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UNITED STATES COURT OF APPEALS

FOR THE SIXTH CIRCUIT

EDWARD ABNEY, BARBARA ALLEN, JAMES DAY, ROBERT GREEN, DELBERT JACKSON, JAMES PUGH, ROGER L. THACKER, and DANIEL HUNTER WEBSTER,

Plaintiffs-Appellants,

v.

AMGEN, INC.,

Defendant-Appellee.

No. 05-6132

Appeal from the United States District Court
for the Eastern District of Kentucky at Lexington.
No. 05-00254—Joseph M. Hood, Chief District Judge.

Argued: February 1, 2006

Decided and Filed: March 29, 2006

Before: MARTIN, NORRIS, and DAUGHTREY, Circuit Judges.

COUNSEL

ARGUED: Alan C. Milstein, SHERMAN, SILVERSTEIN, KOHL, ROSE & PODOLSKY, Pennsauken, New Jersey, for Appellants. Mark D. Gately, HOGAN & HARTSON, L.L.P., Baltimore, Maryland, for Appellee. **ON BRIEF:** Alan C. Milstein, SHERMAN, SILVERSTEIN, KOHL, ROSE & PODOLSKY, Pennsauken, New Jersey, for Appellants. Mark D. Gately, Lauren S. Colton, HOGAN & HARTSON, L.L.P., Baltimore, Maryland, Winston E. Miller, FROST, BROWN, TODD, LLC, Louisville, Kentucky, Keith Moorman, Susan J. Pope, FROST, BROWN, TODD, LLC, Lexington, Kentucky, Catherine E. Stetson, Michele W. Sartori, HOGAN & HARTSON, L.L.P., Washington, D.C., for Appellee.

MARTIN, J., delivered the opinion of the court, in which DAUGHTREY, J., joined. NORRIS, J. (p. 12), delivered a separate opinion concurring in the result.

OPINION

BOYCE F. MARTIN, JR., Circuit Judge. The plaintiffs in this case are eight individuals involved in a clinical drug trial sponsored by Amgen, Inc. When the study was terminated, the plaintiffs sued claiming that Amgen was legally required to continue providing them with the drug. The plaintiffs filed a motion for a preliminary injunction seeking to require Amgen to provide them with the drug immediately. The district court denied the motion and the plaintiffs appealed. For the reasons discussed below, we AFFIRM the district court's denial of the plaintiffs' motion for a preliminary injunction.

I.

The plaintiffs are all Kentucky residents that suffer from Parkinson's disease, a neurogenerative disorder characterized by the progressive loss of dopamine-producing neurons in the brain, resulting in tremors, shaking, slow movement, and muscle stiffness and rigidity. The current treatment for Parkinson's disease focuses on replacing dopamine in the brains of Parkinson's disease sufferers, thus masking the symptoms of the disease. None of these current treatments are curative, however, as none of them halt the loss of dopamine-producing neurons.

A Colorado biotechnology company named Synergen, Inc. designed a protein called gial cell-line derived neutrotropic factor, commonly known as GDNF, which pre-clinical (non-human) studies preliminarily indicated could protect and restore dopamine producing neurons. Believing that GDNF could potentially provide a breakthrough treatment for Parkinson's disease, Amgen purchased Synergen in 1994 for approximately $150 million. Having acquired the drug, however, Amgen was now faced with the problem of how to effectively deliver GDNF to the brain. In 1996, Amgen sponsored two clinical studies of GDNF to determine whether a delivery method known as intracerebroventicular administration (ICV), in which the drug is injected directly into the central fluid-filled cavities of the patient's brain, was effective. Unfortunately, these studies failed to prove that ICV was safe or effective as a delivery method.

Subsequently, Dr. Steven S. Gill of Frenchay Hospital in Bristol, England developed a means of delivering the drug directly to the brain known as bilateral intraputaminal (IPu) infusion. This procedure involves implanting a pump filled with GDNF in the patient's abdomen attached to catheters which, when threaded through the patient's check, neck, and head, deliver the GDNF directly to the putamen region of the brain.

