UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

JACOB GUNVALSON, CHERI AND JOHN GUNVALSON, AS GUARDIANS FOR JACOB GUNVALSON, AND CHERI AND JOHN GUNVALSON, INDIVIDUALLY, Plaintiffs, v. PTC THERAPEUTICS, INC., Defendant.	Civil Action No. 08-3559 (WJM) (MF) *DOCUMENT FILED ELECTRONICALLY* Return Date: August 19, 2008

REPLY BRIEF OF PLAINTIFFS JACOB, JOHN AND CHERI GUNVALSON IN SUPPORT OF THEIR MOTION FOR A PRELIMINARY INJUNCTION

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PRELIMINARY STATEMENT

The core issues in this case are whether PTC promised the Gunvalsons either that: 1) Jacob would not be prejudiced from participating from future trials if he did not enroll in the earlier ones; or 2) PTC would provide Jacob access to PTC124. PTC spends pages arguing the Gunvalsons "fabricated" their claims. However, buried in PTC's opposition is an admission to the very promise that the Gunvalsons assert.

Specifically, PTC's Senior Vice President admits telling Cheri Gunvalson that Jacob would not be precluded from participating in PTC's future clinical trial if he did not enroll in the Phase 2a clinical trial, provided that he met the eligibility requirements. This promise is clear, definite, and the Gunvalsons reasonably relied upon it. Nevertheless, Jacob has been excluded from the current Phase 2a Extension trial on the sole basis that he did not participate in the earlier one.

Similarly, PTC fails to recognize that Dr. Parkin – the only non-party testifying on the subject – also heard Claudia Hirawat promise Jacob access to PTC124, and it hides behind a false diagnosis to avoid treating Jacob with PTC124. Jacob has DMD, a fact of which PTC would be aware if Dr. Finkel had actually examined him, and as PTC itself has repeatedly stated, all available evidence supports PTC124's safety. Jacob cannot wait until PTC124 is publicly available, and does not have the time to let PTC continue to hide behind its story.

PTC claims it had no reason to lead Jacob on, belittling the work of Cheri and Jacob Gunvalson and claiming they seek preferential treatment due to Cheri's "political influence." PTC has it backwards. PTC benefited by the relationships with Senator Wellstone and Representative Peterson, which were formed due to Cheri and Jacob's work to get the 2001 legislation funding Muscular Dystrophy research passed. Cheri was on the panel that designated the Centers of Excellence, and helped write the Senate's funding directives to the NIH. She received honors from the National Genetic Council for her advocacy with PTC's Senior Vice President at her side. Cheri's work ultimately resulted in millions of dollars of federal grants to PTC, giving it ample reason to string along the Gunvalsons, whose contributions were summed up by Senator Wellstone on the Senate floor:

> One DMD child back in Minnesota that I have become especially fond of is Jacob Gunvalson. Jacob is an adorable 10-year-old. He loves to play with his siblings out on his parents' farm, draw pictures for his family's refrigerator and play video games. Jacob and his mother Cheri Gunvalson have made quite an impression on several members of Congress, and Jacob's picture adorns the desks of numerous health care legislative staff throughout Washington. This is because like so many other parents facing the day-to-day experience of living with a child suffering from this debilitating disease, Cheri is focused on leaving no stone unturned in her quest to help improve her son's chance of survival. One day, Jacob drew a picture on himself, and in a cloud above his figure he wrote the words, "What I want most in the world is a cure for Duchenne Muscular Dystrophy". I say to my colleagues, that's what I want, too. Today, we are getting one stop closer to making Jacob's wish come true.

Wolin Decl. Exh. A; see also, Exhs. B (Congressman Colin Peterson), C (Sens. Harkin and Specter); Anderson Decl. ¶¶2-7.

