UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

JACOB GUNVALSON, CHERI and JOHN GUNVALSON as Guardians for Jacob Gunvalson, and CHERI and JOHN GUNVALSON, Individually,	:	
Plaintiffs,	:	District of New Jersey Index No. 08-cv-3559
- against -	:	
PTC THERAPEUTICS, INC.,	:	
Defendants.	:	

AFFIDAVIT OF LANGDON L. MILLER, M.D.

STATE OF NEW JERSEY)
) ss.:
COUNTY OF MIDDLESEX)

LANGDON L. MILLER, M.D., being duly sworn, deposes and says:

1. I am the Chief Medical Officer of defendant PTC Therapeutics, Inc. ("PTC"). I submit this affidavit on behalf of PTC in opposition to the motion of plaintiffs John Gunvalson and Cheri Gunvalson, in their capacity as guardians for Jacob Gunvalson, and Jacob Gunvalson, John Gunvalson and Cheri Gunvalson, individually, for a preliminary injunction forcing PTC to give Jacob Gunvalson access to PTC124 either (i) pursuant to a "protocol exception" permitting him to participate in an ongoing clinical trial for which he is ineligible; or (ii) for use in a proposed "single patient study" by his pediatrician, Dr. John Parkin. I make this affidavit on the basis of my own personal knowledge.

2. I joined PTC as Chief Medical Officer in July 2003. In that capacity, my responsibilities include providing input on the design of the various clinical trials for PTC124 conducted to date and those that are currently ongoing, analyzing the data generated from those trials, presenting those data to other members of the medical community, and obtaining funding necessary to facilitate the development and testing of PTC124.

3. PTC124 is currently under investigation to determine whether it is a safe and effective treatment for patients who have Cystic Fibrosis ("CF") or one of two types of Muscular Dystrophy: Duchenne Muscular Dystrophy ("DMD") or a less-aggressive form of muscular dystrophy known as Becker Muscular Dystrophy ("BMD"). The clinical trials for PTC124 that have been completed to date have yielded positive data suggesting that it demonstrates positive drug activity in some patients with these medical conditions, but those trials have not yielded sufficient data for us to conclude that PTC124 is an effective or safe treatment for any condition.

4. As set forth in greater detail below, enrollment is now ongoing for a pivotal long-term safety and efficacy study for PTC124 as a treatment for DMD and BMD. It is a fundamental axiom of all scientific endeavor, including this study, that to prove any given hypothesis, a study must assume at the outset and be governed by the assumption that the opposite hypothesis is true. Accordingly, because PTC's ongoing controlled clinical trials for PTC124 are designed to show that PTC124 is a safe DMD/BMD treatment that provides a discernible clinical benefit to patients at a given dose, these trials necessarily are governed by the "null" hypotheses that PTC124 is unsafe and ineffective at the dose that will be administered to trial participants. Unless and until the clinical data from this 48-week trial disprove the null hypotheses for PTC124, it is highly unlikely that PTC will ever be able to obtain the requisite FDA approval to market PTC124 as a treatment for DMD/BMD in the United States.

5. Providing PTC124 to Jacob Gunvalson at this stage of our clinical testing would be irresponsible and inconsistent with the underlying premise of our ongoing clinical trials program of the drug as not a safe and effective treatment for DMD/BMD. In essence, it would require PTC to take two diametrically opposed positions. As explained above, in connection with the ongoing trials, in which the null hypothesis must govern, PTC must take the position that the drug does not do what it is intended to do and that it is unsafe. However, if the company were now to make PTC124 available to Jacob Gunvalson, or anyone else with DMD/BMD outside of a trial, it could not do so without creating the perception that the drug is in fact both safe and effective.

6. This is to say nothing of the potentially drastic consequences in terms of PTC's ability to obtain FDA approval for PTC124 that would result if Jacob Gunvalson were given access to PTC as a result of filing this lawsuit. FDA regulations require that a company developing an investigational new drug conduct clinical trials that compare the safety and efficacy of that drug to either placebo (i.e., no treatment at all) or, alternately, another drug that is already on the market. In this case, because there is currently no other drug marketed for the treatment of DMD/BMD, PTC must test PTC124 in clinical trials that involve the administration of placebo to some trial participants to gain sufficient data to be in a position to seek FDA approval for PTC124 as a DMD/BMD treatment.

7. Enrollment in a pivotal clinical 48-week trial that complies with this requirement is currently underway. The subjects in this trial will be divided into three groups. Two of the groups will receive PTC124 (at two different doses), and the third group will receive placebo. This trial is an absolutely necessary step on our path to hopefully someday allow every young man with DMD/BMD who wants to take PTC124 to be able to do so. I applaud the strength,

courage, and compassion of the families who have made the decision to participate in this trial knowing full well that there is a one-third chance their children will receive no treatment at all for nearly a year. However, if the Gunvalsons prevail in this action, it is likely that many families would be unwilling to consider such trials going forward because they could obtain access to the drug through litigation.

8. Thus, if the Gunvalsons' motion were granted, it would compromise PTC's chances of obtaining FDA approval for PTC124 as a DMD/BMD treatment, and the thousands of boys with DMD/BMD who might someday benefit from PTC124 could ultimately lose.

9. I understand that the Gunvalsons have claimed that the population of DMD/BMD patients like Jacob who do not currently have access to PTC124 through a clinical trial is extremely small, and have even gone so far as to suggest that Jacob may be the only child without current access to the drug who might benefit from PTC124. This is untrue. On October 22, 2004, PTC submitted a request to the FDA for orphan drug designation for PTC124 as a treatment for DMD. A copy of PTC's October 22, 2004 Request for Orphan Drug Designation for PTC124 as Treatment for Duchenne Muscular Dystrophy is attached hereto as Exhibit A. Because orphan drug status is unavailable for drugs that will be used to treat more than 200,000 patients in the United States, PTC included in its request a calculation of the number of people in the United States who had the variant of DMD that PTC124 is intended to treat (that is, who had DMD due to a nonsense mutation) to show that PTC124 satisfied the requirements for orphan product designation. (*Id.* at 20.) According to PTC's calculations, in 2004 there were approximately 12,973 DMD patients in the United States, 13% of whom (approximately 1690) might benefit from PTC124. (*See id.*) The number of patients anticipated to participate in PTC's ongoing 2008 clinical trials in DMD and BMD is approximately 200, and this figure includes

participants outside the United States. Thus, far from being the only DMD/BMD patient who cannot participate in those studies, Jacob, in fact, is one of more than a thousand boys and young men in the United States and potentially thousands of others worldwide who currently do not have access to PTC124 through a clinical trial but might benefit from the drug.

The Design and Purpose of Clinical Trials

10. Clinical trials are medical experiments designed to test the safety and efficacy of new drugs that are necessary to secure regulatory approval to market the drug in the United States. Before clinical trials commence, a new drug is subjected to preclinical studies, which involve studying the drug's pharmacological effect and toxicity in animals. The data obtained from preclinical studies are critical in determining that clinical trials, which involve administering the new drug to humans, should go forward.

11. If such a determination is made, the sponsor of a drug must submit an investigational new drug application (an "IND") to the FDA. If the FDA does not raise an objection, the clinical trials can begin.

12. As a general rule, clinical trials involve three distinct phases, each of which is carefully designed to yield specific types of data, and each must be completed before the next may begin. Phase 1 is designed to determine an appropriate and safe dose of the drug for use in later trials. In addition, Phase 1 testing provides information on what happens to the drug when inside a human body, that is, how the drug is metabolized (the "pharmacokinetics" of the drug), how much of it is present in the bloodstream or other organs, and how and when the body excretes the drug. Phase 1 data also provide some preliminary information concerning drug safety.

13. Phase 1 trials typically involve the introduction of a new drug into healthy volunteers. Given the ethical considerations attendant to administering an experimental new drug to children, Phase 1 trials for drugs designed to treat childhood diseases like DMD/BMD are almost always performed in healthy adults.

14. Positive data from Phase 1 justify advancing to Phase 2. The primary goal of Phase 2 studies is to assess the activity of the drug in patients under study. In addition, Phase 2 studies provide additional short-term safety data and pharmacokinetic information.

15. Phase 2 trials are generally followed by Phase 3 trials that compare the drug under investigation to either placebo or another type of control. By agreeing to participate in a controlled trial, a subject has no assurance that he or she will actually receive an investigational drug and assumes the possibility that he or she will be assigned to the control group for the trial and receive either placebo or another available therapy. This possibility is fully set forth in the consent documents that must be reviewed and evaluated by the subject (and/or, as here, his or her parent or guardian) as a condition of trial enrollment.

16. The principal goal of Phase 3 studies is to provide data demonstrating that a drug offers a clinical benefit to patients with the medical condition the drug is intended to treat, either by alleviating their symptoms, prolonging their lives, preventing complications associated with their condition, or some combination thereof. As a general rule, Phase 3 studies tend to be much larger than their predecessor studies and often involve hundreds to thousands of participants. However, if the condition the drug is intended to treat is rare, Phase 3 studies may be somewhat smaller.

17. The nomenclature the FDA uses to describe the phases of clinical investigation do not fully reflect current practices. Although FDA regulations expressly recognize only Phases 1,

2, 3 and 4 (post-marketing studies), a company may conduct Phase 2 trials in two parts, denominating the first part Phase 2a and the latter part Phase 2b. Phase 2b trials may involve the use of placebo or another type of control, and in many respects resemble what FDA regulations call Phase 3 studies.

18. A company that conducts Phase 2b trials that involve a sufficiently large number of participants and the use of placebo or another control may be able to obtain FDA approval without conducting Phase 3 trials, while in other cases additional Phase 3 trials may be required prior to approval. In the United States, the FDA ultimately determines whether a Phase 2b trial provides sufficient data to conclude that an experimental drug is sufficiently safe and effective to justify approval.

19. No matter what they are called, the final set of clinical trials conducted before a company seeks FDA approval for a new drug is governed by the null hypothesis and must assume that the drug under investigation is unsafe and does not work. Unless and until both of these hypotheses are disproved by the data generated from such trials, it is my belief that making PTC124 available outside of these clinical trials poses the potential for unacceptable risks without potential benefits.

PTC124 As A Potential DMD/BMD Treatment

20. DMD/BMD is a progressive form of muscular dystrophy that causes the loss of both muscle function and patient independence. The disease affects only males and it is typically diagnosed within the first few years of life. Boys and young men who have DMD/BMD produce little or no dystrophin, a protein that is important for maintaining the structure of the body's muscle fibers. Proteins, like dystrophin, are comprised of long molecular chains and constitute essential components of all living cells. According to a recent study, medical advances over the

last 20 years have increased the survival rate for DMD patients such that now most DMD patients can be expected to survive into early adulthood. A copy of an Archives of Diseases in Childhood Online article entitled "Update on the Management of Duchenne Muscular Dystrophy" citing this fact is attached hereto as Exhibit B. Patients with BMD would be expected to live considerably longer.

21. The process of protein production involves a number of steps. First, the genetic material contained in a person's DNA is copied to Messenger RNA ("mRNA"). The genetic code contained in the mRNA is then translated by components of cellular machinery known as ribosomes which use the information they receive through the translation process to build proteins.

22. Approximately 10-15% of patients with DMD/BMD have what is known as a "nonsense mutation" in their DNA. The nonsense mutation, when copied to mRNA, inserts a signal into the mRNA to stop protein production before it is complete. This signal is known as a premature stop codon. When translated by the ribosomes, premature stop codons hinder the ribosomes from completing production of the dystrophin protein. The partially completed dystrophin molecules that are created in patients with DMD/BMD are insufficient to serve necessary biological functions.

23. Lacking functional dystrophin, DMD/BMD patients suffer from a loss of structural integrity in their muscles. As the disease progresses, patients lose the ability to use their legs and become non-ambulatory. DMD patients are frequently wheelchair-bound by the age of 10. *See* Ex. B at 2. Eventually, the disease compromises the functioning of the muscles in the patient's torso, including those that facilitate breathing. In the late stages of DMD/BMD,

patients frequently require ventilators to breathe, and cardiac functioning may also be compromised. *Id.* at 7-8.

24. PTC124 is intended to allow the cellular machinery in patients with nonsense mutations to bypass premature stop codons, thereby enabling the production of a complete essential protein. Specifically, for DMD patients, the drug is intended to override the signals that would ordinarily prevent ribosomes from obtaining sufficient information to generate a complete dystrophin molecule, thereby enabling them to produce functional, full-length dystrophin molecules.

Clinical Trials of PTC124

25. Preclinical (animal) studies for PTC124 were initiated in laboratories at the University of Pennsylvania in 2003. Those studies were conducted in mice. Additional toxicology studies were performed in rats and dogs. In PTC's view, the preclinical data generated in these studies justified seeking permission from the FDA to conduct investigations of PTC124 in human subjects.

26. Phase 1 trials for PTC124 were conducted in 2004 and 2005. In those trials, PTC124 was administered to healthy adults for up to 14 days at varying dosages. The purpose of these trials was to gather preliminary safety and pharmacokinetic data on PTC124 and to gain some information on the specificity of drug action – that is, to determine that PTC124 would not read through normal stop codons. The results of the Phase 1 trials indicated the safety and specificity of PTC124 at the studied doses over a short timeframe in healthy adults.

27. In early 2006, PTC initiated a Phase 2a study of PTC124 in subjects who have DMD as a result of a nonsense mutation. The study was conducted at three hospitals: the Children's Hospital of Philadelphia; the Cincinnati Children's Hospital Medical Center; and the

University of Utah. The primary goal of this study was to assess muscle dystrophin expression – that is, the amount of dystrophin present in muscle tissue – in response to treatment with PTC124. Attached as Exhibit C hereto is a copy of a description of the Phase 2a trial and its eligibility requirements that has been posted on the www.clinicaltrials.gov website. PTC worked closely with scientists and investigators to design this study to help evaluate whether the encouraging preclinical (animal) findings for PTC124 translated to the clinical (human) setting.

28. Enrollment in the Phase 2a clinical trials was limited to patients with DMD because they produce virtually no dystrophin and detecting an increase in dystrophin expression as a result of PTC124 treatment would be easier than detecting such an increase in patients with BMD who typically produce more dystrophin than DMD patients.

29. The Phase 2a clinical trials for PTC124 were conducted in three separate and sequential stages. First, a low dose of PTC124 was administered to a group of six ambulatory boys with DMD for 28 days. This initial stage generated pharmacokinetic data concerning the use of PTC124 in young boys. Building on these data, a medium dose of PTC124 was administered to a group of 20 ambulatory boys with DMD for 28 days. Through this portion of the Phase 2a trial, it became apparent that younger children may metabolize PTC124 faster than adults and an additional dosing stage was added to evaluate a higher clinical dose in a group of 12 older boys and young men with DMD, some of whom were ambulatory and others were not, for 28 days.

30. Consistent with the formal eligibility requirements stated in the FDA-approved protocols for that study, whether a given subject was eligible to participate in any of the stages of the Phase 2a study was determined by the principal investigators at each trial site. No one at PTC had the ability to determine whether any specific child could participate.

31. In May 2007, we announced that interim data from the first two stages of the Phase 2a study were positive. In our view, that data suggested that treatment with PTC124 was associated with increases in muscle dystrophin expression in over half of the 26 trial participants. At the time, the data from the third stage of the Phase 2a trial were still being accrued and analyzed and therefore could not be released.

32. In October 2007, after all of the data from each stage of the Phase 2a trial were available and had been analyzed, PTC announced that PTC124 appeared to be well tolerated in all three dose levels that had been administered, and that the target concentrations of the drug in the body – that is, the concentrations that the preclinical studies for PTC124 indicated were necessary for the drug to have effect – were achieved in trial participants who received both the medium dose and the large dose. The results of these trials also added to the growing body of data indicating that PTC124 was safe for human use, but, because they only involved the administration of the drug to DMD patients for 28 days, these trials did not, by any means, provide definitive safety data for PTC124.

33. On April 23, 2008, PTC announced a second Phase 2 trial for PTC124 as a DMD treatment (the "Phase 2b Trial"). Depending on the results of this trial, it may be unnecessary for PTC to conduct Phase 3 trials of PTC124. The Phase 2b trial is designed to demonstrate both the safety and efficacy of PTC124 as a long-term DMD/BMD treatment. Attached as Exhibit D hereto is a copy of a description of the Phase 2b trial and its eligibility requirements that has been posted on the www.clinicaltrials.gov website.

34. The null hypothesis governs this trial. PTC must assume in conducting this trial that PTC124 is neither safe nor effective, and the goal of this trial is to disprove these hypotheses using clinical data. We are hopeful that the Phase 2b study will generate sufficient positive data

to enable us to submit a formal application to the FDA for approval of PTC124 as a DMD/BMD treatment in the United States. However, at this time, we simply do not know if it will.

35. The Phase 2b trial differs in many respects from the Phase 2a trial described above. First, the goals of the trials are different. Unlike the Phase 2a trial which was designed primarily to test muscle dystrophin expression, the Phase 2b trial is designed to demonstrate the efficacy of PTC124 by measuring improvements in the walking ability (ambulation) of its participants. Because one of the primary endpoints of the trial is to measure PTC124's affect on ambulation, the trial is only open to boys or young men with DMD/BMD who can still walk.

36. Second, unlike the Phase 2a trial in which all of the trial participants received PTC124, albeit at varying dose levels, participants in the Phase 2b trial will receive one of two dose levels of PTC124 or placebo. Although enrollment for the Phase 2b trial is still ongoing, we anticipate that the trial will include approximately 165 participants once enrollment is complete. Accordingly, approximately 55 of the subjects who agree to participate in the Phase 2b trial will not receive PTC124 at all for the first 48 weeks of the trial. The Phase 2b trial is double-blinded, meaning that, for the duration of the trial, neither the participants nor the principal investigators conducting the trial will know who is receiving PTC124 and who is receiving placebo. PTC will also not have access to this information until the study is considered completed.

37. Third, each of the participants enrolled in the Phase 2b trial will participate in the trial for nearly a full year (48 weeks), not just 28 days like their Phase 2a counterparts. Because it is contemplated that PTC124 will be administered to DMD/BMD patients throughout their lives, the safety data generated from the Phase 2b trial are crucial, and without those data it

would be irresponsible to administer PTC124 to any child with DMD/BMD for long-term use outside the clinical trial setting.

38. Fourth, unlike the Phase 2a study, which enrolled only patients with DMD, the Phase 2b trial is also open to patients who have been diagnosed with BMD, assuming they satisfy the other eligibility criteria.

39. At the end of 48 weeks, all of the individuals who participate in the Phase 2b trial, whether they receive PTC124 or placebo during the trial, will have access to PTC124 for the next 48 weeks.

40. Although the Phase 2b trial is intended to last a full 48 weeks, preliminary data from the trial will be reviewed by an independent data monitoring committee comprising experts in DMD, biostatistics, and other relevant medical disciplines, after approximately 90 participants have been in the study for approximately 24 weeks. At present, we estimate this will be at some point in the second quarter of 2009. The analysis of those data will provide an interim look at PTC124's safety and efficacy that will determine whether or not to continue the study.

41. The determination of whether the Phase 2b trial should continue after the analysis of the interim data will be based on the recommendations of the data monitoring committee. If the committee finds that the interim data show PTC124 is unsafe or ineffective, the trial will stop. The data monitoring committee may also recommend stopping the trial if the interim data justify a finding of extreme efficacy – that is, that PTC124 works so well it would be virtually unethical not to stop the trial and make the drug available to all Phase 2b study subjects. Finally, the data monitoring committee may determine that the trial should continue until completion – that is, until all subjects are enrolled into the study and have been in the trial for a full 48 weeks; such a recommendation is the most likely of the three alternatives. In this case, the implications

of the committee's decision are that PTC124 is safe enough to continue administering it to trial participants for the remainder of the study and that the drug has not yet proved to be effective. Thus, both the safety and the effectiveness of PTC124 as a long-term DMD treatment will remain uncertain. All we will know at that time is that an independent determination has been made that PTC124 is safe enough to permit the trial to proceed to its scheduled completion in early 2010, at which time definitive conclusions about safety and efficacy will be reached by the FDA after an application for approval of PTC124 has been submitted and reviewed.

42. Although PTC will receive a recommendation from the data monitoring committee after the committee analyzes the interim trial data, PTC will not have direct access to the data divided by subject group, and thus cannot perform a separate analysis of safety or efficacy.

43. It bears mention that, even if the data monitoring committee makes the determination that the Phase 2b trial should be stopped based on a finding of extreme efficacy, before the trial can be stopped, the FDA is requiring PTC to make the interim data from the trial available to the FDA for its own independent review. If the FDA agrees with the data monitoring committee, the trial will stop, but if the FDA disagrees, the trial will continue.

44. It is certainly possible that, even if the Phase 2b trial proceeds until completion, additional trials or studies may be required before PTC124 can receive FDA approval. Thus, maintaining the ability to enroll additional subjects into such trials is important. Such trials could be compromised if the drug were made available outside of the clinical trials setting.

45. In addition to recruiting participants for our Phase 2b trial, we are also currently enrolling subjects who participated in the initial Phase 2a trial into a Phase 2a extension study. This two-year extension study is being conducted pursuant to the IND that was submitted in

connection with the Phase 2a trial. The Phase 2a extension study will provide additional data concerning the long-term safety and efficacy of PTC124 as a treatment for DMD that will be used to support FDA approval of PTC124. Participants in the Phase 2a extension study will receive PTC124 for approximately two years. Because participants in the Phase 2a extension study were all enrolled to the Phase 2a study, only patients with DMD are included.

46. Although the results of clinical trials for PTC124 as a DMD treatment that have been conducted to date have yielded encouraging results about drug activity, it is by no means certain at this point that PTC124 we will be approved by the FDA. According to a recent report by the Director of Economic Analysis at the Tufts Center for the Study of Drug Development at Tufts University, in addition to being complex, time-consuming, and costly, the process of drug development is also "risky in that most compounds that undergo clinical testing are abandoned without obtaining marketing approval." A copy of an article entitled "Risks in New Drug Development: Approval Success Rates for Investigational Drugs," authored by Joseph A. DiMasi, Ph.D, is attached hereto as Exhibit E. That report further notes that about "half of clinical research failures occur in Phase II. This is the case for both the first and second halves of the study period." *Id* at 302. This indicates that, despite the great hope we have that PTC124 will be approved by the FDA as a DMD treatment, it is wholly premature at this point to expect that the drug is sufficiently safe and effective such that it will be approved.

Funding for PTC124 Trials

47. The clinical development and testing of PTC124 thus far has largely been funded by grants from various organizations, governmental entities, and private investors. To date, the company has received grants from the Muscular Dystrophy Association, Cystic Fibrosis Foundation Therapeutics, Inc., and the FDA's Office of Orphan Products Development. In

addition, indirect support for certain types of infrastructure at the clinical sites was made available by the National Center for Research Resources. To the best of my knowledge, Cheri Gunvalson was not involved in any of our efforts to obtain the clinical grants we have received from any of these entities.

