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UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

JACOB GUNVALSON, CHERI AND JOHN GUNVALSON, AS GUARDIANS FOR JACOB GUNVALSON, AND CHERI AND JOHN GUNVALSON, INDIVIDUALLY, Plaintiffs, v. PTC THERAPEUTICS, INC., Defendant.	Civil Action No. 08-3559 (WJM) (MF) **DECLARATION OF CHERI GUNVALSON** ***DOCUMENT FILED ELECTRONICALLY***

CHERI GUNVALSON, of full age, declares as follows:

1. I reside at 11617 506th Street, Gonvick, Minnesota 56644. I am married to John Gunvalson, and we have three children, Ben (20), Jacob (16) and Kelsey (13), all of whom live with us. I am a Registered Nurse with a Master's Degree in Adult Health Nursing, and John is a farmer.

2. At an early age Jacob began displaying symptoms of Muscular Dystrophy, and in 1999, he was diagnosed. We had two gene sequencing studies undertaken, which both

confirmed that Jacob has Duchene Muscular Dystrophy due to a Nonsense Mutation in the dystrophin gene. One study was undertaken at the City of Hope Hospital in Los Angeles on behalf of Ohio State University and the other study was undertaken by the University of Utah Medical Center. True and correct copies of the reports from these two studies are attached hereto as Exhibits A and B, respectively.

3. Duchene Muscular Dystrophy is a progressive muscular disorder which is the most prevalent of the muscular dystrophies and the most common lethal genetic disorder diagnosed during childhood. One in every 7,000 children is born with Duchene Muscular Dystrophy. There is no treatment for Muscular Dystrophy, and the life expectancy is under 25 years, with death usually caused by deterioration of the pulmonary system. A true and correct copy of a printout of the DMD entry from the Medline Plus website is attached hereto as Exhibit C.

4. Jacob was an A student at school and was ambulatory – that is, he was able to walk – until a year ago. Since March of 2007, Jacob has been confined to a wheelchair and is losing his upper body strength. Today, he cannot lift a glass of water, feed himself, use a urinal on his own or transfer himself, and needs help to sit up. A true and correct copy of the report on Jacob's physical taken at Cincinnati Children's Hospital in December of 2007 is attached hereto as Exhibit D.

5. Approximately fifteen percent (15%) of the patients with Duchene Muscular Dystrophy have the condition due to the presence of a "nonsense mutation" in the dystrophin gene. (See Exhibit E.) The nonsense mutation is called a "stop codon" because the mutation instructs the ribosome within the dystrophin gene to prematurely stop the production of the protein which provides the connective structure for muscle tissue. (See Exhibit F.) The

mutation is in the X chromosome. Because girls have two X chromosomes, and because only one chromosome is necessary to produce the protein, it is a disease that is carried by girls but affects boys. (See Exhibit C.) A true and correct copy of a PTC press release discussing DMD and how the FDA has accorded PTC124 "fast track" status is attached hereto as Exhibit E. A true and correct copy of an article in the Journal *Nature* concerning the nonsense mutation and a treatment therefore is attached hereto as Exhibit F.

6. However, there are few approaches to treating DMD which have been tried or being evaluated. One approach is the use of Gentamicin. Gentamicin is an intravenously administered antibiotic that, in sufficient doses, is believed to allow the ribosome in the gene to read through the "stop codon" and continue to develop the protein for muscular connective tissue. (See Exhibit F.) On information and belief, Jacob is one of less than ten (10) children with DMD in the United States who have been under long term treatment of Gentamicin, from January of 2003 to June of 2007.

7. The most promising treatment for DMD is PTC124, a drug that masks the stop codon and allows the ribosome to direct that the dystrophin be produced to a mature cell. (See Exhibits F-G.) Dr. Lee Sweeney, a physiology professor at the University of Pennsylvania Medical School who works with PTC Therapeutics, Inc. ("PTC Therapeutics" or "PTC"), the Parent Project for Muscular Dystrophy ("PPMD"), and with the clinical trials for PTC124, has told me that PTC124 is twelve times as effective as Gentamicin and may actually restore dystrophin to functional levels. A true and correct copy of an FAQ web page from the PTC Therapeutics website concerning PTC124 is attached hereto as Exhibit G.

8. PTC124 is manufactured by PTC Therapeutics. On information and belief, PTC Therapeutics is currently the only company conducting clinical trials on any drug targeted at the

nonsense mutation-caused DMD. PTC Therapeutics participates in a novel joint venture with a parent group known as PPMD. PTC and PPMD have a close working relationship. (See Exhibit H.) I joined PPMD in 2001 and have been very active in the organization. PPMD is composed of approximately 3,000 parents and relatives of children with Muscular Dystrophy, 50 of which have contributed at least $25,000 for research. (See Exhibit H.) PPMD has contributed at least $3 million to PTC Therapeutics for research. (See Exhibit I.) A true and correct copy of an article from *Nature Biotechnology* magazine is attached hereto as Exhibit H. A true and correct copy of a PPMD press release is attached hereto as Exhibit I.

9. PPMD and PTC describe their collaboration as "Project Catalyst". (See Exhibit I.) According to *Nature Biotechnology*, "Project Catalyst" creates several benefits for PTC, including increased access to government funding and advocacy intervention with the FDA and other regulators, and the PPMD parents have played a critical roll in getting NIH funding for PTC Therapeutics. (See Exhibit H.)

10. In 2001, I joined the Government Relations Board of PPMD. I helped draft the Muscular Dystrophy CARE Act, the purpose of which is to equalize funding for Muscular Dystrophy patients. I also persuaded two of my Congressmen at the time -- Representative Collin Peterson and the late Senator Paul Wellstone -- to be primary authors for the legislation. (See Exhibit J.) A true and correct copy of an article from the *Star Tribune* concerning my involvement in the push for DMD research funding is attached hereto as Exhibit J.

11. In 2001, I personally met with dozens of Senators and Representatives and spent the entire year on the telephone calling Congressional offices. Jacob and I persuaded 235 Representatives and 49 Senators to co-author the Muscular Dystrophy CARE Act, which was the only disease specific legislation enacted by the 107th Congress. (See Exhibit J.)

12. Prior to passage of the Muscular Dystrophy CARE Act, Muscular Dystrophy patients, on a per patient basis, received but a small fraction of grants and funds, from the National Institutes of Health and other sources, when compared to other diseases with similar morbidity outcomes. In 2001, only $14.3 million was allocated by the National Institutes of Health to Muscular Dystrophy research. The legislation doubled the research in the first year and grew to $54 million by 2006. (See Exhibit J.)

13. The legislation also required the National Institutes of Health to establish and fund Centers of Excellence for treatment of Muscular Dystrophy. After the law was signed on December 18, 2001, I was appointed to the NIH Review Board to designate the Centers of Excellence. (See Exhibit J.)

14. Since 2001 I have continued to advocate in Congress and with the National Institutes of Health in an effort to increase funding for Duchenne Muscular Dystrophy. Each year I worked with Bettilou Taylor, the staff director of the Senate Labor, Health and Human Services Appropriation Committee from 2003 to 2006, in preparing the annual Committee Report which directs the National Institutes of Health as it relates to grants and funding proposals. My mission was to make sure that Muscular Dystrophy research was funded at least equal to other diseases with similar morbidity outcomes.

15. In 2005, PTC Therapeutics began its first clinical trial – the Phase I trial – of PTC124, primarily to determine patient tolerance to the drug. I recall a meeting with Claudia Hirawat, the Senior Vice President for Corporate Development, at a PPMD meeting, where she told me that one of the hurdles in bringing a drug like PTC124 to market was raising the money necessary to pay for the clinical trials that test the efficacy and safety of a new drug. Thereafter, I urged Dr. Langdon Miller, the Chief Medical Officer of PTC, to file applications for grants

from the National Institutes of Health. He was skeptical of the suggestion, noting that the applications were very complicated and bureaucratic. Having served on a Peer Review Committee with NIH in 2003, I was adamant that PTC should file an application. I told him that ten percent (10%) of the NIH grant money has to go to private companies and that very few private companies were applying for it. Based on my direction, PTC applied for, and received, government grants. Within a year and a half, PTC Therapeutics received a $15.4 million research grant by NIH to build upon the research paid for by Project Catalyst. (See Exhibit I.)

16. The Phase I trial was administered to healthy adults only. As such, Jacob was not enrolled. The findings of the Phase I study were very promising.

17. PTC Therapeutics also initiated Phase II trials in late 2005 (see Exhibit E), but once again, Jacob was not enrolled in the clinical trial. In the Phase II trial, patients would receive only a 28-day dosage of PTC124. However, prior to its commencement, I asked several people affiliated with PTC if Jacob should be enrolled. Both Dr. Richard Finkel, head of pediatric neurology at the Children's Hospital of Pennsylvania (who was the trial's "primary investigator") and Claudia Hirawat, PTC's Senior Vice President, told me it was not worth taking Jacob off of Gentamicin for only a 28-day dosage of PTC124. Specifically, I was told that, "One in the hand is better than two in the bush." Had we wanted to enter Jacob in the trial, he almost certainly would have met the criteria (another boy with the same mutation was entered), but he did not have a muscle biopsy to confirm this. At the time, I asked Ms. Hirawat if there were any adverse effects on Jacob for not participating in the trial, and she told me there were none. I did not have a biopsy performed on Jacob nor attempt to enroll him in the Phase II trial in reliance on this statement.

18. On March 30, 2006, PTC Therapeutics announced that the FDA had granted "fast track status" to the development of the drug.

19. Jacob continued to deteriorate, and concerned with this, I went to Dr. John Parkin, Jacobs's pediatrician in Bemidji, Minnesota, and asked him if he would apply for a "Compassionate Use" exemption from the FDA on behalf of Jacob. In order to qualify for a "Compassionate Use" exemption the pharmaceutical company must agree to make the drug available to the physician. (See Exhibit K.) A true and correct copy of a FDA web page concerning the FDA's "treatment IND" program is attached hereto as Exhibit K.

20. Accordingly, in March or April of 2006, Dr. Parkin wrote to Dr. Langdon Miller, the Chief Medical Officer of PTC, requesting that the company make the drug available to him for a single patient investigative study. (Dr. Parkin's letter is attached to his declaration, which has also been submitted herewith.) On April 14, 2006, Dr. Miller responded to Dr. Parkin by letter, stating that the results of the Phase IIa clinical trials would not be known until the end of 2006. Dr. Miller continued that, once patient safety is confirmed with the study, the parties could discuss an IND "compassionate use" proposal. I was copied on Dr. Miller's April 14, 2006 reply letter. (Dr. Miller's letter is attached to Dr. Parkin's declaration, which has also been submitted herewith.)