Additionally, PTC ignores 21 C.F.R. §312.34, which expresses a strong public policy in favor of compassionate use, and hides behind its unsupported assertion that patients will leave its clinical trials, fabricate promises and litigate for drug access. This hypothesis deliberately overlooks that compassionate use exceptions are not available to patients who qualify for trials. As to PTC's "fairness" concerns, perhaps it should have thought about them before promising the Gunvalsons Jacob would not be prejudiced by staying out of the Phase 2a trial. PTC did not, and fairness to Jacob should now preclude it from breaking its word.

ARGUMENT

I. PTC BROKE ITS PROMISE ABOUT FUTURE CLINICAL TRIALS

One of plaintiffs' primary claims is that PTC violated multiple common laws as a result of statements it made to Cheri Gunvalson. Specifically, when determining whether to enroll Jacob in either the Phase 2 or Phase 2a clinical trial, Cheri asked PTC's Claudia Hirawat whether there were any adverse effects on Jacob for not participating in the trial, and was told there were none. See Gunvalson Decl. ¶17, 25. Among PTC's opposition papers is the Affidavit of Claudia Hirawat, which admits this is exactly what she told Cheri:

> I informed Mrs. Gunvalson that Jacob's non-enrollment in Phase 2a trials would not by itself preclude him from participating in all of PTC's anticipated future clinical trials for PTC124, assuming he satisfied the eligibility requirements for those trials.

Hirawat Aff., ¶16. The Phase 2a trial was 28 days in length. After the completion of that trial PTC announced the positive results at the Child Neurology Society's Annual Meeting. Wolin Decl. Exh. G. PTC also stated the safety profile of PTC124 in the Phase 2a study "supports continued testing in longer-term studies." Id. PTC then announced a 96-week (672-day) Phase 2a Extension study. Jacob meets all qualifications except for the fact that he was not enrolled in the earlier Phase 2a trial.[1] However, PTC told him he was not eligible for that trial, directly contradicting the representation and promise Ms. Hirawat made to the Gunvalsons.

Because it is undisputed that PTC made a clear and definite promise to the Gunvalsons that Jacob would not be excluded from future trials only because he did not participate in the earlier ones, and the Gunvalsons reasonably relied on those statements to their detriment, plaintiffs have established a *prima facie* case of promissory estoppel. Insofar as PTC's representation was knowingly or negligently untrue when it was made, plaintiffs have established a *prima facie* case of either fraudulent or negligent misrepresentation.

II. JACOB HAS DMD AND WAS ELIGIBLE FOR PTC124

The Phase 2a Extension study in Cincinnati is restricted by its protocol to the 26 patients who participated in the 28-day Phase 2a study. Those patients will receive PTC124 for 96 weeks. PTC now argues that Jacob did not qualify for the

[1] PTC erroneously contends that there are other reasons why Jacob does not qualify for the Extension. This is addressed in Point II of Plaintiffs' Reply, at pp. 4-6.

earlier Cincinnati study because Dr. Finkel from the University of Pennsylvania, who has never examined Jacob, determined in 2006 that Jacob has Becker Muscular Dystrophy ("BMD"), not DMD. Opp. at 14. Had Dr. Finkel actually examined Jacob – like Dr. Brenda Wong, the Primary Investigator from Cincinnati study, did – he would have determined that Jacob was eligible, and could have been in the Cincinnati trial. Dr. Wong has examined Jacob multiple times (the most recent being last week), has confirmed that Jacob has DMD, and has noted that prior physicians failed to undertake the appropriate tests:

> Although Jacob has been labeled as a Becker Muscular Dystrophy, he **clearly** has the phenotype of a patient with **Duchenne** Muscular Dystrophy with regards to his presentation and the profile of his declining motor function to the loss of independent ambulation at age 15½...Apparently, no quantification of dystrophin was done with Western blot or immunobloting studies. Such immunochemical staining has been seen in our clinic patients with **Duchenne** Muscular Dystrophy. MRI muscle done at this visit...and DEXA studies...are also consistent with a diagnosis of **Duchenne** Muscular Dystrophy. The age at loss of ambulation at 15½ is quite consistent with **DMD** patients treated with daily steroids...**I discussed with mom the option of discontinuing gentamicin especially in the light of up coming PTC124 clinical trials.**

Gunvalson Decl. Exh. N, pp. 3-5. She noted that Jacob had no "racing heart" and his kidney function was normal. Id. pp. 2, 4. Nothing in Dr. Wong's report says that Jacob would not qualify. Dr. Finkel's misdiagnosis of Jacob should not be used by PTC to excuse its promises and exclude Jacob from his only hope for life.