In 2000, Amgen supported an open-label trial in the United Kingdom for the administration of GDNF using IPu with five patients suffering from Parkinson's disease. Although the study yielded favorable results because the study was open-label, meaning study participants knew they were receiving GDNF and no participants received a placebo, Amgen concluded that more research was necessary. Another open-label study was also conducted at the University of Kentucky medical center in which GDNF was administered via IPu to ten patients.[1] All ten of these patients showed benefits after six months of treatment but, it was unclear whether this improvement was the result of the GDNF or a placebo effect as there was no control group in the study.

[1]The study was originally designed and initiated by physicians at the University of Kentucky. In September 2002, however, Amgen became a sponsor of the study, meaning it funded the study and provided the study drug.

Based on the result open-label studies, in 2003 Amgen sponsored a multi-center Phase II, randomized, double-blind,[2] placebo-controlled study of GDNF using the IPu method of delivery in order to test its safety and efficacy. As part of this study, Amgen and the University of Kentucky entered into a Clinical Trial Agreement. Under the Agreement, Amgen agreed to sponsor the University as one of the study center locations and the University agreed to carry out Amgen's Protocol for the trial. Amgen's Protocol, which was approved by the Institutional Review Board at the University, indicated that the trial would begin with each participant having a pump inserted in their abdomen and the catheter inserted through a hole drilled in their skull. The participants would then receive treatment or a saline placebo solution for approximately thirty-three weeks. At the end of the study, the Protocol indicated that the participants "may elect to continue treatment for up to an additional 24 months."

The plaintiffs in this case elected to participate in the clinical trial at the University. Each plaintiff signed an Informed Consent Document, indicating that they were aware of the risks of the clinical trial and agreeing to participate. Like the Protocol, the Informed Consent Document indicated that study participants could elect to continue treatment for 24 months after the end of the study. The Informed Consent Document also informed participants in the study that they might be required to withdraw from the study "if they find that your being in the study is more risk than benefit to you, if you are not able to follow the directions they give you, or if the agency funding the study decides to stop the study early for a variety of reasons." The Informed Consent Document was signed by each participant and by the physician investigators leading the study.

Using the Unified Parkinson's Disease Rating Scale,[3] Amgen hoped to see a 25% increase in motor scores relative to the placebo after six months of treatment. In June 2004, the study results showed only a 10.01% increase in the group using GDNF and a 4.52% increase in the group being administered the placebo. Seven of the thirty-four subjects demonstrated dramatic improvement, but four of the seven were receiving the placebo.

Despite these less than stellar results, Amgen decided to continue with the clinical trial but convert it into an open-label study with all thirty-four patients receiving GDNF. The plaintiffs contend that after GDNF was administered, they experienced marked physical, cognitive, and emotional improvement. The plaintiffs also have submitted affidavits from several patients from other study locations attesting to similar improvements. Moreover, the plaintiffs have submitted affidavits from all of the doctors participating in the University of Kentucky study and principal investigators involved in the New York and Chicago studies that unanimously state that GDNF is safe and effective.

Despite the plaintiffs' belief that GDNF was working, in September 2004, Amgen announced that it was terminating all clinical use of GDNF based on two scientific concerns. The first was the discovery that several study participants had developed neutralizing antibodies. Antibodies are proteins produced by the immune system that attack substances such as viruses, bacteria, and in some cases, synthetic proteins like GDNF. Such neutralizing antibodies could clear the drug from a patient's system, neutralizing the effects of the drug. More worrisome to Amgen, however, was that the antibodies could attack naturally occurring GDNF in the body. While it is unclear what naturally occurring GDNF does, animal studies have shown that an absence of GDNF during development causes irreversible damage to vital organs.

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[2]This means that neither the patient volunteers nor the physician investigators know which patients are receiving the study drug and which patients are merely receiving the placebo.

[3]UPDRS is a standard instrument widely used to determine the severity of a patient's Parkinson's disease. It measures a patient's behavior, mood ability to accomplish daily activities, and motor skills.

The second disturbing discovery was that several primates used in a long-term toxicology study of IPu delivered GDNF developed lesions in the cerebullum, an area of the brain critical for movement and coordination. Based on these concerning scientific findings along with the lack of efficacy shown by the study, Amgen made the decision to terminate the study. Amgen consulted the FDA regarding discontinuation of the study and the FDA indicated that given the evidence termination of the study was reasonable.