21. On April 24, 2006, I received an email from Dr. Russell Katz, the head of the FDA's neuron-pharmacological division, suggesting that Jacob apply for a compassionate use exception in order to receive PTC124 without disturbing any of PTC's clinical trials. A true and correct copy of this email is attached hereto as Exhibit L. In his email, Dr. Katz explains that there are several vehicles through which a patient can get access to an investigational drug if he or she is not already enrolled in, or eligible for including in, a clinical trial. One approach is

through a "protocol exception" in which the pharmaceutical company will approve the participation of a patient who otherwise is not qualified to participate in the clinical study if, without access to the drug, the patient may die or suffer serious consequences. In a protocol exception, the data from the "excepted" patient would not be part of the report of the original study, but the patient could be monitored by investigators already familiar with the drug. Another approach is to obtain approval from the FDA for a single patient IND (a single-patient study), which also requires the approval of the pharmaceutical company.

22. In his email, Dr. Katz noted that the FDA normally supports requests for compassionate use exceptions. He also explained that Jacob's best option would be to request a protocol exception.

23. Claudia Hirawat is Senior Vice President for Corporate Development at Defendant PTC. The website for PTC indicates that she is directly responsible for fund raising and commercial development of the company. I consider Claudia to be my friend.

24. On July 13, 2006, the Gunvalsons attended the Annual PPMD Conference. At the conference Jacob had a long conversation with PTC's Chief Medical Officer, Dr. Miller. The next day my husband and I had a private conference with Dr. Miller. As with all PTC representatives, Dr. Miller expressed great appreciation to me for my work in Washington and getting public funding for DMD research. As noted in the *Nature Biotechnology* magazine NIH funding was critical to success of the company. (See Exhibit H.) During the conversation, I asked Dr. Miller if Jacob would get PTC124. Dr. Miller said that the boys in the Phase II trial metabolized the drug faster than expected and that PTC would need to conduct another 28-day trial at a higher dose. He told me that the Company did not know the right dosage level yet and they need to get the safety data back. Dr. Miller also said that they needed to figure out the right

dosage level and to do so they may need to do another short trial at higher doses. He reassured me that, once positive results were back from the trial, Jacob will get PTC124.

25. At this time, I again asked PTC if Jacob should be in the Phase IIa trial. As she had earlier, Claudia Hirawat again told me not to discontinue Jacob's then-current Gentamicin treatment. We were told that Jacob had no better or worse chance to be treated in the future based on his non-enrollment in the Phase IIa trial. My husband and I decided to listen to the advice of medical professionals and not place Jacob in the trial.

26. On September 27, 2006, I was recognized for my work in getting funding for Muscular Dystrophy at the Annual Gala of the National Genetic Alliance in Washington, D.C. Claudia Hirawat, the PTC Senior Vice President in charge of fundraising and corporate development, also attended the Gala. At the event, Ms. Hirawat expressed great appreciation to me for my work in getting federal funding for research. At the event I explained to her that I was frustrated with the delay in getting Jacob access to PTC124. She assured me that Jacob would get access to PTC124. Ms. Hirawat and a board member of PPMD then invited me to attend a meeting the next day in Philadelphia to hear a presentation on the results of the Phase IIa clinical study.

27. The next day I took a train to Philadelphia where PTC announced the successful results of the Phase II clinical study of PTC124, which were eventually released to the media the next month. (See Exhibit M.) The preliminary findings were that the children in the study tolerated the medication and showed increased development of dystrophin, and that there were no significant adverse effects. (See Exhibit M.) A true and correct copy of an email attaching a press release announcing these preliminary findings is attached hereto as Exhibit M.

28. That evening a dinner was held at the Loew's Hotel. Dr. Stewart Peltz, the President and Chief Executive Officer of PTC, sat next to me at the dinner. Dr. Peltz thanked me for my leadership in getting federal funding for Muscular Dystrophy treatment. I asked Dr. Peltz if Jacob could get the drug. Dr. Peltz agreed that Jacob would have access to it.

29. Thereafter I participated in a conference call between Dr. John Parkin and Ms. Hirawat. I believe the call was made in October of 2006. During the conversation, Ms. Hirawat made a commitment that Jacob would be given access to PTC124. During this discussion it was also noted that Jacob was being administered Gentamicin and that, to be enrolled in the PTC124 trial, Jacob would have to get off of Gentamicin for at least 90 days.

30. In or around March 2007, Jacob lost the ability to walk and has since been confined to a wheelchair. In May of 2007, Jacob was examined by Dr. Brenda Wong, a child neurologist at Cincinnati Children's Hospital. Dr. Wong is a primary investigator in the PTC124 clinical studies at her hospital. Dr. Wong recommended that Jacob discontinue his dosage of Gentamicin, and that he prepare for enrollment in a PTC124 clinical trial. A true and correct copy of Dr. Wong's report on her examination of Jacob is attached hereto as Exhibit N. At that time, Jacob had been taking Gentamicin with positive results, but PTC124 was a more promising treatment for his condition because it appears more effective than Gentamicin and the side effects of PTC124 are much less severe than Gentamicin.

31. On July 11, 2007, PTC and PPMD announced that PTC and the University of Pennsylvania had jointly received a $15.4 million research grant to develop PTC124. (See Exhibit I.) The next day, I attended the annual PPMD Conference in Philadelphia. At the conference, on July 14, 2007, I had another conversation with Dr. Peltz, the CEO of PTC. Dr. Peltz once again thanked me for my role in getting funding for Muscular Dystrophy research in

general and PTC Therapeutics in particular. I asked Dr. Peltz if Jacob could get the drug. Dr. Peltz responded that Jacob should have been enrolled in a previous clinical trial. Distressed by that comment, I went to Claudia Hirawat, who then invited Jacob and me to visit her at her home and tour the company headquarters.

32. Jacob and I then stayed with Ms. Hirawat at her home. During the visit, Claudia again represented to Jacob and I that the company was working to include Jacob in a trial.

33. In October and November of 2007, Ms. Hirawat and I exchanged a number of e-mails concerning Jacob. On October 10, 2007, she told me that she was thinking of Jacob, and reminisced about our stay at her home and Jacob's desire to eat a New York pizza. (See Exhibit O.) On October 25, 2007, Hirawat told us by email that PTC was in final discussions with the FDA regarding next steps for its clinical studies, and what those steps could mean for Jacob; additionally, she wrote that she and her husband were touched by our visit to their home, she kept all of Jacob's photos at the top of her desk, and that she considered the Gunvalson family to be her friends. (See Exhibit P.) True and correct copies of these emails are attached hereto as Exhibits O and P, respectively.

34. On October 18, 2007, PTC announced the results of its Phase IIa clinical trial involving many patients administered PTC124. The drug was reported to be successful, with improved dystrophin presence, increased physical activity and no serious side effects reported.

35. Throughout this process PTC Therapeutics led me to believe that Jacob was going to be enrolled in a trial or at least to have access to the drug by January of 2008. Bolstered by the news concerning the Phase IIa trial, especially in light of Dr. Miller's earlier promises regarding access to PTC124 once safety and efficacy were reported, I contacted PTC's patient liaison, Diane Goetz, about Jacob receiving PTC124 through a compassionate use exception. On

November 26, 2007, I had a conversation with Ms. Goetz, who advised me that Jacob could not use the drug under an expanded use protocol but that he would be able to get the drug in a different way. I was ecstatic and I called a number of people to let them know that we were getting into a clinical trial and Jacob would be receiving PTC124.

36. Despite Ms. Goetz's promises, I was told by Claudia Hirawat that Jacob's status was still up in the air. Concerned by this, I emailed Ms. Goetz on December 30, 2007 and asked her what Ms. Hirawat had meant by her statement. (See Exhibit Q.) Ms. Goetz responded that Jacob did not qualify for the Phase IIb trial because patients have to be ambulatory in order to measure their progress. (See Exhibit R.) She began the process of backpedaling off of PTC's commitment to provide PTC124 to Jacob by stating that the company was looking for another study that Jacob might be able to enroll. Finally, she admitted that, as patient liaison, she was not aware of what "protocol exception" meant. True and correct copies of these emails are attached hereto as Exhibits Q and R, respectively.

37. By December 29, 2007, I also had learned that PTC was enrolling patients in an extension of the Phase IIa clinical trial. As I understand it, this Phase IIa trial extension is only available to those patients previously enrolled in the initial Phase IIa 28-day trial. Therefore, despite Ms. Hirawat's promises to us to the contrary, Jacob is now denied from participating in the Phase IIa extension based on its protocol.

38. On January 1, 2008, I replied to Ms. Goetz's December 29 communication by email, indicating that Dr. Russell Katz, the director of the FDA's neuron-pharmacological division, had suggested that Jacob receive PTC124 through a protocol exception and that he would consider an expedited review of Jacob's need for PTC124. I explained that my understanding was that the FDA wanted to expand use of protocol exceptions, especially in rare

subgroups such as Jacob's, to provide more safety data in a controlled setting. I then reiterated my request that Jacob be allowed access to PTC124 in the Phase IIa extension as a protocol exception. A true and correct copy of this email is attached hereto as Exhibit S.

39. On January 4, 2008, without explanation as to why Jacob could not receive a protocol exception, Ms. Goetz, on behalf of PTC, denied our request. A true and correct copy of this email is attached hereto as Exhibit T.

40. Not satisfied with this response, I contacted Bettilou Taylor, staff director of the Senate Labor, Health and Human Services Appropriations Committee. On January 14, 2008, Ms. Taylor sent Ms. Goetz an email specifically asking why PTC "won't grant a protocol exception for Jacob", especially because the FDA was "encouraging companies to grant exceptions to provide as much [information] as possible about the side effects from the drug". Eleven days later, on January 25, 2008, Diane Goetz responded to Ms. Taylor by stating, again without explanation, that PTC would not provide PTC124 to Jacob in connection with a protocol exception. A true and correct copy of the email string containing both of these emails is attached hereto as Exhibit U.

41. Finally, on April 12, 2008, I was told that the company did not know when or if Jacob would ever get the drug. On April 23, 2008, PTC announced the commencement of yet another clinical study, this one a Phase IIb study. A true and correct copy of PTC's press release announcing this study is attached hereto as Exhibit V. The Phase IIb study has already commenced. It is an international study, and one of the criteria is that the patient still be ambulatory. Jacob is no longer ambulatory, so he is not eligible under the study protocol to participate.