PTC alternatively argues, referring again to Dr. Finkel, that the Gunvalson family chose *on their own* to forego the initial 28-day trial. First, Finkel admits

that he advised Cheri to do this, Finkel Aff. ¶7, and PTC's own officers further belie that claim. Ms. Hirawat, PTC's Senior Vice President, swears that at her first meeting with Ms. Gunvalson several years ago, Cheri expressed the desire for immediate access to PTC124 and since that time she was "uniquely" relentless in her effort to get access to it. Hirawat Aff. ¶¶17-19. Dr. Peltz, PTC's CEO, swears that Cheri cornered him after the Phase 2a trial commenced and asked why Jacob was not in a trial. Peltz Aff. ¶16. Jacob has always wanted access to PTC124, and but for a mistaken exclusion from the 28-day trial, he would be getting it.

III. PTC124 IS SAFE ENOUGH FOR COMPASSIONATE USE

PTC repeatedly asserts that PTC124 either is not safe or that PTC has safety concerns. See, e.g., Opp. at 2, 7-8, 13. PTC misleads the Court on multiple fronts. First, PTC124 has been used to treat patients with nonsense mutations for both DMD and Cystic Fibrosis ("CF"). PTC has conducted numerous clinical trials, for both DMD and CF. Yet nowhere in PTC's brief does it discuss the various CF trials it has conducted and the safety data from them. The simple fact is that PTC, as demonstrated by its governmental submissions and press releases on its web site, has conducted Phase I clinical trials with PTC124, Phase 2 and Phase 2a clinical trials with PTC124 for DMD, and multiple national and international clinical studies of PTC124 for CF. See Wolin Decl. Exhs. E-J. Under a protocol exception, Jacob would be treated the same as all patients in the study. Thus, if it

is safe enough for them, then it is safe enough for Jacob.

Second, PTC argues that the clinical trials for PTC124 have been only for 14 to 28 days. *See* Opp. at 6-7. Indeed, one international study of PTC124 in Israel lasted for 3 months. For that study, PTC has stated, "PTC124 was generally well tolerated, resulting in excellent mean compliance with the treatment regimen". Wolin Decl. Exh. J. However, this is all conspicuously absent from PTC's brief.

Third, PTC's positive report on the 3-month trial is entirely consistent with its earlier press releases concerning other clinical trials. See id. Exh. E ("...there were no safety concerns identified in patients' physical examinations"), F (finding "supportive safety data in more than 50 patients participating in Phase 2 trial program"), G ("these results add to the growing body of safety data for PTC124 which has now been evaluated in more than 150 subjects...The safety profile has consistently shown that PTC124 appears well tolerated"), H ("Coupled with the emerging safety profile of PTC124, these data provide the impetus for moving forward rapidly to initiate longer-term studies..."), I ("we believe that the safety profile of PTC124...clearly support[s] the initiation of this longer-term...study").

PTC's brief also completely ignores 21 C.F.R. §312.34(a), which states that one of the primary purposes of "compassionate use" exceptions "is to obtain additional data on the drug's safety[.]" Providing Jacob with a protocol exception would provide PTC with valuable data that it implies it now lacks. PTC also fails

to address PTC124's "fast track" status, meaning the FDA determined that PTC124 "is reasonably likely to predict clinical benefit," 21 U.S.C. §356(b)(1), or that Genzyme has already paid PTC $100 million for a drug PTC now argues may be unsafe. The inescapable conclusion is that PTC's "spin" on PTC124's safety to this Court is radically different than what it represented to the FDA and Genzyme.