The plaintiffs claim that the drug is effective and that Amgen has exaggerated the safety risks of GDNF. The plaintiffs submitted to the district court an affidavit from the principal investigator of the New York study suggesting that the primates's legions were not a cause for alarm as the primates received larger doses of GDNF than study participants received and because the primates, unlike the study participants, were rapidly withdrawn from GDNF. The affidavit also disagreed with Amgen's placebo effect theory and asserted that the antibodies found in several study participants were not harmful.

The plaintiffs assert that Amgen's reasons for ending the study were financial rather than safety and efficacy. They allege that because of the prolonged time it took Amgen to develop a delivery method for GDNF, Amgen has little time left before its patent on the drug expires. Moreover, based on the invasive means of delivering the drug, only those with severe Parkinson's disease would use the drug, leading to less profit. Finally, GDNF has a short shelf life and thus Amgen would constantly be required to produce new proteins. The plaintiffs claim that all of these considerations led Amgen to conclude that it was financially untenable to bring the drug to market and thus Amgen terminated the study. Amgen vehemently disputes the plaintiffs' claims.[4]

After deciding to terminate the study, several investigators and Amgen met with the FDA to consider whether to permit "compassionate use," meaning use of a drug even if the drug is proven unsafe, of GDNF for the participants. The FDA stated that it would permit compassionate use of GDNF but left the decision up to Amgen. After seeking advice of eight external experts (three bioethicists and five Parkinson's disease experts), seven of whom advised Amgen to terminate the use of the drug, Amgen decided not to allow compassionate use of GDNF.

The plaintiffs filed suit on June 17, 2005, naming Amgen as the sole defendant. The district court had jurisdiction based on diversity of citizenship, and none of the plaintiffs' causes of action arise under federal law. On June 24, the plaintiffs moved for a preliminary injunction requiring Amgen to provide the physicians at the University of Kentucky with GDNF and to allow the doctors to administer it to the plaintiffs. None of the plaintiffs have received GDNF treatment since September 2004.

The plaintiffs advanced three legal theories to support their motion for a preliminary injunction. First, they claimed that GDNF is beneficial to them, and that Amgen is contractually obligated to supply them with GDNF. Second, they argued that Amgen is liable under a theory of promissory estoppel as Amgen promised to continue to provide the plaintiffs with GDNF and the plaintiffs detrimentally relied on this promise. Third, they asserted that Amgen owes them a fiduciary duty, and that is has breached that duty by unreasonably denying them access to GDNF. In response, Amgen denied that it made any such enforceable promises to the plaintiffs and denied owing the plaintiffs any fiduciary duty.

The district court held a hearing on the plaintiffs' motion on July 5 and on July 8 denied the motion. The district court concluded that the plaintiffs had failed to demonstrate a strong likelihood

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[4]Amgen submitted evidencing disputing the plaintiffs' claims regarding the safety and efficacy of GDNF. Moreover, Agmen submitted evidence indicating that it would have been in the company's best financial interest to bring GDNF to market quickly.

of success on the merits based on any of their claims. The district court also concluded that the plaintiffs could not prove that they would suffer irreparable harm if they did not obtain a preliminary injunction nor could they establish that public policy would be furthered by issuing the injunction. Thus, the district court denied the plaintiffs' motion for a preliminary injunction. This appeal ensued.

The district court's decision to deny the plaintiffs' motion for a preliminary injunction relied in part on a decision from the Southern District of New York in a nearly identical case, *Suthers v. Amgen, Inc.*, 372 F. Supp. 2d 416 (S.D.N.Y. 2005). In *Suthers*, two Parkinson's disease sufferers who participated in the Amgen study at the New York University site filed suit against Amgen in the Southern District of New York and sought a preliminary injunction requiring Amgen to provide them with GDNF. The plaintiffs in *Suthers* advanced nearly identical legal claims as this case: breach of contract, promissory estoppel, and breach of fiduciary duty. The district court denied the plaintiffs' motion on grounds similar to the district court's reasoning here. Specifically, the *Suthers* court concluded that the plaintiffs "have shown neither a likelihood of success nor a sufficiently serious showing of merits to warrant the extraordinary relief of a preliminary injunction." *Id.* at 419. The court found that the plaintiffs' breach of contract claim was unlikely to succeed because the plaintiffs could not show any contract between the plaintiffs and Amgen. While their Informed Consent document arguably gave them a right to GDNF, the court concluded that this agreement was between the plaintiffs and New York University rather than the plaintiffs and Amgen, and that the principal investigators did not have the authority to bind Amgen. The court also concluded that the plaintiffs' promissory estoppel argument had little chance of success as Amgen had made no direct promises to the plaintiffs. Finally, the court held that under the facts of the case, Amgen did not have a fiduciary duty to continue treatment. As a result of these determinations the district court did not address whether the plaintiffs or the defendants would suffer irreparable harm based on the district court's decision. The plaintiffs in *Suthers* initially appealed the district court's decision but later withdrew their appeal.