42. PTC is also extending the Phase IIa study for a longer-term (96-week) review of PTC124 on children with DMD. This study is taking place at three locations – the Cincinnati Children's Hospital, the University of Utah, and the Children's Hospital of Philadelphia. The only children eligible for inclusion in this Phase IIa extension are those that participated in the previous Phase IIa study. Because we were told not to enroll Jacob in that study and he did not participate in it, Jacob is not eligible to participate under the Phase IIa protocol. The start of each individual child's treatment is staggered, although parents of children enrolled in Phase IIa have been told the study will commence in late July or August. Prior to receiving PTC124, each child much undergo a thorough examination by one of the physicians running the study. Included in this examination is an invasive muscle biopsy to examine the child's dystrophin levels. (As a note, other non-ambulatory children with Jacob's form of DMD will be enrolled in this Phase IIa extension study.)

43. There is a six-month waiting list for an appointment with Dr. Brenda Wong, the lead researcher for the Phase IIa study at Cincinnati Children's Hospital. Jacob has an appointment with Dr. Wong on August 6, 2008. At that time, Dr. Wong will perform a thorough examination of Jacob. She could also perform a muscle biopsy, although because it is very invasive, we would only do this if it could lead to Jacob receiving PTC124. At that time, therefore, Jacob could be prepared – from a medical perspective – to begin treatment on PTC124. However, Dr. Wong would still need some authorization to provide Jacob PTC124 outside the study protocols.

44. On information and belief, there are less than a dozen children – Jacob is perhaps the only one – that could participate as a protocol exception in the Phase IIa trial extension because so few children have DMD due to the nonsense mutation (the only form of DMD that

PTC124 treats). Children with DMD die by 25, with some dying as young as 13. Usually, children younger than 15 are still ambulatory and are therefore eligible for the Phase IIb study. On information and belief, many over 18 are on a ventilator and therefore would not participate. Further, to participate in the studies, a child must not only receive a DMD diagnosis but have his genes sequenced – this is very expensive and thus many patients forego it. Finally, most, perhaps all, of those children who meet these criteria were already in the Phase IIa study, and are therefore already eligible for the extension of the study.

45. If Jacob cannot be enrolled as a protocol exception to the Phase IIa study, we would alternatively place him in a single-patient IND under the care of Dr. John Parkin or another physician who could supervise the study, on approval from the FDA.

46. As part of the conditions of Jacob's treatment with PTC124, Jacob, John and I will sign a full release concerning liability and any necessary "informed consent" document, pay for PTC124 and its administration, undertake the necessary applications to secure approval from the FDA for a "compassionate use" exception, and complete any other task necessary to secure Jacob access to PTC124.

47. We have requested that PTC Therapeutics enroll Jacob as a protocol exception in the Phase IIa study extension or permit him to undergo a single-patient IND. Unfortunately, on July 1, 2008, I was told by Dr. Miller and others at PTC that the company would not permit Jacob to receive the drug as either a protocol exception or single-patient IND. PTC Therapeutics also told me that no new trials with different inclusion criteria are being planned or even contemplated, meaning it is probably a number of years before such studies would begin due to inherent and necessary procedures to commence them.

48. Jacob was ambulatory until March 2007. At that time, he fell and we believe that he probably suffered a compression fracture of the spine. He was then fitted with Kafo braces which permitted him to stand up and walk. In March of 2007 Jacob could pick up a glass of water and drink it. He could use the toilet by himself. He could sit up in bed without help and transfer himself to a chair. Throughout 2007 Jacob could utilize a scooter.

49. By March of 2008 – just one year later – Jacob was no longer able to utilize his braces in an efficient manner, as his musculature has deteriorated such that the Kafo braces are of no more assistance. Jacob now has to use a power chair. He has continued to deteriorate to the degree that he needs assistance to transfer from the power chair to the toilet and he can no longer lift a glass of water. As a registered nurse with 26 years of experience, it is my opinion that Jacob's condition will continue to deteriorate and that, without intervention, he will die within the foreseeable future. Unless he has access to PTC124 in the near future, through either a protocol exception in the Phase IIa study extension (at Cincinnati Children's Hospital) or a single-patient IND, Jacob will not be alive, or at least will be so incapacitated that he will not be able to participate, by the time any future clinical trial begins.

50. In reliance upon PTC's statements that there would be no negative impact on Jacob based upon not participating in the Phase II or Phase IIa 28-day studies, John and I did not enroll him in those studies. However, based on the Phase IIa study extension's protocol requirement that a patient have been previously enrolled in a PTC124 study, it is clear that Jacob has been shut out for the simple reason that we listened to, believed and acted upon PTC's promises.

51. On repeated occasions, Dr. Miller, Dr. Peltz, Ms. Hirawat, and Ms. Goetz told me that Jacob would have access to the drug.

52. In reliance upon Jacob having access to the drug, his dosage of Gentamicin was terminated in June of 2007.

53. Over the past two and one half years, representatives of PTC repeatedly raised my expectations about Jacob's access to PTC124. At several points it was made clear to me, by word and by deed, that the biggest obstacle to getting Jacob access to the PTC124 was to finance the clinical trials necessary to demonstrate efficacy and safety. PTC made it clear to me that my work on Capitol Hill was key to getting DMD funding. I was successful in getting funding for Muscular Dystrophy, and the clinical trial results have been positive, but PTC will still not give my son access to PTC124.

54. The longer Jacob does not have access to PTC124, and the more he deteriorates, the less likely he is to benefit from the drug.

I certify that the foregoing statements made by me are true. I am aware that if any of the foregoing statements made by me are willfully false, I am subject to punishment.

Cheri Gunvalson

CHERI GUNVALSON

Dated: 7-22-08

EXHIBIT A

[redacted]

MEDICAL CENTER

October 26, 2000

Dear Parents of Jacob Gunvalson,

We have finally completed the DNA study looking for stop codons in the Duchenne muscular dystrophy gene. The study has been grueling but rewarding in many ways. We worked with an outstanding laboratory of molecular genetics in California under the supervision of Dr. Steve Sommer. Due to his expertise we have found more mutations of the dystrophin gene than ever predicted from previous studies. In the population we studied we found about 75% of patients had a mutation of the dystrophin gene. More than one-third of these are stop codons and two-thirds represent other types of mutations. The note below will indicate either (A) stop codon or (B) other type of mutation.

We feel that you should have this information but you must understand that this was a research study and we cannot be liable for the results of the study. Every result should be verified in a commercial laboratory before using the information for any reason in the future. For example, if this information is to be used to guide treatment for the disease, or applied to other family members for carrier detection, or used for prenatal diagnosis, the findings must be rechecked. We take no responsibility for the results.

In the case of your son, the finding from the research study indicated (A) Stop codon mutation: **A causative mutation was found in the dystrophin gene representing a nonsense mutation in exon 5, C119, with an Amino Acid Change of gln>ter. The information is summarized below.**

Exon	NT No.	NT Change	Codon	A Change	Type	Hemi/Het
5	563	C>T	119	gln>ter	*Nonsense*	Hemi

If you have any questions, please call my office at 614-293-4962. We would also be happy to see you for an appointment to further explain the results of this study.

614-722-2203

Sincerely,

Jerry R. Mendell, MD
Kurtz Chair and Professor of Neurology

EXHIBIT B

THE UNIVERSITY OF UTAH

Department of Human Genetics

Ms. Cheri Gunvalson
Rt. 1, Box 206
Gonwick, MN 56644

Re: Jacob Gunvalson
DOB: 10/5/91

October 27, 2003

Dear Ms. Gunvalson:

Some time ago you consented to participate in a research study to identify mutations or changes in genes responsible for inherited neurologic diseases. In your family we searched for mutations in the dystrophin gene, which cause both Duchenne and Becker muscular dystrophies. We have developed a new testing method that allows us to identify dystrophin gene mutations not previously detectable with current, commercially available testing techniques.

We are writing to inform you that we have completed sequencing the dystrophin gene for Jacob and the results are below.

Jacob's test results demonstrated a disease-causing premature stop mutation:

Exon	Nucleotide*	Nucleotide change	Codon	Amino acid	Amino acid change	Mutation type
5	355	C → T	CAG → TAG	119	Gln → STOP	Premature stop

*The nucleotide position is based on the numbering from the translation initiation site (start codon) of the dystrophin mRNA sequence which encodes the major isoform in muscle (Dp427m). This reference sequence is available in GenBank under the accession number NM_004006.

It is important for you to understand that this testing was performed in a research laboratory and results should be verified in a commercial laboratory before using the information for any reason in the future. For example, if this information is to be applied to other family members to determine carrier status, or used for prenatal diagnosis, the findings should be re-confirmed in a clinical laboratory.

Genetic counseling regarding this information is available to you. Please contact Karin Dent, Genetic Counselor, at the number below with any questions or concerns you might have. We can also provide contact information for genetic counselors available to you in your area. Again, please do not hesitate to contact us with questions regarding this information.

Sincerely,

Kevin M. Flanigan, MD
Assistant Professor of Neurology, Pathology, Human Genetics and Pediatrics
(801) 587-9540

Karin M. Dent, MS
Certified Genetic Counselor
Department of Pediatrics
(801) 581-6956

Eccles Institute of Human Genetics
15 North 2030 East, Room 2100
Salt Lake City, Utah 84112-5330
(801) 581-4422
FAX (801) 581-7796

EXHIBIT C

Medical Encyclopedia

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Duchenne muscular dystrophy

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X-linked recessive genetic defects

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Definition Return to top

Duchenne muscular dystrophy is an inherited disorder, characterized by rapidly-worsening muscle weakness that starts in the legs and pelvis, and later affects the whole body.

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Duchenne muscular dystrophy is a rapidly-worsening form of muscular dystrophy. It is caused by a defective gene for dystrophin (a protein in the muscles). However, it often occurs in people without a known family history of the condition. This disorder is marked by worsening loss of muscle function, which begins in the lower limbs.

Duchenne muscular dystrophy is inherited in what is known as an X-linked recessive pattern. The defective gene is found on the X chromosome. Because women have two X chromosomes, if one contains a normal copy of the gene, that gene will make enough of the protein to prevent symptoms. But boys have an X chromosome from their mother and a Y from father, so if the X chromosome is defective, there is no second X to make up for it and they will develop the disease.

The sons of carrier females (women with one defective chromosome but no symptoms themselves) each have a 50% chance of having the disease, and the daughters each have a 50% chance of being carriers.

Symptoms usually appear before age 6 and may appear as early as infancy. There is progressive muscle weakness of the legs and pelvis, which is associated with a loss of muscle mass (wasting). Muscle weakness also occurs in the arms, neck, and other areas, but not as severely or as early as in the lower half of the body.