48. I understand that the Gunvalsons are alleging that Cheri Gunvalson urged me to file an application for a grant from the National Institutes of Health ("NIH") and that Mrs. Gunvalson helped PTC to apply for federal grant money. Neither of these assertions is true. First, PTC has never applied for an NIH grant to facilitate the clinical development of PTC124. The only grant we have received from the NIH that was used to fund PTC124 research went almost entirely to the University of Massachusetts, and was used to fund *in vitro* studies of PTC124. Mrs. Gunvalson had no involvement in procuring this grant. Second, to the extent that PTC124 applied for and received money from the FDA, as set forth above, Mrs. Gunvalson was not involved in the process.

PTC Makes A Formal Record that Expanded Access Is Not Yet Available

49. I understand that the Gunvalsons also are claiming that PTC has somehow failed to provide required information concerning its policies with respect to expanded access. This is untrue.

50. Prior to the commencement of the Phase 2b trial for PTC124, PTC posted the eligibility requirements for that trial on www.clinicaltrials.gov. *See* Ex. D. In connection with that posting, PTC employees filled out a web form indicating as a matter of formal record that there was no expanded or non-protocol access available for this trial. A copy of the web form PTC completed for the Phase 2b trial is attached hereto as Exhibit F.

Jacob Gunvalson's Access to PTC124

51. I understand that the Gunvalsons have alleged that, in response to the request of Jacob Gunvalson's pediatrician, Dr. John Parkin, I stated that once patient safety was confirmed by the Phase 2 clinical trials that were ongoing at the time, I would discuss making PTC124 available to Jacob Gunvalson. That also is not true. Attached as Exhibits G and H, hereto respectively, are a copy of the letter I received from Dr. Parkin seeking pre-approval access to PTC124 and my April 14, 2006 letter to Dr. Parkin responding to his request.

52. Specifically, after apprising Dr. Parkin of the results of the clinical trials that had been conducted as of that time, I told him:

> Given this situation, implementation of an expanded access program at this time would be premature. While we are encouraged that the available data may suggest proof of concept in CF, these data were obtained in only a small number of adult patients receiving PTC124 for a short period of time. We cannot be sure that the preliminary results in CF will indicate long-term clinical benefit in CF, nor can we surmise that the preliminary CF findings will predict clinical benefit in patients with DMD.
>
> We want to avoid unacceptable risks for patients and be certain that we do not jeopardize the development of PTC124. Our clinical development plan is designed to ensure that PTC124 becomes available for all patients who might benefit if its efficacy and safety are eventually proven. Thus, we must finish the additional toxicology studies and complete accrual to the current Phase 2 clinical trials in CF and DMD. We expect to complete our further toxicology studies and Phase 2 clinical trials in CF and DMD by the end of 2006, with data available following completion.
>
> I would like to suggest that we plan to be in touch in early 2007 once more information is available.

Ex. H at 1.

53. As is clear from my letter, all that I did was suggest that Dr. Parkin and I speak once the data from the Phase 2a clinical trials were complete and had been evaluated. At that time, I anticipated that PTC's Phase 2a trials would be fully completed in 2006. As it turns out, however, the data from those trials were not accrued and analyzed until the third quarter of 2007.

54. In no way was my letter to Dr. Parkin intended to suggest, nor do I believe it can reasonably be interpreted as suggesting, that Jacob would receive pre-approval access to PTC124 to enable Dr. Parkin to administer PTC124 to Jacob under a single-patient IND if our Phase 2a trials yielded positive data.

55. I understand that the Gunvalsons also have claimed that at some point during the July 13, 2006 annual conference of Parent Project Muscular Dystrophy, I assured Mrs. Gunvalson that once PTC had positive data from the ongoing Phase 2a trials, Jacob would have access to PTC124. I made no such statement and it is, quite frankly, beyond any realm of possibility that I would ever make such a statement. The only manner in which any boy or young man with DMD/BMD can or could at the time receive PTC124 is through participation in a clinical trial for the drug. Study participation is predicated on evaluation by a clinical investigator to determine whether a prospective subject meets the enrollment criteria set forth in an FDA-approved protocol for that trial. Thus, neither I nor anyone else at PTC can determine the eligibility of a specific trial candidate. For Jacob Gunvalson to have received PTC124 at that time, or any time since, he would have to have been selected to participate in the clinical trial by one of the primary investigators who conducted that trial.

Langdon L. Miller

Langdon L. Miller, M.D.

Sworn to before me this
11th day of August, 2008

Brian P. Sharkey

~~Notary Public~~ Attorney-At-Law

Exhibit A

REQUEST FOR ORPHAN DRUG DESIGNATION FOR PTC124 AS TREATMENT OF DUCHENNE MUSCULAR DYSTROPHY

22 October 2004
PTC Therapeutics, Inc.
South Plainfield, NJ

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AUTHORS

Samit Hirawat, MD – Director, Clinical Development, PTC Therapeutics, Inc.

Gary L. Elfring, MS – Biostatistical Consultant to PTC Therapeutics, Inc.

Eileen M. Leonard, MD – Regulatory Consultant to PTC Therapeutics, Inc.

Langdon L. Miller, MD – Chief Medical Officer, PTC Therapeutics, Inc.

1. REQUEST FOR ORPHAN DRUG DESIGNATION

Pursuant to Section 526 of the Federal Food, Drug, and Cosmetic Act, PTC Therapeutics, Inc. requests that PTC124 be designated as an orphan drug for the treatment of Duchenne muscular dystrophy (DMD) resulting from a nonsense mutation (premature stop codon) in the dystrophin gene.

2. SPONSOR AND DRUG PRODUCT

2.1. Sponsor Information

Address

PTC Therapeutics
100 Corporate Court
South Plainfield, NJ
USA 07080

Contact

Langdon L Miller, MD
Chief Medical Officer
Tel: (908) 222-7000 x 152
Fax: (908) 222-7231
E-mail: lmiller@ptcbio.com

2.2. Drug Product

Generic Name

PTC124

Trade Name

To be determined

2.3. Sites of Manufacture

Drug Substance

Rhodia-Annan
Three Trees Road
Newbie, Annan, Dumfriesshire
Scotland DG12 5QH

or

Rhodia-Dudley:
Dudley, Cramlington, Northumberland
England NE23 7QG

Drug Product

Patheon, Inc.
2100 Syntex Court
Mississauga, Ontario
Canada L5N 7K9

3. DISEASE DESCRIPTION, THERAPEUTIC RATIONALE, AND PROPOSED INDICATION

3.1. Disease Description and Current Therapies

DMD is an X-linked disorder caused by defects in the gene for dystrophin, a protein that is critical to the structural stability of myofibers in skeletal and cardiac muscle [1]. Dystrophin is a high-molecular-weight cytoskeleton protein localized at the inner surface of the muscle membrane. It is part of a dystrophin-glycoprotein complex that also includes dystroglycans and

sarcoglycans. The complex provides a bridge across the muscle membrane; dystrophin couples F-actin in the cytoplasm with dystroglycan, which, in turn, binds merosin (laminin-2) in the extracellular matrix. Dystrophin deficiency destabilizes the dystrophin-glycoprotein complex, impairing localization of the dystroglycans and sarcoglycans to the muscle membrane, and compromising the structural integrity of the membrane. The absence of normally functioning dystrophin results in sarcolemmal breakdown, calcium ion influx, phospholipase activation, oxidative muscle injury, and, ultimately, myonecrosis. As muscle damage progresses, connective tissue and fat replace muscle fibers.

The diagnosis of DMD is based on the typical muscular manifestations, a family history (although one-third of patients have spontaneous mutations with no family history), and the presence of a substantially elevated serum creatine kinase level [1]. The diagnosis can be confirmed by muscle biopsy in moderately weak muscles that still have sufficient muscle tissue for evaluation. Immunofluorescence staining reveals the conspicuous absence of dystrophin and other molecules of the dystrophin complex at the sarcolemmal membrane. Standard histological features include widespread muscle necrosis, fiber size variation, and regenerating cells in different stages of atrophy and regrowth. Initially, macrophages and CD8-positive T lymphocytes invade necrotic muscle fibers and then are replaced by fibrotic and fatty tissue. Total sequencing of the dystrophin gene to confirm the presence of mutations is now available for research studies by the University of Utah, Salt Lake City, UT [2].

DMD usually manifests in boys approximately 3-7 years of age when they are noted to develop lordosis, a waddling gait, and the Gower sign (a characteristically abnormal method of rising from a supine to a standing position) [1]. Inexorable progressive weakness is seen in the proximal musculature, initially in the lower extremities but later involving the neck, shoulders, and arms. By the age of 8 years, most patients have difficulty with ascending stairs, and many are wheelchair-bound by 10-12 years of age as they develop increasing weakness and contractures of the iliotibial bands, hip flexors, and Achilles tendons. Wheelchair-induced immobility creates a vicious cycle, with further loss of strength and formation of additional contractures. As respiratory and cardiac muscle strength decline, FVC and cardiac output decrease, leading to terminal respiratory or cardiac failure, often by late adolescence.

At this time, there is no available systemic therapy to improve or correct dystrophin production and function. The primary goal of DMD treatment is palliation through supportive care measures such as bracing, joint-stretching exercises to avoid onset of contractures, tendon-release surgery, and eventual wheelchair use and application of assisted ventilation. Although not specifically FDA-approved for use in DMD, corticosteroids, working through unknown mechanisms, have been the only medications to demonstrate a benefit in ameliorating the disease [3, 4]. Clinical improvement, as measured by strength testing, is seen approximately 1 month after starting treatment and disease progression appears to be slowed for $\geq$6 months [3, 4]. To date, only modest creatine kinase improvements have been observed with steroid use, perhaps due to the extreme variability in this marker. Because chronic steroid use in children with DMD is typically associated with serious sequelae, steroids are not universally employed. Most patients receiving steroids experience weight gain (which is problematic given the need to reduce muscle load-bearing), growth inhibition (which may offer benefit by minimizing torque on muscle groups), and Cushingoid habitus [4]. Osteopenia, stomach ulcers, rashes, and glucose intolerance are also commonly observed. Clinical tests have been developed, standardized, and validated as helpful tools in following the course of the disease and evaluating clinical benefit in

studies [5, 6]. The tests are primarily useful in ambulatory patients and involve physical-therapist-administered determinations of strength in 34 specific muscle groups as well as timed evaluations of walking, stair climbing, and rising from a supine position

3.2. Therapeutic Rationale for Nonsense Mutation Suppression as a Therapy for Duchenne Muscular Dystrophy

Nonsense mutations are single-point alterations in DNA that, when transcribed, result in conversion of a messenger RNA triplet (eg, CAG) that codes for an amino acid to a triplet (eg, UAG) that is interpreted as a termination codon. The presence of such a malpositioned stop codon leads to premature cessation of translation, with protein truncation and consequent disease due to loss of enzymatic function or a structural deficit. Nonsense mutations are the basis for approximately 10% to 15% of the individual cases of most inherited diseases, including DMD [7].

Drug treatment approaches that selectively promote ribosomal readthrough of nonsense mutations have the potential to treat genetic disorders such as DMD. It has recently been described in preclinical systems that existing drugs such as the aminoglycoside group of antibiotics, which have translation-modifying mechanisms of action, can suppress the effects of nonsense mutation in the mRNA for the dystrophin gene. In the nonsense-containing dystrophin gene in the mdx mouse model of DMD, animals treated with high-dose gentamicin have produced full-length dystrophin protein, and have shown evidence of reduced muscle stress injury [8].

Administration of gentamicin has also shown evidence of nonsense mutation suppression in pilot clinical studies. While some clinical results have been equivocal [9], there is also evidence that intravenous (IV) gentamicin can induce full-length dystrophin production as shown by immunofluorescence of biceps muscle biopsies [10].

Because serious renal and otic toxicities and the need for parenteral administration preclude the long-term clinical use of high-dose gentamicin, there has been considerable interest in the identification of more suitable small-molecular-weight synthetic compounds with the ability to promote readthrough of disease-causing nonsense mutations.

PTC124 is a new chemical entity that selectively promotes ribosomal readthrough of mRNA containing a nonsense mutation, and thus may have the potential to treat a proportion of patients with DMD. The molecule was identified by PTC Therapeutics, a drug discovery company based in South Plainfield, NJ, that is focusing on the identification and development of small-molecule drugs that can treat human disease by selectively binding to RNA targets or to proteins that interact with RNA. It is expected that because of its mechanism of action, PTC124 will be able to overcome the basic causative defect responsible for the disease in a subset of patients and provide a new, more definitive therapy for the treatment of DMD.

3.3. Proposed Indication

PTC Therapeutic's development program hypothesis is that PTC124, administered by daily oral dosing to maintain target plasma concentrations, will modify disease-specific pharmacodynamic markers and will safely offer clinical benefit. PTC Therapeutics' development program for PTC124 is intended to support an indication for:

Treatment of patients with Duchene muscular dystrophy resulting from a nonsense mutation (premature stop codon) in the dystrophin gene

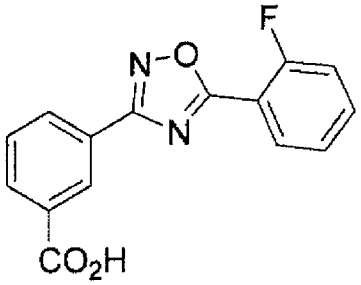
4. DESCRIPTION OF DRUG AND RATIONALE FOR USE

4.1. Drug Properties

4.1.1. Drug Substance

As shown in Figure 1, PTC124 is a 1,2,4-oxadiazole linked to 2 ring structures: fluorobenzene and benzoic acid. Its chemical name is 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazole-3-yl]-benzoic acid. The structure has been confirmed by ^{1}H-NMR and IR, and the molecule has no chiral centers. Of note, the compound has no structural similarity to gentamicin or other aminoglycoside antibiotics.

Figure 1. Structure of PTC124



The drug substance is a white, crystalline powder with a molecular weight of 284.2 Daltons, a mean particle size of 7-8 μm, and a melting point of approximately 244°C. Its pKa and partition coefficient (octanol/water) have not yet been determined. A preliminary evaluation of the solubility profile of PTC124 in various organic solvents has shown the substance is readily solubilized in dimethyl sulfoxide (DMSO) and ethanol.

PTC124 is a Biopharmaceutical Classification System Case 2 compound, possessing low aqueous solubility (<1 μg/mL) and high permeability across a Caco-2 cell layer. The permeability results from 2 studies, expressed as apparent permeability (P_{app}), were 22.8×10^{-6} and 27.6×10^{-6} cm/sec, respectively, for the free acid.

Two cGMP batches of PTC124 have been manufactured by Rhodia Pharma Solutions, Malvern, PA. Additional batches of drug will also be manufactured by Rhodia Pharma Solutions.

4.1.2. Drug Product

The drug product is being provided by Patheon, Inc., Ontario, Canada, as powder in a bottle for reconstitution, formulated with a suspending agent and a surfactant. Future formulation development will address any potential palatability issues noted in Phase 1 studies. It is anticipated that the Phase 2-3 formulations may employ the components contained in the Phase 1 formulation but with the possible addition of flavoring and/or coloring agents.

4.2. Preclinical Characterization of PTC124

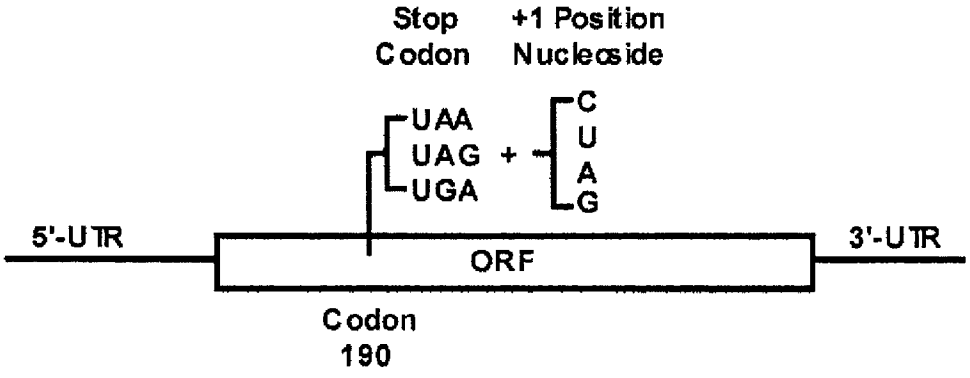
The focus of the preclinical pharmacological evaluation of PTC124 has been to determine essential characteristics of its activity that will influence future development, to evaluate its mechanism of action and specificity, and to build a body of evidence supporting its clinical testing in DMD.

4.2.1. In Vitro Activity

4.2.1.1. Cell-based Translation Assay

Building on the established use of firefly luciferase as a biological reporter system, a functional cell-based translation assay was developed as a means of identifying and quantifying the activity of compounds that can induce ribosomal readthrough of nonsense stop codons in mRNA. In this assay, a reporter construct has been prepared that permits quantitative assessment of the level of translation readthrough based on luciferase-mediated chemoluminescence. Human embryonic kidney cells (293 cells) growing in media containing fetal bovine serum (FBS) have been stably transfected with the luciferase gene containing a premature termination codon at amino acid position 190. In place of the threonine codon (ACA) normally present at this site, each of the 3 possible nonsense codons (UAA, UAG, or UGA) and each of the 4 possible nucleotides (C, U, A, G) at the contextually important downstream +1 position following the nonsense codon have been introduced by site-directed mutagenesis. Figure 2 provides a diagram of the types of luciferase mRNA resulting from this construct.

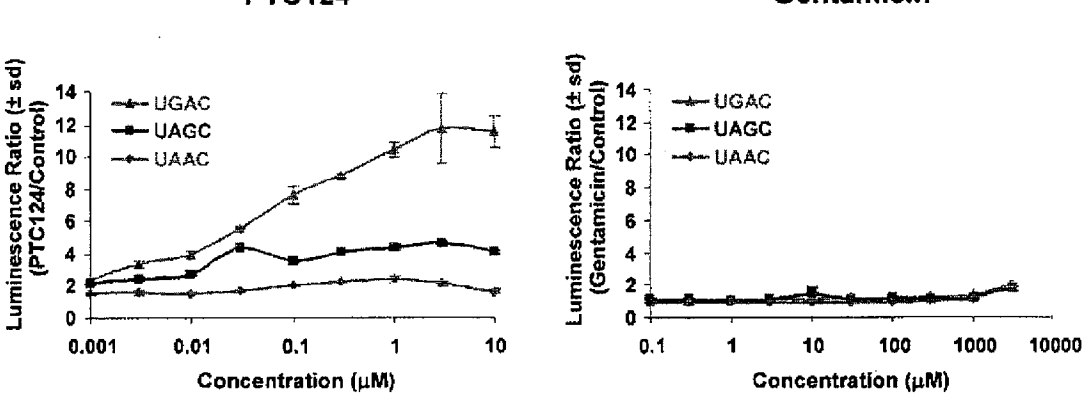
Figure 2. Luciferase Reporter mRNA Constructs



Abbreviations: A = adenosine, C = cytidine, G = guanosine, U = uridine, mRNA = messenger ribonucleic acid, ORF = open reading frame, UTR = untranslated region

Treatment of the reporter assay cells for 20 hours with increasing concentrations of PTC124 resulted in dose-dependent readthrough of full-length, functional luciferase as measured by chemoluminescence (Figure 3). Readthrough was best with UGA, was less with UAG, and was least with UAA. With each stop codon, the minimal concentration showing discernable readthrough was in the range of 0.1 μM (28 ng/mL) while the effective concentration achieving 90% of peak activity (EC_{90}) was approximately 1.0 μM (284 ng/mL). In this system, when compared with gentamicin, PTC124 demonstrated greater and more potent nonsense suppression.

Figure 3. Relative Activity of PTC124 and Gentamicin by Stop Codon Type and Concentration in Cell-based Luciferase Reporter Assay



Abbreviations: A = adenosine, C = cytidine, G = guanosine, U = uridine
Assays performed in triplicate

Additional studies have documented that continuous, unabated exposure to PTC124 appears important in maximizing that activity and that protein binding does not appear to overtly influence PTC124 efficacy.

4.2.1.2. mdx Myotube Assay

In order to obtain confirmatory in vitro evidence in a model system containing a nonsense mutation relevant to human disease, PTC Therapeutics provided PTC124 to investigators, Dr. Elisabeth Barton and Dr. Lee Sweeney, at the University of Pennsylvania. These collaborators assessed the activity and dose response of PTC124 in myocytes obtained from mdx mice. These mice have a nonsense mutation in exon 23 of the dystrophin gene that generates a premature UAA stop codon in dystrophin mRNA. Consequent loss of full-length protein results in histological and functional abnormalities of muscle that are reminiscent of findings associated with DMD in humans.

In this system, primary myoblasts were derived from neonatal mdx mice. After adherence to plastic dishes, cells were allowed to differentiate into myotubes in serum-containing media to which PTC124 (500 ng/mL [1.8 μM] to 30,000 ng/mL [106 μM]) or gentamicin (300,000 ng/mL [313 μM]) was added. Media and drug were replenished every other day and cells were assayed for dystrophin and myosin by immunofluorescence at 12 days. Respective negative and positive controls comprised untreated mdx and wild-type C57/B10 mouse primary muscle cultures. The degree of staining was assessed using a -, +1, +2, +3, +4 semiquantitative scale.

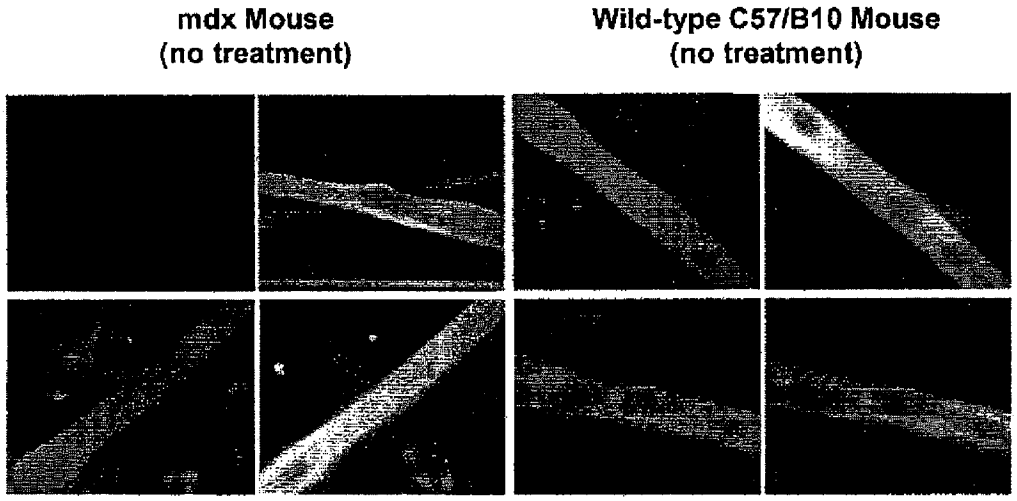
As shown in Table 1, successful readthrough, documented by production of dystrophin, was evident at all doses of PTC124 tested, with dystrophin appearing convincingly at PTC124 concentrations of 500 ng/mL (1.8 μM) and reaching a maximum at concentrations of 10,000 (35 μM) to 20,000 ng/mL (70 μM), values higher than the range associated with activity in the luciferase reporter assays. At 30,000 ng/mL (106 μM), a drop-off in activity was observed due to cytotoxicity that becomes evident with high drug concentrations in this in vitro system [8].

