UNITED STATES COURT OF APPEALS
for the
THIRD CIRCUIT

Case No. 08-3575

JACOB GUNVALSON; and CHERI and JOHN GUNVALSON,
Individually and as Guardians for Jacob Gunvalson, A Minor

Plaintiffs-Appellees,

– v. –

PTC THERAPEUTICS, INC.,

Defendant-Appellant.

On Appeal From The United States District Court
For The District Of New Jersey

BRIEF OF *AMICI CURIAE* JACQUI AND NICHOLAS FUCA, INDIVIDUALLY AND AS GUARDIANS FOR NICOLAS FUCA, A MINOR, SUPPORTING DEFENDANT-APPELLANT PTC THERAPEUTICS, INC. AND SEEKING REVERSAL

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TABLE OF CONTENTS

TABLE OF AUTHORITIES

FEDERAL CASES

FEDERAL STATUTES AND REGULATIONS

FEDERAL REGISTER

LAW REVIEWS AND INTERNET WEBSITES

AFFIDAVITS AND DECLARATIONS

STATEMENT OF *AMICI CURIAE*

Nicolas Fuca is 13 years old. On February 3, 1999, when he was 4, Nicolas was diagnosed with Duchenne Muscular Dystrophy (or "DMD"). As a result of his muscular dystrophy, Nicolas now cannot walk and is wheelchair-bound.

DMD affects only boys and typically is diagnosed in early childhood. In the United States, roughly 13,000 boys and young men suffer from DMD, and about 1,700 of them, including both plaintiff Jacob Gunvalson and Nicolas, have DMD due to a genetic defect known as a nonsense mutation. There is no known cure for DMD, and DMD patients generally do not live beyond their middle twenties. *Amici curiae* Jacqui and Nicholas Fuca are Nicolas Fuca's parents.

Amici curiae submit this brief in support of defendant-appellant PTC Therapeutics, Inc.'s (or "PTC") appeal from the district court's preliminary injunction. PTC has developed PTC124, an investigational new drug that may treat nonsense mutation DMD. The Fucas want PTC124 (or any other drug that is safe and effective for treating DMD) to be approved and marketed as quickly as possible so that Nicolas Fuca and more than a thousand other boys and young men who suffer from the same form of DMD in the United States may benefit. The Fucas believe that litigation-

based access to PTC124 will hinder efforts to recruit subjects into clinical trials of PTC124, including PTC's Phase 2b trial, which is currently enrolling subjects, and possible future clinical trials.

In addition, PTC has freely shared information with the Fucas about its development and testing of PTC124, just as PTC has been candid with the Gunvalsons and other DMD families. The Fucas fear that, if parents of terminally ill children succeed in bringing promissory-estoppel claims like the Gunvalsons', then PTC and other manufacturers of novel, potentially life-saving drugs will have no choice but to reduce or eliminate communication with patients and their relatives.

While PTC consents to the filing of this brief, the Gunvalsons do not. The Fucas are seeking leave to file this brief in the accompanying motion.

INTRODUCTION

Few questions are more wrenching than when children suffering from a life-threatening condition should receive a drug such as PTC124 that, while not shown to be safe or effective, is a potential cure. The Gunvalsons believe that Jacob should get the drug immediately. PTC believes that Jacob, and others in his situation, should receive the drug as soon as possible, but not until PTC's clinical trials are fully enrolled and there is better evidence that the drug is safe and effective.

Because the Fucas have a son who, like Jacob Gunvalson, suffers from nonsense mutation DMD and might benefit from access to PTC124, these *amici curiae* understand the seriousness of this question only too well. But the Fucas, unlike the Gunvalsons, believe it is too early to provide access to PTC124 outside the ongoing clinical trial for two reasons.

First, allowing access to PTC124 via litigation when the drug is being tested in placebo-controlled clinical trials could devastate the clinical trial program. Why would anyone enroll (or remain) in a clinical trial that presents a substantial risk of receiving a useless placebo pill when, through litigation, one can be certain of receiving what could be a life-saving drug? The problem is compounded where, as here, the underlying condition is thankfully rare and, therefore, the universe of potential clinical trial participants is small. We currently do not know whether PTC124 is safe or effective for treating nonsense mutation DMD; if this lawsuit and the ones that may follow on its heels are successful, we may never find out.

Second, PTC has been extremely open in dealing with the Gunvalsons, the Fucas, and others by providing frequent updates and open channels of communication about PTC124's development and progress. If this lawsuit – based on what parents of a terminally-ill child say they heard from drug company employees – is successful, then neither PTC nor other

pharmaceutical manufacturers will continue to provide patients and their families with the degree of access and information they now receive. That result benefits no one.