Calf muscles initially grow larger – the enlarged muscle tissue is eventually replaced by fat and connective tissue (a condition called pseudohypertrophy). Muscle contractures occur in the legs. Thus, the muscles are unusable because the muscle fibers shorten and fibrosis (scarring) occurs in connective tissue.

By age 10, braces may be required for walking, and by age 12, most patients are confined to a wheelchair. Bones develop abnormally, causing skeletal deformities of the spine and other areas.

Muscular weakness and skeletal deformities contribute to frequent breathing disorders. Cardiomyopathy occurs in almost all cases. Intellectual impairment may occur, but it is not inevitable and does not worsen as the disorder progresses.

Duchenne muscular dystrophy occurs in approximately 2 out of 10,000 people. Because this is an inherited disorder, risks include a family history of Duchenne muscular dystrophy. In contrast, Becker muscular dystrophy is a form that progresses (gets worse) much more slowly.

Symptoms *Return to top*

- Muscle weakness
  - Rapidly progressive
  - Frequent falls
  - Difficulty with motor skills (running, hopping, jumping)
- Progressive difficulty walking
  - Ability to walk may be lost by age 12
- Fatigue
- Intellectual retardation (possible)
- Skeletal deformities
  - Chest and back (scoliosis)
- Muscle deformities
  - Contractures of heels, legs
  - Pseudohypertrophy of calf muscles

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Muscle wasting (atrophy) begins in the legs and pelvis, then progresses to the muscles of the shoulders and neck, followed by loss of arm muscles and respiratory muscles. Calf muscle enlargement (pseudohypertrophy) is quite obvious.

Cardiomyopathy is commonly present, but signs of congestive heart failure or arrhythmias (irregular heartbeats) are rare. Respiratory disorders are common during the later stages, including pneumonia and aspiration of food or fluid into the lungs.

- A serum CPK is highly elevated.
- A neurological exam shows weakness and lack of coordination or balance.
- An EMG (electromyography) shows that weakness is caused by destruction of muscle tissue, rather than nerve damage.
- A muscle biopsy confirms the diagnosis.

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There is no known cure for Duchenne muscular dystrophy. Treatment is aimed at control of symptoms to maximize the quality of life. Gene therapy may become available in the future.

Activity is encouraged. Inactivity (such as bedrest) can worsen the muscle disease. Physical therapy may be helpful to maintain muscle strength and function. Orthopedic appliances (such as braces and wheelchairs) may improve mobility and the ability for self-care.

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EXHIBIT D

Cincinnati Children's

NEW PATIENT VISIT ENDOCRINOLOGY

Division of Endocrinology 12/08/2007

Stuart Handwerger, MD
Director

Philippe Backeljauw, MD
Nancy Crimmins, MD
Lawrence M. Dolan, MD
Deborah A. Elder, MD
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David J. Klein, MD, PhD
David R. Repaske, PhD, MD
Susan R. Rose, MD
Mellan Rutter, MD
Peggy Stenger, DO

Deb Neumann, CPA
Business Director

RE: GUNVALSON, JACOB
DOB: 10/05/1991
MRN#: 1360556
ACCT#: 167023852
DOV:
Requesting Physician: WONG, BRENDA, M.D.

Reason for consultation: Evaluation of endocrine issues associated with Duchenne muscular dystrophy and its treatment, in particular, severe growth failure and pubertal delay.

Medications: Deflazacort 6 mg daily, AndroGel 1.25 grams (1 actuation via pump) daily (since September 2007), vitamin D 1000 iu daily, OTC multivitamin 1 tablet daily, Cozaar 50 mg daily, metoprolol 25 mg daily, Fosamax 35 mg weekly, calcium 600 mg daily, MiraLax 34 mg daily, Xanax 0.25 mg tablet, half-tablet as needed, Juven 2 packets twice daily.

History of present illness: I had the pleasure of seeing Jacob, aged 16-years-2-months, for initial consultation for evaluation of endocrine issues associated with treatment for Duchenne muscular dystrophy. Jacob has been on steroid therapy from the age of 8 years, initially with prednisone, followed by daily deflazacort from age 9 years. Jacob's main concerns were his short stature and lack of growth, as well as his pubertal delay. His questions included wanting to know why he was not growing, whether he could start growth hormone, potential benefits and concerns related to growth hormone use, whether his testosterone dose was appropriate, and whether testosterone therapy at this stage would compromise his height potential. Jacob was previously of average height (around the 50th percentile) and "skinny" before starting steroids. He has had no appreciable gain in height since he was 8 years old (2nd grade). He is concerned about his short stature, and would be very interested in growth hormone therapy if possible. He has had weight gain since starting steroids, but this has not been excessive. There has been no evidence of pubertal development, and biochemical testing confirmed prepubertal levels of testosterone on May 31, 2007. After discussion with myself and Dr. Wong, a low-dose of AndroGel was started on September 16, 2007. Growth hormone stimulation testing was undertaken, and this showed normal stimulated growth hormone levels. Jacob also has a history of osteoporosis; he had a "presumed spine compression fracture" in March 2007, although this was not confirmed on CCHMC x-rays. Uncorrected lumbar spine Z-scores by DEXA scan were -3.5, or -2 when corrected for a bone age of 9 years, low for age.

Birth history: Born at 38-weeks' gestation by normal vaginal delivery. Birth weight 7 pounds, 15-1/2 ounces. Neonatal period normal.

Development: Early milestones normal, but walked around 15 months.

Social history: Jacob lives in northern Minnesota. He is in 10th grade, an A-grade student, and is actually top of his class.

Past medical history: Duchenne muscular dystrophy, although was initially diagnosed with Becker muscular dystrophy. Glucocorticoid therapy from aged 8 years, initially prednisone, followed by the deflazacort from age 9 years. After decline in motor function in 2004, he was

treated with intravenous gentamicin, but this was eventually discontinued. He experienced loss of independent ambulation at 15-1/2 years. Other issues include vitamin D deficiency, concern for insulin resistance, and asymptomatic cataracts. He has sinus tachycardia, treated with a beta-blocker and losartan. He has an 11 degree scoliosis.

Family history: Mother stands at 5 feet, 7 inches. Father stands at 6 feet, 2 inches. His midparental height is 185.6 cm (90th percentile). Mother had early puberty, but father had a history of constitutional delay of growth and development. There is no other significant family history.

Review of systems: Otherwise noncontributory.

Physical examination: Height unable to obtain (unable to stand straight unassisted). Weight 41.1 kg (< 3rd percentile). Arm span 144 cm (measured by myself, approximately -3.6 SDS). Body mass index 19.8 kg/m2. Body surface area 1.3 m2. Vital signs: Pulse 106 per minute, blood pressure 100/64. Jacob was an extremely intelligent, delightful young man. He had mild Cushingoid features. There was no acanthosis nigricans. There was no significant facial hair. Oropharynx was clear. His thyroid was not enlarged. Cardiovascular, respiratory and abdominal systems appeared normal. He had no axillary hair or apocrine secretion. He declined genital examination, and details will be obtained from his primary care physician. He was nonambulatory, although he had long-leg braces for standing.

Laboratory evaluation: Results from his endocrine evaluation in May and June 2007 are as follows: Peak growth hormone following provocative stimulation with arginine and clonidine was 17.5 ng/mL (normal). IGF-1 was 591.2 ng/mL (358.0 to 870.0) and IGFBP-3 was 5.1 mg/L (3.5 to 10.0). Total T4 was 10.1 mcg/dL, free T4 was 2.3 ng/dL, and TSH was 0.9 mlu/mL (normal thyroid function). Total testosterone was 12 ng/dL (prepubertal level), LH was 4.2 mlu/mL and FSH was 7.8 mlu/mL. Fasting insulin was 22.9 microunits/mL and glucose was 78 mg/dL (normal fasting glucose; insulin level is slightly elevated for prepubertal state, nondiagnostic but suggestive of insulin resistance), 25-hydroxyvitamin D was 18.9 ng/mL (suboptimal).

Results from this visit: Fasting glucose 79 mg/dl, insulin 26.4 microUn/ml, total cholesterol 208 mg/dl, HDL 59 mg/dl, LDL 111 mg/dl (upper normal range), triglycerides 191 mg/dl (elevated), 25-hydroxyvitamin D 41.5 ng/ml (good levels), urine Ca/Cr 0.56 (elevated), testosterone 220 ng/dl, LH 3.0 mUn/ml, FSH 13.4 mUn/ml.

Spine x-rays on May 30, 2007 showed levoscoliosis of 11 degrees, demineralized bones, but no definite compression fracture. Spine x-rays at this visit showed no significant spinal curvature on the AP view. There was loss of height of the L3 through L5 vertebrae when compared to his prior study. His bones looked osteoporotic.

Bone age on May 30, 2007 was 9 years (read by myself), very delayed and consistent with age of starting glucocorticoid therapy.

Assessment:
1. Duchenne muscular dystrophy.
2. Chronic glucocorticoid therapy since age 8 years.

3. Severe short stature / growth failure (no appreciable height gain since age 9 years), with arm span -3.6 SDS. Growth hormone testing implies he is growth hormone sufficient. The pathogenesis of his growth failure, while idiopathi, is likely related to his chronic glucocorticoid administration.
4. Excess weight for height.
5. Delayed puberty, on testosterone since September 2007.

Plan:
1. Laboratory evaluation, including testosterone level (see above).
2. Review bone age (see above).
3. Obtain previous growth records and report of pubertal staging from primary care physician.
4. Continue testosterone at 1.25 grams AndroGel daily.
5. Start growth hormone. We discussed in detail the results of Jacob's growth hormone stimulation testing, and the etiology of his growth failure likely related to chronic high-dose glucocorticoid administration. We discussed the potential benefits of height gain and improved body composition with growth hormone, and supporting literature on the positive effects of growth hormone therapy in patients with glucocorticoid induced growth failure (such as juvenile rheumatoid arthritis) as well as idiopathic short stature. We discussed potential side effects of growth hormone, including fluid retention, headache, slipped capital femoral epiphysis, scoliosis, carbohydrate intolerance/diabetes. We discussed potential concerns in Jacob's situation of pre-existing mild scoliosis, with risk of progression due to his neuromuscular condition, and that this would have to be carefully monitored. We discussed additional potential benefits on neuromuscular function including pulmonary function and bone mineralization.
6. I plan to see Jacob about 4 to 6 months after starting growth hormone, when he is next back in Cincinnati.