Table 1. Dystrophin Immunofluorescence by PTC124 and Gentamicin Concentration in Primary Myotube Cell Cultures

		Untreated Controls		Treatments								
		mdx Mouse	C57/B10 Mouse	PTC124								Gentamicin
Drug Concentration	ng/mL	0	0	100	500	1,000	2,500	5,000	10,000	20,000	30,000	300,000
	µM	0	0	0.35	1.8	3.5	8.8	18	35	70	106	313
Dystrophin Staining		-	++++	+/-	++	++	++	+++	++++	+++	++	++++

Figure 4 depicts immunofluorescence images of the myotubes with dystrophin stained red and myosin (a reference standard) stained green. Substantial production of dystrophin is observed with PTC124 treatment and with high-dose gentamicin treatment.

Figure 4. Immunofluorescence Images of Dystrophin (red) and Myosin (green) Staining in Primary Myotube Cell Cultures



4.2.2. Mechanism of Action

Chemical footprinting has been used to map sites of interaction of small molecules with ribosomal RNA (rRNA). Such an analysis was undertaken with several molecules that were precursors to PTC124 to map sites of interaction with human rRNA. In this analysis, ribosomes prepared from HeLa cells were incubated with 100 µM of each compound or controls and then treated with 2 chemical modifying agents (either dimethyl sulfate or kethoxal) that alter the structure of rRNA. Following the chemical modification reaction, rRNA was isolated and primer extension analysis was performed using end-labeled oligonucleotides that hybridize to different regions of the human 18S, 28S, and 5S rRNAs. The products of the primer extension were resolved on 6% polyacrylamide gels. Accessibility of the rRNA to chemical modification by dimethyl sulfate or kethoxal was visualized as the presence or absence of bands on the gel.

The regions of the ribosomal RNA that showed altered patterns of chemical modification with the compounds included several sites of the 28S rRNA known to be modified in prokaryotic models of nonsense suppression. Interactions with other areas of the 28S rRNA, or with the 18S and 5S rRNAs were not observed. These data suggest that the mechanism of action of PTC124-like compounds is mediated through interactions with specific regions of the 28S rRNA and that these areas are distinct from those of gentamicin, which binds to the 18S rRNA.

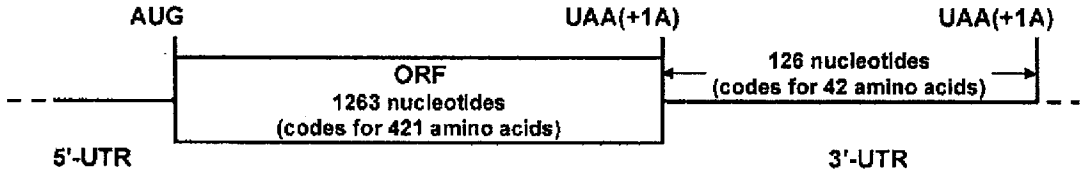
4.2.3. Selectivity

An important question regarding PTC124 relates to its selectivity for ribosomal readthrough of premature stop codons relative to normal stop codons. While such selectivity might be expected based on the extensive understanding of translational processes that has been developed in recent years, the potential for PTC124 to read through normal stop codons has been evaluated experimentally in several systems.

4.2.3.1. Evaluation of Normal β-Tubulin Stop Codon Readthrough

To specifically evaluate the potential for normal stop codon readthrough, the mdx mouse model of Duchenne muscular dystrophy was employed as a model. It is known that both PTC124 and gentamicin can induce readthrough of the UAA nonsense stop codon in dystrophin mRNA in these animals. It is also known that the mRNA for β-tubulin (an abundant protein in mouse muscle) has a UAA (+1A) termination codon at the end of the ORF and a second in-frame UAA (+1A) stop codon downstream in its 3'-UTR. Between these 2 stop codons is an intervening sequence of 126 nucleotides that, theoretically, could code for a 42-amino-acid extension of the mouse β-tubulin protein. A schematic of the β-tubulin mRNA is provided in Figure 5. If PTC124 were to have the capacity to induce ribosomal read of the normal stop codons, it would be expected that the β-tubulin protein would be increased in size by >42 amino acids (approximately 5 kiloDaltons [kD]) and that this change would be detectable by Western blotting.

Figure 5. Mouse β-Tubulin mRNA

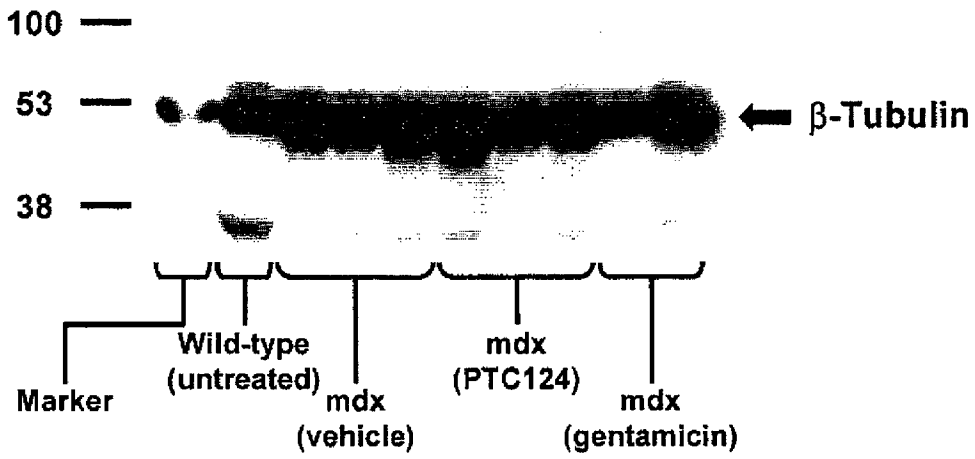


Abbreviations: A = adenosine, G = guanosine, U = uridine,
mRNA = messenger ribonucleic acid, ORF = open reading frame, UTR = untranslated region

In the experiment, mdx mice were treated daily for 28 days with PTC124 (150 mg/kg orally [PO]), gentamicin (34 mg/kg subcutaneously [SC]) or PO vehicle, after which muscle tissue was collected. Muscle from wild-type C57/B10 mice was also analyzed. As expected, immunofluorescence analysis in the PTC124- and gentamicin-treated mdx mice and in the wild-type mice revealed evidence of dystrophin production and localization in muscle membranes. However, as shown in Figure 6, Western blotting of muscles from drug-treated mice did not reveal an upward shift in the location of the β-tubulin that would suggest that the protein had

been aberrantly extended due to readthrough of the initial normal stop codon. Thus, the results of this experiment indicate that PTC124, while suppressing a UAA nonsense mutation in dystrophin, does not promote readthrough at a normal UAA translation termination codon in β-tubulin.

Figure 6. Western Blot of Mouse β-Tubulin



4.2.3.2. Evaluation of Normal Stop Codon Readthrough by 2-Dimensional Gel Electrophoresis

While the β-tubulin experiment provided a detailed evaluation of PTC124 action on a single abundant transcript, a more general approach to the theoretical problem of normal stop codon readthrough was performed using 2-dimensional gel electrophoresis. If substantial PTC124-induced ribosomal readthrough of normal stop codons were to abnormally elongate proteins, shifts in protein staining patterns due to increases in molecular weight and/or electric charge would be expected. To test this hypothesis, duplicate samples of 293 cells harboring a UGA (+1C) stop codon at the 190 amino acid position of the luciferase reporter were treated with PTC124 (5 μM [1420 ng/mL]) or vehicle for 48 hours. Aliquots of cells were assayed to ensure evidence of PTC124-induced ribosomal readthrough of luciferase in the standard cell-based reporter assay. Frozen cell preparations were then shipped to Kendrick Laboratories, Inc. (Madison, WI) for 2-dimensional gel electrophoresis and computerized analysis using Phoretix software.

Gel membranes, stained with Coomassie Blue, resolved 494 proteins migrating in a pH range of 3.5 to 10 and a molecular weight range of 14 to 250 kD. Computer analysis indicated that there were no substantive changes in the electrophoretic pattern in PTC124-treated cells compared to control. The exception was the appearance of a 62-kD band that is in the appropriate molecular weight and electrophoretic mobility position consistent with production of full-length luciferase.

4.2.3.3. Bacterial Suppression Studies

A number of aminoglycoside antibiotics are active in inducing nonsense mutation suppression [11, 12, 13], raising the question of whether a drug like PTC124, although not structurally

similar to the aminoglycosides, might have antibacterial properties. Accordingly, the antimicrobial activity of PTC124 against a battery of logarithmically growing gram-negative (*Escherichia coli, Pseudomonas aeruginosa*) and gram-positive (*Staphylococcus aureus, Staphylococcus epidermidis, Enterococcus faecium, Enterococcus faecalis*) bacteria was determined. Two aminoglycosides (tobramycin, kanamycin) and a penicillin (ampicillin) were included as positive controls. The concentrations achieving 90% bacterial growth suppression (IC_{90}) of test compounds were determined.

PTC124 did not prevent the growth of any of the tested bacterial strains at concentrations up to 250,000 ng/ml (880 μM). The expected pattern of bacterial susceptibility to the positive controls was observed. These results confirm that nonsense suppression activity is separable from antimicrobial activity and that PTC124 does not have any significant antimicrobial activity.

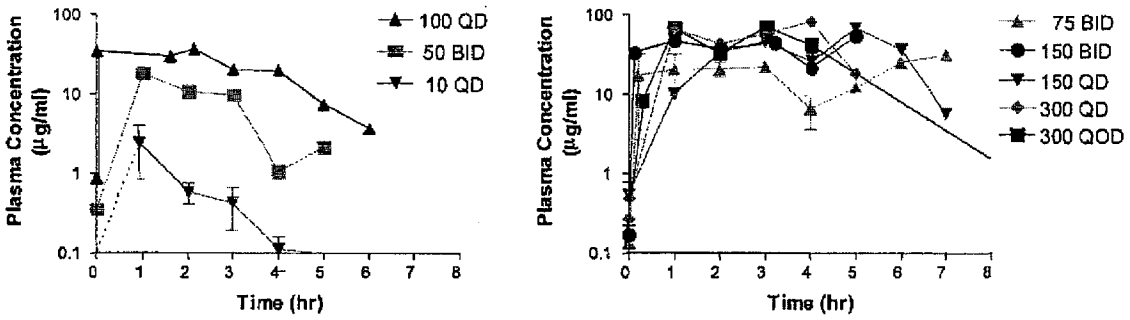
4.2.4. In Vivo Activity

In follow-up to the studies evaluating PTC124's effects on mdx myotubes in vitro, its activity in vivo was also assessed. Studies were performed working in collaboration with Dr Elisabeth Barton and Dr. Lee Sweeney at the University of Pennsylvania. Because the nonsense mutation in the mdx mouse is a UAA (+1A), this model represents a particularly stringent test of efficacy.

In this study, 10 groups of mdx mice (n=20 per group) were stratified by age; the youngest mice were age 7-9 weeks (n=8 per group), the intermediate mice were age 10-13 weeks (n=6 per group), and the oldest mice were age 15-19 weeks (n=6 per group) at the start of the study. Groups treated with PTC124 were as follows: 10 mg/kg QD SC, 50 mg/kg BID SC, 100 mg/kg QD SC, 75 mg/kg BID PO, 150 mg/kg QD PO, 300 mg/kg QOD PO, 150 mg/kg BID PO, 300 mg/kg QD PO. Negative control animals comprised mice treated with vehicle PO QD. Positive control animals comprised mice treated with 34 mg/kg QD of gentamicin. After 28 days of treatment, tibialis anterior muscles were removed and processed for dystrophin immunofluorescence staining. Dystrophin expression in myofiber membranes was quantitatively assessed using image intensity software. Values reported are membrane intensities normalized to membrane intensities in bright revertant fibers, taking into account nonspecific background. Selection of membranes for imaging was performed with the observer blinded as to study treatment. Blood was collected from each animal to assess effects on CK. PTC124 plasma concentrations were determined in selected animals at selected timepoints in order to generate a concentration-time curve for each group.

As shown in Figure 7, animals receiving PTC124 SC had dose-dependent increases in plasma exposure between 10, 50 and 100 mg/kg SC, while animals receiving PTC124 PO in the relatively limited dose range tested showed no clear differences in plasma exposure with each dose in this experiment.

Figure 7. PTC124 Plasma Concentration-Time Curves by Route and Dose Level in mdx Mice



Abbreviations: QD = once per day, BID = twice per day, QD = once per day, QOD = every other day, PO=oral, SC = subcutaneous

As depicted in Figure 8, treatment with PTC124 and with gentamicin was associated with positive dystrophin immunofluorescent staining localized to the membrane of muscle fibers.

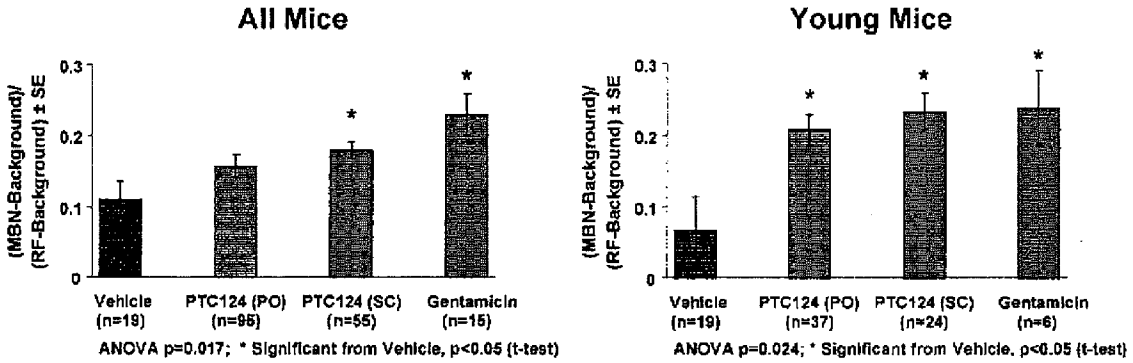
Figure 8. Immunofluorescence Images of Dystrophin in Muscle Fibers from mdx Mice Treated for 28 Days

Vehicle	PTC124 50 mg/kg BID SC	PTC124 150 mg/kg QD PO	Gentamicin 34 mg/kg QD SC

Abbreviations: BID = twice per day, PO = oral, QD = once per day, SC = subcutaneous

Overt differences in dystrophin expression among the various dose-schedule subgroups were not readily discernable. Summary data by drug and route of administration are presented in Figure 9. Dystrophin increases with PTC124 and gentamicin were observed when all animals were considered; however, the young animals contributed most substantially to the treatment effect. In the middle-aged and older mice, fiber loss with relatively high levels of background staining was observed.

Figure 9. Summary of Dystrophin Immunofluorescence Quantitation by Treatment Group in Muscle Fibers from mdx Mice



Abbreviations: ANOVA = analysis of variance; MBN = membrane intensity; PO = oral; RF = revertant fiber intensity; SC = subcutaneous

Significant changes in creatine kinase values were not seen due to a high level of variability in this parameter. PTC124 appeared generally safe; no weight loss was observed after 28 days of treatment.

4.2.5. Preclinical Toxicology and Safety Pharmacology

PTC124 has undergone comprehensive preclinical toxicology and toxicokinetic testing to support initiation of clinical studies. Studies that have been completed to date include 1-day, 7-day, and 28-day good laboratory practices (GLP) evaluations of oral PTC124 doses up to 2000 mg/kg/day in rats aged 4 to 8 weeks and up to 1500 mg/kg/day in dogs aged approximately 5 to 6 months. GLP safety pharmacology has been assessed with a neurological (Irwin) study in rats, a pulmonary study in rats, and a cardiovascular (telemetry) study in dogs. GLP in vitro determinations of genotoxicity and human ether-à-go-go-related gene (hERG)-channel function, and assessment of unintended pharmacological effects have been performed. GLP metabolism studies have included in vivo assessment of drug disposition following administration of 14C-PTC124 to rats, and in vitro evaluations of cytochrome P450 interactions, hepatic metabolism, and protein binding.

In the 1-, 7-, and 28-day toxicology studies, PTC124 was generally well tolerated even at high dose levels. The NOAEL for 28 days of treatment was considered to be 1800 mg/kg in the rat and 1500 mg/kg in the dog. The most consistent clinical findings were transient decreases in weight gain and decreased food consumption during the first several days of treatment at the highest doses tested (≥1800 mg/kg/day in rats and ≥1500 mg/kg/day in dogs), with recovery generally beginning by 1 week despite continued therapy. In dogs treated for 28 days, episodic vomiting and liquid feces were noted but were observed in both control and treated animals.

Variations in clinical pathology findings were often within the ranges typically observed for animals of these ages, were not always dose related, and were universally modest in extent. Possible compound-related findings observed in rats receiving 1800 mg/kg/day of PTC124 for 28 days were minimal decreases in hemoglobin and hematocrit, minimal increases in alanine aminotransferase and alkaline phosphatase, and minimal increases in cholesterol and

triglycerides. In dogs receiving 1500 mg/kg/day of PTC124 for 28 days, there was also the suggestion of minimal increases in alkaline phosphatase, triglycerides, and cholesterol.

Increases in liver weights were apparent, particularly in rats treated at ≥1800 mg/kg for 7 or 28 days but also in dogs treated at 1500 mg/kg/day for 28 days. Also notable were decreases in submandibular salivary gland weights after 28 days of treatment in both rats and dogs at the highest dose levels. In rats, statistically significant decreases in thymus weights were noted in the 7-day study at the highest dose level. Significant decreases in thymus weights were not present in the rat 28-day study. When evaluated for 28 days at the 1800-mg/kg dose level in rats, males were noted to have moderately decreased prostate weights, while females were noted to have moderately decreased heart, ovary, and adrenal weights. The organ weight changes were not accompanied by any adverse microscopic pathology abnormalities and all organ weight changes reversed upon drug withdrawal.

There were no notable macroscopic pathology findings at either the end-of-treatment or end-of-recovery sacrifices. On histopathologic examination, hyperkeratosis of the nonglandular stomach was observed in rats receiving PTC124 for 7 and 28 days at doses ≥1800 mg/kg. Hepatocellular hypertrophy was seen at the end-of-treatment sacrifice for rats given 1800 mg/kg/day, but was not considered adverse. No microscopic findings were noted at the recovery sacrifices.

Available TK data (from the 1-, 7-, and 28-day studies in rats and dogs) indicate that these toxicology findings where obtained in the context of substantial exposures to PTC124 over the duration of these studies. PTC124 was orally absorbed with time of maximum concentration (T_{max}) values of ~4 to 8 hours in both species. Day 1 C_{max} values averaged >200 μg/mL in rats receiving ≥1800 mg/kg and >150 μg/mL in dogs receiving 1500 mg/kg. The respective AUC_{0-24} values at these same dose levels were ~4000 μg·hours/mL in the rat and 2000 μg·hours/mL in the dog. PTC124 plasma levels steadily declined after reaching C_{max}, and the mean terminal-phase $t_{1/2}$ was ~3 hours in both the rat and the dog. While the C_{max} and AUC_{0-24} values rose with dose, increases were generally less than dose proportional. In rats, the C_{max} and AUC_{0-24} values were increased by ~150-200% on Day 7 and Day 28 relative to Day 1. By contrast, in dogs the C_{max} and AUC_{0-24} values were decreased by ~40% on Day 7 and Day 28 relative to Day 1. The TK profiles appeared similar in males and females of both species.

In safety pharmacology studies, no adverse neurological or pulmonary effects were noted in rats and no adverse cardiovascular effects were noted in dogs. The NOAELs for Irwin observations and for pulmonary function effects were both considered to be 2000 mg/kg in the rat, while the NOAEL for cardiovascular effects was 1500 mg/kg/day in the dog.

In order to address the possibility that PTC124 might nonspecifically permit ribosomes to read through normal stop codons in vivo, protein elongation assessments were also performed in special rat and dog toxicology studies. PTC124 was given by daily oral gavage over 14 days at doses ranging from 200 to 1800 mg/kg/day in male and female rats, and from 500 to 1500 mg/kg in male dogs. Vehicle-treated and pair-fed animals comprised controls. Tissues (heart, kidney, liver, lung, small intestine, mandibular salivary glands, thymus, and peripheral blood mononuclear cells) were collected between 2 and 8 hours after the last daily PTC124 dose. Tissue extracts were evaluated by Western blotting to determine if PTC124 induced abnormal elongation of selected high-abundance proteins (vimentin, α-actin, U1 small nuclear

ribonucleoprotein A, and cofilin in the rat; glyceraldehyde-3-phosphate dehydrogenase, β-actin, and cofilin in the dog) representing each type of stop codon (UAA, UAG, UGA). Despite the expected occurrence of toxicological effects and high drug exposure levels, there was no evidence of a PTC124 effect on nonspecific ribosomal readthrough of normal stop codons.

Evaluations of PTC124 in the Ames test in several bacterial tester strains and with the chromosomal aberration test in Chinese hamster ovary (CHO) cells indicate that PTC124 is unlikely to be mutagenic or genotoxic. Testing for clastogenic potential of PTC124 in the rat micronucleus assay was similarly negative at all doses tested including the maximum dose of 1600 mg/kg.

The hERG-channel assay demonstrates that PTC124 is unlikely to induce QT interval prolongation. Similarly, PTC124 showed no evidence of substantial ancillary pharmacological activities against clinically relevant enzymatic and receptor targets, as assessed in the routine off-target pharmacological profiling panel performed by NovaScreen Biosciences Corporation, Cleveland, OH.

Evaluation of PTC124 in long-term GLP toxicological studies in rats and dogs is in progress.

4.2.6. Drug Metabolism

Administration of ^{14}C-PTC124 PO to rats resulted in recovery of approximately 80% of administered radioactivity in feces and approximately 20% in urine. The radioactive pharmacokinetic (PK) profile had 2 C_{max} values, suggesting the prospect of absorption at ≥1 site in the gastrointestinal tract and/or enterohepatic circulation. There were no apparent gender-related differences in absorption, distribution, or elimination in rats. In vitro metabolism studies document that approximately 15% of PTC124 is converted to a methyl ester by human hepatocytes; this metabolite has been shown to have minimal activity in in vitro assays of nonsense suppression. As expected given its low solubility, PTC124's protein binding was high in all species. PTC124 does not appear to interfere with the metabolism of known cytochrome P450 substrates in a hepatic microsome assay.