FACTUAL BACKGROUND

PTC124 is an investigational new drug developed by PTC that may treat, among other things, nonsense mutation DMD. (Affidavit of Langdon L. Miller at ¶ 3 (JA 235) ["Miller Aff."]). Based on favorable results in preclinical studies of PTC124 in animals, the FDA approved PTC124 for testing as an investigational new drug in human clinical trials. (*Id.* at ¶¶ 25-26 (JA 242)). There are three pre-approval clinical trial phases: (1) Phase 1, which involves giving the drug to healthy volunteers to explore how the drug is metabolized in and affects humans; (2) Phase 2, which may include separate "a" and "b" subparts and involves (i) giving the drug to small numbers of subjects suffering from the condition the drug may treat to establish appropriate dosing levels, and (ii) gathering preliminary safety and efficacy data; and (3) Phase 3, which gives the drug to larger numbers of subjects to establish safety and efficacy. *See* 21 C.F.R. § 312.21.

PTC124 currently is in the middle of Phase 2 trials, and only very limited safety and efficacy data are available. Results of a Phase 1 trial involving 62 healthy adults given PTC124 for two weeks were positive and,

in 2006, PTC began a Phase 2a clinical trial that involved giving low, medium, and higher PTC124 doses to 38 boys or young men for four weeks. (*See* Miller Aff. at ¶¶ 26, 29 (JA 242-43)). The Phase 2a trial results were released in late 2007 and showed that the drug was associated with increased production of the protein that nonsense mutation DMD patients cannot otherwise produce and that the drug was tolerated at the levels given over four weeks. (*Id*. at ¶¶ 31-32 (JA 244)).

On April 23, 2008, PTC announced a 165-subject Phase 2b PTC124 trial, which will look for improvements in walking ability over two, 48-week periods. (*Id*. at ¶¶ 35, 37, 38 (JA 245-46)). The Phase 2b trial currently is enrolling subjects. That trial will be placebo-controlled for the first 48 weeks, which means that 55 boys with nonsense mutation DMD enrolled in the study will receive a placebo – an inactive pill. (*Id*. at ¶ 36 (JA 245)). PTC and its experts plan to review interim data from the Phase 2b trial to determine whether the study should stop, proceed, or, if there is "extreme efficacy," provide PTC124 to all study participants. (*Id*. at ¶ 41 (JA 246-47)).

To qualify for the Phase 2b PTC124 study and for two of the three parts of the Phase 2a study, subjects had to be able to walk. (*Id*. at ¶¶ 29, 35 (JA 243, 245)). Nicolas Fuca is wheelchair-bound, so he did not try to enroll.

Because of the sparse safety and efficacy data available, as well as the need to enroll subjects in the current and future clinical trials, PTC currently has no expanded access program to provide PTC124 to DMD patients who are not participating in clinical trials. PTC will consider providing PTC124 to DMD patients outside the clinical trials when subjects for Phase 3 clinical trials are enrolled and there is more safety and efficacy data. (*See* Affidavit of Claudia Hirawat at ¶ 30 ["Hirawat Aff."] (JA 344)).

The Fucas have been in contact with PTC and have closely followed the company's development and testing of PTC124. PTC hosted Jacqui Fuca for a breakfast, a tour of its facility, and a PowerPoint presentation about PTC124, and the company sends the Fucas e-mail updates on the status of PTC124.

ARGUMENT

I. THE DISTRICT COURT'S ORDER GRANTING THE GUNVALSONS INTERIM RELIEF WILL HURT OTHER DMD PATIENTS AND FAMILIES.

Like the plaintiffs in this action – and every other DMD family – the Fucas desperately want a safe and effective drug to treat their son's life-threatening condition. And they want their son to have that treatment as soon as humanly possible. But, as the FDA has said, "[t]he most efficient and effective way to make a drug available to all those who can benefit from

the drug, is to market it." *Expanded Access to Investigational Drugs for Treatment Use,* 71 Fed. Reg. 75,147, 75,151 (Dec. 14, 2006).

The Gunvalsons' lawsuit and the district court's order granting preliminary relief hurt the Fucas and other DMD families in two ways. First, allowing patients to obtain PTC124 through litigation creates perverse incentives that will hinder efforts to recruit subjects for clinical trials that are essential to PTC124 becoming generally available. Second, allowing judicially-mandated access to PTC124 based on alleged promises that parents of a terminally ill child say they heard will likely cause PTC to sharply reduce or even eliminate communications with DMD families and to stop providing those families with information about PTC124's progress.