Signed: Meilan M. Rutter, M.D.
12/19/2007 10:12 EST

Meilan M Rutter, M.D.
Assistant Professor of Pediatrics
Division of Endocrinology

D: 12/08/2007 12:15:26 Job #27608409 T: 12/08/2007 12:46:35 Doc #21919726 MMR/dts483009

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EXHIBIT E

PTC Therapeutics Receives Fast Track Designation for PTC124 in the Treatment of DMD

SOUTH PLAINFIELD, NJ March 30, 2006 - PTC Therapeutics, Inc. (PTC), a biopharmaceutical company focused on the discovery, development, and commercialization of small-molecule drugs that target post-transcriptional control processes, today announced that the company has been granted Fast Track designation from the United States Food and Drug Administration (FDA) for the development of PTC124 for the treatment of Duchenne muscular dystrophy (DMD) due to a nonsense mutation in the dystrophin gene. In December 2004, PTC124 was granted Orphan Drug designation by the FDA for the treatment of DMD. PTC124 is currently in Phase 2 clinical trials in DMD and cystic fibrosis (CF) in cases in which a nonsense mutation is the cause of the disease. PTC expects to complete these Phase 2 clinical trials in the second half of 2006.

The Fast Track program is designed to facilitate the development and expedite the review of new drugs that are intended to treat serious or life-threatening conditions and that demonstrate the potential to address unmet medical needs. Development programs receiving Fast Track designations typically receive FDA priority review (6-month vs. standard 10-month review).

"Fast Track designation in DMD is an additional important element in the development of PTC124," said Stuart W. Peltz, Ph.D., President and CEO of PTC. "DMD is an unmet medical need where only palliative options are currently available. We hope PTC124 will represent a therapeutic option for patients with DMD due to a nonsense mutation."

ABOUT PTC THERAPEUTICS, INC.

PTC is a biopharmaceutical company focused on the discovery, development, and commercialization of orally administered, proprietary small-molecule drugs that target post-transcriptional control processes. Post-transcriptional control processes are of central importance to the regulation of the rate and timing of cellular protein production. PTC has assembled proprietary technologies and extensive knowledge of post-transcriptional control processes that it applies in its drug discovery and development activities. PTC's current pipeline of clinical and preclinical product candidates addresses multiple indications, including genetic disorders, oncology, and infectious diseases.

ABOUT PTC124

PTC124 is an orally delivered investigational product candidate in development for the treatment of genetic disorders due to nonsense mutations. Nonsense mutations are single-point alterations in the genetic code that prematurely halt the translation process, producing a shortened, non-functional protein. In pre-clinical trials, the administration of PTC124 allowed the restoration of the production of full-length, functional proteins. PTC124 has demonstrated activity in preclinical genetic disease models harboring nonsense mutations. In Phase 1 clinical trials, PTC124 was generally well tolerated, achieved target plasma concentrations that have been associated with activity in preclinical models, and did not induce ribosomal readthrough of normal stop codons. Pharmacokinetic modeling of the Phase 1 results allowed development of a dosing regimen for the Phase 2 studies in cystic fibrosis (CF) and Duchenne muscular dystrophy (DMD). It is estimated that 10% of the cases of CF and 15% of the cases of DMD are due to nonsense mutations. PTC believes that PTC124 is potentially applicable to a broad range of other genetic disorders in which a nonsense mutation is the cause of the disease. The FDA has granted PTC124 Fast-Track designation and Orphan Drug designations for the treatment of CF and DMD due to nonsense mutations. PTC124 has also been granted orphan drug status for the treatment of DMD and CF by the Committee for Orphan Medicinal Products (COMP) of the European Medicines Agency (EMEA). PTC124's development is supported by grants from the Muscular Dystrophy Association (MDA), Cystic Fibrosis Foundation Therapeutics, Inc. (CFFT), FDA's Office of Orphan Products

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EXHIBIT F

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PTC124 targets genetic disorders caused by nonsense mutations

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Nonsense mutations promote premature translational termination and cause anywhere from 5–70% of the individual cases of most inherited diseases[1]. Studies on nonsense-mediated cystic fibrosis have indicated that boosting specific protein synthesis from <1% to as little as 5% of normal levels may greatly reduce the severity or eliminate the principal manifestations of disease[2,3]. To address the need for a drug capable of suppressing premature termination, we identified PTC124—a new chemical entity that selectively induces ribosomal readthrough of premature but not normal termination codons. PTC124 activity, optimized using nonsense-containing reporters, promoted dystrophin production in primary muscle cells from humans and *mdx* mice expressing dystrophin nonsense alleles, and rescued striated muscle function in *mdx* mice within 2–8 weeks of drug exposure. PTC124 was well tolerated in animals at plasma exposures substantially in excess of those required for nonsense suppression. The selectivity of PTC124 for premature termination codons, its well characterized activity profile, oral bioavailability and pharmacological properties indicate that this drug may have broad clinical potential for the treatment of a large group of genetic disorders with limited or no therapeutic options.

Nonsense mutations give rise to in-frame UAA, UAG or UGA codons in the messenger RNA coding region, lead to premature translational termination and truncated polypeptide products, and promote mRNA destabilization by nonsense-mediated mRNA decay (NMD)[1]. The NMD pathway depends on a set of three conserved factors that modulate both transcript stability and translation termination efficiency[4,5]. Inactivation of any of these stabilizes nonsense-containing transcripts and promotes nonsense codon readthrough[6–10]. Such observations indicated that a nonsense-containing mRNA might produce significant amounts of functional protein if either its decay rate or extent of premature termination is altered.

High concentrations of aminoglycosides such as gentamicin promote readthrough of premature nonsense codons in mammalian cells[11] and in animal models of nonsense mutation diseases. Gentamicin treatment of the *mdx* mouse—a model of Duchenne muscular dystrophy (DMD)—and of a mouse model of cystic fibrosis led to its evaluation in patients[12–16]. Treatment of patients harbouring nonsense mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) or dystrophin genes promoted production of the respective missing proteins; however, the lack of potency, the potential renal and otic toxicities, and the need for intravenous or intramuscular gentamicin administration have limited the clinical usefulness of this approach. These proof-of-concept experiments, and the effects of the NMD pathway on mRNA turnover and premature translation termination efficiency, strongly indicated that an orally bioavailable, non-toxic, small-molecule drug that promotes selective and specific readthrough of disease-causing premature termination codons might alleviate the pathologies of nonsense-mediated diseases and we therefore sought an alternative approach.

Two high-throughput screens (comprising ~800,000 low molecular weight compounds) were performed to identify compounds that promoted UGA nonsense suppression. Chemical scaffolds were identified and optimized through extensive medicinal chemistry efforts. Minimally toxic compounds demonstrating UGA readthrough activity were intensively characterized (see Supplementary Information). These analyses identified PTC124 (3-[5-(2-fluorophenyl)-[1,2,4]oxadiazol-3-yl]-benzoic acid; $C_{15}H_9FN_2O_3$) as a candidate for further development. PTC124 is a 284.24 Da, achiral, 1,2,4-oxadiazole linked to fluorobenzene and benzoic acid rings (Supplementary Figs 1 and 2). The compound has no structural similarity to aminoglycosides or other clinically developed drugs, and its anhydrous free carboxylic acid form, despite having low aqueous solubility ($<1\ \mu g\ ml^{-1}$), is orally bioavailable when prepared in aqueous suspension.

PTC124 promoted dose-dependent readthrough of all three nonsense codons in stable cell lines harbouring *LUC-190* nonsense alleles. Levels of suppression correlated inversely with established termination efficiencies[11,17–19], with the highest readthrough at UGA, followed by UAG and then UAA (Fig. 1a). Differences in transcript levels do not account for the observed differences in readthrough (Supplementary Fig. 3a). The minimal concentration of PTC124 showing discernable readthrough was 0.01–0.1 μM (2.8–28 $ng\ ml^{-1}$), whereas the concentration promoting maximal activity was approximately 3 μM (852 $ng\ ml^{-1}$). Because gentamicin is only active at much higher concentrations (Fig. 1b, and data not shown), PTC124 is a more potent nonsense-suppressing agent in this system.

Termination efficiencies are also influenced by the nature of the nucleotide following the nonsense codon (the +1 position)[18–20]. Like

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gentamicin[11], PTC124 was most active when a pyrimidine (in particular cytosine, C) was located in the +1 position (data not shown). The UGAG termination context was the only efficiently suppressed exception to this trend. Additional experiments with *LUC-190* constructs established that PTC124 did not suppress multiple proximal nonsense codons and that continuous exposure to PTC124 maximizes and maintains suppression activity (Supplementary Fig. 3c–e).

PTC124 promoted suppression of human and mouse nonsense alleles of the dystrophin gene. Drug-treated and untreated primary muscle cell cultures from DMD patients or *mdx* mice were subjected to immunocytochemistry with an antibody recognizing a carboxy-terminal dystrophin epitope. Readthrough of dystrophin mRNA premature nonsense codons was evident in all samples and at all PTC124 concentrations tested. Dystrophin was present at the myofibre membrane, the location critical for maintenance of muscle structural integrity. Consistent with the stable cell line reporter assay (Fig. 1a), the most efficient readthrough was observed in cultures treated with 5 $\mu g\,ml^{-1}$ (17 μM) of PTC124, and there was no further increase at 10 $\mu g\,ml^{-1}$ (Fig. 2). The ratio of dystrophin:myosin obtained at 5 $\mu g\,ml^{-1}$ of PTC124 was 40–60% of normal ($n = 2$; Fig. 2 and data not shown). For the *mdx* samples, the dystrophin:myosin ratio was approximately 35% of normal at 10 $\mu g\,ml^{-1}$ ($n = 8$). Normal myotubes were unaffected by PTC124, and the DMD and *mdx* myotubes had no detectable expression in the absence of drug (Fig. 2).

The ability of PTC124 to promote nonsense suppression was also assessed using *mdx* mice; this analysis required a dosing regimen that would maintain target plasma concentrations of 5–10 $\mu g\,ml^{-1}$. Oral feeding of PTC124 by a liquid diet achieved significantly better blood exposure than when administered by intraperitoneal injection (Supplementary Fig. 4). However, to prolong PTC124 exposure during the day (sleep period), the drug was administered intraperitoneally three times per day in addition to oral ingestion by the liquid diet. Using this combination regimen, plasma levels remained >10 $\mu g\,ml^{-1}$ at nearly all measured time points (Supplementary Fig. 4).

The functional effects of PTC124 were monitored in *mdx* mice treated with oral, intraperitoneal or combined dosing for 2–8 weeks (during which time there was no significant difference in weight gain among the treatment and control groups). As shown in Fig. 3a, 4 weeks of PTC124 treatment by any of the 3 treatment regimens partially rescued the functional strength deficit (decreased force per cross-sectional area) characteristic of the *mdx* mouse. Equivalent results were obtained at 2 and 8 weeks (data not shown).