4.3. Rationale for Use

Based on the preclinical activity and mechanism of action studies available to date, PTC124 has demonstrated the potential to offer an orally bioavailable therapy for patients with nonsense-mutation-induced DMD by specifically and selectively promoting ribosomal readthrough of dystrophin mRNA containing a premature stop codon. Furthermore, preclinical toxicity, toxicokinetic, safety pharmacology, genotoxicity, and drug metabolism studies confirm that PTC124 has the potential to treat DMD and other genetic disorders safely.

4.4. Proposed Clinical Development of PTC124

4.4.1. Overview

In the initial stages of the clinical development program, PTC Therapeutics proposes to conduct clinical trials leading toward registration of PTC124 in the treatment of patients who have nonsense-mutation-mediated DMD. Based on currently available information, the preliminary clinical development plan for DMD calls for conduct of 4 clinical trials to evaluate PTC124's

safety, activity, and PK, and to document its ability to significantly improve relevant surrogate markers and clinical benefit endpoints. These studies include 2 Phase 1 studies in healthy volunteers, and 1 Phase 2 and 1 Phase 3 study to evaluate activity, efficacy, and safety in patients with DMD. The plan for clinical studies is outlined below and is expected to evolve as additional preclinical and clinical data become available, further opinion is obtained from experts in the therapy of DMD and other genetic disorders, and consultation with the FDA occurs.

The drug's mechanism of action and the available preclinical data suggest that PTC124 may be effective in the treatment of other genetic disorders mediated by nonsense mutations. PTC Therapeutics anticipates developing this product for use in cystic fibrosis. The company submitted an application and was granted orphan product designation for use of PTC124 in the treatment of cystic fibrosis resulting from a nonsense (premature stop codon) mutation in the cystic fibrosis transmembrane conductance regulator gene [14].

4.4.2. Healthy-Volunteer Phase 1 Studies

4.4.2.1. Phase 1 Single-Dose Study

Phase 1 clinical testing began with a single-site, randomized, double-blind, placebo-controlled, escalating single-dose safety and PK study of PTC124 in healthy young adult volunteers. This study was initiated in June of 2004 and completed accrual in August 2004. The trial was designed to evaluate safety, PK, palatability, and the influence of food on drug absorption. The trial was conducted in 2 stages: dose finding was performed in Stage 1 over a range of PTC124 doses from 3 to 200 mg/kg, and food effects were evaluated in Stage 2 in subjects receiving a PTC124 dose of 50 mg/kg.

The results indicate that oral administration of single doses of PTC124 through doses of 100 mg/kg can safely achieve target plasma concentrations exceeding the 10- to 20-μg/mL values that were maximally active in vitro in mdx myocytes (see Section 4.2.1.2). Transient mild gastrointestinal events (nausea, vomiting, and diarrhea) and headache were commonly noted at drug levels of 150 and 200 mg/kg and appeared to be drug-related. Findings of dizziness in several subjects, and delayed elevations of serum ALT and AST in a single subject treated at 200 mg/kg were of uncertain relationship to study drug. Other events without a dose-response relationship and with alternative medical explanations included eye pain, eye swelling, eye burning, nipple sensitivity, breast tenderness, musculoskeletal chest pain, elevated serum CK, elevated LDH, elevated aldolase, and elevated serum triglycerides; these events appeared unlikely to be drug-related. The formulation was generally palatable; there was no odor reported and objectionable bitterness and grittiness were noted only at doses >100 mg/kg. Based on evaluation of all adverse events, laboratory parameters, ECGs, and palatability assessments, the maximum well-tolerated dose was estimated to be 100 mg/kg.

PTC124 PK followed a 1-compartment model. Based on values from the model, mean T_{max} occurred at ~1 to ~3 hours and the mean $t_{1/2}$ ranged from ~2 to 5 hours. At the maximum well-tolerated dose of 100 mg/kg, the mean C_{max} was 206.7 μg/mL and the mean AUC_{0-24} was 2047 μg·hours/mL. Increases in C_{max} were generally proportional to PTC124 dose. Increases in AUC values were somewhat greater than dose proportional as the dose increased from 3 mg/kg to 150 mg/kg but were less than dose proportional in the transition from 150 mg/kg to 200 mg/kg. No

sex-related differences in PK parameters were observed. Ingestion of a high-fat, high-calorie meal just prior to administration of 50 mg/kg of PTC124 did not alter C_{max}. The meal only modestly increased AUC by shifting the mean T_{max} from a fasting value of ~1.2 hours to a fed value of ~1.8 hours and by lengthening the mean $t_{1/2}$ from 3.4 hours to 4.2 hours.

4.4.2.2. Phase 1 Multiple-Dose Study

This will be a Phase 1 escalating multiple-dose, single-site, safety, and PK study in healthy volunteers ≥18 and ≤30 years of age. Enrollment and follow-up are planned to occur from October to January 2005. The study will be conducted in 2 stages. In Stage 1, the safety and PK profile during 7 consecutive days of dosing will be evaluated over a range of PTC124 doses in 4 cohorts of 6 subjects each (3 males, 3 females). Based on available nonclinical and clinical pharmacology, safety, and PK data, planned dose levels in Stage 1 are 10, 20, 30, and 50 mg/kg twice per day (BID) given with food over the planned 7 days (resulting in total daily doses of 20, 40, 60 and 100 mg/kg/day). Once the subjects enrolled to the highest safe dose level in Stage 1 have completed the required follow-up, 6 newly recruited subjects (3 males and 3 females) will be enrolled in Stage 2 to evaluate the effect of 14 consecutive days of dosing on the safety and PK of PTC124. These subjects will also receive PTC124 BID with food. In Stage 2, the dose level will be determined by the study monitor based on analysis of the collective safety and PK data from Stage 1 of the study.

4.4.3. Duchenne Muscular Dystrophy Phase 2 and 3 Studies

PTC Therapeutics proposes to conduct 2 clinical trials leading to registration of PTC124 in the treatment of patients who have nonsense-mutation-mediated DMD (as determined by sequencing of each patient's dystrophin gene to document the presence of a premature stop codon).

4.4.3.1. Phase 2 Pharmacodynamic Study

The first study will be a 6-month, Phase 2, randomized, dose-ranging efficacy, safety, and PK study in 18 to 24 boys (ages ≥3 years). This study will be conducted in 2 stages: in Stage 1, the activity, safety, and PK effects of a range of 2 dose levels will be evaluated in each patient during two 6-week cycles (4 weeks on therapy followed by 2 weeks of rest); in Stage 2, efficacy and safety parameters will be followed in the same patients during continuous PTC124 therapy administered for 3 months at the highest individually tolerable dose level identified in Stage 1. The primary endpoint will be evaluation of immunofluorescence for dystrophin protein in the skeletal muscle (eg biceps or tibialis anterior). Pharmacological activity will also be assessed by effects on additional efficacy measures (serum creatine kinase, urinary creatinine excretion, standardized muscle strength evaluations, timed function tests, overall functional grade for upper and lower extremities, and maximum hand-held weight that can be lifted while sitting). In addition, patients will undergo evaluations for PTC124 PK.

4.4.3.2. Phase 3 Clinical Benefit Study

Following the Phase 2 study, PTC Therapeutics proposes to sponsor a 6-month, Phase 3, randomized, placebo-controlled, double-blind, efficacy and safety study in 48 boys (ages ≥3 years) to document PTC124-mediated quantitative improvements in muscle strength as the primary endpoint. Additional measures of clinical benefit (timed function tests, overall

functional grade for upper and lower extremities, and maximum hand-held weight that can be lifted while sitting), will also be evaluated. Pharmacological activity will also be assessed by confirmation of dystrophin expression by muscle biopsy, change in serum creatine kinase, and urinary creatinine excretion. If successful, data from the Phase 2 and Phase 3 studies will form the basis for submission of the New Drug Application to the FDA.

PTC Therapeutics will working closely with the Division of Neuropharmacology Drug Products to ensure early conformance with applicable regulatory requirements and acceptability of the study design of the clinical studies prior to their initiation.

5. CLINICAL SUPERIORITY

As noted in Section 3.1 above, current therapies for DMD are palliative and supportive, offering only partial relief from disease-related symptoms. Most DMD patients will suffer substantial morbidity, compromised quality of life, and a greatly reduced life expectancy. New, more effective therapies aimed at correcting the DMD phenotype by inducing production of full-length, functional dystrophin protein are clearly needed. Nonsense mutations are the basis for approximately 10-15% of the individual cases of DMD [7]. Drug treatment approaches that selectively promote ribosomal readthrough of nonsense mutations in mRNA have the potential to treat genetic disorders such as DMD.

As has been shown in preclinical systems, existing drugs such as the aminoglycoside group of antibiotics, which have translation-modifying mechanisms of action, can suppress the effects of nonsense mutation. Intravenous administration of gentamicin has been shown to induce full-length dystrophin production as shown by immunofluorescence staining for protein in the biceps muscle in a pilot study [10]. While these data are encouraging in documenting proof of concept, the serious renal toxicities, otic toxicities, and the inconvenience of parenteral administration, preclude the long-term clinical use of high-dose gentamicin.

Based on the high unmet medical need and the inadequacies of chronic aminoglycoside therapy for DMD, there has been considerable interest in the identification of more suitable, small-molecular-weight, synthetic, orally bioavailable compounds with the ability to promote readthrough of disease-causing nonsense mutations. PTC124 represents such a drug; development of PTC124 offers a unique approach to the treatment of DMD, coupling the testing for a specific type of gene defect with an orally bioavailable, practical-to-deliver small molecule therapy that has the potential to correct the phenotypic expression of that genetic defect, and thus to significantly improve disease-related morbidity and mortality.

6. MEDICAL PLAUSIBILITY OF SUBSET

Given the specificity of PTC124 for nonsense mutation suppression, its activity is expected to be limited to patients with DMD who have a premature stop codon in the dystrophin gene as the basis for disease. Activity is not anticipated in patients who have DMD due to deletions, missense, or frameshift mutations in the alleles of the gene. This contention is supported by a proof-of-concept study in which topical application of intranasal gentamicin was evaluated for anatomic and functional activity in patients with cystic fibrosis [15]. Only those patients with at least 1 nonsense mutation in the cystic fibrosis transmembrane regulator gene responded to gentamicin nonsense suppression therapy. Patients with other mutation types (eg, deletions or missense mutations) showed no evidence of protein production or activity. Given the nature of

its mechanism of action, Phase 2 and Phase 3 clinical development of PTC124 in DMD must be limited to patients with nonsense mutations who have the potential to have some clinical benefit. Accordingly, product labeling would be similarly restricted to a subset of patients with DMD.

7. REGULATORY STATUS & MARKETING HISTORY

In the United States, PTC Therapeutics submitted an Investigational New Drug Application (IND 48,648) to the Division of Pulmonary and Allergy Drug Products in May 2004 and the Phase 1 clinical program was initiated in mid-June 2004. This IND is supporting the Phase 1 single-dose trial and Phase 1 multiple-dose trials (see Section 4.4.2). As appropriate, it is intended that PTC Therapeutics will have an end-of-Phase 1 meeting with the Division to discuss plans for the Phase 2 and Phase 3 studies in patients with cystic fibrosis. The company also plans to hold a pre-IND meeting with the Division of Neuropharmacology Drug Products and file an IND (PIND 68,431) in the first quarter of 2005 to support the initiation of a Phase 2 study in DMD.

There have been no clinical studies, regulatory filings or regulatory actions in any other country, and PTC124 has never been marketed for any purpose.

8. PREVALENCE OF THE DISEASE

It is possible to estimate the prevalence of patients with DMD who might be eligible for PTC124 treatment in the United States in the Year 2004 by constructing a model based on birth rate data, the projected annual incidence of the disease, the projected median survival for the disease over time, and the proportion of patients who have a nonsense mutation as the basis for the disease. An upper bound on the number of people in the United States with DMD in 2004 was estimated based on the following information and assumptions.

- The numbers of yearly live births in the United States since 1960 were obtained from official sources [16]. From 1960 to 2002, yearly data regarding the number of births are available. Given the fact that the number of births in 2002 was actually lower than in 2001, the number of births in 2003 and 2004 (years for which data are not yet available) were assumed to be the same as in 2002.
- The number of yearly live male births in the United States was calculated by multiplying the number of births in a given year by the proportion of those births expected to be male. This proportion (1048 male births for every 1000 female births) has not appreciably changed over the last half century [16].
- Based on data generated in several locations in the United States and over several decades [17], it was assumed the incidence of DMD was constant over the period 1960 to 2004 at 300 per 10^6 live male births. The use of this figure may provide a slight overestimate because most incidence calculations fall in the range between 250 and 300 per 10^6 live male births [17].
- As shown in Table 2, published data provide estimates of survival in patients with DMD by decade over the time span between 1960 and 2002 [18]. These data indicate a survival improvement that has been attributed primarily to introduction of ventilatory support during adolescence [18,19]. It has also been speculated that other supportive therapies may have played a role (eg, medical reduction of cardiac afterload, early application of antibiotics for

infections, corticosteroid use to main muscle strength, and spinal surgery to improve posture) [18, 20]. All of these treatments have become established as part of routine care by the 1990s. From these data, a linear function can be derived that estimates the median survival for any given calendar year:

Median survival (years) = 0.2025*Year-383.09

Using this equation, the median survival in 2004 can be projected as 22.8 years.

Table 2. Estimated Median Survival Since 1960 in Patients with DMD

Time Period	Median Survival (years)
1960-1969	14
1970-1979	18
1980-1989	19.5
1990-2002	20.5
2004	22.8*

*Projected using linear equation (y=0.2025 *Year-383.09)
Reference [18]
Abbreviation: DMD = Duchenne muscular dystrophy

- For each year of birth from 1960 to 2004, the number of patients with DMD born in that year who are still alive in 2004 was estimated from an exponential survival curve defined by the median survival obtained from the above function.

Table 3 depicts the estimated prevalence of DMD in 2004, based on these assumptions.

Table 3: Estimated Prevalence of DMD in the Year 2004 Based on Birth Data and Survival Estimates Since 1960

Year	Number of Live Male Births	Number of Births with DMD	Median DMD Survival (yrs)	Probability of Surviving to 2004	Number of DMD Patients Still Alive in 2004	Cumulative Total Number of DMD Patients Still Alive in 2004
1960	2231113	669	13.9	0.111	74	74
1961	2236603	671	14.1	0.121	81	155
1962	2183698	655	14.3	0.131	86	241
1963	2147362	644	14.5	0.141	91	332
1964	2110405	633	14.7	0.152	96	428
1965	1970428	591	14.9	0.163	96	524
1966	1889688	567	15.1	0.175	99	623
1967	1844983	553	15.3	0.187	104	727
1968	1834820	550	15.5	0.200	110	837
1969	1886508	566	15.7	0.214	121	958
1970	1955246	587	15.9	0.227	133	1091
1971	1863328	559	16.1	0.242	136	1227
1972	1707407	512	16.3	0.257	131	1358
1973	1643770	493	16.5	0.272	134	1492
1974	1655818	497	16.7	0.288	144	1636
1975	1647560	494	16.9	0.305	151	1787
1976	1659921	498	17.1	0.322	160	1947
1977	1743155	523	17.3	0.340	178	2125
1978	1746638	524	17.5	0.358	187	2312
1979	1831065	549	17.7	0.377	207	2519

Table 3: Estimated Prevalence of DMD in the Year 2004 Based on Birth Data and Survival Estimates Since 1960

Year	Number of Live Male Births	Number of Births with DMD	Median DMD Survival (yrs)	Probability of Surviving to 2004	Number of DMD Patients Still Alive in 2004	Cumulative Total Number of DMD Patients Still Alive in 2004
1980	1892823	568	17.9	0.396	224	2743
1981	1901721	571	18.1	0.415	237	2980
1982	1928601	579	18.3	0.436	252	3232
1983	1906801	572	18.5	0.456	261	3493
1984	1922630	577	18.8	0.477	275	3769
1985	1970534	591	19.0	0.499	295	4064
1986	1968431	591	19.2	0.521	308	4372
1987	1996122	599	19.4	0.544	325	4697
1988	2048583	615	19.6	0.567	349	5046
1989	2117462	635	19.8	0.591	375	5421
1990	2178903	654	20.0	0.615	402	5823
1991	2154115	646	20.2	0.640	414	6237
1992	2130067	639	20.4	0.665	425	6662
1993	2096126	629	20.6	0.690	434	7096
1994	2071250	621	20.8	0.716	445	7541
1995	2043385	613	21.0	0.743	455	7996
1996	2039143	612	21.2	0.770	471	8467
1997	2033588	610	21.4	0.797	486	8953
1998	2065374	620	21.6	0.825	511	9464
1999	2074735	622	21.8	0.853	531	9995
2000	2126819	638	22.0	0.882	562	10557
2001	2109589	633	22.2	0.911	577	11134
2002	2107384	632	22.4	0.940	594	11728
2003	2107384	632	22.6	0.970	613	12341
2004	2107384	632	22.8	1.000	632	12973

Abbreviation: DMD = Duchenne muscular dystrophy

The resulting Year 2004 prevalence for the United States was calculated to be 12,973 patients. This figure appears to correspond appropriately with data regarding known DMD patients documented in the Muscular Dystrophy Association (MDA) registry. The Year 2004 estimated value of 12,973 compares with an MDA registry value of approximately 8,100 patients (Dr. Sharon Hesterlee, MDA – personal communication). These values are consistent when it is considered that the projected prevalence number for the total population is probably an overestimate due to use of a high incidence rate and the registry value almost certainly represents an underestimate due to underreporting.

It has been estimated that 13% of the patients with DMD in the United States have the disease secondary to a nonsense mutation [7]. Because PTC124 therapy can only be applied in this proportion of the total population with DMD, the estimated prevalence of patients for which the drug will be indicated is <2000 in 2004. This figure is well below the 200,000 upper bound for orphan product designation.

9. PARTY OF INTEREST IN DEVELOPMENT, MANUFACTURING, AND SALES

PTC Therapeutics, Inc. is the sole party of interest in the development, manufacturing, and intended sales of PTC124 in the United States.

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Exhibit B

Update on the management of Duchenne muscular dystrophy

Adnan Y Manzur, Maria Kinali and Francesco Muntoni

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Update on the management of Duchenne muscular dystrophy

Adnan Y Manzur, Maria Kinali, Francesco Muntoni

Dubowitz Neuromuscular Centre, Department of Paediatric Neurology, Great Ormond Street Hospital for Children, Institute of Child Health, London, UK.

Disclosures

Adnan Manzur is the lead clinician for UK North Star Clinical Network for Paediatric Neuromuscular Disorders, which is in part funded by Muscular Dystrophy Campaign UK. Francesco Muntoni and Maria Kinali are involved in the phase I/IIa trial using morpholino antisense oligomers in DMD. The study is funded by the Department of Health and Imperial College London is the study sponsor.

The three authors have no financial competing interests to declare.

Correspondence to:

Dr Adnan Y Manzur

Consultant Paediatric Neurologist

Great Ormond Street Hospital for Children NHS Trust

Great Ormond Street,

London WC1N 3JH

Email: manzua@gosh.nhs.uk

Summary

Duchenne Muscular Dystrophy (DMD) is familiar to paediatricians as the most common childhood muscular dystrophy, leading to severe disability and early death in late teenage years, if untreated. Improvement in general care, glucocorticoid corticosteroid treatment, non-invasive ventilatory support, cardiomyopathy and scoliosis management have significantly changed the course of the DMD in treated individuals, so that survival into adulthood is now a realistic possibility for most DMD patients. This has important implications for the medical and social sectors to provide transition to adult medical services, suitable employment, and social care. Multidisciplinary team working for optimal management of the DMD-specific multisystem complications is essential, and collaboration in disease specific national clinical networks is recommended. Several curative therapeutic strategies including cell and gene therapy in DMD are being pursued, but these are still at an experimental stage.

Key words: Duchenne muscular dystrophy, management, therapy, North Star clinical network.

Introduction

Duchenne Muscular Dystrophy (DMD) affects 1 in every 3,500 live male births. Paediatricians are familiar with the course of *untreated* DMD: common presentation is with abnormal gait, calf hypertrophy and difficulty in rising from the floor between 2 to 5 years of age [1]. Progression of muscle weakness and leg contractures leads to loss of walking and complete wheelchair dependence, at a mean age of 9.5 years, and the ensuing early teenage years are marked by development of progressive scoliosis. The leading cause of death is respiratory insufficiency in the late teens or early twenties, though a minority demise because of cardiac complications such as dilated cardiomyopathy. Feeding difficulties and weight loss are common in the late stages of the disease.

No curative treatment for DMD is yet known, but advances in management over the last two decades have altered the natural history of DMD, so that most of these individuals can now be anticipated to survive into adulthood. The multisystem complications of DMD necessitate a multidisciplinary team approach for optimal surveillance and management (table 1). This review describes the advances in management and outlines the challenges to paediatric practice to achieve early diagnosis, the best possible outcome, quality of life and transition to adulthood.

Table 1. The multidisciplinary team for management of DMD. The predictable evolution of disease course and multisystem complications in DMD allows a plan for input from various disciplines at the appropriate time.

	Core team. Continuous follow up through childhood	Complication dependent follow up
Doctors	Paediatrician	Geneticist
	Neurologist	Muscle histopathologist
	GP	Orthopaedic surgeon
		Pulmonolgist / intensivist
		Cardiologist
		General surgeon
Therapists	Physiotherapist	Orthotist
		Dietitian
		Speech and language therapist
		Occupation therapist
		Wheel chair specialists
		Psychologist
Other associated professionals	Hospital / community nurse	Family care officer
		Social services worker

Genetics and Pathophysiology

A brief review of the molecular genetic basis of DMD is necessary to understand the approach to diagnosis and limitations of the various diagnostic techniques. DMD is caused by mutations in the Dystrophin gene on the X chromosome at Xp21. The dystrophin locus contains 85 exons and encodes for a large but low abundance protein, named dystrophin [2]. Dystrophin is a rod shaped molecule, which localises at the cytoplasmic side of the sarcolemma: one end binds to the dystrophin associated glycoprotein complex at the sarcolemma while the other end binds to the cytoskeletal actin. Dystrophin is postulated to be essential for force transduction by providing a indirect link between the contractile apparatus in the muscle fibre with the extracellular matrix. The mutations in the dystrophin gene which result in DMD cause disruption of the reading frame, resulting in a severe reduction or complete absence of dystrophin in the skeletal and cardiac muscle, which in tum leads to mechanically induced sarcolemmal damage, loss of intracytoplasmic calcium homeostasis, and muscle fibre degeneration. Several dystrophin Isoforms are also expressed in brain and their

deficiency in this tissue is responsible for the mental retardation which complicates the course of DMD in approximately 1/3 of cases.