II.

The plaintiffs assert that the district court erred in denying their motion for a preliminary injunction. We review a district court's grant of a preliminary injunction for an abuse of discretion. *Tucker v. City of Fairfield*, 398 F.3d 457, 461 (6th Cir.2005). "A district court abuses its discretion when it relies on clearly erroneous findings of fact, improperly applies the law, or uses an erroneous legal standard." *Id.* A district court errs "only if it incorrectly applied the law, or relied on clearly erroneous findings of fact." *Ramsey v. Formica Corp.*, 398 F.3d 421, 423 (6th Cir. 2005). We review the district court's conclusions of law de novo and its findings of fact for clear error. *Golden v. Kelsey-Hayes Co.*, 73 F.3d 648, 653 (6th Cir.1996).

To determine whether to grant a preliminary injunction, a district court must consider: "(1) the plaintiffs' likelihood of success on the merits; (2) whether the plaintiff may suffer irreparable harm absent the injunction; (3) whether granting the injunction will cause substantial harm to others; and (4) the impact of an injunction upon the public interest." *Deja Vu of Nashville, Inc. v. Metro. Gov't of Nashville & Davidson County*, 274 F.3d 377, 400 (6th Cir.2001). "None of these factors, standing alone, is a prerequisite to relief; rather, the court should balance them." *Golden*, 73 F.3d at 653. Thus, even though a finding of no likelihood of success "is usually fatal[,]" *Gonzales v. Nat'l Bd. of Med. Exam'rs*, 225 F.3d 620, 625 (6th Cir. 2000), a district court should ordinarily analyze all of the factors. *Leary v. Daeschner*, 228 F.3d 729, 739 n.3 (6th Cir. 2000). We will review the district court's analysis as to each of these factors in order to ensure that the district court did not abuse its discretion in denying the plaintiffs' motion for a preliminary injunction.

A.

The first factors to be considered is whether the plaintiffs have demonstrated a likelihood of success on the merits. The plaintiffs identify three grounds on which they allege that Amgen is legally obligated to provide them with GDNF — breach of contract, promissory estoppel and fiduciary duty. The district court concluded that the plaintiffs had little chance of success on any of these grounds. We find nothing in the record that suggests the district court abused its discretion in reaching such a conclusion.

i.

Turning first to the plaintiffs' breach of contract claim, the district court concluded that there was no breach of contract by Amgen because no contract ever existed between the plaintiffs and Amgen that required Amgen to continue to provide the plaintiffs with GDNF. The court found that the Informed Consent Document that the plaintiffs rely upon as evidence of a contract between them and Amgen did not directly bind Amgen because neither Amgen nor any agent of Amgen signed the Informed Consent Document. We find no abuse of discretion in the district court's conclusion on this point.

Under Kentucky law, "in order to recover in any action based on breach of a contract, a plaintiff must show the existence and the breach of a contractually imposed duty." *Lenning v. Commercial Union Ins. Co.*, 260 F.3d 574, 581 (6th Cir. 2001) (citing *Strong v. Louisville & Nashville R. Co.*, 43 S.W.2d 11, 13 (Ky. 1931)). Thus, the plaintiffs must show by clear and convincing evidence proof of an actual agreement between them and Amgen. *See Auto Channel, Inc. v. Speedvision Network, LLC*, 144 F.Supp.2d 784, 790 (W.D. Ky. 2001).