The major functional deficit in dystrophic muscles of *mdx* mice (and, most likely, in DMD patients) is increased susceptibility to contraction-induced injury, especially in muscle that is simultaneously stretched[20]. This susceptibility results in repeated cycles of degeneration–regeneration, ongoing inflammation and necrosis, with the eventual destruction of muscle. Thus, the best predictor of long-term therapeutic outcome may be protection from contraction-induced injury. The mean percentage drop in force after five eccentric contractions of extensor digitorum longus (EDL) muscles from PTC124-treated or control animals is shown in Fig. 3b. Either intraperitoneal injections or oral dosing alone of PTC124 for 4 weeks resulted in partial protection against contraction-induced injury in the EDL muscles. The effects at 2 and 8 weeks were similar (data not shown). When oral and intraperitoneal dosing were combined (Fig. 3b), a further improvement in protection against contraction-induced injury was observed, such that the decrement in force was not different to that of wild-type (C57) mice.

Elevated levels of creatine kinase are found in the serum of both *mdx* animals and DMD patients. Over 8 weeks, vehicle-treated *mdx* mice showed little change in serum creatine kinase values (data not shown), but those treated with combined oral and intraperitoneal dosing demonstrated significant reductions in serum creatine kinase values by 2 weeks (Fig. 3c), which were maintained for up to 8 weeks. These data corroborate the findings of reduced eccentric contraction injury in the EDLs and suggest that PTC124 leads to decreased muscle fragility.

The functional recovery was associated with dystrophin production, as measured by western blotting. Full-length dystrophin was detected in both C57- and PTC124-treated *mdx* mice (Fig. 3d). *mdx* animals treated with the combined regimen had dystrophin levels approximately 20–25% that of muscles from C57 mice (Fig. 3d). PTC124-treated *mdx* mouse muscles also exhibited increased levels of γ-sarcoglycan (Fig. 3d), consistent with production of dystrophin and stabilization of the dystrophin-associated membrane complex, which is missing in the absence of dystrophin. To confirm the proper membrane localization of dystrophin and associated proteins, striated muscles were subjected to immunohistological analyses. Partial restoration of dystrophin to the membrane was detected in

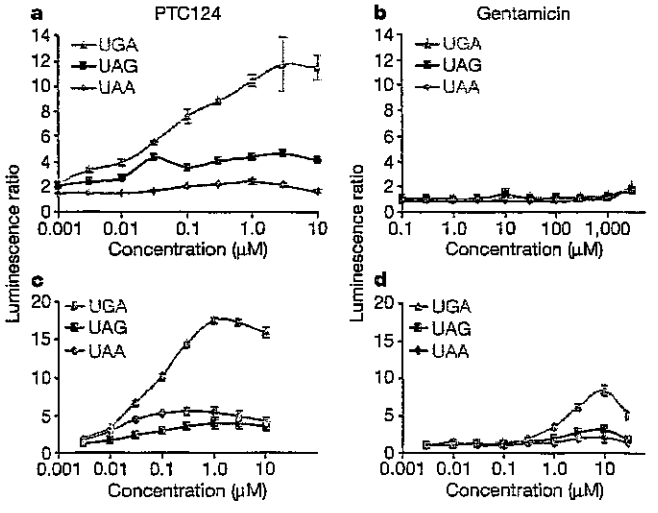


Figure 1 | PTC124 suppresses premature nonsense codons. **a**, **b**, Cultured HEK293 cells harbouring UAA, UAG or UGA *LUC-190* nonsense alleles were treated with increasing concentrations of PTC124 (**a**) or gentamicin (**b**) for 16 h, and assayed for luciferase activity. **c**, **d**, Synthetic *LUC* mRNAs, each harbouring different premature termination codons, were incubated with HeLa cell-free extract supplemented with varying concentrations of PTC124 (**c**) or gentamicin (**d**), and assayed for luciferase activity after 4 h. Luminescence ratio, drug-treated:control; error bars (±s.d.) are derived from three independent experiments.

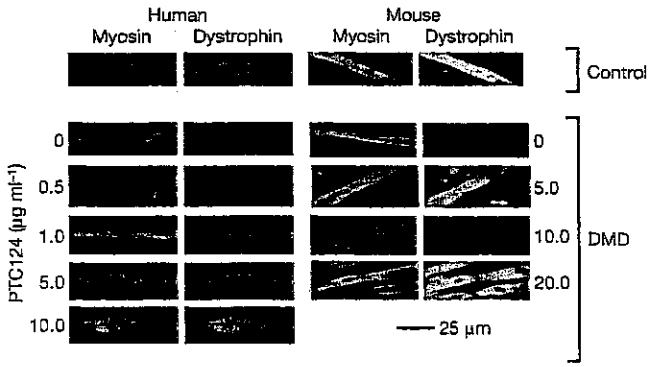


Figure 2 | Full-length dystrophin is produced in PTC124-treated cultured myotubes. Immunohistochemistry of myotubes from primary cell cultures derived from muscle biopsies. Left panel, a non-DMD individual (control) and a patient with a premature UGA codon in exon 28 of the dystrophin gene (*DMD*). Right panel, wild-type C57 mice (control) and *mdx* mice containing a premature UAA codon in exon 23 of the dystrophin gene (*Dmd*). The effect of adding varying amounts of PTC124 on levels of detectable dystrophin (green) is shown. Myosin (red) levels remain unchanged.

all skeletal muscles examined, including tibialis anterior, diaphragm and cardiac muscle (Fig. 3e). The intensity of fluorescence in drug-treated animals, compared with revertant fibres (white arrow, Fig. 3e), is indicative of lower levels of protein than in wild-type animals, consistent with the data of Fig. 3d.

In principle, nonsense suppression could result from an increase in stop codon readthrough, a decrease in mRNA turnover, or both[7–10]. To elucidate PTC124's mechanism of action, we monitored its effects on the translation and stability of nonsense-containing mRNAs *in vitro*. PTC124 promoted readthrough at each of the nonsense codons (Fig. 1c), showing maximal activity with UGA, while having no effect on mRNA levels (data not shown). Unlike the stable cell line assays (Fig. 1a, b), PTC124 did not discriminate significantly between the UAG and UAA mRNAs. PTC124 was a more potent nonsense-suppressing agent than gentamicin (Fig. 1d), and exhibited 4- to 15-fold stimulation of *in vitro* readthrough relative to the controls (Fig. 1c) at levels similar to those in the stable cell reporter assays. These results indicate that PTC124 modulates termination efficiency at premature nonsense codons.

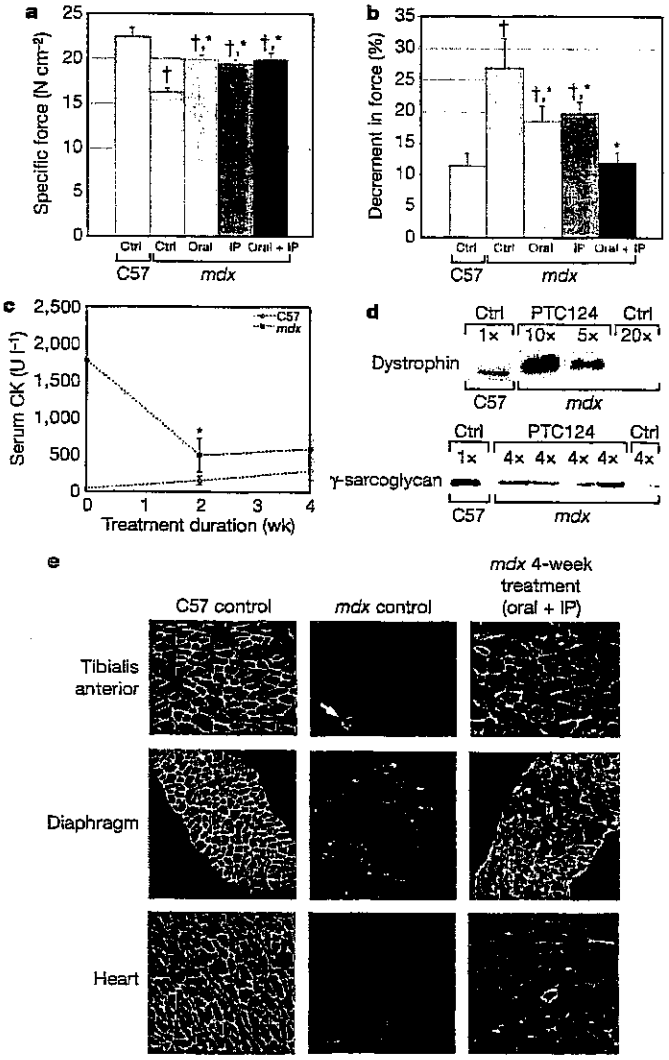
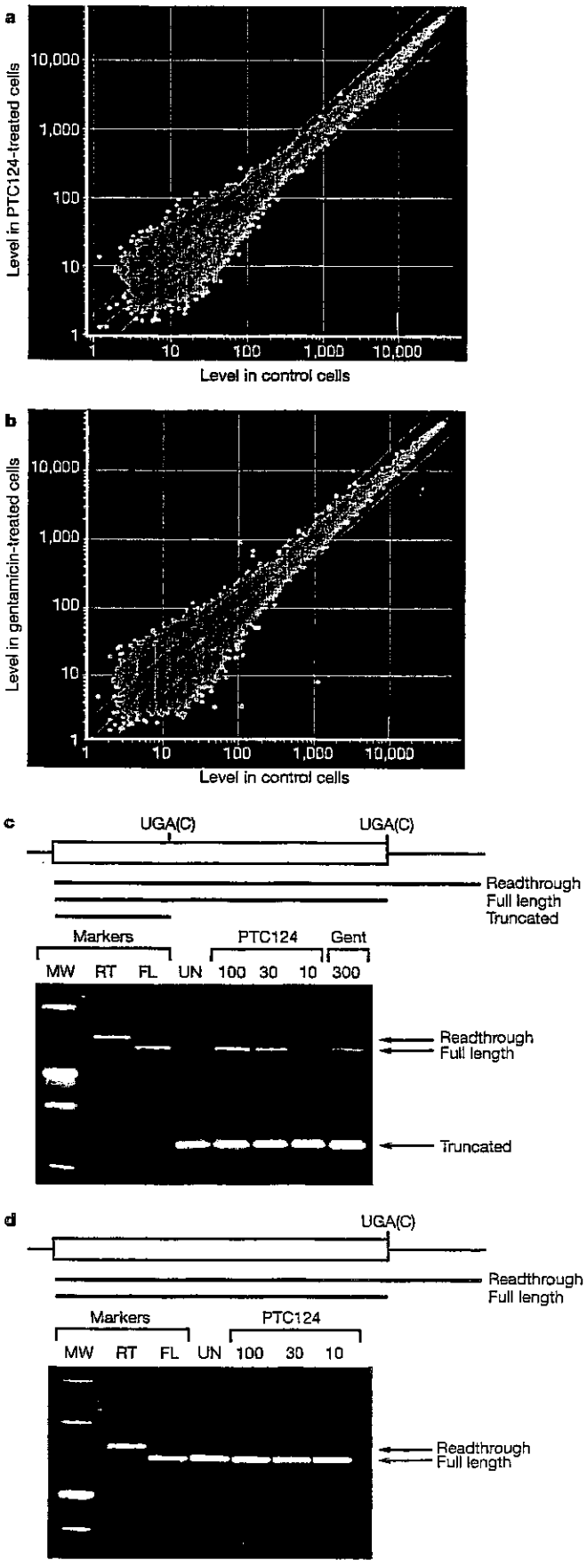