Approximately 65% of patients with DMD have intragenic out-of-frame (gross rearrangements) deletions and approximately another 10% have duplications of one or more exons of the dystrophin gene. The remaining patients have point mutations or other smaller gene rearrangements (pure intronic deletions, insertions of repetitive sequences, splice site mutations). As a general rule out-of-frame dystrophin gene mutations lead to a severe reduction or absence of dystrophin in the muscle resulting in DMD phenotype, whereas in-frame mutations lead to the expression of abnormal but partly functional truncated dystrophin protein, resulting in the milder Becker muscular dystrophy (BMD). The frame shift hypothesis holds true for over 90% of cases and is commonly used both for diagnosis and for differentiating between DMD and BMD. There are important exceptions to the frame shift rule; in-frame mutations in the gene coding for the crucial actin-binding domain of dystrophin protein may cause the Duchenne severity phenotype, where as some out of frame mutations are associated with BMD [2].

The X linked recessive inheritance of DMD is well recognized, but there is a high incidence of new mutations and two-thirds of the cases do not have a positive family history at presentation.

Diagnosis

Delay in diagnosis of cases without a family history, to over four and half years of age, continues to be a problem [3]. The principal reasons for missing the diagnosis on parents initial contact with the health professionals, is the failure to see the child "running" and rising from the floor (thereby missing the valuable clues of waddling gait and Gowers' manoeuvre). In addition it is often not appreciated that that global developmental delay is a frequent early presentation of DMD [4]. Table 2 lists the various presentations of DMD.

Table 2. The various presentations of DMD

Motor Presentations
• Walking delayed beyond 18 months
• Frequent falls
• Foot posture abnormalities / deformities
• Toe walking
• Waddling gait
• Difficulty running / rising from the floor

Non-motor Presentations*

- Global developmental delay
- Severe learning difficulties / "Autism"
- Failure to thrive
- "Liver disease" – Elevated ALT, AST discovered incidentally during investigation of intercurrent or other illness
- Myoglobinuria, rhabdomyolytic hyperkalemic, malignant hyperthermia-like reaction to suxamethonium, halothane or other halogenated inhaled anaesthetics during anaesthesia

* Motor difficulties are present when specifically looked for, but are often missed because the clinical presentation is dominated by other issues.

Serum Creatine Kinase (CK) is massively elevated (10-100 x normal since birth) and should be the first investigation when DMD is suspected. A high CK should prompt urgent specialist referral for confirmation. A normal CK at presentation excludes the diagnosis. CK levels fall with disease progression reflecting muscle wasting and reduced physical activity. CK therefore is not a reliable screening test in late presenters who are already constant wheelchair users. Electromyography (EMG) has no role in the investigation of DMD and should not be requested.

The last decade has seen important advances in molecular genetic testing to identify Dystrophin gene mutations. As most DMD patients carry deletions in two mutational hot spots of the gene, the screening of only 19 exons, following amplification of genomic DNA, could identify mutations in over 65% of cases with DMD [5]. An important limitation of the technique is not only the inability to identify rarer mutations but also the breakpoint of several common deletions. More recently other testing, such as multiplex ligation dependent probe amplification method [6], or more recently a combinatorial strategy using the fluorescent multiplex quantitative PCR followed by conformation sensitive capillary electrophoresis (CSCE) of the same PCR products on a multi-capillary genetic analyser[7] , have increased the efficiency of mutation detection close to 100%. These techniques have the additional advantage of being able to unequivocally detect mutations in carrier females, allowing a precise genetic counselling of affected families. Molecular genetic documentation of a dystrophin mutation confirms dystrophinopathy (dystrophin gene related muscular dystrophy); determination of the endpoints of the mutation establish the in/out-of-frame status, and may allow assignment of the severity with regards to Duchenne or Becker phenotype, but exceptions to the frame shift hypothesis have been described [2]. Establishing the precise diagnosis of DMD is therefore best achieved by a combination of clinical observation of the patient's strength and functional abilities,

ascertainment of dystrophin levels on muscle biopsy and knowledge of the gene mutation[8].

Dystrophin protein assay on muscle biopsy in DMD shows severe reduction or complete absence and allows the most robust diagnosis. Muscle sample can be obtained by a needle biopsy under oral sedation [9]. It is our unit policy at the Dubowitz Neuromuscular Centre to offer a muscle biopsy (in addition to molecular genetic testing) as the first and confirmatory test to boys with suspected DMD, unless there is positive family history in a sibling, or the presentation is late (after 7 years of age) when the disease course is clearly in the Duchenne severity range.

Female carriers of DMD: The advances in molecular genetics now allow precise evaluation of carrier status of the relevant females in the family. In addition to accurate counselling and antenatal diagnosis, determination of carrier status is important as carriers have a 10% life time risk of developing cardiomyopathy [10], and this allows institution of appropriate surveillance and treatment protocols.

Physiotherapy and orthoses

Physiotherapy to promote walking and prevent joint deformities, remains important and detailed recommendations are available [11]. Rehabilitation in knee ankle foot orthoses (KAFOs) is offered to DMD boys at the end of independent ambulation, and is effective in prolonging walking for an average of 18 months to two years [12]. The technique entails custom-built KAFOs, and used to require surgical release of the tendon Achilles, to reduce ankle contracture, to allow fitting of KAFOs, and is generally well tolerated [13]. We have recently shown that serial casting of the ankles can be offered instead of the surgical release of the Achilles tendons in many cases[14].

Glucocorticoid corticosteroids

To date, glucocorticoid corticosteroids have been the most effective medication in DMD, and a Cochrane systematic review of the glucocorticoids in DMD is available [15].

Randomised controlled trials (RCT) have shown that treatment with prednisone can stabilise of strength and function for 6 months to 2 years [15]. Prednisone has been the most widely used medication and the starting dose of 0.75mg/kg/day. Non-randomised studies with prednisone or deflazacort, have documented prolongation of walking ability, preservation of respiratory function and reduction in the incidence of scoliosis and cardiomyopathy in Duchenne boys who tolerated long-term daily dose corticosteroids [16].

Predictably, the daily glucocorticosteroid therapy has significant side effects, notably, in the short-term weight gain can be a bothersome side effect and dietetic input from initiation of steroid therapy helps prevent/ ameliorate this side effect. Vertebral fractures are a significant side effect in approximately a third of the long-term treated patients [17]. The Dubowitz intermittent regime was recommended to reduce the adverse effects associated with the daily steroid regimes; a six month RCT of Prednisone 0.75 mg/kg/day for the 1st 10 days of every month, demonstrated slowing of functional deterioration [18], and international RCT to compare daily dose prednisone and deflazacort with intermittent prednisone regime is planned [19].

A consensus on the role of corticosteroids in DMD is emerging after careful consideration of pros and cons of long-term steroid treatment, based on expert and evidence based reviews [19, 20]. Corticosteroids should preferably be started in all early ambulant cases (4 - 6 years) and in most of the older ambulant children, unless contraindicated. Treatment needs to be monitored for benefit, adverse effects. The optimal starting dose of prednisolone 0.75 mg/kg/day is often not tolerated in the long term and, over the course of years, careful dose adjustment is required. Regular reviews, in collaboration with specialist centre allows for appropriate monitoring, dosing and adverse effects management. Optimising bone health in corticosteroid treated patients includes dietary advice regarding calcium and vitamin D, and supplementation if plasma Vitamin D levels are low [21]. There is currently no evidence that oral bisphosphonates should be used prophylactically in children receiving steroids; however their acute administration is recommended in the treatment of vertebral fractures, where they are very effective.

In the UK, North Star Clinical Network for Paediatric Neuromuscular Disorders (NSCN) is a Muscular Dystrophy Campaign UK (MDC) sponsored collaboration between 16 specialist centres caring for boys with DMD (http://www.muscular-dystrophy.org/research/northstar/). The clinicians on the NSCN have a consensus on the treatment and standardised assessment protocols for the use of glucocorticosteroids in DMD, and are prospectively collecting data on a web based database to allow audit of clinical practice and refinement of the protocols. It is anticipated that this approach will standardize the steroid related DMD management in the UK regardless of postcode.

Management of respiratory complications

The teenage years in DMD are marked by worsening respiratory reserve and sleep hypoventilation, which is a sequel of respiratory muscle weakness, REM sleep, related

hypoxemic dips [22] and obstructive apnoeas [23]. The resulting symptoms may include morning drowsiness, poor appetite, headaches, nausea, fatigue, tiredness, poor concentration at school, failure to thrive, reduced coughing ability or overt respiratory failure in the course of "minor" respiratory infections. In untreated patients who become hypercapnic, the survival is less than a year[24] .

Until recent decades, the onset of symptomatic sleep hypoventilation signified imminent demise, as the only way to prolong life was mechanical ventilation through tracheostomy, and this was limited by the complex ethical issues of invasive ventilation of patients with totally incapacitating and incurable disease. In the recent years, domiciliary non-invasive ventilation (NIV) has proven effective in symptom relief and prolonging survival [25]. The patient's breathing at night is augmented with breaths delivered by a compact, portable ventilator with a snugly fitting facial or nose mask. NIV corrects sleep hypoventilation and affords symptom relief without significant encroachment on living space or restriction of travel. NIV, and if needed, the use of cough assist devices, can extend average survival to mid-twenties and in some cases to the fourth decade [26, 27]. This has led to the opinion that denying NIV to hypercapnic DMD patients is unethical [28 25].

Forced vital capacity (FVC) predicts the development of hypercapnia and survival [29]. Regular monitoring for symptoms of sleep hypoventilation, FVC, and overnight sleep studies when the FVC falls below 50% allow for timely initiation of NIV. Gradual initiation of NIV in individuals with nocturnal hypercapnia but daytime normocapnia is a valid approach, as waiting for daytime ventilatory failure exposes patients to minor chest infections and uncontrolled decompensation[24].

Management of cardiac complications

Dilated cardiomyopathy (DCM) occurs in up to 90% of DMD individuals ≥18 years [30]. The severity of the physical disability of DMD boys in the late teens and later on masks the clinical symptoms of cardiac failure unless these are very florid; traditionally cardiomyopathy was considered responsible for death in up to 20% of DMD individuals; however this proportion is likely to increase over the coming years in individuals in whom NIV prevents respiratory related mortality. The optimal timing of introducing therapy for DCM remains an unresolved issue. Duboc et al [31] reported that early treatment with perindopril delayed the onset and progression of prominent LV dysfunction, and was associated with lower mortality [32] in DMD. Some cardiologists suggest that treatment is not necessary for a complication that is often asymptomatic for a long time before deteriorating into clear-cut cardiac failure [33] , although this view

is at odds with the current evidence on related forms of DCM, in which early treatment is clearly superior compared to late therapy[34]. Indeed considering the well-described incidence and clinical course of DCM in DMD, and the recent suggestions from several groups of the positive effect of therapeutic intervention, the most logical approach appears to intervene before a too severe damage has occurred.
While awaiting the results of RCT, the published consensus documents recommend the use of Angiotensin converting enzyme (ACE) inhibitors, beta blockers and diuretics [(79)] in patients with early cardiomyopathy [34]. It is important to look for and treat co-existing nocturnal hypoventilation, which aggravates cardiac function.

The risk of cardiac involvement in carriers of DMD is approximately 10%, and this may occur in the absence of muscle weakness[35]. Genetic counselling should include informing the carriers of the cardiac risks and plan for surveillance and treatment.

Scoliosis management

Scoliosis usually develops after loss of walking, shows rapid progression during pubertal growth spurt and adversely affects respiratory function, feeding, seating and comfort. The reduced incidence and severity of scoliosis in glucocorticosteroid treated boys [16] is likely to be secondary to prolongation of walking and increase in truncal muscle strength.
Progression of the spinal curve is the indication for surgical spinal fusion, and the optimum time for making the decision is when the range of the curve's Cobb angle is $20^0 - 40^0$ [36]. Multidisciplinary team input to make the decision to offer surgery, and pre-operative assessment are essential to ensure that the operation is safe and choosing a time when the FVC is above 30% predicted for height, and the cardiac function, as demonstrated by echocardiogram, is good. Spinal surgery can be performed when the FVC is between 20-30%, but the risks are greater, and this should be undertaken in specialized centres [37].
Spinal brace (jacket) does not prevent progression of scoliosis, but may be useful in postural management, especially in cases where spinal surgery is contraindicated or is not acceptable to the patient.

Nutritional aspects

Nutritional difficulties include initial presentation with failure to thrive, obesity during the late ambulant phase, especially in corticosteroid treated individuals, and severe wasting

in the spinal surgery post-operative period and the late teenage years. Regular weight monitoring and dietary advice to avoid obesity should be available to all DMD patients, especially when treated with daily corticosteroids.

Young adults with DMD may have chewing and swallowing difficulties, prolonged mealtimes, choking on food, and failure to thrive [38]. Appropriate facilities for weighing the wheel chair dependent adolescents should be available in the clinics to allow for regular weight monitoring. Patients with failure to thrive and/or swallowing difficulties benefit by dietetic and speech and language therapist's assessment for nutritional supplementation; observation of mealtimes and swallowing videofluoroscopy allow further advice about postural management, feeding aids or gastrostomy insertion.

Survival and transition of care

The improvements in general care and the frequent provision of NIV from 1990s, has improved the mean survival of DMD patients in the UK to 27 years [26, 27], and further prolongation of survival is anticipated as the currently corticosteroid treated cohort matures and accrues the long-term beneficial effects, particularly on respiratory function [16]. This change in natural history of treated DMD means that most of these adolescents are now anticipated to reach adulthood. This underlines the need for development of robust protocols for transition of care to the adult medical teams, and in particular, for the drive to enable improvement in rehabilitation, employment, social participation and social services for the adult with DMD [39]

"Gene therapy" for DMD

The major advances in understanding of the molecular genetics, and pathogenesis of DMD has raised expectation of a curative treatment with gene therapy. Research in this area has been greatly facilitated by the improved understanding of the disease pathogenesis and the use of two naturally occurring animal models; the dystrophic golden retriever dog (GRMD), which suffers a fatal clinical course akin to the humans and the *mdx* mouse which has a stop codon in exon 23 resulting in dystrophin deficient muscle fibres but is not overtly weak, and its survival only minimally limited compared to wild type. A detailed discussion of the various genetic strategies aimed at restoration of dystrophin in the affected muscle [40] is beyond the scope of this article, but they are listed with a basic description and current status in table 3.

Table 3. Strategies for gene therapy in Duchenne Muscular Dystrophy			
Research Strategy	**Action**	**Effect**	**Current Status**
Adeno-associated virus (AAV) vector	Using AAV as a vehicle to transfer "mini-dystrophin" Gene into the affected muscles	Expression of truncated but partly effective Dystropin protein in muscle	Pilot study initiated in Ohio (USA) http://genetherapy.unc.edu/.
Utrophin up-regulation	Utrophin up-regulation in skeletal muscle by pharmacological means	Increased utrophin levels, which has 85% homology with dystophin protein, binds to the dystrophin-glycoprotein complex, and ameliorates dystrophic pathology in transgenic mice	Future clinical trials are planned with VOXC1100 a drug discovered by a UK company VASTox.
Myoblast transplantation	Direct injection of myoblasts in DMD muscle	Studies in the *mdx* mice resulted in expression of dystrophin	No significant dystrophin expression in human studies
Stem cell transplantation	Delivery of stem cells to muscle to give rise to progenitor or precursor cells before differentiating to other cells	*mdx* mice study has shown that human derived pericytes, can differentiate into satellite stem cells	Clinical trials using pericytes are now being planned in DMD
Modification of dystrophin mRNA splicing (Exon skipping)	Antisense oligonucleotides (AOs) used to redirect splicing and induce exon skipping	Temporary restoration of reading frame to allow dystrophin production	Two European Consortia are testing safety and local efficacy of Intramuscular AOs with the view of performing systemic AOs trials in 2008
Read- through of stop codon mutations	Aminoglycosides and the recently produced PTC124 can cause misreading of the RNA code, allowing insertion of alternative amino acids at the site of the mutated codon.	Transcription and dystrophin protein formation in *mdx* mouse muscle. Gentamicin not effective in human study	PTC-124, an orally administered Molecule, is currently being piloted in a Phase II clinical trial in DMD underway. Techinque relevant to ~ 10% of DMD patients who have nonsense point mutations.

Of particular interest is the UK Department of health funded "molecular patch therapy" trial, utilizing the exon skipping approach (http://www.muscular-dystrophy.org/research/), which is a good example of collaborative efforts of basic and clinical scientists, parent and patient organisations, the governmental funding bodies and pharmaceutical industry. The strategy behind the "molecular patches" is the modification of dystrophin mRNA splicing using antisense oligonucleotides (AOs). These small RNA like molecules prevent the normal splicing of the gene by masking crucial areas of the messenger RNA during the splicing process, and induce exon skipping. In DMD patients with out of frame deletions (which represent ~ 65% of all boys) the manipulation of exon skipping can result in deletions that maintain the open reading frame, similar to what is found in the milder BMD. The early proof of concept studies on the role of this approach was obtained in cell cultures of the *mdx* mouse and subsequently demonstrated in DMD cells. Systemic administration of AOs in the *mdx* mouse also resulted in appreciable induction of exon skipping which resulted in dystrophin expression of functional levels in body-wide skeletal muscles of the *mdx* mouse, with corresponding improvement in muscle function [41]. There are several limitations of AOs. Firstly, different deletions will require different AOs and secondly

the treatment is not permanent but limited to the period in which the AO persist in the tissue. AO treatment will therefore require repeated administrations for the entire life of the DMD boys, and whether this will be associated with any toxicity is not known. AOs nevertheless have a fairly good safety profile from data available on human trials. Two European Consortia are currently testing safety and local efficacy of intramuscularly administered AOs with the view of performing systemic AOs trials in 2008. One group is based in Holland (http://prosensa.eu/news/news_may10_06.pdf), and the other in UK (http://clinicaltrials.gov/ct/gui/show/NCT00159250). The results of these studies are expected in 2007, and this will inform the feasibility of future systemic delivery studies.

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Exhibit C

Safety and Efficacy Study of PTC124 in Duchenne Muscular Dystrophy

This study is ongoing, but not recruiting participants.

Sponsors and Collaborators:	**PTC Therapeutics** Muscular Dystrophy Association
Information provided by:	PTC Therapeutics
ClinicalTrials.gov Identifier:	NCT00264888

Purpose

In some patients with Duchenne muscular dystrophy (DMD), the disease is caused by a nonsense mutation (premature stop codon) in the gene that makes the dystrophin protein. PTC124 has been shown to partially restore dystrophin production in animals with DMD due to a nonsense mutation. The main purpose of this study is to understand whether PTC124 can safely increase functional dystrophin protein in the muscles of patients with DMD due to a nonsense mutation.

Condition	Intervention	Phase
Duchenne Muscular Dystrophy	Drug: **PTC124**	Phase II

Genetics Home Reference related topics: Duchenne and Becker muscular dystrophy L1 syndrome

MedlinePlus related topics: Muscular Dystrophy

U.S. FDA Resources

Study Type: Interventional
Study Design: Treatment, Non-Randomized, Open Label, Dose Comparison, Single Group Assignment, Safety/Efficacy Study

Official Title: A Phase 2 Study of **PTC124** as an Oral Treatment for Nonsense-Mutation-Mediated **Duchenne Muscular Dystrophy**

Further study details as provided by PTC Therapeutics:

Primary Outcome Measures:

- Dystrophin expression as assessed by immunofluorescence evaluation of tissue obtained by biopsy of the extensor digitorum brevis (EDB) muscle of the foot or tibialis anterior (TA) muscle of the leg

Secondary Outcome Measures:

- Presence of dystrophin mRNA and dystrophin-related proteins on EDB or TA muscle biopsy, muscle function, compliance with treatment, safety and PTC124 pharmacokinetics

Estimated Enrollment: 38
Study Start Date: December 2005
Estimated Study Completion Date: April 2007

Detailed Description:

In this study, patients with DMD due to a nonsense mutation will be treated with a new investigational drug called PTC124. To determine if a patient qualifies for the study evaluation procedures will be performed within 21 days prior to the start of treatment; these procedures include: history, physical examination, blood and urine tests to assess organ function, electrocardiogram (ECG), muscle biopsy for evaluation of dystrophin protein, and DMD-specific tests of muscle function (for patients who are able to perform such tests). Eligible patients who elect to enroll in the study will then participate in a 28-day treatment period and a 28-day follow-up period (56 days total). The first 6 patients to be enrolled will take PTC124 treatment 3 times per day with meals for 28 days at doses of 4 mg/kg (breakfast), 4 mg/kg (lunch) and 8 mg/kg (dinner); these patients will then be observed during a 28-day follow-up period without treatment. Next, 18 additional patients will be enrolled to take PTC124 treatment 3 times per day with meals for 28 days at doses of 10 mg/kg (breakfast), 10 mg/kg (lunch), and 20 mg/kg (dinner); these patients will then be observed during a 28-day follow-up period without treatment. Subsequently, 6-12 additional patients will be enrolled to take PTC124 treatment 3 times per day with meals for 28 days at doses of 20 mg/kg (breakfast), 20 mg/kg (lunch), and 40 mg/kg (dinner); these patients will then be observed during a 28-day follow-up period without treatment. There will be a 2-night stay at the clinical research center at the beginning and at the end of the 28 days of PTC124 treatment. To assess efficacy, patients will have an end-of-treatment biopsy and will undergo DMD-specific tests of muscle function (for patients who are able to perform such tests). To assess safety and pharmacokinetics, safety assessments, blood and urine tests, and ECGs will be performed at prespecified timepoints during the 28-day treatment period and the 28-day follow-up period. At the end of the 56 days, patients will be assessed periodically regarding their general health status; these evaluations will be performed by telephone contact at approximately 6-month intervals in the first 2 years and at approximately 12-month intervals in subsequent years (up to 5 years total).