A. Granting Patients Access To Experimental Drugs Through Litigation Impedes Enrollment In Clinical Trials.

"Persons intending to market a drug must first file" with the FDA "full reports of investigations into the drug's safety and effectiveness ...." *Colacicco v. Apotex, Inc.*, 521 F.3d 253, 257 (3d Cir. 2008) (citing 21 U.S.C. § 355(b)(1)). The "investigations" are, in practice, "a series of clinical trials." *N.J. Carpenters Pension & Annuity Funds v. Biogen IDEC Inc.*, 537 F.3d 35, 39 (1st Cir. 2008) (citation omitted).

Not all persons in clinical trials receive the test drug. Instead, clinical trial subjects generally "are randomly assigned to one of two groups: one group exposed to the drug of interest and the other not exposed. After a period of time the study participants in both groups are evaluated ...." *In re Bextra & Celebrex Mktg. Sales Practices & Prod. Liab. Litig.*, 524 F. Supp. 2d 1166, 1173 (N.D. Cal. 2007) (citation omitted).

Obviously, clinical trials require subjects. For drugs being tested for rare conditions, the population of patients from whom clinical trial participants may be recruited is, by definition, very limited. Moreover, subjects in clinical trials take a risk that, if they are randomized to receive a placebo (or dummy) pill and the study drug proves effective, they will have sacrificed a chance for treatment of their life-threatening illness.

Allowing access outside the trials to an investigational drug being tested in clinical trials creates a powerful, yet perverse incentive for prospective participants not to enroll (or remain) in trials. (*See* Declaration and Opinion of Jonathan D. Moreno at ¶¶ 11, 12 (JA 419)). Every expanded access patient receives the active drug, while subjects in clinical trials may be randomly selected to receive only dummy pills.

As the FDA observed, "it is important to ensure that expanded access use does not compromise enrollment in the trials needed to demonstrate

the safety and effectiveness of the drug.... Patients may find participation in a clinical trial less desirable than receiving the drug for treatment" because "clinical trial participants may receive a treatment other than the study drug." *Expanded Access to Investigational Drugs for Treatment Use,* 71 Fed. Reg. 75,147, 75,150-51 (Dec. 14, 2006). "[T]he challenges associated with subject recruitment and retention are well documented," and "[c]linical trial enrollment involves both hassle (in the form of screening procedures required to assess eligibility) and risk (in placebo-controlled trials, the patient may not receive the active drug) that terminally ill patients may be unwilling to contemplate." Peter M. Currie, "Restricting Access To Unapproved Drugs: A Compelling Government Interest?," 20 *J.L. & Health* 309, 319, 321 (2006/2007) (footnote omitted).

Not surprisingly, the expanded access statute and regulations reflect the seriousness of the concern about clinical trial recruitment. The statute permits individual patient access only after the FDA "determines that provision of the investigational drug ... will not interfere with the initiation, conduct, or completion of clinical investigations to support marketing approval." 21 U.S.C. § 360bbb(b)(3). And, while the regulation permits limited expanded use during Phase 2 trials in "appropriate circumstances," "a drug ordinarily may be made available for treatment use ... during Phase

3 investigations or after all clinical trials have been completed." 21 C.F.R. § 312.34(a).

Here, PTC currently is enrolling subjects in a Phase 2b PTC124 trial that will be placebo-controlled. (*See* Miller Aff. at ¶ 36 (JA 245)). Every subject who enrolls in the PTC124 Phase 2b trial knows that he has a roughly one-in-three chance of *not* receiving what may prove to be a life-saving drug. If the Gunvalsons' lawsuit is successful, potential and existing clinical trial enrollees may conclude that they, too, should seek access to PTC124 through legal action. Unlike enrolling in the Phase 2b clinical trial, which presents a 33 percent chance of receiving a placebo, a court order would guarantee access to PTC124. Thus, the district court's preliminary injunction would make efforts to fill the clinical trial more difficult and encourage those enrolled in the trial to withdraw.

Moreover, if the Phase 2b PTC124 clinical trial that currently is enrolling subjects provides some evidence of safety and efficacy, additional trials may be needed to establish that PTC124 is safe and effective and obtain the FDA's approval to market the drug. Given the thankfully small number of boys and young men who suffer from nonsense mutation DMD, allowing litigation-based access to PTC124 could mean that future clinical trials will not be able to enroll enough subjects. Indeed, the very limited

universe of potential enrollees is very likely why, in response to the Gunvalsons' pleas to PTC for PTC124 for Jacob, PTC deferred the issue of access to the drug outside the clinical trial program until after enrollment for Phase 3 clinical trials is completed and more safety and efficacy data become available. (Hirawat Aff. at ¶ 30 (JA 344)).