Figure 3 | Rescue of the dystrophic phenotype in muscles of the *mdx* mouse. **a**, The effects of oral dosing, intraperitoneal (IP) injections or combined dosing of PTC124 on the force per cross-sectional area (specific force) of the EDL muscle after 4 weeks of drug treatment. **b**, The effects of 4 weeks of oral dosing, IP injections or combined dosing of PTC124 on preventing loss-of-force production in the EDL muscle following five successive eccentric contractions. **c**, Serum creatine kinase (CK) changes in *mdx* mice after PTC124 dosing. †$P < 0.05$ for comparisons to untreated C57 mice; *$P < 0.05$ for comparisons to untreated *mdx* mice. **d**, Western blot analysis of quadriceps and tibialis anterior muscles for dystrophin and γ-sarcoglycan. Protein load of each lane is indicated relative to the load of C57 wild-type (1×). Ctrl, control. **e**, Immunohistochemistry of indicated muscle cross-sections to visualize dystrophin in the tibialis anterior, diaphragm and heart. The white arrow in the tibialis anterior negative control designates a revertant fibre. **a–c**, Data expressed as means ± s.e.m.; $n = 8$.

LUC-190 transcripts were also monitored by quantitative PCR with reverse transcription (RT–PCR) in cells treated with PTC124 or cycloheximide, a well characterized translation inhibitor that promotes mRNA stabilization[21]. These experiments showed that nonsense-containing *LUC* mRNA levels increased 11-fold in cycloheximide-treated cells, but were unaffected in PTC124-treated cells (data not shown). These observations were extended to a larger pool of mRNAs—including known NMD substrates[22]—by using oligonucleotide microarrays to analyse mRNA expression profiles in HEK293 cells treated for 48 h with or without PTC124 or gentamicin. The averages of six independent comparisons of >54,000-probe sets suggested that very few transcripts deviated from equivalent expression in PTC124-treated versus control cells (Fig. 4a); only 12 transcripts with increased levels and ten with decreased levels were identified in PTC124-treated cells (Supplementary Table 1). None of these are known NMD substrates[22] and all 22 were among the lowest expressing cellular mRNAs; that is, they were normally subject to the largest experimental error. No observed differences were detectable by subsequent northern analysis (data not shown). In contrast, six independent comparisons of cells treated or not treated with gentamicin indicated increases in the abundance of 20 transcripts and decreases in the abundance of 11 additional transcripts, including several for which the fold-change was substantial (Fig. 4b; Supplementary Table 2; Supplementary Fig. 5). There was no overlap of transcripts with altered levels in PTC124-treated cells versus gentamicin-treated cells (Supplementary Tables 1 and 2). These results indicate that: (a) the synthesis and stability of few, if any, cellular mRNAs are altered in response to levels of PTC124 that promote nonsense suppression; (b) PTC124 demonstrates little off-target activity at the level of transcription or mRNA stability; and (c) PTC124 and gentamicin have distinct effects on gene expression. Consistent with the latter conclusion, PTC124 does not manifest antibacterial activity (Supplementary Table 3).

Nonsense-suppressing drugs could theoretically promote non-specific readthrough of normal termination codons, but available evidence suggests that normal and premature termination differ mechanistically[9,10,23], thereby implying a basis for selectivity. To test directly for the selectivity of PTC124-promoted readthrough, we monitored the accumulation of truncated, full-length and readthrough luciferase polypeptides in drug-treated HEK293 cells, and also assayed for the presence of specific readthrough polypeptides in humans, rats and dogs. Cells harbouring the *LUC-190-CD40* construct (Fig. 4c, d) were treated with PTC124, and luciferase immunoprecipitated from cell lysates was analysed by western blotting. In the absence of drug, translation of the *LUC-190-CD40* mRNA yielded only a 25 kD amino-terminal truncated luciferase fragment, but treatment of cells with PTC124 led to a dose-dependent accumulation of full-length luciferase (Fig. 4c). Importantly, no luciferase was detected that corresponded in size to the product expected from readthrough of the normal terminator (Fig. 4c). The absence of a detectable readthrough product was unlikely to be a consequence of its instability because the control readthrough protein, generated by replacing the termination codon with CGA, was efficiently expressed in the same cells (Fig. 4c, d). Similar analyses also failed to detect polypeptides corresponding to putative readthrough products in multiple tissues isolated from PTC124-treated human subjects, rats and dogs (Supplementary Fig. 6). For example, western blotting analyses of pooled peripheral blood mononuclear cells from subjects treated with 200 mg kg^{-1} of PTC124 elicited only wild-type β2 microglobulin and no additional, longer polypeptides that would



have originated from termination codon readthrough (Supplementary Fig. 6c). These results indicate that PTC124 promotes readthrough of premature termination without affecting normal termination, even at drug exposure levels substantially greater than the values achieving maximal activity. Consistent with this conclusion, two-dimensional gel analyses of HEK293 cells incubated with or without PTC124 showed no significant differences in the relative amounts or shapes of the respective spots representing several hundred polypeptides (Supplementary Fig. 7).

Systemic delivery of PTC124 was achieved without any obvious toxicity, consistent with the findings of preclinical safety pharmacology and toxicology studies in rats and dogs[24]. Given the significance of NMD as a genomic surveillance mechanism[25], PTC124's lack of effect on this pathway may be an important component of its safety. The safety of PTC124 may also be related to the observation that its readthrough activity is specific for premature stop codons. Such selectivity might be expected from the apparent mechanistic differences between premature and normal termination[23], but may also be enhanced by the inability of PTC124 to efficiently promote readthrough of the multiple stop codons normally present in mRNA 3′-UTRs[26], and by the specific mRNA decay mechanism known to be activated when translation extends into the 3′-UTR[27,28].

Clinical trials of PTC124 have been initiated and their successful completion may ultimately allow therapy of subsets of patients in a large and diverse group of genetic disorders for which the primary disease defect is the presence of a nonsense mutation. As such, this approach is among the first to test the model of personalized medicine, in which the focus shifts from treatment of a disease to treatment of a specific genetic defect.

METHODS SUMMARY

PTC124 was identified by a combination of high-throughput screening of a small-molecule chemical library and subsequent lead optimization of compounds exhibiting significant nonsense suppression activity and low toxicity. Optimization protocols selected for high oral bioavailability, lack of *in vitro* off-target activity, *in vivo* safety and suitability for pharmaceutical formulation. Nonsense suppression analyses in the screening and early characterization steps monitored the production of luciferase from *LUC* nonsense-containing mRNAs expressed in HEK293 cells or incubated as synthetic transcripts in cell-free lysates. Suppression of dystrophin nonsense alleles, in patients and in *mdx* mice, was assayed by established procedures, including those monitoring dystrophin accumulation *in vivo* and in cultured myotubes, and those analysing dystrophin function as inferred from the mechanics of isolated mouse EDL muscles. Levels of cellular mRNAs were quantified by high-density microarray analysis and northern blotting, and readthrough of normal termination codons was assessed by western blotting using antibodies targeted to either full-length polypeptides or to putative readthrough-dependent C-terminal extension peptides. Detailed protocols for all assays can be found in Methods.

Figure 4 | PTC124 activity is selective for readthrough of premature translation termination codons. a, b, Microarray analyses of mRNA levels in HEK293 cells treated with 5 μM of PTC124 (**a**) or ~300 μM of gentamicin (**b**). The relative level of each transcript in the drug-treated samples was normalized to that in the untreated samples and the resulting expression ratios from 5/6 independent replicates were averaged and plotted on a logarithmic scale for pair-wise comparisons. The centre line indicates the line of equivalence and the outer lines indicate a twofold difference in expression. **c, d,** PTC124 does not promote readthrough of normal termination codons. Shown are a cartoon depicting *LUC* reporter constructs, and western blot analysis of *LUC* readthrough protein. Cells harboured *LUC* nonsense (UGAC) or wild-type alleles with 6×-histidine and Xpress epitope tags, inserted in frame with the *LUC* coding region, as well as a CD40 3′-UTR. Cultures were treated with PTC124 (100 μM (28.4 μg ml^{-1}), lane 5; 10 μM (2.8 μg ml^{-1}), lane 6; and 1.0 μM (0.28 μg ml^{-1}), lane 7) for 72 h, and luciferase protein was purified and analysed by western blotting. Readthrough marker protein was derived by mutating the normal termination codon to CGA. M_r, relative molecular mass marker; RT, readthrough protein marker; FL, full-length protein marker; UN, untreated.

Full Methods and any associated references are available in the online version of the paper at www.nature.com/nature.

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Supplementary Information is linked to the online version of the paper at www.nature.com/nature.

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EXHIBIT G

1. **Q: What are nonsense mutations and how does PTC124 overcome them?**

A: A nonsense mutation is a type of mutation that causes a genetic disorder by inducing a defect in the production of a critical protein. This type of mutation is an alteration in DNA that, when copied to mRNA, tells the ribosomes (the cellular machinery responsible for translating mRNA to make proteins) to prematurely stop production of that protein. This results in a protein that is too short to perform its necessary function.

PTC Therapeutics discovered PTC124 by looking for a drug that allows the ribosome to read through, or bypass, the premature stop signals in mRNA and continue the translation process to make a full-length and functional protein. PTC is currently analyzing results of the PTC124 Phase 2a clinical trials in patients with cystic fibrosis and in Duchenne muscular dystrophy.

Approximately 5-15% of cases of most inherited diseases, including cystic fibrosis, Duchenne muscular dystrophy, spinal muscular atrophy, hemophilia, neurofibromatosis, retinitis pigmentosa, lysosomal storage diseases, Hurler's Syndrome and a variety of other genetic disorders, are due to nonsense mutations.