Finally, the key cases relied upon by PTC are easily distinguished. In Abney v. Amgen, 443 F.3d 540, 552 (6th Cir. 2006), the defendant, unlike PTC, provided "clinical evidence indicating that there may be scientific reasons to be concerned about the safety of" the drug, and the FDA agreed that the studies should be terminated. Here, to the contrary, all evidence regarding the safety of PTC124 is positive and the FDA continues to approve additional studies. Moreover, Abigail Alliance v. Von Eschenbach, 495 F.3d 695, 701 (D.C. Cir. 2007), merely determined there was no constitutional right to drugs that had gone only through a Phase I clinical trial. By contrast, between DMD and CF, PTC124 has gone through at least 7 clinical trials, all with positive data.

In short, PTC has put no evidence before the Court that PTC124 is not safe, and all available evidence supports that it is. Therefore, PTC should not be able to use that as basis to deny Jacob access to it.

IV. PTC CONTINUALLY STRUNG ALONG THE GUNVALSONS

Each of PTC's affiants has a financial tie to the company. Even its ethicist

is a professor at a university that has received substantial sums of money in connection with PTC's research. The only affiant who is truly independent is Dr. John Parkin, who swore under oath that he heard Claudia Hirawat promise that PTC would give Jacob access to PTC124. Parkin Decl. ¶7.

Indeed, approximately 25 e-mails were submitted with the various affidavits and numerous communications between Cheri and PTC executives exist, yet those relied upon by PTC never say that Jacob is foreclosed from getting PTC124 as PTC claims. Instead, each dangles eventual treatment. See Hirawat Aff. Exh. F (not enough data "at this time"); Miller Aff. Exh. H (plan to be in touch with Dr. Parkin in early 2007 to discuss access); Goetz Aff. Exhs. B (trying to find way for Jacob to participate in another study), C ("we're saying no because we're trying to create an even better yes. When it's all over you'll know exactly what I mean and why"). In January 2008, Dr. Lee Sweeney, Director of the University of Pennsylvania's Center of Excellence, emailed Cheri: "As far as I can tell, they are planning to include Jacob in the 2A extension." Supp. Gunvalson Decl. Exh. A. Not until April 2008 did PTC tell Cheri that Jacob may never get PTC124.

PTC's promises are no less binding simply because they strung along the Gunvalsons, as made clear in a case PTC relies upon:

> CIGNA also maintains that it made no representations to Tiberi upon which he could reasonably rely for the purposes of equitable estoppel. CIGNA claims that the statements that its promises to correct COMPAR's problems were so vague, and left unfulfilled for such a long period of time, that Tiberi

> could not have relied on them. In essence, CINGA argues that the court should not allow equitable estoppel to attach because it was not serious about the promises it made to Tiberi. This would allow CIGNA 'to profit from its own fraud.' Such a result is inherently inequitable.

Alexander v. CIGNA Corp., 991 F. Supp. 427, 439 (D.N.J. 1998) (quotation omitted). Indeed, the closest factual scenario to PTC's promises of access remains Dahl v. Hem Pharms. Corp., 7 F.3d 1399, 1401 (9th Cir. 1993), which holds that a promise to provide an investigational drug is enforceable.