▶ Eligibility

Ages Eligible for Study: 5 Years and older
Genders Eligible for Study: Male
Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:

- Diagnosis of DMD based on a clinical phenotype presenting by age 5, with increased serum CK and decrease of dystrophin on a muscle biopsy
- Presence of a nonsense mutation in the dystrophin gene
- Physical examination or radiographic imaging documenting the presence of EDB or TA muscles in both legs
- Ability to ambulate, or if non-ambulatory, then not requiring ventilator support
- Male sex
- Age $\geq$ 5 years
- Willingness to abstain from sexual intercourse or employ a barrier or medical method of contraception during the study drug administration and follow-up periods in subjects known to be sexually active

- Willingness and ability to comply with scheduled visits, drug administration plan, laboratory tests, study restrictions, and study procedures (including muscle biopsies, myometry, and PK sampling)
- Ability to provide written informed consent (parental/guardian consent if applicable)/assent (if <18 years of age)

Exclusion Criteria:

- Prior or ongoing medical condition (e.g., concomitant illness, psychiatric condition, alcoholism, drug abuse), medical history, physical findings, ECG findings, or laboratory abnormality that, in the investigator's opinion, could adversely affect the safety of the subject, makes it unlikely that the course of treatment or follow-up would be completed, or could impair the assessment of study results
- Clinical symptoms and signs of congestive cardiac failure
- Positive hepatitis B surface antigen, hepatitis C antibody test, or human immunodeficiency virus (HIV) test
- Hemoglobin <10 g/dL
- Serum albumin <2.5 g/dL
- Abnormal GGT or total bilirubin (>laboratory's upper limit of normal)
- Abnormal renal function (serum creatinine >1.5 times laboratory's upper limit of normal)
- History of solid organ or hematological transplantation
- Ongoing immunosuppressive therapy (other than corticosteroids)
- Exposure to another investigational drug within 28 days prior to start of study treatment
- Ongoing participation in any other therapeutic clinical trial
- Ongoing use of thiazolidinedione peroxisome proliferator-activated receptor gamma (PPAR γ) agonists, e.g., rosiglitazone (Avandia® or equivalent) or pioglitazone (Actos® or equivalent)
- Change in systemic corticosteroid therapy (e.g., initiation of treatment; cessation of treatment; change in dose, schedule, or type of steroid) within 3 months prior to start of study treatment.
- Treatment with systemic aminoglycoside antibiotics within 4 weeks prior to start of study treatment

▶ Contacts and Locations

Please refer to this study by its ClinicalTrials.gov identifier: NCT00264888

Locations

United States, Ohio
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio, United States, 45229-3039

United States, Pennsylvania
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania, United States, 19104-4399

United States, Utah
University of Utah
Salt Lake City, Utah, United States, 84112

Sponsors and Collaborators

PTC Therapeutics

Muscular Dystrophy Association

Investigators

Principal Investigator: Richard Finkel, MD Children's Hospital of Philadelphia

More Information

Study ID Numbers: PTC124-GD-004-DMD
First Received: December 9, 2005
Last Updated: April 19, 2007
ClinicalTrials.gov Identifier: NCT00264888
Health Authority: United States: Food and Drug Administration

Keywords provided by PTC Therapeutics:
Duchenne muscular dystrophy
Nonsense mutation
Premature stop codon

Study placed in the following topic categories:

Muscular dystrophy, Duchenne and Becker type	Genetic Diseases, Inborn
Muscular Dystrophies	Muscular Dystrophy, Duchenne
Muscular Diseases	Genetic Diseases, X-Linked
Becker's muscular dystrophy	Duchenne muscular dystrophy
Muscular Disorders, Atrophic	Atrophy
Musculoskeletal Diseases	Muscular dystrophy
Neuromuscular Diseases	

Additional relevant MeSH terms:
Nervous System Diseases
Muscular Dystrophy, Duchenne

ClinicalTrials.gov processed this record on August 11, 2008

Exhibit D

Phase 2b Study of PTC124 in Duchenne/Becker Muscular Dystrophy (DMD/BMD)

This study is currently recruiting participants.
Verified by PTC Therapeutics, July 2008

Sponsored by:	**PTC Therapeutics**
Information provided by:	PTC Therapeutics
ClinicalTrials.gov Identifier:	NCT00592553

Purpose

Duchenne/Becker muscular dystrophy (DMD/BMD) is a genetic disorder that develops in boys. It is caused by a mutation in the gene for dystrophin, a protein that is important for maintaining normal muscle structure and function. Loss of dystrophin causes muscle fragility that leads to weakness and loss of walking ability during childhood and teenage years. A specific type of mutation, called a nonsense (premature stop codon) mutation is the cause of DMD/BMD in approximately 10-15% of boys with the disease. PTC124 is an orally delivered, investigational drug that has the potential to overcome the effects of the nonsense mutation. This study is a Phase 2b trial that will evaluate the clinical benefit of PTC124 in boys with DMD/BMD due to a nonsense mutation. The main goals of the study are to understand whether PTC124 can improve walking, activity, muscle function, and strength and whether the drug can safely be given for a long period of time.

Condition	Intervention	Phase
Duchenne Muscular Dystrophy **Becker Muscular Dystrophy**	Drug: **PTC124**	Phase II Phase III

Genetics Home Reference related topics: Duchenne and Becker muscular dystrophy L1 syndrome

MedlinePlus related topics: Muscular Dystrophy

U.S. FDA Resources

Study Type: Interventional
Study Design: Treatment, Randomized, Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor), Placebo Control, Parallel Assignment, Safety/Efficacy Study

Official Title: A Phase 2b Efficacy and Safety Study of **PTC124** in Subjects With Nonsense-Mutation-Mediated **Duchenne Muscular Dystrophy** and **Becker Muscular Dystrophy**

Further study details as provided by PTC Therapeutics:

Primary Outcome Measures:

- To determine the effect of PTC124 on ambulation in subjects with nonsense-mutation-mediated DMD/BMD (as assessed by changes in the distance walked during a 6-minute walk test) [Time Frame: 12 months] [Designated as safety issue: No]

Secondary Outcome Measures:

- Activity in the community setting [Time Frame: 12 months] [Designated as safety issue: No]
- Proximal muscle function [Time Frame: 12 months] [Designated as safety issue: No]
- Muscle strength [Time Frame: 12 months] [Designated as safety issue: No]
- Muscle fragility [Time Frame: 12 months] [Designated as safety issue: No]
- Biceps muscle dystrophin expression [Time Frame: 12 months] [Designated as safety issue: No]
- Quality of Life [Time Frame: 12 months] [Designated as safety issue: No]
- Cognitive ability [Time Frame: 12 months] [Designated as safety issue: No]
- Cardiac function [Time Frame: 12 months] [Designated as safety issue: No]
- Frequency of accidental falls during ambulation [Time Frame: 12 Months] [Designated as safety issue: No]
- Treatment satisfaction [Time Frame: 12 Months] [Designated as safety issue: No]
- Safety [Time Frame: 12 months] [Designated as safety issue: Yes]
- Compliance with treatment [Time Frame: 12 months] [Designated as safety issue: No]
- PTC124 pharmacokinetics [Time Frame: 12 months] [Designated as safety issue: No]

Estimated Enrollment:	165
Study Start Date:	February 2008
Estimated Study Completion Date:	August 2010
Estimated Primary Completion Date:	April 2010 (Final data collection date for primary outcome measure)

Arms	Assigned Interventions
1: Active Comparator	Drug: **PTC124** **PTC124** Low Dose
2: Active Comparator	Drug: **PTC124** **PTC124** High Dose
3: Placebo Comparator	Drug: **PTC124** Placebo

Detailed Description:

This study is a Phase 2b, multicenter, randomized, double-blind, placebo-controlled, dose-ranging, efficacy and safety study, designed to document the clinical benefit of PTC124 when administered as therapy of patients with DMD/BMD due to a nonsense mutation (premature stop codon) in the dystrophin gene. It is planned that ~165 boys who are at least 5 years of age and can walk at least 75 meters (80 yards) will be enrolled. Study subjects will be enrolled at sites in North America, Europe, Israel, and Australia. They will be randomized in a 1:1:1 ratio to either a higher dose of PTC124, a lower dose of PTC124, or placebo. Subjects will receive study drug 3 times per day (at breakfast, lunch, and dinner) for 48 weeks. Subjects will be evaluated at clinic visits every 6 weeks. Additional safety laboratory testing, which may be performed at the investigational site or at an accredited local laboratory or clinic, is required every 3 weeks for the first 24 weeks of the study. At the completion of blinded treatment, all compliant participants will be eligible to receive open-label PTC124 in a separate extension study.

Eligibility

Ages Eligible for Study: 5 Years and older
Genders Eligible for Study: Male
Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:

- Ability to provide written informed consent (parental/guardian consent if applicable)/assent (if <18 years of age)
- Male sex.
- Age ≥5 years.
- Phenotypic evidence of DMD/BMD based on the onset of characteristic clinical symptoms or signs (ie., proximal muscle weakness, waddling gait, and Gowers' maneuver) by 9 years of age, an elevated serum creatinine kinase level, and ongoing difficulty with walking.
- Documentation of the presence of a nonsense point mutation in the dystrophin gene as determined by gene sequencing from a laboratory certified by the College of American Pathologists (CAP), the Clinical Laboratory Improvement Act/Amendment (CLIA) or an equivalent organization.
- Ability to walk ≥75 meters unassisted during the screening 6-minute walk test.
- Documentation that a baseline renal ultrasound has been performed.
- Confirmed screening laboratory values within the central laboratory ranges (hemoglobin, adrenal, renal and serum electrolytes parameters)
- Willingness and ability to comply with scheduled visits, drug administration plan, study procedures, laboratory tests, and study restrictions.

Exclusion Criteria:

- Treatment with systemic aminoglycoside antibiotics within 3 months prior to start of study treatment.
- Initiation of systemic corticosteroid therapy within 6 months prior to start of study treatment or change in systemic corticosteroid therapy (eg, initiation, change in type of drug, dose modification not related to body weight change, schedule modification, interruption, discontinuation, or reinitiation) within 3 months prior to start of study treatment.
- Any change (initiation, change in type of drug, dose modification, schedule modification, interruption, discontinuation, or reinitiation) in prophylaxis/treatment for congestive heart failure within 3 months prior to start of study treatment.
- Treatment with warfarin within 1 month prior to start of study treatment.
- Prior therapy with PTC124.
- Known hypersensitivity to any of the ingredients or excipients of the study drug (Litesse® UltraTM [refined polydextrose], polyethylene glycol 3350, Lutrol® micro F127 [poloxamer 407], mannitol 25C, crospovidone XL10, hydroxyethyl cellulose, vanilla, Cab-O-Sil® M5P [colloidal silica], magnesium stearate).
- Exposure to another investigational drug within 2 months prior to start of study treatment.
- History of major surgical procedure within 30 days prior to start of study treatment.
- Ongoing immunosuppressive therapy (other than corticosteroids).
- Ongoing participation in any other therapeutic clinical trial.
- Expectation of major surgical procedure (eg, scoliosis surgery) during the 12 month treatment period of the study.
- Requirement for daytime ventilator assistance.

- Clinical symptoms and signs of congestive heart failure (American College of Cardiology/American Heart Association Stage C or Stage D) or evidence on echocardiogram of clinically significant myopathy
- Prior or ongoing medical condition (eg, concomitant illness, psychiatric condition, behavioral disorder, alcoholism, drug abuse), medical history, physical findings, electrocardiogram findings, or laboratory abnormality that, in the investigator's opinion, could adversely affect the safety of the subject, makes it unlikely that the course of treatment or follow-up would be completed, or could impair the assessment of study results.

Contacts and Locations

Please refer to this study by its ClinicalTrials.gov identifier: NCT00592553

Contacts

Contact: Diane Goetz 908-912-9256 dgoetz@ptcbio.com

Show 38 Study Locations

Sponsors and Collaborators

PTC Therapeutics

More Information

Responsible Party:	PTC Therapeutics, Inc. (Langdon Miller, MD, Chief Medical Officer)
Study ID Numbers:	PTC124-GD-007-DMD
First Received:	January 1, 2008
Last Updated:	July 24, 2008
ClinicalTrials.gov Identifier:	NCT00592553
Health Authority:	United States: Food and Drug Administration

Keywords provided by PTC Therapeutics:

Duchenne muscular dystrophy	Premature stop codon
Becker muscular dystrophy	DMD/BMD
Nonsense mutation	**PTC124**

Study placed in the following topic categories:

Muscular dystrophy, Duchenne and Becker type	Genetic Diseases, Inborn
Muscular Dystrophies	Muscular Dystrophy, Duchenne
Muscular Diseases	Genetic Diseases, X-Linked
Becker's muscular dystrophy	Duchenne muscular dystrophy
Muscular Disorders, Atrophic	Atrophy
Musculoskeletal Diseases	Muscular dystrophy
Neuromuscular Diseases	

Additional relevant MeSH terms:

Nervous System Diseases
Muscular Dystrophy, Duchenne

ClinicalTrials.gov processed this record on August 11, 2008

Links to all studies - primarily for crawlers

Exhibit E

Risks in new drug development: Approval success rates for investigational drugs

Joseph A. DiMasi, PhD *Boston, Mass*

The drug development process is known to be complex, costly, and time-consuming.[1-3] The process is also risky in that most compounds that undergo clinical testing are abandoned without obtaining marketing approval. The rate at which pharmaceutical firms market new therapies in the United States is an important measure of the viability of the drug development process.[4] The cost of new drug development is also critically dependent on the proportion of drugs that fail in clinical testing.[5-7] Estimates of industry success rates can be used in benchmarking exercises for project planning purposes. Given the length and cost of the drug development process, careful consideration of all factors that have a significant impact on the process is needed to appropriately allocate research and development resources.

In a series of studies of new drug development in the United States, the Tufts Center for the Study of Drug Development (CSDD) and others have provided descriptive data on how cumulative success rates for new chemical entities (NCEs) vary with time from investigational new drug application (IND) filing.[1,8-14] Several studies have also examined clinical success rates for biotechnology-derived drugs.[15-17] Statistical modeling can be helpful in analyzing success rates for recent periods because many of the compounds will still be in active testing at the time of the analysis. Tufts CSDD has also conducted a number of studies that use this approach to predict final success rates for groups of compounds for which the ultimate fate of some of the compounds in the data set is not known.[4-7,18-20]

This study provides updated success rate analyses for NCEs. Success rate trends and variations in success rates by therapeutic class are presented. The hypothesis that pharmaceutical firms have been moving compounds through the process to either marketing approval or research abandonment more quickly is also examined. In addition, attrition rates for compounds entering clinical development phases are obtained. Finally, statistics on the reasons compounds fail in development are given.

METHODS

Data used for this study were obtained primarily from a Tufts CSDD database that contains information from ongoing surveys of pharmaceutical firms. The data provided for the most recent survey come from firms that have declined in number over the study period, as mergers have resulted in the combination of some of them. The data used for this study were obtained from the units and subsidiaries of what are now 24 parent firms. These firms provided data on NCEs first investigated in humans anywhere in the world or NCEs for which they were the first to file a US IND since 1963. The data gathered include IND filing dates, the dates on which IND research was abandoned, reasons for termination of research, the latest phase compounds were in when research was abandoned, and the date of new drug application approval. A description of additional information included in this database is available elsewhere.[1] Data were also obtained from public sources.[21,22] Current success rates for these NCEs were examined (as of December 31, 1999), and statistical analysis was applied to data on past rates of research abandonment and approval to predict future success rates. Analyses were conducted for NCEs with INDs first filed in 3- and 6-year periods from 1981 to 1992. Data on more recent INDs were available but, given the length of the NCE development

From the Director of Economic Analysis, Tufts Center for the Study of Drug Development, Tufts University.
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Reprint requests: Joseph A. DiMasi, PhD, Tufts Center for the Study of Drug Development, Tufts University, 192 South St, Suite 550, Boston, MA 02111.
Clin Pharmacol Ther 2001;69:297-307.

0009-9236/2001/$35.00 + 0 13/1/115446
doi:10.1067/mcp.2001.115446

process, they are too recent to use for a comprehensive statistical analysis of success rates.

Inclusion criteria. For purposes of this study, an NCE is defined as a new molecular compound not previously tested in humans. Excluded are new salts and esters of existing compounds, surgical and diagnostic materials, vaccines and other biologic agents, certain externally used compounds (such as disinfectants, antiperspirants, and sunscreens), and nutritional compounds (such as natural forms of vitamins and sweetening agents). Our definition of an NCE differs from the FDA's definition of a new molecular entity. The most notable difference is that the FDA's definition includes diagnostics, whereas our definition of an NCE does not.

Statistical analysis of success rates. For the statistical analyses, residence time (the length of time from IND filing to either abandonment of research without marketing approval or to new drug application approval) was calculated for NCEs with INDs first filed in successive 3-year intervals from 1981 to 1992. Approval dates were available through December 31, 1999, and were used in determining observed success rates. Residence times were also calculated as of the end of 1999. Observed and predicted cumulative approval success rates were calculated at each year from IND filing.

NCEs were stratified according to source (self-originated versus licensed-in or otherwise acquired) and therapeutic class. An NCE is defined as self-originated if it was developed entirely under the auspices of the responding firm. We define acquired NCEs to be compounds that were obtained by the developing firm through licensing, purchase, barter, or other means. To determine whether trends in success rates exist, we analyzed the data by the period during which the IND was filed.

Predicted success rates for IND filing periods were determined from a 2-stage model of the approval process. NCEs with research still active as of December 31, 1999, constitute right-censored observations for our data set. Survival analysis can make use of information provided by censored data,[23] NCEs were assumed to survive until either research was terminated without approval or marketing approval was achieved. Details of the selected models and the computational approach used to estimate final success rates are provided in the Appendix.

The survey data also provided information on the latest development or regulatory phase that abandoned NCEs were in at the time of termination. These data allow us to determine the distribution of research terminations by phase. In combination with predicted approval rates for IND filing intervals, they also permit us to estimate the probability of approval once a compound enters a given clinical phase and phase attrition rates (the percentage of compounds that enter a phase that are abandoned before the next phase is initiated).

RESULTS

Included in the CSDD database of investigational compounds are the development histories of 671 NCEs for which survey firms had filed a first IND from 1981 to 1992. Of these, 508 were identified as self-originated and 163 were identified as acquired. Of the 508 self-originated NCEs, 350 were initially investigated in humans in the United States. By the end of 1999, 20.9% of the NCEs with INDs filed from 1981 to 1992 had been approved for marketing in the United States. For this period, the current US approval success rates for NCEs that were acquired, self-originated, and self-originated and first tested in humans in the United States are 33.1%, 16.9%, and 8.6%, respectively. These results illustrate the significance of previous testing on measured US success rates; success rates on IND filings are higher for compounds that were licensed-in or first tested abroad.

Time to research termination. Even though some of the drugs in our database are still active, survival analysis can be used to establish the rates at which the NCEs with INDs filed during a given period will be dropped from active testing. The mean and median times to research termination for self-originated NCEs that were abandoned with INDs first filed during the periods from 1981 to 1983, 1984 to 1986, 1987 to 1989, and 1990 to 1992 are shown in Fig 1. Because NCEs in the later intervals had less time for research to be terminated, the averages for the later periods may be somewhat understated relative to the earlier periods. However, previous research and our current data suggest that the likelihood of approval, as opposed to abandonment, increases with time from IND filing. If we could add termination times for NCEs that will eventually be terminated, the impact should be much less on the median than on the mean.

Even with these qualifications, the results at least suggest that, over time, pharmaceutical firms have made quicker decisions on research failures. Mean residence time decreased 30% (1.5 years) from the 1981–1983 to the 1990–1992 IND filing intervals. Median time to research abandonment decreased 20% (0.8 years) for INDs filed in the early 1990s relative to the early 1980s.

Further evidence that the ultimate fate of investigational NCEs has tended to be resolved more rapidly

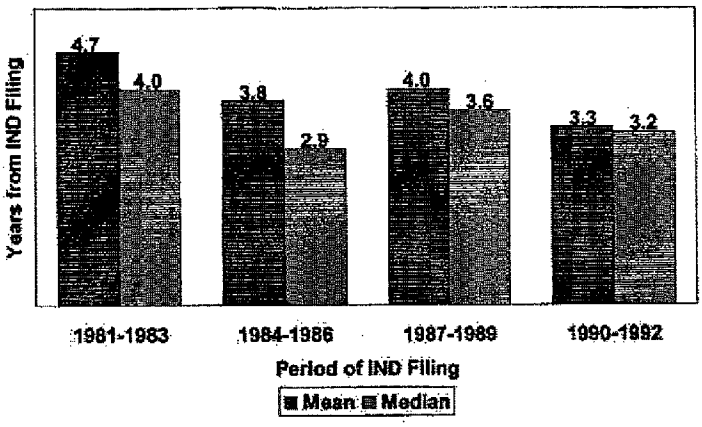

Fig 1. Mean and median time to research abandonment for self-originated new chemical entities (NCEs) with a first investigational new drug application (IND) filed during a given period.

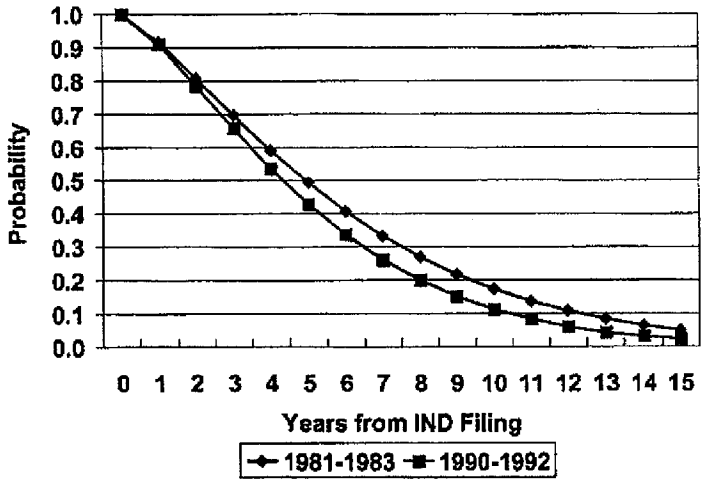

Fig 2. Estimated survival curves for self-originated NCEs with a first IND filed during a given period. The curves show the percentage of NCEs that had not been abandoned or approved for marketing in the United States (ie, still active) a given number of years from the date of IND filing. The data were fitted to Weibull distributions.

over time is shown in Fig 2. The *curves* in the figure are estimated survival curves for the 1981–1983 to 1990–1992 IND filing intervals. A *point* on the curve represents the probability that an investigational NCE will still be active a given number of years from IND filing. An NCE is inactive at a given point in time if either research has been abandoned without marketing approval or the compound has received FDA approval for marketing. It should be noted that the estimated survival curves account for censored data; that is, information regarding still active NCEs is used to estimate final survival rates.

Median survival time decreased from 4.9 years to 4.3 years (12%) for the 1981–1983 to 1990–1992 filing intervals, respectively. Faster action is also evident in the figure for different amounts of time from IND filing. The percentages of NCEs for the 1990–1992 filing period that are still active are 6 to 7 percentage points lower than those for the 1981–1983 filing period at 4 to 10 years from IND filing.

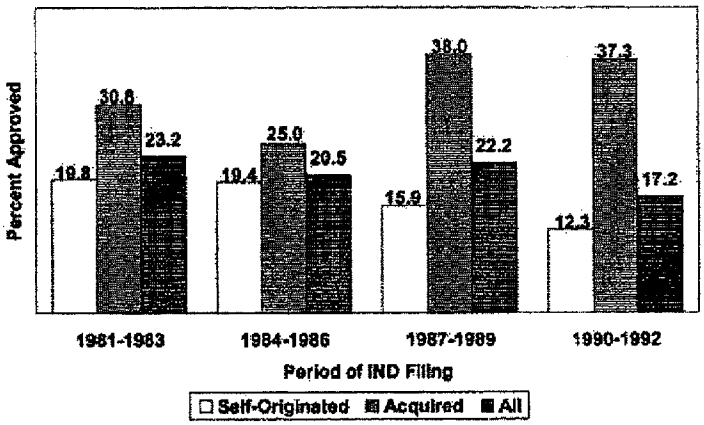

Fig 3. Current clinical approval success rates for NCEs by origin and period during which a first IND was filed.