The plaintiffs admit that Amgen did not sign the Informed Consent Document, which the plaintiffs point to as the primary basis for their breach of contract claim. Moreover, there are no other documents that create a contractually enforceable duty for Amgen to continue to provide GDNF to the plaintiffs. The Clinical Trial Agreement was not signed by the plaintiffs but rather was signed by Amgen, the University of Kentucky, and the principal investigators. Thus, the plaintiffs' claim that Amgen is directly contractually obligated to provide the plaintiffs with GDNF is unlikely to succeed on the merits because "it is axiomatic that courts cannot bind a non-party to a contract because that party never agreed to the terms set forth therein." *EEOC v. Frank's Nursery & Crafts, Inc.*, 177 F.3d 448, 460 (6th Cir. 1999).[5]

Moreover, the principal investigators in the University of Kentucky study were not in a position to enter into a binding contract with the plaintiffs on Amgen's behalf, as the district court correctly concluded that the principal investigators were independent contractors rather than Amgen's agents. Under Kentucky law, whether a principal/agent relationship is created rather than merely a principal/independent contractor relationship is determined by examining the following factors:

> (a) the extent of control which, by the agreement, the master may exercise over the details of the work;
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> (b) whether or not the one employed is engaged in a distinct occupation or business;

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[5]Even if the Informed Consent Document or the Clinical Trial Agreement created a contract between Amgen and the plaintiffs, Amgen would still have no duty to provide the plaintiffs with GDNF. As the district court correctly noted, the Informed Consent Document allows Amgen to terminate the study for scientific reasons, which is at least arguably what occurred in this case. In addition, the Clinical Trial Agreement specifically allowed Amgen to terminate the agreement "immediately upon written notice."

> (c) the kind of occupation, with reference to whether, in the locality, the work is usually done under the direction of the employer or by a specialist without supervision;
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> (d) the skill required in the particular occupation;
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> (e) whether the employer or the workman supplies the instrumentalities, tools, and the place of work for the person doing the work;
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> (f) the length of time for which the person is employed;
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> (g) the method of payment, whether by the time or by the job;
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> (h) whether or not the work is a part of the regular business of the employer; and
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> (i) whether or not the parties believe they are creating the relationship of master and servant.

Sam Horne Motor & Implement Co. v. Gregg, 279 S.W.2d 755, 756-757 (Ky. 1955). Of these factors, the most critical element in determining whether an agency relationship exists is whether the alleged principal has the right to control the details of the agent's work. *Grant v. Bill Walker Pontain-GMC, Inc.*, 523 F.2d 1301, 1305 (6th Cir. 1975); *Bottled Gas, Inc. v. Borg Warner Corp.*, 56 F.3d 726, 736 (6th Cir. 1995).

Here, the above factors suggest that the district court did not abuse its discretion in concluding that the plaintiffs had little chance of success based on their agency theory of contract liability. As the district court properly pointed out: "The [Clinical Trial] Agreement provides that the 'Institution agrees to act as an independent contractor without the capacity to legally bind Amgen and also agrees that it is not acting as an agent or employee of Amgen.' Because the Kentucky doctors were employees of the University of Kentucky, they too were independent contractors lacking the power to bind Amgen." *Abney v. Amgen, Inc.*, No. 5:05-CV-254-JMH, 2005 WL 1630154 (July 8, 2005 E.D.Ky.) (citing *Berry v. Delta Airlines, Inc.*, 260 F.3d 803, 812 (7th Cir. 2001), for the proposition that "an employee of an independent contractor typically cannot be considered an agent of the employer").

Other factors also indicate that the principal investigators were independent contractors and not agents of Amgen. The set up of the Kentucky study, consistent with federal regulations, left the principal investigators in charge of the details of the work. *See* 21 C.F.R. § 312.60 (indicating that in a clinical drug trial "[a]n investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation."). Furthermore the principal investigators drafted and implemented the Protocol for the study themselves, not Amgen. Moreover, the doctors were highly specialized professionals with extensive experience in their field. The study took place at the University of Kentucky, not at an Amgen facility. The University also received a set amount of money from Amgen as a result of the study. Finally, as the documents regarding the study indicated, the study was structured such that Amgen's sponsorship of the study would be independent of control over the study. Thus, the above factors indicate that the district court did not abuse its discretion in concluding that it was unlikely that any direct agency relationship existed between Amgen and the University of Kentucky or its physicians.

