were exposed to Brethine in utero between 2001 and 2011, a significant subset of which, like the Hamiltons, developed cognitive/behavioral disorders as a result. It is difficult to think of a more morally blameworthy course of conduct than that. (E.g., *Conte*, *supra*, 168 Cal.App.4th at p. 106 ["If Wyeth intentionally, or even negligently, excluded a warning from its product information, it may be morally culpable for the resulting harm."].)

Regarding the next *Rowland* factor—the policy of preventing future harm—Novartis will inevitably argue that a ruling in the Hamiltons' favor would cause every brand-name drug manufacturer who divests a drug to remain liable in perpetuity for drugs that bear insufficient labeling.

But as this case shows, any post-divesture liability will only attach where, as here, (1) the label was already inadequate *before* it was divested, and (2) the divesting company had reason to anticipate that subsequent manufactures would be unlikely to update the label. Thus, if, prior to December 2001, Novartis did not have reason to know that Brethine's label was inadequate by virtue of its failure to warn about risks to fetal health associated with Brethine use, or if Novartis had a reasonable basis to

believe that aaiPharma would update the label with a suitable warning, Novartis would not be liable for the Hamiltons' injuries.

But Novartis is correct that a judgment in favor of the Hamiltons would give rise to potentially indefinite liability for drug companies who, like Novartis, (1) know that a drug label fails to address foreseeable risks, (2) shirk their obligations under state and federal law to ameliorate that fact, and then (3) place the proverbial keys to that drug in the hands of company it has reason to suspect is similarly unlikely to provide a necessary warning. Rather than cause for alarm, assigning liability to such companies is cause for *celebration*, as it will strongly encourage drug manufacturers to provide required warnings before divesting their drugs, and would thus promote the important national policy of "protect[ing] the public health" by "assur[ing] the safety, effectiveness, and reliability of drugs." (*Levine*, *supra*, 555 U.S. at p. 567.)

The next *Rowland* factor assesses the defendant's ability to mitigate risk through insurance or alternative courses of conduct. Here, there is no doubt that Novartis "had alternative courses of conduct to avoid tort liability" at its disposal. (*Randi W.*, *supra*, 14 Cal.4th at p. 1078.) In particular, Novartis could have simply refrained from falsely promoting Brethine for the nonapproved use as a tocolytic and taken the simple step of amending its label to note potential hazards to fetal health when used as a tocolytic. Doing so would have had required little more than simple compliance with federal law, would have spared Novartis any liability to future victims like the Hamiltons, and most

importantly, would have spared countless future children physical injury from prenatal exposure to Brethine.

The final *Rowland* factor addresses "the extent of the burden to the defendant and consequences to the community of imposing a duty to exercise care with resulting liability for breach." (*Randi W.*, *supra*, 14 Cal.4th at p. 1077.) In terms of "burden," a judgment against Novartis on the Hamiltons' complaint would stand for the proposition that brand-name manufacturers have the burden to carefully and continuously review scientific data to detect reasonable evidence of health hazards associated with foreseeable uses of their drugs. But drug manufacturers already have those obligations under federal law. (See 21 C.F.R. §§ 201.57(c)(6)(i), 314.80(b).) Thus, a finding in favor of the Hamiltons would not impose any new burdens on drug manufacturers that they do not already have.

Moreover, the consequences to the community would only be positive. By reinforcing manufacturer's existing obligations to carefully and continuously review scientific data to detect reasonable evidence of health hazards associated with foreseeable uses of their drugs, a decision in favor of the Hamiltons would simply reinforce the important public policy of "protect[ing] the public health" by "assur[ing] the safety, effectiveness, and reliability of drugs." (*Levine*, *supra*, 555 U.S. at p. 567.)

CONCLUSION

Novartis had a duty under state and federal law to not misrepresent Brethine's safety and efficacy to the public.

Novartis breached those duties by promoting Brethine "off label" as a maintenance tocolytic among the obstetric profession even though it knew that Brethine was dangerous to the fetal brain and not effective when used outside an acute period. It further breached that duty by failing to include warnings on Brethine's label that the drug was potentially hazardous to fetal health before it sold the rights to Brethine to aaiPharma for $26.6 million in December 2001.

Novartis's breach of those duties was a substantial factor in the Hamiltons' eventual exposure to Brethine in utero. Had Novartis never promoted Brethine as a maintenance tocolytic, it is likely that it never would have gained traction in the obstetrics profession for that purpose. Alternatively, as a consequence of the one-way ratchet nature of federal labeling law, had Novartis included a warning regarding the risks to fetal health prior to December 2001, it almost certainly would have remained in place by 2007. And, had Brethine's product information contained such a warning, it most likely would not have been prescribed to Jude Hamilton while she was pregnant with Plaintiffs.

Because Novartis could foresee that aaiPharma had $20 million worth of annual sales riding on Brethine's popularity as a tocolytic and was thus quite unlikely to update Brethine's label, Novartis should have foreseen that doctors would continue to rely on its promotional efforts and Brethine's deceptive warning label

in choosing to prescribe Brethine to pregnant women indefinitely in the future.

Simply put, by failing to do as state and federal law required, Novartis could have thus foreseen the exact result that transpired here—a pregnant woman was given Brethine as a maintenance tocolytic, only to give birth to twin boys with severe cognitive disabilities.

Reserving the judgment of dismissal would thus require nothing more remarkable than underscoring the well-established rule in California that tortfeasors are liable for the foreseeable consequences of their conduct. Accordingly, the Hamiltons' pray this Court will ***reverse*** the judgment of dismissal in Novartis's favor, and remand this case for further proceedings (including, if necessary, leave for the Hamiltons to file an amended complaint).

September 18, 2015 By: _____

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CERTIFICATE OF COMPLIANCE

As required by California Rules of Court, rule 8.360, subdivision (b)(1), I certify that, according to the word-count feature in Microsoft Word 2011, this Opening Brief contains **11,457** words, including footnotes, but excluding the tables, this certificate, and any attachments permitted under California Rules of Court, rule 8.204, subdivision (d).

September 18, 2015 By: _____

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PROOF OF SERVICE

I, the undersigned, say: I am over 18 years of age, employed in the County of San Diego, California, and not a party to the subject cause. My business address is 2550 Fifth Ave., Ste. 1100, San Diego, California, 92103.

On September 18, 2015, I served the attached **Appellants' Opening Brief**, of which a true and correct copy of the document filed in the cause is affixed by placing a copy thereof in a separate envelope for each addressee named hereafter, addressed to each such addressee respectively as follows:

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Each envelope was then sealed, and with the postage thereon fully prepaid, deposited in the United States mail by me at San Diego, California, on September 18, 2015.

I declare under penalty of perjury that the foregoing is true and correct, and this declaration was executed at San Diego, California, on September 18, 2015.

_____

Diane DeCarlo