V. PLAINTIFFS ARE LIKELY TO SUCCEED ON THEIR CLAIMS

PTC's promises were clear and definite. Ms. Hirawat's guarantee that Jacob's non-enrollment in the Phase 2a trial would not preclude him from future ones is abundantly clear. Similarly, PTC's repeated promises, by different employees, that it would provide Jacob PTC124 can be interpreted no other way. Clear statements are enforced despite missing details if the promise is clear without them. Peck v. Imedia, Inc., 293 N.J. Super. 151, 168 (App. Div. 1996) (promissory estoppel based on "reasonable reliance on full-time employment" despite at-will status); Jenkins v. Region Nine Housing Corp., 306 N.J. Super. 258, 263-65 (App. Div. 1997) (same). None of PTC's cited cases dispute this, instead only illustrating that a promise is not "clear and definite" if it is too vague, see Carthan v. Alliance, 2007 WL 316464, at *5-6 (D.N.J. Jan. 29, 2007) (discussion about serving as carrier not enough to support damages for tractor-trailer and insurance when no promises were made as to any work at all); it is qualified or contingent,

see Malaker Corp. v. First Jersey Nat'l Bank, 163 N.J. Super. 463, 479-80 (App. Div. 1978) (no guarantee of loan, with statement collateral would be required); or no specific promise is identified, Automated Salvage v. NV Koninklijke, 106 F. Supp. 2d 606, 622 (D.N.J. 1999) (multiple misrepresentations do not amount to "single concrete promise"). Taken to its logical conclusion, PTC's argument, that its promises were not sufficient because they lacked duration or timing, would preclude the nephew in Hamer v. Sidway who refrained from all vices from recovering his uncle's windfall because the date and method of payment were never specified. To be sure, PTC's promises were sufficiently clear and definite.

Further, PTC's false promises to the Gunvalsons were not "opinions or expectations," "conditional and contingent" or "truthful present intentions." Promissory estoppel applies if a defendant makes a clear promise and then reneges on it in the future, as did PTC. Royal Assocs. v. Concannon, 200 N.J. Super. 84, 88-91 (App. Div. 1985) (promise tenants could keep dog "so long as they took care of it" enforced to stop later eviction). PTC's cases do not address its clear promises, but instead concern "puffery," see Alexander, 991 F. Supp. at 436 ("COMPAR would take CIGNA into the twenty-first century and beyond"); contained a reservation of rights, Del Sontro v. Cendant Corp., 223 F. Supp. 2d 563, 575 (D.N.J. 2002) (promise explicitly reserved right to rescind or alter terms); made clear they were not guarantees, see Kopp v. United Techs., 223 N.J. Super.

548, 553 (App. Div. 1988); or concern a scienter element necessary only for a fraud damages claim,[2] see CapitalPlus Equity v. Prismatic Dev. Corp., 2008 WL 2783339, at *8 (D.N.J. July 16, 2008).

The Gunvalsons' reliance was reasonable. To claim it was not, despite Ms. Hirawat's response to specific questions from Cheri and repeated promises by multiple, high-ranking employees for the only company developing a drug for Jacob's condition, is disingenuous. PTC's brief tacitly admits that it, not the investigators, chooses trial protocols. PTC officials developed close relationships with Cheri, even going so far as to host her at one's home, and provided direction concerning life-altering medical decisions. PTC made these statements directly and individually to the Gunvalsons, not as broad press releases to the public like those in footnote 19 of PTC's Opposition. Even now, PTC claims sole authority to allow Jacob PTC124. See Opp. at 9. The Gunvalsons reasonably relied upon PTC, and based on the same actions, PTC owed them an explicit duty of care.

Jacob will suffer irreparable harm without an injunction. PTC's arguments to the contrary are offensive. Jacob is dying; there is no other treatment

[2] Without citation, PTC deceptively claims that Plaintiffs must prove additional, unnecessary elements on their fraudulent misrepresentation claim, Opp. at 22 & n.13, but neither scienter nor intent is required when seeking equitable relief. Jewish Ctr. v. Whale, 86 N.J. 619, 625 (1981). Similarly, neither is required for Plaintiffs' other two claims, although the facts show they are present nonetheless.

for his condition.[3] In about a year, he went from walking to being unable to hold a glass of water. All available data supports PTC124's efficacy, and PTC124 represents an excellent (and the only) opportunity for Jacob to extend his life.