Moreover, the record suggests that the district court was similarly correct in concluding that it was unlikely that the principal investigators had any apparent authority to bind Amgen. Apparent authority, which may be possessed by an independent contractor, is "the authority the agent is held

out *by the principal* as possessing. It is a matter of appearance on which third parties come to rely." *Mill St. Church of Christ v. Hogan*, 785 S.W.2d 263, 267 (Ky. Ct. App. 1990) (emphasis added). Nothing in the record nor in the plaintiffs' brief demonstrates any representations made *by Amgen to the plaintiffs* that could have led the plaintiffs to believe that the principal investigators were agents of Amgen for purposes of the study. Nothing suggests that Amgen even had any contact with any of the plaintiffs as it was the principal investigators who controlled the study and were in charge of the plaintiffs' care. Thus, the district court did not abuse its discretion in concluding that the plaintiffs' claim based on apparent authority had little chance of success on the merits.

ii.

The plaintiffs' second claim is that Amgen is legally required to provide them with GDNF based on promissory estoppel. The plaintiffs' promissory estoppel argument is premised on their claim that the principal investigators informed them that they would make decisions based upon the patients's best interests and that if GDNF proved to be safe and effective, study participants could continue to receive the medication following termination of the study. The district court concluded that "the plaintiffs have not shown a strong likelihood of success on the merits because the plaintiffs have not submitted any evidence of a clear promise by Amgen." The district court did not abuse its discretion in reaching such a conclusion.

Promissory estoppel requires "(1) a promise; (2) which the promisor should reasonably expect to induce action or forbearance of a definite and substantial character on the part of the promisee; (3) which does induce such action or forbearance; and (4) injustice can be avoided only by enforcement of the promise." *Bergman v. Baptist Healthcare Sys., Inc.*, 344 F. Supp. 2d 998, 1003 (W.D.Ky. 2004) (analyzing Kentucky law). Where there is no evidence of a promise, promissory estoppel cannot be established.

In this case, there is no evidence of a promise by Amgen to continue to provide the plaintiffs with GDNF following the termination of the study. The plaintiffs do not assert that Amgen directly promised to continue to provide them with GDNF. Instead, they assert that the principal investigators promised that the plaintiffs would continue to receive the medication and that subsequently Amgen is bound by those promises. This theory is untenable, however, because, as discussed above, neither the University of Kentucky nor the principal investigators were agents of Amgen. There is also no evidence that the University or the principal investigators had the apparent authority to bind Amgen via their promises to the plaintiffs. As a result, the district court did not abuse its discretion in concluding that there is little chance that the plaintiffs will succeed on the merits of this claim.

iii.

The plaintiffs' final claim is that Amgen, working through the principal investigators, breached its fiduciary duty to ameliorate their pain and treat their illness with the best medicine available. The district court held that Amgen had no fiduciary duty to continue to supply the plaintiffs with GDNF. The district court did not abuse its discretion in concluding that the plaintiffs' likelihood of success on this claim is minimal.

Under Kentucky law, while there is no set formula for determining whether a fiduciary duty exists, "as a general rule, [courts] can conclude that such a relationship is one founded on trust or confidence reposed by one person in the integrity and fidelity of another and which also necessarily involves an undertaking in which a duty is created in one person to act primarily for another's benefit in matters connected with such undertaking." *Steelvest, Inc. v. Scansteel Serv. Ctr.*, 807 S.W.2d 476, 485 (Ky. 1991); *Layne v. Bank One, Ky., N.A.*, 395 F.3d 271, 281 (6th Cir. 2005). While "[f]iduciary relationships can be informal, [] they must evidence circumstances showing both

parties agreed that one party would be acting in the interest of the other." *In re Sallee*, 286 F.3d 878, 892 (6th Cir. 2002).

In this case, the record does not demonstrate that Amgen and the plaintiffs agreed that Amgen would be acting primarily for the benefit of the plaintiffs. Amgen had various reasons for the undertaking sponsorship of the University of Kentucky study. While benefitting the plaintiffs could arguably be described as one of those reasons, there is nothing to suggest that the parties agreed that this would be the primary reason for Amgen's sponsorship of the study. Thus, the district court did not abused its discretion in concluding that there is no evidence Amgen has a fiduciary duty to the plaintiffs.