Success rate trends. To estimate final success rates, results from the survival analyses must be combined with those from qualitative choice models of the conditional probability of approval at given residence times. The parameter estimates for both stages of the model are highly statistically significant, and goodness-of-fit measures indicate strong agreement with the data. The parameter estimates used to determine the predicted final success rates reported here and the accompanying statistical results are available upon request.

Current success rates (as of December 31, 1999) for self-originated, acquired, and all NCEs by IND filing interval are shown in Fig 3. Licensed compounds generally have undergone some testing before licensing and have been shown to be promising candidates for marketing approval. The results support the hypothesis of such a screening effect for acquired NCEs; current success rates for acquired NCEs are notably higher than those for self-originated NCEs.

A screening effect also appears to apply to self-originated compounds that have undergone some clinical testing abroad before an IND has been filed in the United States. The success rates for self-originated NCEs that were first tested in humans in the United States are much lower than the success rates for all self-originated NCEs. Current success rates by IND filing interval for self-originated NCEs first tested in the United States are 33% to 65% lower than for self-originated NCEs as a whole.

Censoring has an impact on the results for all IND filing intervals, but the effect is much greater for the more recent intervals. The proportions of NCEs that are currently active are substantially higher for these later periods. Thus the lower current success rates for self-originated NCEs in the 1987–1989 and 1990–1992 intervals may simply reflect the shorter amount of time available for the ultimate fate of those NCEs to have occurred. Trend analysis for these later periods must be aided by the application of statistical techniques to forecast approval rates for the active NCEs.

Current success rates, maximum possible success rates (assuming all active NCEs are approved), and predicted final success rates for self-originated NCEs by IND filing interval are shown in Fig 4. The predicted final success rates fall between current and maximum possible success rates for all filing intervals. Although both predicted and maximum possible success rates are lower for the 1987–1989 interval relative to the intervals in the earlier 1980s, the predicted success rate for the 1990–1992 interval is 16% higher than for the interval with the next highest predicted success rate.

Comparison of predicted and actual success rates for the early time periods can validate the performance of the statistical model. For NCEs with INDs first filed from 1981 to 1983, the model predicts a cumulative success rate of 19.5% at 16 years from IND filing (the maximum amount of time available for all compounds in the group); the actual success rate for this group at 16 years from IND filing is 19.8%. Similarly, NCEs with INDs first filed from 1984 to 1986 have a predicted success rate of 18.8% at 13 years from IND filing and an actual success rate of 19.4%.

Therapeutic classes. Previous research has indicated that success rates for NCEs vary by therapeutic

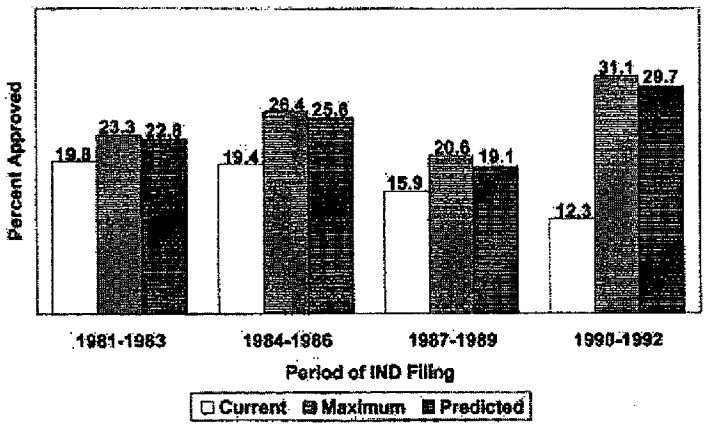

Fig 4. Current (as of December 31, 1999), maximum possible, and predicted final clinical approval success rates for self-originated NCEs by period during which a first IND was filed. Maximum possible success rates were determined under the assumption that all active compounds are eventually approved for marketing. Predicted success rates were constructed with use of estimates for a survival analysis of residence time (time from IND filing to abandonment or US marketing approval) with a Weibull distribution specification and estimates for the conditional probability of approval for a given residence time with a probit specification.

Table I. Current and maximum possible success rates by therapeutic class for self-originated NCEs with INDs first filed from 1981 to 1992*

Therapeutic class	*NCEs*	*Approved NCEs*	*Open NCEs†*	*Current success rate†*	*Maximum success rate‡*
Analgesic/anesthetic	49	10	4	20.4%	28.6%
Anti-infective	57	16	3	28.1%	33.3%
Antineoplastic	38	6	6	15.8%	31.6%
Cardiovascular	120	21	6	17.5%	22.5%
Central nervous system	110	16	14	14.5%	27.3%
Endocrine	33	6	4	18.2%	30.3%
Gastrointestinal	15	3	2	20.0%	33.3%
Immunologic	13	2	0	15.4%	15.4%
Respiratory	25	3	0	12.0%	12.0%
Miscellaneous	43	3	4	7.0%	16.3%

NCE, New chemical entity.
*Therapeutic class information is missing for five compounds.
†As of December 31, 1999.
‡Assumes that all open NCEs will eventually be approved.

class.[6,20] The current and maximum possible success rates by IND filing interval for self-originated NCEs in 9 specific therapeutic categories are shown in Table I. Because the number of compounds available for analysis is greatly reduced when the data are stratified into therapeutic categories, the entire study period (1981–1992) is used. For the immunologic and respiratory categories the fate of all of the NCEs is known so that current, maximum, and final success rates are the same.

For many of these therapeutic classes, the number of compounds with IND filings in an interval is too small for accurate statistical estimation. However, we had enough data and the fits with the statistical model described above were sufficiently good for us to estimate predicted final success rates for the analgesic/anesthetic, anti-infective, cardiovascular, and central nervous system categories. The current, maximum possible, and predicted final success rates for these 4 classes are shown in Fig 5. Relative success rate results for these

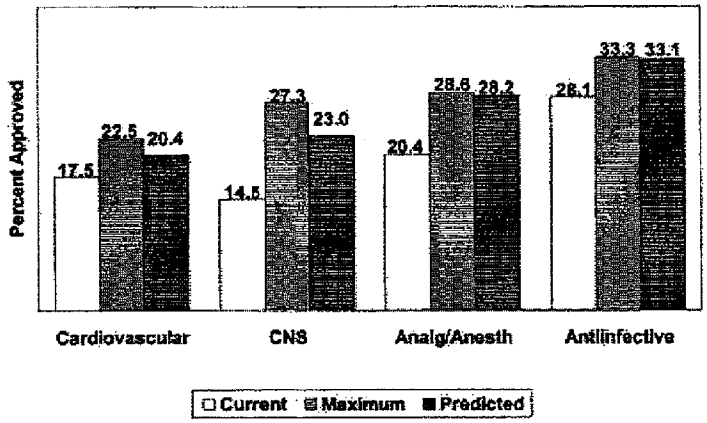

Fig 5. Current (as of December 31, 1999), maximum possible, and predicted final clinical approval success rates by therapeutic class for self-originated NCEs with a first IND filed from 1981 to 1992. Maximum possible success rates were determined under the assumption that all active compounds are eventually approved for marketing. Predicted success rates were constructed with use of estimates for a survival analysis of residence time (time from IND filing to abandonment or US marketing approval) with a Weibull distribution specification and estimates for the conditional probability of approval for a given residence time with a probit specification.

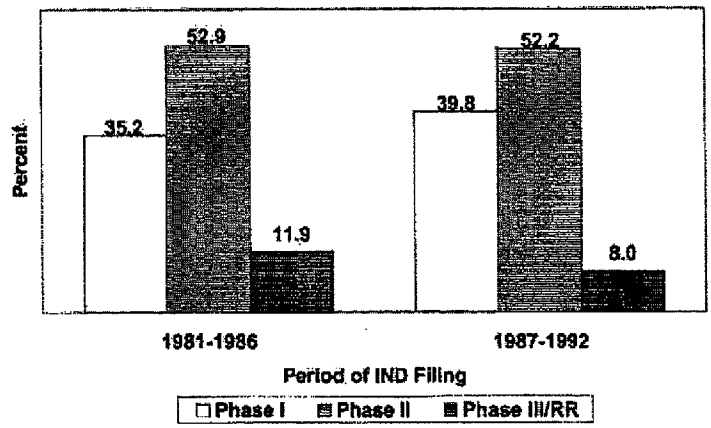

Fig 6. Distribution of research terminations for self-originated NCEs by clinical phase and period during which a first IND was filed.

classes are likely unaffected by time trends inasmuch as the number of filings for the last half of the study period as a percentage of total filings for the whole period for each of these 4 classes varied only from 47% to 55%. The predicted success rates range from approximately 1 in 5 for cardiovascular NCEs to 1 in 3 for anti-infectives.

Clinical phase attrition rates. Clinical approval success rates yield patterns of success for the clinical development process as a whole, but they do not inform us of success and failure patterns during the clinical development process. Our data on the latest phase that an abandoned NCE was in at the time of termination give us a distribution of research terminations by phase. The distribution for self-originated NCEs is shown in Fig 6. Approximately half of clinical research failures occur in phase II. This is the case for both the first and second halves of the study period. For the later IND fil-

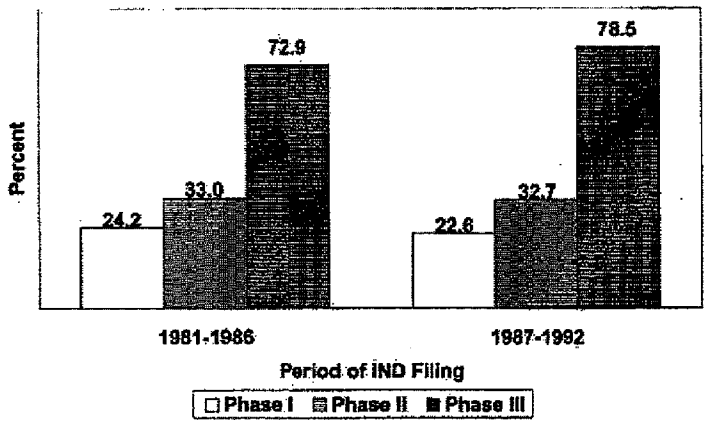

Fig 7. Approval success rates for self-originated NCEs entering a given clinical phase.

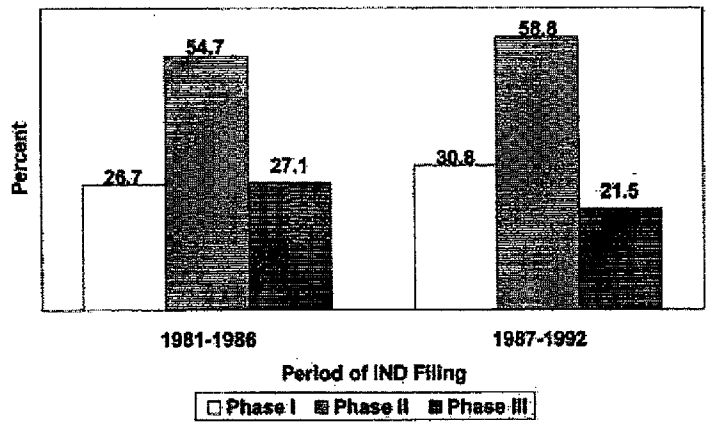

Fig 8. Phase attrition rates (percentage of compounds entering a phase that fail in the phase) for self-originated NCEs by period during which a first IND was filed.

ing period, however, proportionately more research failures occurred in phase I and proportionately fewer occurred in phase III or regulatory review.

Statistical analysis yields predicted final success rates for self-originated NCEs for the 1981–1986 and 1987–1992 filing intervals of 24.2% and 22.6%, respectively. Current approval and termination rates for these periods, along with the assumption that currently active NCEs that are predicted to eventually fail will do so in phase III or regulatory review, allow us to predict approval rates for NCEs that enter a clinical phase (Fig 7). Although approval rates are similar for the early clinical phases in both periods, the likelihood of approval increased by 5.6 percentage points for phase III. This is consistent with the results displayed in Fig 6, which showed relatively more terminations in phase I and relatively fewer in phase III or later.

The data on research terminations by phase and predicted success rates also allow us to determine phase attrition rates. Fig 8 shows that attrition rates are greatest in phase II in which more than half of the investigated compounds fail. During the study period, failure rates increased for phases I and II but declined for phase III.

Reasons for research abandonment. The database contained information on the reasons research was abandoned for NCEs that had research terminated without marketing approval. We grouped the responses into 3 major categories: safety (eg, "human toxicity" or "ani-

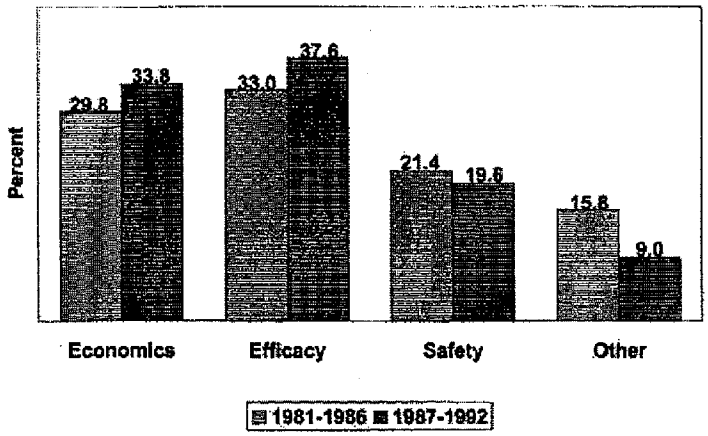

Fig 9. Percentage of research terminations for all NCEs by period of first IND filing and by primary reason for abandonment.

mal toxicity"), efficacy (eg, "activity too weak" or "lack of efficacy"), and economics (eg, "commercial market too limited" or "insufficient return on investment"). A relatively small number of the compounds that had been abandoned had reasons for termination that were not specific enough to be placed in 1 of these 3 categories. The shares of all reasons for abandonment for each of these categories by IND filing interval are shown in Fig 9.

For the last half of the study period, economic and efficacy issues became relatively more prevalent, while safety issues became relatively less prevalent, as reasons for research termination. Because the time available for the fate of the compounds to have been determined is limited, the abandonment results for the interval from 1987 to 1992 are biased toward causes that tend to be revealed relatively soon after filing. This censoring effect also applies to the earlier interval but with much less impact. The economic share increased, even though research on NCEs terminated for economic reasons tends to occur later in the development process than is the case for safety and efficacy (eg, for filings from 1981 to 1986, 45% of the economic terminations occurred at least 6 years from filing compared with 35% of efficacy and 17% of safety terminations).

The censoring effect also applies when the data are analyzed by the phase that a compound was in when it was abandoned. This bias will tend to be lower if earlier periods are examined. Considering the first half of the study period (NCEs that had an IND first filed from 1981 to 1986), compounds that had failed for economic or efficacy reasons were terminated much more frequently in late clinical testing phases. The percentage of failed compounds that were abandoned in phase III or during the regulatory review period was 26.6% for economic failures, 24.0% for efficacy failures, and 8.3% for safety failures.

Table II shows mean and median abandonment times for all NCEs by IND filing period and by the primary reason for termination. Average times to abandonment are lower for the later filing period, but this can result in part from the shorter period during which abandonments can occur for this interval. For either period, however, both the mean and median time to research abandonment is longer for NCEs that were terminated primarily for economic than for other reasons. The data also show that economic considerations were the most frequent determinants underlying decisions to terminate late-stage clinical research. During the entire study period, 39% of the terminations that occurred at least 4 years from filing were for economic reasons, 32% were related to efficacy issues, and only 16% were for safety problems (13% were for other reasons).

DISCUSSION

A statistical model of the rate at which new drugs proceed through clinical testing to marketing approval was estimated for three 4-year and two 6-year IND filing intervals. Estimated approval success rates for self-originated NCEs varied from 19% to 30% during the study period. The highest predicted success rate was for the most recent filing period (1990–1992). The results suggest that approval rates have not declined over time and, quite possibly, have increased. A general improvement in success rates can result from bet-

Table II. Time to research abandonment (in years) for NCEs by IND filing period

	1981-1986			*1987-1992*		
Reason	*n*	*Mean (y)*	*Median (y)*	*n*	*Mean (y)*	*Median (y)*
Economics	64	4.4	4.0	45	3.7	3.2
Efficacy	71	3.6	2.3	50	2.7	2.6
Safety	46	2.6	2.5	26	2.1	1.2
Other	34	3.5	2.3	12	2.7	2.2

IND, Investigational new drug application.

ter preclinical screening. The implications for the development process are significant because the clinical costs for some research failures will not be borne if success rates increase. However, these savings would have to be balanced against any additional costs associated with a better preclinical screening process.

Success rates for self-originated NCEs differed significantly by therapeutic class. Predicted or actual final success rates varied from 12% for respiratory drugs to 33% for anti-infectives. Cardiovascular and central nervous system drugs also had predicted success rates that were substantially below that for anti-infectives. Some of the differences in success rates by therapeutic class might be explained generally by differences in the uncertainty with which regulatory standards would be satisfied. For example, efficacy end points for anti-infectives are usually clearly defined and relatively easy to assess. In contrast, the difficulties in establishing efficacy for psychotropic compounds have been well described.[24,25]

The length of time that an NCE spent in clinical testing or regulatory review before the fate of the drug (abandonment or approval) was determined decreased during the study period. Estimated median survival times for self-originated NCEs decreased 0.6 years for IND filings in the early 1990s compared with those a decade earlier. These results are consistent with data on shorter US clinical development times for late 1990s approvals.[2,3] In addition, our data on the time to research termination for compounds that have been abandoned suggest that pharmaceutical firms have been abandoning unsuccessful compounds more quickly. Faster failures and shorter development times for drugs that do get approved imply, other things being equal, lower research and development costs per approved new drug. However, these gains can easily be offset if the out-of-pocket costs of conducting clinical trials have increased.

Our data on clinical phase attrition rates not only support the hypothesis that pharmaceutical firms have acted more quickly in terminating development on unsuccessful compounds but also allow us to better pinpoint when in the process these gains were made. Development costs are reduced more if a compound that ultimately fails is abandoned sooner. Our results indicate that firms have indeed tended to abandon their failed compounds earlier in the process. Reductions in failure rates for phase III and regulatory review appear to be associated with corresponding increases in failure rates for phase I. It should be noted, however, that quicker decisions to abandon projects may also increase the likelihood of making a type II error (accepting the hypothesis that an investigational drug will not meet efficacy and safety standards and earn a reasonable return when in fact it would have done so if pursued). Furthermore, failure rates for phase II testing remained essentially constant. Some expensive phase III trials may be avoided if phase II testing can be made more informative so as to weed out more of those compounds that will fail to achieve regulatory approval.

Our results indicate that commercial factors became relatively more important over time as the primary reason for abandoning development of investigational NCEs. Censoring may affect the results for the more recent time periods. NCEs that failed for economic reasons, however, tended to last longer in testing than NCEs that failed for efficacy or safety reasons. Thus the censoring in the data suggests that the final results will show that the trend for economics is even steeper than currently observed. Given that economic factors increased in importance as a reason for research termination and that these commercial considerations have tended to be a deciding factor relatively late in the development process, the improvement in attrition rates that we have observed is all the more impressive.

Clinical success rates and phase attrition rates for new drugs are important indicators of how effectively pharmaceutical firms are using the resources that they devote to research and development. The proficiency with which this is done is a consequence of a complex set of regulatory, economic, and firm-specific factors. Reliable success rate and phase attrition rate estimates are an important tool for evaluation of the efficiency with which industry conducts clinical drug development. Our results on the risks in drug development should aid in this process.

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APPENDIX

Success rates are predicted by combining 2 separate statistical estimation procedures. Specifically, the cumulative probability of approval at t years from IND filing is given by the following:

$$S(t) = \int_0^t f(u) \cdot P(u) \cdot du \qquad (1)$$

in which f(u) is the probability density function for the survival-time data, P(u) is the probability of approval given a residence time of u.

The density function, f(u), can be estimated by a parametric survival analysis. Various theoretical distributions (ie, exponential, Weibull, log-normal, and log-logistic) were fitted to the survival-time data. Estimated survival and hazard rate curves derived from nonparametric techniques, such as life-table analysis or the Kaplan-Meier technique, can be used as a first step in determining whether the data are consistent with these parametric forms. Likelihood ratio tests based on the log-likelihood values obtained from fitting particular parametric forms to the data can also be used to test whether one distribution fits the data better than another. The estimated survival and hazard rate curves from life-table analyses and the likelihood ratio tests suggested that Weibull distributions best fit the data.

Specification of the Weibull distribution (a generalization of the exponential distribution) requires esti-

mates of two parameters. In particular, the probability density function for the Weibull distribution is given as follows:

$$f(u) = \gamma \cdot \alpha \cdot u^{\gamma-1} \cdot e^{-\alpha \cdot u^{\gamma}} \qquad (2)$$

$$u \geq 0 \quad \alpha,\gamma > 0,$$

where u is residence time. For this distribution, statistical software gives estimates of μ and σ where $\gamma = 1/\sigma$ and $\alpha = e^{-\mu/\sigma}$. The values obtained are maximum likelihood estimates in which a Newton-Raphson algorithm is used to solve the first-order conditions.

NCEs with a given residence time have terminated with either research abandonment or marketing approval. Because the possible responses are qualitative and binary, qualitative choice modeling is an appropriate and feasible method for estimating P(u). Parametric forms that have proved useful in many applications of this type are the probit and logit specifications. We examined both of these specifications. The parameters were estimated by a maximum likelihood technique in which a modified Newton-Raphson algorithm was used to solve the first-order conditions. Log-likelihood values for the estimations can be used to discriminate among the models. The log-likelihood values suggested the probit form for P(u). In general, however, the results were not sensitive to the choice of model.

In the context of this application, the probit model posits that the cumulative probability of approval varies with residence time according to the cumulative standard normal distribution evaluated at a linear function of residence time. In particular, we estimated the parameters, α and β, of the following function:

$$P(\alpha + \beta \cdot u) = \int_{-\infty}^{\alpha+\beta\cdot u} (1/\sqrt{2 \cdot \pi}) \cdot e^{-z^2/2} \cdot dz, \qquad (3)$$

where u is residence time. This specification has the property that the conditional probability of approval increases (in a sigmoidal fashion) with the time from IND filing.

Once parameter estimates are obtained, equations 2 and 3 can be substituted into equation 1 to determine a success rate at a given number of years from IND filing. We are also interested, though, in final success rates for NCEs with INDs filed during a given interval. Both the Weibull density function and the conditional probability of approval determined from the probit specification vary with time and, in theory, no ceiling can be placed on the time from IND filing. Thus the two-stage model predicts as a final success rate (S_F) the following limit:

$$S_F = \lim_{t \to \infty} S(t) \qquad (4)$$

assuming that the limit exists. Unfortunately, we do not have a closed-form solution for equation 1. However, if the limit does exist, we can then use numerical techniques to adequately approximate S_F with S(T) for large enough T. In choosing T, we adopted two criteria. First, T must be large enough so that the probability density function (2) integrated up to T is within one-half of 1% of one. Second, the estimated cumulative probability of success [S(t)] must have stopped increasing out to 3 places after the decimal point. Thus our approximation of S_F should be accurate to within one-tenth of 1%. For all of the predicted success rate estimates given here, T = 30 years easily meets the two criteria. Therefore all of the survival and predicted cumulative success rate curves presented here are shown out to 30 years from IND filing.