VI. THERE ARE NO PUBLIC POLICY CONCERNS PRESENT

PTC, without any evidentiary showing whatsoever, claims that permitting Jacob access to PTC124 would jeopardize the Phase 2b study and would be unfair. PTC's argument completely misses the point.

Jacob cannot jeopardize the Phase 2b study because he does not qualify for it. There is a critical difference between Jacob and the Phase 2b patients, who must be able to walk under that study's inclusion criteria. Jacob has been unable to walk for 1½ years. Ineligibility aside, PTC ignores a more significant point: Jacob's condition is much worse than the Phase 2b candidates. Because DMD is progressive, they all have something Jacob does not: more time. PTC's Diane Goetz told Cheri "no" to a compassionate use so PTC can "create a better yes". Goetz Aff. ¶9. Now Goetz says the "better yes" means Jacob must wait for the additional clinical trials from which he is excluded to conclude. Id. ¶6. The Phase

[3] Contrast Jacob's situation with the cases cited on page 26 of PTC's brief. Both Smith v. Shalala, 954 F. Supp. 1, 3 (D.D.C. 1996), and Graham v. Med. Mut. Of Ohio, 130 F.3d 293, 296-97 (7th Cir. 1997), found irreparable harm lacking only because plaintiffs failed to undergo other accepted and effective treatments for their illness, and because Smith had already tried the experimental drug for some time without any benefit. In Zervos v. Verizon N.Y., 2001 WL 253377, at *7 (S.D.N.Y. Mar. 14, 2001), studies had actually concluded the drug was "ineffective and potentially harmful."

2a extension runs for 96 weeks and the Phase 2b study will be finish in August 2010. Hatch Decl. Exh. 8. How is it a "better yes" if Jacob doesn't live that long?

Moreover, the FDA's Dr. Russell Katz made it clear that "a protocol exception allows some patients who are ineligible to participate in a study to be treated with the investigational drug." Gunvalson Decl. Exh. L. This echoed Dr. Robert Temple, FDA Associate Director for the Center for Drug Evaluation, who in a 2001 statement to the House Committee on Government Reform explained:

> In cases where a patient cannot be enrolled in an existing protocol because of some factor that makes the patient ineligible to participate in the study, research sponsors often can make a protocol exception to treat the patient.

Wolin Decl. Exh. D. Patients in a clinical trial and those with protocol exceptions are in mutually exclusive categories, and therefore, it a fallacious concern that providing Jacob a protocol exception will damage the clinical trials. The FDA regulatory structure prevents the alleged harm that PTC articulates from occurring.

Even assuming, that the categories were not mutually exclusive, if PTC permitted Jacob access to PTC124, the Phase 2b trial would not be jeopardized because the FDA - not PTC or its ethicist - must approve the compassionate use before it is implemented and the FDA has the ability to put it on a clinical hold. 21 C.F.R. §312.42(b)(3). Thus, if the clinical trials become hindered by an inordinate number of compassionate use applications, the FDA itself would put a stop to it.

Here, however, there is no such problem. PTC asserts that there are about

1,690 boys with Jacob's condition. Opp. at 8. While this may be statistically accurate, PTC offers no proof whatsoever that any children besides Jacob are being turned away from clinical trials and/or compassionate uses. There a number of reasons for this. See Pl. Brf. at 23. Indeed, PTC admits that since February 2008 it has been unable to fill the Phase 2b study with 165 participants, Opp. at 28, even though it spans 11 different countries. Simply put, DMD is a very rare disease and therefore, there are extremely few, if any, boys in Jacob's unfortunate position.

Finally, PTC's argument that providing Jacob with a protocol exception will not serve the public interest is utter nonsense. Indeed, by providing PTC124 to Jacob, PTC would receive additional data regarding both the safety and efficacy of the drug, thereby providing it with more information that will enable it to bring its product to market quicker. Nothing could serve the public interest more.

CONCLUSION

For the foregoing reasons and those in their initial brief, plaintiffs respectfully request that the Court grant their motion for a preliminary injunction.

Respectfully submitted,

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