The plaintiffs cite *Grimes v. Kennedy Krieger Institute, Inc.*, 782 A.2d 807 (Md. 2001), in support of their fiduciary duty claim. *Grimes*, however, is distinguishable from this case as the district court correctly decided. The manner in which the district court in *Suthers* distinguished *Grimes* from Amgen's GDNF study is helpful:

> In *Grimes*, the Maryland Supreme Court found that medical researchers owed a duty sounding in tort to children whose parents had been induced to live in homes containing lead paint so that the paint's effects could be measured against a control population without such exposure. The researchers in *Grimes* designed the study, recruited the subjects, and obtained their consent. Understandably, the Maryland Supreme Court was concerned about a "vulnerable research subject" who may have been provided information to induce consent that was "incomplete in a material respect." *Grimes* concluded that there was a duty to the research subject independent of the consent, and that a consent form could not be utilized to immunize the researchers from liability. The *Grimes* court did not characterize the duty as that of a fiduciary or offer any other characterization.
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> The dissimilarities between this case and *Grimes* are many. Here, a therapeutic treatment was tested in a manner so that the tests would comply with FDA regulations. To avoid the potential that a pharmaceutical company with a financial interest in the outcome would place participants at risk of needless harm, independent research institutions and their physicians conducted the clinical trials. In *Grimes*, the participants were in direct contact and privity with the party who was found to have owed them a duty. Here no claim is asserted against the principal investigator [] with whom plaintiffs had their dealings.

Suthers, 372 F.Supp.2d at 427. This analysis applies with equal force to this case. Neither the *Grimes* case nor Kentucky case law suggests that Amgen had a fiduciary duty to the plaintiffs. Thus, the district court did not abuse its discretion in concluding that the plaintiffs had little chance of success as to this claim.

Although we express no ultimate view, it appears that the plaintiffs might have considered suit against the University of Kentucky's Institutional Review Board and the physician investigators involved in the clinical trial. It was the University that was legally bound by the Informed Consent Document and thus arguably legally obligated to continue to administer the treatment to the plaintiffs. Moreover, as discussed above, under the FDA's regulatory scheme it is not the pharmaceutical companies that are charged with ensuring trial participants' well being. Rather, it is the Institutional Review Board that is meant to "protect the rights and welfare" of trial participants during a clinical trial. 21 C.F.R. § 56.101 (requiring university conducting clinical trials to establish institutional review boards for the purpose of "protect[ing] the rights and welfare of human subjects involved in" clinical trials); *see also* 21 C.F.R. § 56.103 (requiring institutional review boards to approve all clinical trials before initiation and requiring continuing review of clinical trials while

they are being conducted). Thus, while the plaintiffs' arguments have little merit against Amgen, they may have merit against the University and its Institutional Review Board.[6]

B.

The second factors under the preliminary injunction test is whether the plaintiffs will suffer immediate and irreparable harm absent injunctive relief. The plaintiffs assert that absent a preliminary injunction they would suffer immediate, irreparable harm because without GDNF they allege that their health will continue to deteriorate as a result of their Parkinson's disease. The district court concluded that "the plaintiffs [] failed to meet their burden in proving that they would suffer immediate, irreparable harm if an injunction is not granted." While there is evidence in the record that supports the plaintiffs' claim, the district court did not abuse its discretion in concluding that the plaintiffs failed to show irreparable harm absent a preliminary injunction.

To demonstrate irreparable harm, the plaintiffs must show that unless GDNF treatments resumed immediately, they will suffer "actual and imminent" harm rather than harm that is speculative or unsubstantiated. *See Monsanto Co. v. Manning*, 841 F.2d 1126, 1998 WL 19169, at *6 (6th Cir. Mar. 8, 1998); *Heideman v. South Salt Lake City*, 348 F.3d 1182, 1189 (10th Cir. 2003) (citing *Wisconsin Gas Co. v. FERC*, 758 F.2d 669, 674 (D.C. Cir. 1985)). Here there is no question that the plaintiffs' health will continue to deteriorate as a result of their Parkinson's disease. Nonetheless, there is no guarantee that the plaintiffs' condition will improve or at least deteriorate at slower rate if they are prescribed GDNF. Admittedly, the plaintiffs have provided evidence suggesting that GDNF is effective. There is evidence in the record that the plaintiff subjectively felt an improvement in their symptoms after being administered GDNF. In addition, there is evidence in the record that the principal investigators believe GDNF to be a safe and effective treatment for the type of severe Parkinson's disease that the plaintiffs are afflicted with.