Exhibit F

ClinicalTrials.gov
Protocol Registration System

View Protocol Record

Main Menu Select Preview Spelling Download XML Check Records

Record Status: Released	In Progress Completed Approved Released **Owned by:** kdonnelly **Last updated:** 07 2008 12:54 by kdonnelly **Initial release:** 01/01/2008 **Last release:** 2008 Download Receipt (PDF)
Comments:	5/16/08 "DMD/BMD" was expanded in Brief Title ClinicalTrials.gov QA5 07/08/08 Changed "maneuver" to "me ria" in Eligibility Criteria Change made by ClinicalTrials.gov
Unique Protocol ID:	PTC124-GD-007-DMD
Secondary IDs:	
ClinicalTrials.gov ID:	NCT00592553 ClinicalTrials.gov Archive Identification Status
Brief Title:	Phase 2b Study of PTC124 in Duchenne Muscular Dystrophy (DMD BMD)
Official Title:	A Phase 2b Efficacy and Safety Study of PTC124 in Subjects With Nonsense-Mutation-Mediated Duchenne Muscular Dystrophy and Becker Muscular Dystrophy
Study Type:	Interventional
FDA Regulated Intervention?	Yes
IND/IDE Protocol?	Yes
IND/IDE Information:	Grantor CDER IND IDE Number 68,431 Serial Number #0090 Has Expanded Access? No
Section 801 Clinical Trial?	No
Delayed Posting?	
Sponsor:	PTC Therapeutics
Collaborators:	
Responsible Party:	Name Official Title Langdon Miller, MD, C Medical Officer Organization PTC Therapeutics, Inc. Phone 908-912-9152 Ext Email lmiller@ptcthera.com
Review Board:	Approval Status Approved Approval Nur 07-12-14 Board Name Institutional Review Board Ch its Children's Hospital Medical Center Board Affiliation Cincinnati Children's Hos Medical Center Phone 513-636-8039 Email:
Data Monitoring Committee?	Yes
Oversight Authorities:	United States: Food and Drug Administratio
Brief Summary:	Duchenne/Becker muscular dystrophy (DMD/BMD) is a genetic disorder that develops in boys. It is caused by a mutation in the gene for dystrophin, a protein that is important in maintaining normal muscle structure and function. Loss of dystrophin causes muscle fragility that leads to weakness and loss of walking ability during childhood and teenage years. A specific type of mutation called a nonsense (premature stop codon) mutation is the cause of DMD/BMD in approximately 10-15% of boys with the disease. PTC124 is an orally delivered, investigational drug that has the potential to overcome the effects of the nonsense mutation. This study is a Phase 2b trial that will evaluate the clinical benefit of PTC124 in boys with DMD/BMD due to a nonsense mutation. The main goals of the study are to understand whether PTC124 can improve walking activity, muscle function, and strength and whether the drug can safely be given for a long period of time.
Detailed Description:	This study is a Phase 2b, multicenter, randomized, double-blind, placebo-controlled, dose-ranging, efficacy and safety study. It is designed to document the clinical benefit of PTC124 when administered as therapy of patients with DMD/BMD due to a nonsense mutation (premature stop codon) in the dystrophin gene. It is planned that 165 boys who are at least 5 years of age and can walk at least 75 meters (80 yards) will be enrolled. Subjects will be enrolled at sites in North America, Europe, Israel, and Australia. They will be randomized in a 1:1:1 ratio to receive study drug 3 times per day (at breakfast, lunch, and dinner) for 48 weeks. Subjects will be evaluated at clinic visits every 3 weeks. Additional safety laboratory testing may be performed at the investigational site or at an accelerated local laboratory clinic, is required every 3 weeks for the first weeks of the study. At the completion of blinded treatment, all compliant participants will be eligible to receive open-label PTC124 in a separate extension study.
Record Verification Date:	July 2008
Overall Status:	Recruiting
Study Start Date:	February 2008
Primary Completion Date:	April 2010 [Anticipated]
Study Completion Date:	August 2010 [Anticipated]
Study Design:	Primary Purpose: Treatment Study Phase: Phase 2 Phase 3 Intervention Model: Parallel Assignment

Number of Arms 3
Masking Double Blind (Subject, Caregiver, ...igator, Outcomes Assessor)
Allocation Randomized
Control Placebo Control
Endpoint Classification Safety, Efficacy Stu...
Enrollment 165 [Anticipated]

Outcome Measures:

Primary Outcome Measure:

Measure	To determine the effec... PTC124 on ambulation in subjects with nonsense-mutation-mediated DMD/BM... as assessed by change ...e distance walked during a 6-minute walk test
Time Frame	12 months
Safety Issue?	No

Secondary Outcome Measures:

Measure	Activity in the commun... ...tting
Time Frame	12 months
Safety Issue?	No
Measure	Proximal muscle funct...
Time Frame	12 months
Safety Issue?	No
Measure	Muscle strength
Time Frame	12 months
Safety Issue?	No
Measure	Muscle fragility
Time Frame	12 months
Safety Issue?	No
Measure	Biceps muscle dystrop... ...pression
Time Frame	12 months
Safety Issue?	No
Measure	Quality of Life
Time Frame	12 months
Safety Issue?	No
Measure	Cognitive ability
Time Frame	12 months
Safety Issue?	No
Measure	Cardiac function
Time Frame	12 months
Safety Issue?	No
Measure	Frequency of accidents... during ambulation
Time Frame	12 Months
Safety Issue?	No
Measure	Treatment satisfaction
Time Frame	12 Months
Safety Issue?	No
Measure	Safety
Time Frame	12 months
Safety Issue?	Yes
Measure	Compliance with treati...
Time Frame	12 months
Safety Issue?	No
Measure	PTC124 pharmacokine...
Time Frame	12 months
Safety Issue?	No

Conditions:
Duchenne Muscular Dystrophy
Becker Muscular Dystrophy

Keywords:
Duchenne muscular dystrophy
Becker muscular dystrophy
Nonsense mutation
Premature stop codon
DMD/BMD

PTC124

Arms:
1 Active Comparator
2 Active Comparator
3 Placebo Comparator

Interventions:
Drug: PTC124

PTC124 Low Dose

Arms: 1
Drug: PTC124

PTC124 High Dose

Arms: 2
Drug: PTC124

Placebo

Arms: 3

NOTE: Intervention Other Names have n n specified
NOTE: Intervention Other Names have n n specified
NOTE: Intervention Other Names have n n specified

Eligibility Criteria:
Inclusion Criteria

- Ability to provide written informed co parental guardian consent if applicable) assent (if < 18 years of age)
- Male sex
- Age 5 years
- Phenotypic evidence of DMD/BMD b in the onset of characteristic clinical symptoms or signs (e proximal muscle weakness, waddling gait, and Gowers recovery by 9 years of age, an elevated serum creatinine kinase level, and ongoing difficulty with walking
- Documentation of the presence of a m e point mutation in the dystrophin gene as determined by gene sequencing fr laboratory certified by the College of ean Pathologists (CAP), the Clinical Laboratory Improvement Act Amendme (CLIA), or an equivalent organization
- Ability to walk 75 meters unassisted g the screening 6-minute walk test
- Documentation that a baseline renal ul nd has been performed
- Confirmed screening laboratory value in the central laboratory ranges (hemoglobin, adrenal, renal, and serum electro parameters)
- Willingness and ability to comply wit duled visits, drug administration plan, study procedures, laboratory tests, and restrictions

Exclusion Criteria

- Treatment with systemic aminoglycos tibiotics within 3 months prior to start of study treatment
- Initiation of systemic corticosteroid th within 6 months prior to start of study treatment or change in systemic corticosteroid therapy (eg, initiation, c in type of drug, dose modification not related to body weight change, schedu modification, interruption, discontinua or reinitiation) within 3 months prior to start of study treatment
- Any change (initiation, change in type ng, dose modification, schedule modification, interruption, discontinuation, o reinitiation) in prophylaxis treatment f gestive heart failure within 3 months prior to start of study treatment
- Treatment with warfarin within 1 mon or to start of study treatment
- Prior therapy with PTC124
- Known hypersensitivity to any of the i ients or excipients of the study drug (Lutrol® [Ultra]M [refined polydextro polyethylene glycol 3350, Lutrol® mi 27 [poloxamer 407], mannitol 25C, crospovidone XL 10, Hydroxyethyl cellu vanilla, Cab-O-Sil® M5P [colloidal si magnesium stearate)
- Exposure to another investigational dr thin 2 months prior to start of study treatment.
- History of major surgical procedure w 30 days prior to start of study treatment
- Ongoing immunosuppressive therapy than corticosteroids).
- Ongoing participation in any other the tic clinical trial
- Expectation of major surgical procedu , scoliosis surgery) during the 12-month treatment period of the study ce
- Clinical symptoms and signs of conge heart failure (American College of Cardiology/American Heart Association St or Stage D) or evidence on echocardio of clinically significant myopathy
- Prior or ongoing medical condition (eg comorbid illness, psychiatric condition, behavioral disorder, alcoholism, drug abuse), medical history, physical findi lectrocardiogram findings, or laboratory abnormality that, in the investigator opinion, could adversely affect the saf the subject, makes it unlikely that the course of treatment or follow-up would completed, or could impair the assess of study results

Gender: Male

Minimum Age: 5 Years

Maximum Age:

Accepts Healthy Volunteers? No

Central Contact:
Diane Goetz
Telephone: 908-912-9256
Email: dgoetz@ptcbio.com

Study Officials/Investigators:

NOTE: Study Official is required by the and ICMJE

Locations:
Facility: Cincinnati Children's Hospital M l Center
Cincinnati, Ohio, United States
Contact: Paula Morehart

Telephone 513-636-8967
Email Paula.Merchart@cchmc.org
Recruitment Status: Recruiting

Facility: The Children's Hospital
Aurora, Colorado, United States
Contact: Melissa Gibbons
Telephone 303-724-2354
Email gibbons.melissa@tchden.org
Recruitment Status: Recruiting

Facility: University of Rochester
Rochester, New York, United States
Contact: Alexis Smirnow
Telephone 585-275-4715
Email alexis_smirnow@urmc.rochester
Recruitment Status: Recruiting

Facility: Children's Hospital of Boston H Medical School
Boston, Massachusetts, United States
Contact: Erica Sanborn
Telephone 617-355-2752
Email Erica.Sanborn@childrens.harvar
Recruitment Status: Recruiting

Facility: University of Utah
Salt Lake City, Utah, United States
Contact: Brianna McGerty
Telephone 801-585-1299
Email bmcgerty@genetics.utah.edu
Recruitment Status: Recruiting

Facility: Southwestern University
Dallas, Texas, United States
Contact: Medrith Green
Telephone 214-456-8072
Email medrith.greene@childrens.com
Recruitment Status: Recruiting

Facility: University of Iowa Healthcare
Iowa City, Iowa, United States
Contact: Carrie Stephan
Telephone 319-356-2673
Email carrie-stephan@uiowa.edu
Recruitment Status: Recruiting

Facility: Child Neurology Center of Pens
Pensacola, Florida, United States
Contact: Holley Moseley
Telephone 850-484-6060
Email holley.moseley@childneurology .com
Recruitment Status: Recruiting

Facility: Duke University Medical Cente
Durham, North Carolina, United States
Contact: JoAnne Mackey
Telephone 919-684-2036
Email mackey003@mc.duke.edu
Recruitment Status: Recruiting

Facility: University of Kansas Medical C
Kansas City, Kansas, United States
Contact: Victoria Watts
Telephone 913-588-5479
Email vwatts@kumc.edu
Recruitment Status: Recruiting

Facility: Washington University School dicine
Saint Louis, Missouri, United States
Contact: Betsy Malkus
Telephone 314-362-1624
Email malkusb@neuro.wustl.edu
Recruitment Status: Recruiting

Facility: University of Minnesota
Minneapolis, Minnesota, United States
Contact: Cameron Naughton
Telephone 612-625-4882
Email naugl009@umn.edu
Recruitment Status: Recruiting

Facility: Children's Hospital of Philadelp
Philadelphia, Pennsylvania, United States

Contact: Lindsey Dorsey
Telephone 267-426-7623
Email: dorsey@email.chop.edu
Recruitment Status: Recruiting

Facility: Columbia University Medical [illegible]
New York City, New York, United State
Contact: Jackie Montes
Telephone 212-342-5767
Email JMontes@neuro.columbia.edu
Recruitment Status: Recruiting

Facility: University of California-Davis
Sacramento, California, United States
Recruitment Status: Not yet recruiting

Facility: Shriners Hospital for Children
Portland, Oregon, United States
Contact: Lora Wahl
Telephone 503-221-3473
Email lwahl@shrinenet.org
Recruitment Status: Recruiting

Facility: University Hospital KU Leuve
Leuven, Belgium
Contact: Greet Van Leemputten
Telephone 32 16 34 38 45
Email greet.vanleemputten@uz.kuleu [illegible].be
Recruitment Status: Recruiting

Facility: Alberta Children's Hospital
Calgary, Alberta, Canada
Recruitment Status: Not yet recruiting

Facility: London Health Sciences Cent
London, Ontario, Canada
Contact: Ashrafunissa Janmohammad
Telephone 519-685-8207
Email ashrafunissa@lhsc.on.ca
Recruitment Status: Recruiting

Facility: Groupe Hospitalier La Pitie-S [illegible]ere
Paris, France
Contact: Denis de Castro
Telephone 33 1 42165863
Email d.decastro@institut-myologie.
Recruitment Status: Recruiting

Facility: Service de Neuropediatrie, hô [illegible]a Timone
Marseille, France
Contact: Cecile Halbert
Telephone 33 491386739
Email cecilehalbert@yahoo.fr
Recruitment Status: Recruiting

Facility: Neuromuscular center of Nant
Nantes, France
Contact: Raphaelle Chassereau
Telephone 33 240083617
Email Raphaelle.Chassereau@chu-n[illegible].fr
Recruitment Status: Recruiting

Facility: University Hospital
Freiburg, Germany
Contact: Ursula Wenn
Telephone 49 761 2707711
Email ursula.wenn@unikliniik-freiburg
Recruitment Status: Recruiting

Facility: University Clinic for Children [illegible]ersity of Essen
Essen, Germany
Contact: Barbel Leiendecker
Telephone 49 201 7232508
Email baerbel.leiendecker@uk-essen
Recruitment Status: Recruiting

Facility: Hadassah Medical Center, He [illegible]University Hospital
Jerusalem, Israel
Recruitment Status: Not yet recruiting

Facility: Ospedale Pediatrico Bambino
Rome, Italy
Recruitment Status: Not yet recruiting

Facility: U O Complessa di Neuropsichia[illegible]fantile
Rome, Italy
Contact: Marika Pane
Telephone 39 347 934 7864
Email marika.pane@rm.unicatt.it
Recruitment Status: Recruiting

Facility: Ospedale Maggiore Policlinico [illegible]n
Milan, Italy
Contact: Stefania Corti
Telephone 39 025 503 3807
Email stefania.corti@unimi.it
Recruitment Status: Recruiting

Facility: Hospital Universitari La Fe
Valencia, Spain
Recruitment Status: Not yet recruiting

Facility: Hospital Sant Joan de deu
Barcelona, Spain
Recruitment Status: Not yet recruiting

Facility: Queen Silvia Children's Hospital
Goteburg, Sweden
Contact: Ulrica Sterky
Telephone 46 31 3438207
Email ulrika.sterky@vgregion.se
Recruitment Status: Recruiting

Facility: Astrid Lindgren Pediatric Hospi[illegible]
Stockholm, Sweden
Contact: Erika Trulsson
Telephone 46 8 51777479
Recruitment Status: Recruiting

Facility: Univ of Newcastle, Institute of H[illegible] Genetics
Newcastle, United Kingdom
Contact: Jane Barnes
Telephone 44 191 246 4672
Email jane.barnes@ncl.ac.uk
Recruitment Status: Recruiting

Facility: Imperial College London, Hamm[illegible]th Hospital
London, United Kingdom
Recruitment Status: Not yet recruiting

Facility: Robert Jones and Agnes Hunt Or[illegible]edic NHS Trust
Shropshire, United Kingdom
Contact: Meredith James
Telephone 0044 1691 404047
Email Meredith.James@rjah.nhs.uk
Recruitment Status: Recruiting

Facility: Institute For Neuromuscular Res[illegible] The Children's Hospital at Westmead
Westmead, Australia
Recruitment Status: Not yet recruiting

Facility: Royal Children's Hospital
Parkville, Victoria, Australia
Contact: Monique Ryan
Telephone 61 3 9345 4633
Email JMontes@neuro.columbia.edu
Recruitment Status: Recruiting

Facility: British Columbia Children's Hosp[illegible]
Vancouver, British Columbia, Canada
Recruitment Status: Not yet recruiting

The Children's Hospital: NOTE: missin[illegible] valid postal code
University of Rochester: NOTE: missing[illegible] valid postal code
Children's Hospital of Boston/Harvard Medi[illegible]al School: NOTE: missing or invalid postal code
University of Utah: NOTE: missing or in[illegible] postal code
Southwestern University: NOTE: missin[illegible] valid postal code
University of Iowa Healthcare: NOTE:[illegible]g or invalid postal code
Child Neurology Center of Pensacola: N[illegible] missing or invalid postal code
Duke University Medical Center: NOTE[illegible]sing or invalid postal code
University of Kansas Medical Centre: N[illegible] missing or invalid postal code
Washington University School of Medicine: NOTE: missing or invalid postal code
University of Minnesota: NOTE: missing[illegible] valid postal code
Children's Hospital of Philadelphia: NO[illegible] missing or invalid postal code
Columbia University Medical School: N[illegible] missing or invalid postal code
University of California-Davis: NOTE[illegible]g or invalid postal code

Exhibit G

John R. Parkin M.D.
1705 Anne St NW
Bemidji, MN 56601
[218] 333-4710
[218] 333-4728 FAX

Langdon Miller M.D.
Chief Medical Officer
PTC Therapeutics
100 Corporate Court
South Plainfield, NJ 07080

Dear Dr. Miller,

I am writing as the initial step of a compassionate use application of PTC 124 as a single patient IND for a patient of mine. As the first step, we would need agreement from PTC to provide the medication

Jacob Gunvalson [DOB 10/05/91] has been a patient of mine since birth. In early childhood he was diagnosed with Muscular Dystrophy [MD] secondary to a nonsense stop codon mutation of his dystrophin gene. Fortunately he has not had any major medical complications from his MD but his motor functions are deteriorating in spite of aggressive therapy. He does show stunted growth and Cushingoid features from the long term steroids.

His major medications at this time include Deflazacort, Fosamax, Enalopril and Prevacid. He also has been treated with an experimental protocol of IV gentamycin 3 times weekly. This has slowed the progression of his disease but appears to be losing effectiveness.

His general health remains good thus far. Specifically his most recent echocardiogram [11/03/05] was normal with an ejection fraction of 79%. Pulmonary functions were last tested [12/30/04] and were also normal. He has not had pneumonias. Dexascan [5/19/04] did show decreased but improving bone density and he has not had any fractures. His most recent creatinine clearance was normal at 86 ml/minute.

I am aware of the cystic fibrosis trials and the current MD trial in progress. If the MD trial shows any promise, I would like to see Jacob start PCT 124 as soon as possible before any further deterioration occurs.

Jacob is a pleasant, bright adolescent who is motivated to succeed. He has been cooperative in his therapy and treatments. He can still walk short distances with a pronounced abnormal gait and uses an electric scooter for longer walks.

His parents are very knowledgeable about MD and understand the potential risks of a phase 2 drug such as PTC 124. They have also been very active politically in getting research funds for MD.

I feel that Jacob would be an ideal candidate for a single patient IND under compassionate use. It is important that this be started as soon as possible before further deterioration occurs.

I would be glad to answer any questions or discuss this further by any means you wish. I appreciate your careful consideration of my request. Thank you.

Sincerely

John R. Parkin M.D.
johnparkin@meritcare.com

Exhibit H

April 14, 2006

John R. Parkin, MD
MeritCare Bemidji
1705 Anne Street NW
Bemidji, Minnesota 56601

Dear Dr. Parkin:

Thank you for your inquiry regarding a single-patient protocol for Jacob Gunvalson. I would like to provide you with some details about the current clinical development of PTC124.

At this point we have Phase 2 studies ongoing in cystic fibrosis (CF) and in Duchenne muscular dystrophy (DMD). In the CF Phase 2 program, we have performed an interim analysis of data from the first 15 patients who have received two 14-day courses of PTC124.

The findings show evidence that PTC124 can increase chloride channel activity in some patients. In the DMD Phase 2 study, we are not yet in the position to perform an analysis and therefore have no indication of PTC124's activity in DMD patients. The safety data for CF and DMD are also limited and are awaiting data monitoring committee review. Therapy in the Phase 2 clinical trial program is currently limited to a total of 28 days, based on the duration of preclinical toxicology data available to date. A long-term preclinical toxicology program is in progress as a prelude to conducting longer-term clinical trials in CF and DMD.

Given this situation, implementation of an expanded access program at this time would be premature. While we are encouraged that the available data may suggest proof of concept in CF, these data were obtained in only a small number of adult patients receiving PTC124 for a short period of time. We cannot be sure that the preliminary results in CF will indicate long-term clinical benefit in CF, nor can we surmise that the preliminary CF findings will predict clinical benefit in patients with DMD.

We want to avoid unacceptable risks for patients and be certain that we do not jeopardize the development of PTC124. Our clinical development plan is designed to ensure that PTC124 becomes available for all patients who might benefit if its efficacy and safety are eventually proven. Thus, we must finish the additional toxicology studies and complete accrual to the current Phase 2 clinical trials in CF and DMD. We expect to complete our further toxicology studies and Phase 2 clinical trials in CF and DMD by the end of 2006, with data available following completion.

I would like to suggest that we plan to be in touch in early 2007 once more information is available. In the meantime, should you have any questions, please do not hesitate to contact us. In my role I am often traveling and I did not have an opportunity to see your letter until late last week. The best point of contact here at PTC Therapeutics is Ms. Kerri Donnelly (kdonnelly@ptcbio.com; 908-222-7000, x112). Ms. Donnelly will ensure you receive a prompt reply and she is always able to reach me and anyone else within PTC Therapeutics who could be of assistance.

Best regards,

Langdon L. Miller, MD

Langdon L. Miller, M.D.
Chief Medical Officer
PTC Therapeutics

cc: Ms. Kerri Donnelly
Ms. Cheri Gunvalson