As the FDA observed in connection with its expanded access program, "a system of blindly permitting uncontrolled access to investigational drugs could make it difficult or impossible to enroll adequate numbers of subjects in clinical trials to establish the safety and effectiveness of the drug for marketing approval." *Expanded Access to Investigational Drugs for Treatment Use,* 71 Fed. Reg. 75,147, 75,150 (Dec. 14, 2006). Given the limited universe of nonsense mutation DMD patients coupled with the life-threatening nature of the disease, litigation-based access to PTC124 could easily destroy the PTC124 clinical trial program and render impossible FDA approval that would permit access to the drug for all patients.

B. The District Court's Order Will Have A Chilling Effect On PTC That Likely Will Cause PTC To Stop Communicating With DMD Families.

The Fucas have received – and want to continue to receive – information from PTC about its development of PTC124 and any other potentially life-saving drugs for Nicolas. PTC has worked closely not only

with the Fucas, but with other DMD families to provide support and information. For example, PTC gave Jacqui Fuca a tour of its facility, as well as a presentation about PTC124, and the Gunvalsons' allegations in their lawsuit reflect that PTC worked with them closely, too. Indeed, the company has been so open and transparent with patients' families that it has received awards from patient advocacy groups for these efforts. (Affidavit of Stuart W. Peltz at ¶ 6 (JA 324-25)).

The Fucas are concerned that, if the Gunvalsons prevail on their promissory estoppel claim, PTC will have no choice but to terminate its current practice of communicating openly and freely with patients and families about PTC124. Litigation, of course, involves not just the words that PTC speaks, but the words that DMD patients (or their families) believe they hear. The district court decision rewards parents for believing in good faith that they heard more than PTC actually said, or for shading the truth to offer hope to their terminally ill children. Pharmaceutical manufacturers should not fear that every phone call, every e-mail, and every interaction with patients or their families will be the basis for claims based on supposed promises that patients or their families may think they heard.

The concern that this lawsuit and ones like it will change the way PTC operates is well founded. PTC's founder, president, and CEO said that: "If statements made by [PTC's] employees can be misinterpreted, mischaracterized, or simply made up, to form the basis for lawsuits like this one, it would be inadvisable for [PTC] to continue to have such extensive interactions with patient families and the larger DMD[] community in the future. If similar lawsuits follow this one, as [he] think[s] will happen if the Gunvalsons obtain the extraordinary relief they are seeking, then [PTC] will have no alternative but to drastically curtail [PTC's] interaction with the DMD[] community." (*Id.*).

Indeed, the district court's ruling prompted an educational program titled "Compassionate Use: Changes You Should Make Following *Gunvalson, et al. v. PTC Therapeutics*" that addresses the question: "Should you make changes to your compassionate use policies?" (http://www.thompsoninteractive.com/upcoming.asp?topic=enc&id=940&priority=FKYG50731 (last visited Sept. 29, 2008)). The program's answer is unequivocal: "Based on an August ruling in [d]istrict court, the answer is yes." (*Id.*). Neither silencing PTC nor limiting its communications with DMD families to formal, disclaimer-filled and lawyer-drafted communications serves any good purpose.

CONCLUSION

This Court should reverse and vacate the district court's preliminary injunction.

September 30, 2008

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CERTIFICATION OF BAR MEMBERSHIP

Pursuant to Third Circuit Local Appellate Rule 28.3(d), we certify that we are members of the bar of the United States Court of Appeals for the Third Circuit.

/s/ Mark Herrmann
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CERTIFICATION PURSUANT TO FED. R. APP. P. 32(a)(7)(C)

I certify that this brief complies with the type-volume limitations set forth in Federal Rule of Appellate Procedure 32(a)(7)(B). This certification is based on the word count of the word processing system used to prepare this brief. The number of words contained in this brief, excluding parts of the brief exempted by Fed. R. App. P. 32(a)(7)(B)(iii), is 2,886, according to that word processing system. This brief also complies with the typeface and type style requirements of Fed. R. App. P. 32(a)(5) and 32(a)(6) because it was prepared using Microsoft Office Word 2003 with proportionally-spaced Georgia typeface in 14-point font.

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CERTIFICATIONS PURSUANT TO 3D CIR. LOC. APP. R. 31.1(c)

I certify that the text of the electronic brief is identical to the text in the paper copies. I also certify that a virus check was performed using McAfee VirusScan Enterprise Workstation, version 8.5.0.781, and that no virus was detected.

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CERTIFICATE OF SERVICE

I certify that, on September 30, 2008 and by Federal Express, (a) ten copies of the foregoing Brief of *Amici Curiae* were sent to the Clerk's Office; and (b) two copies of that brief were sent to:

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