Nonetheless, there is also evidence in the record that rebuts the plaintiffs' claim that GDNF is safe and effective. Amgen has submitted clinical evidence indicating that there may be scientific reasons to be concerned about the safety of GDNF based upon: (1) cerebullum lesions developed by primates on GDNF and (2) neutralizing antibodies found in some patients taking GDNF. More importantly, there is evidence in the record suggesting that even if the plaintiffs were provided with GDNF their health might not improve. The clinical data submitted by Amgen suggests that GDNF adminstered via IPu proved ineffective in clinical trial. The data can arguably be read as indicating that any improvement in study participants was based merely on a placebo effect. Thus, in the record there is simply conflicting evidence as to whether GDNF would really prevent irreparable harm to the plaintiffs if immediately administered. Therefore the district court did not abuse its discretion in concluding that the plaintiffs failed to establish they would suffer irreparable harm absent a preliminary injunction.

C.

The third factor we must consider is whether substantial harm to others will occur if the injunction is granted. As to the third factor of the preliminary injunction test the district court concluded that "on balance, the court would side with the plaintiffs on this prong." Like the second

[6]Moreover, the litigation in this case indicates that the University, through its Informed Consent Document, and its other representations to the plaintiffs did a poor job informing the plaintiffs as to the grounds upon which the study would terminate and their access to GDNF would be denied. We urge the University's Institutional Review Board, and other review boards throughout the Circuit, to take additional measures to ensure that patients fully understand that even if they or their physicians believe an experimental treatment to be safe and efficacious there may circumstances under which they will be denied continued access to treatment. If this fact had been properly explained to the plaintiffs in this case prior to the outset of the clinical trial (and spelled out clearly in the Informed Consent Document) perhaps the litigation in this case could have been avoided.

factor, there is conflicting evidence on the record as to whether others would be harmed if the plaintiffs' motion for a preliminary injunction was granted. On the one hand, Amgen asserts several harms that it would face if a preliminary injunction was awarded, including: (1) exposing Amgen to future civil liability; (2) undermining Amgen's role as the sponsor of clinical trials under federal regulations requiring Amgen to terminate trials found to present unreasonable and significant risk to patients. On the other hand, these concerns are at least partially obviated by the plaintiffs' assertions that they will assume all risks of taking GDNF and the fact that the FDA informed Amgen that it would permit compassionate use of Amgen. Given that there is conflicting evidence in the record, we conclude that the district court did not abuse it discretion in finding that this factor weighed in the plaintiffs' favor.

D.

The final factor is whether the public interest would be served by granting the plaintiffs' motion for a preliminary injunction. Before the district court, the plaintiffs asserted that the public interest weighed in favor of granting the preliminary injunction because it should be physicians (who in this case the record suggests were in favor of compassionate use of GDNF) who decide whether a drug should be given to their patients and not pharmaceutical companies. The plaintiffs also claimed that a denial of their motion for an injunction would cause them unnecessary suffering thereby disrepecting human subjects and deterring other patients from participating in clinical trials. In response, Amgen claimed that forcing them to provide GDNF to the plaintiffs is contrary to the FDA's regulatory scheme and that it is up to the FDA, and not doctors or their patients, to determine whether a drug is safe and effective. The district court found that public interest was not served by granting an injunction in this case.

The district court's opinion made several insightful points regarding this prong. The district court acknowledged that there may be some deterrent concern as to patient participation in clinical trials if the plaintiffs are not provided with compassionate use of GDNF. The district court was quick to point out, however, that granting the plaintiffs' motion for a preliminary injunction could also deter pharmaceutical companies from sponsoring clinical trials as clinical trial sponsors might be required to continue to produce and distribute a drug they believed to be dangerous. Additionally, the plaintiffs' claim that physicians should be the sole arbiter of patient care wholly undermines the purpose and value of the FDA. The public has a strong interest in ensuring that the FDA rather individual doctors has the power to decide what drugs meet baseline levels of safety and efficacy. Thus, the district court did not abuse its discretion by concluding that the public interest would not be served by granting the plaintiffs' motion for preliminary injunction.

III.

Based on the analysis above, the district court did not abuse its discretion in the denying the plaintiffs' motion for a preliminary injunction. We therefore AFFIRM the district court's ruling.

CONCURRENCE

ALAN E. NORRIS, Circuit Judge, concurring in the result. I agree with the majority affirming the district court's denial of the plaintiff's motion for a preliminary injunction, with the exception of the inclusion in the opinion of the last paragraph of section A iii and footnote 6.