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2. **Q: How is PTC's approach to genetic disorders different from existing therapies such as gene therapy or enzyme replacement?**

A: Gene therapy attempts to treat the disease by replacing the defective gene with one that produces the correct protein. For example, genes can be attached to modified versions of viruses that have the ability to penetrate into the nucleus of a cell, become incorporated into the cell's existing DNA, and synthesize new proteins.

Enzyme replacement refers to the administration of purified or synthesized protein to patients in whom that particular enzyme is deficient or absent. Currently this therapy often involves patients receiving periodic intravenous or intramuscular injections of the replacement enzyme.

PTC124 is a small-molecule drug that can be taken by mouth, and so does not suffer from the delivery challenges that have limited gene therapy and enzyme replacement therapy. In addition, it does not necessitate the delivery of foreign genetic material or viruses. It is anticipated that PTC124, by addressing the underlying cause of the disease, might decrease dependence on palliative interventions and ameliorate debilitation and decrease mortality in patients with genetic disorders due to nonsense mutations.

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3. **Q: If nonsense mutations cause multiple disorders, would PTC124 be able to treat different diseases? Are there plans for studying PTC124 in other diseases?**

A:

PTC124 may have the potential to treat many genetic disorders in which a nonsense mutation is the basis for the disease. PTC has catalogued over 1,800 distinct genetic disorders where nonsense mutations are the cause of the disease in a significant percentage of patients. Nonsense mutations inactivate gene function and are known to cause anywhere from five to 70 percent of the individual cases of most inherited diseases, such as cystic fibrosis (10%) and Hurler's syndrome (70%). Other genetic disorders where a percentage of the cases are due to nonsense mutations include spinal muscular atrophy, hemophilia, neurofibromatosis, and retinitis pigmentosa.

We are currently conducting clinical studies in cystic fibrosis and Duchenne muscular dystrophy. If these clinical trials yield positive results we hope eventually to expand development to multiple genetic disorders. In the meantime, we are continuing our preclinical research in order to assess the potential clinical utility of PTC124 in other genetic diseases.

If you are interested in determining if your condition is caused by a nonsense mutation, we recommend that you speak with your

treating physician or genetic counselor. This requires gene-sequencing, also called genotyping, determined from a blood sample. Facilities that perform gene sequencing, by condition, can be located through the NIH sponsored website, Gene Tests (www.genetests.org). The Laboratory Directory permits searches by disease and location. For patients with cystic fibrosis, full-length gene sequencing is available through Ambry Genetics (http://www.ambrygen.com). For patients with Duchenne muscular dystrophy, information regarding full-length gene sequencing is available through the University of Utah (http://www.genome.utah.edu/DMD).

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4. **Q: Does PTC expect PTC124 to work in patients with genetic disorders who do not have nonsense mutations as the cause of the disease?**

   A: No, based on its mechanism of action, PTC124 will not work in patients whose genetic disorder is caused by a mutation other than a nonsense mutation, such as a missense, deletion, or duplication mutation.

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5. **Q: If PTC124 reads through a nonsense mutation (also known as a premature stop codon), can it also read through the normal stop codon near the end of the mRNA?**

   A: Theoretically, inappropriate readthrough of normal stop codons could result in abnormally long proteins being made. For this reason, PTC has carefully analyzed this issue in studies of high doses of PTC124 in tissue culture systems, in animals, and in humans. These studies have demonstrated no evidence of production of abnormal proteins with PTC124 administration. Thus, the information available at this time indicates that PTC124 specifically acts to allow ribosomes to read through nonsense mutations (premature stop codons) but does not induce ribosomes to read through normal stop codons.

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6. **Q: Is this approach similar to the studies conducted with the antibiotic, gentamicin, in bypassing nonsense mutations to treat genetic disorders? Is PTC124 related to gentamicin?**

   A: Yes, the approach is similar, but PTC124 is not related to gentamicin. Like gentamicin, PTC124 allows ribosomes to read through premature stop codons to produce full-length, functional proteins. However, PTC124 is from a distinct structural class that we believe acts at a different location on the ribosome than gentamicin, and PTC124 does not have antibiotic properties. Although the results involving gentamicin have provided proof of concept for the readthrough of nonsense mutations as a therapeutic approach to treating genetic disorders, gentamicin has serious dose-limiting toxicities and requires intravenous administration, making it an unattractive long-term treatment for genetic disorders. We do not expect PTC124, which is orally administered, to have the serious dose-limiting toxicities associated with gentamicin.

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7. **Q: How can it be determined whether a patient has a nonsense mutation or a different kind of mutation as the cause of his or her disease?**

   A: Gene sequencing, also called genotyping, can determine if a patient has the disease because of a nonsense mutation. This is one of the first instances where knowledge of genetic sequence may prove useful in determining if a patient may benefit from a drug. Patients who wish to determine what type of mutation is responsible for their disease should consult with their physician about the possibility of having the relevant gene sequenced. Usually, a small amount of blood is required to perform gene sequencing. The blood sample will be sent to a specialized laboratory, sometimes at a university hospital that has expertise in studying patients with a particular disease. For patients with cystic fibrosis, full-length gene sequencing is available through Ambry Genetics (http://www.ambrygen.com). For patients with Duchenne muscular dystrophy, information regarding full-length gene sequencing is available through the University of Utah (http://www.genome.utah.edu/DMD).

For other genetic disorders, we recommend that you speak with your treating physician or genetic counselor. Facilities that perform gene-sequencing can be located through the NIH-sponsored website, Gene Tests (www.genetests.org). The Laboratory Directory at this site permits searches by disease and location.

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8. **Q: Are any clinical studies of PTC124 currently recruiting patients?**

A: No new Phase 2a trials are currently planned in Duchenne muscular dystrophy. We have initiated a new Phase 2a study in cystic fibrosis at Hôpital Necker-Enfants Malades, in Paris, France. An additional site in Belgium may join the French study. The study is similar in design to the recently completed Phase 2 cystic fibrosis studies and will enroll patients 6 years of age and older. Please visit www.clinicaltrials.gov and type"PTC124" in the search area for more information on the locations and enrollment criteria for these studies.

In addition, we have completed enrollment and treatment in a Phase 2 extension study in cystic fibrosis ongoing in Israel at the Hadassah Medical Center, Jerusalem and are currently analyzing the results.

We are continually engaged in discussions with regulatory authorities regarding PTC124. With the completion of the Phase 2a studies and data analysis, we hope to begin Phase 2b/3 studies by the end of the year.

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9. **Q: What studies of PTC124 have been performed and where?**

A: After completing two Phase 1 clinical trials in healthy volunteers to characterize the general safety, palatability and effects of food on PTC124 as well as its pharmacokinetics in order to understand its absorption into the bloodstream, we initiated the Phase 2a trials in late 2005.

Three Phase 2a trials were initiated in late 2005. In cystic fibrosis, we sponsored two studies, one study at five sites in the United States and a similar study at one site in Israel. In Duchenne muscular dystrophy, we sponsored one study in three sites in the United States. The study centers were primarily university hospitals selected for their expertise in performing specialized clinical trials in cystic fibrosis or Duchenne muscular dystrophy.

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10. **Q: What were the goals of the PTC124 Phase 2a studies in cystic fibrosis and Duchenne muscular dystrophy?**

A: The main goals in Phase 2a were to obtain indications of pharmacological activity and to assess dose response, safety, and pharmacokinetics in patients.

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11. **Q: How does PTC Therapeutics identify patients with nonsense mutations for the clinical trials?**

A: To confirm the diagnosis of a nonsense mutation for the clinical trials in cystic fibrosis, PTC Therapeutics employed the gene sequencing test offered by Ambry Genetics (www.ambrygen.com).

For the clinical trial in Duchenne muscular dystrophy, we used the test offered by the University of Utah (http://www.genome.utah.edu/DMD/clinical_test.shtml).

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12. **Q: What are the goals of the PTC124 Phase 2 studies in cystic fibrosis and Duchenne muscular dystrophy?**

A:

Phase 2a studies are typically conducted on a relatively small number of patients, with the goal of determining drug activity,

evaluating short-term side effects, and assessing pharmacokinetics in patients. The duration of several of the initial Phase 2a studies has been based on knowledge that PTC124 is safe when given for up to 28 days to animals and because it has been expected that early drug effects in patients might be observed within this duration of treatment.

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13. Q: In what form was PTC124 provided to patients?

A: In the Phase 2a studies the drug has been supplied as a vanilla-flavored powder. The powder is mixed in water, apple juice or milk to form a suspension that the patient drinks. PTC124 is being dosed based on patient body weight (i.e., milligrams of drug per kilograms of patient body weight) in order to accommodate the varying size range of the children, adolescents, and young adults who will be treated.

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14. Q: Are any results of the cystic fibrosis Phase 2a trials available?

A:

In November 2006, we presented data from the PTC124 cystic fibrosis clinical trials in Israel and the U.S. Cystic fibrosis is caused by a lack of the cystic fibrosis transmembrane conductance regulator (CFTR) protein. To determine whether PTC124 was inducing production of active CFTR protein in patients, we measured nasal transepithelial potential difference (TEPD). TEPD is assessed by means of a standardized procedure in which a small plastic catheter is used to assess electrical differences across the cell membrane of the skin in each nostril. Cystic fibrosis patients with nonsense mutations have abnormalities in the electrical difference measured by the TEPD test because they lack sufficient CFTR protein and thus have a defect in the movement of chloride ions across the cells (the chloride conductance). A change in the chloride conductance towards normal during PTC124 treatment would suggest that PTC124 is inducing the cells to make full-length, functional CFTR protein. Also assessed were circulating blood neutrophil and liver enzyme values, lung function, and body weight, as well as safety, compliance, and pharmacokinetics.

Patients received two sequential two-week courses of treatment, first at a lower and then at a higher dose level. Across the two studies, at both PTC124 dose levels tested, we observed statistically significant improvements of mean CFTR-dependent chloride secretion in the airways. By the end of the first cycle of treatment, 18 out of 42 patients had responded with a change of at least -5 mV in chloride secretion TEPD and 15 out of 42 patients had chloride secretion TEPD values in the generally accepted normal range (more electrically negative than -5 mV). CFTR chloride secretion responses were observed in both the U.S. and Israel among several of the most common nonsense mutation genotypes affecting patients with cystic fibrosis. In evaluating the studies separately, the results from the Israeli study demonstrated statistical significance for chloride secretion TEPD response for the population as a whole, while the interim results from the U.S. study demonstrated such responses in several patients but the trends did not reach statistical significance. The potential causes of these differences are now being studied.

Blood neutrophil counts were also monitored before and during PTC124 treatment because cystic fibrosis is a neutrophil-mediated disease, and reductions in blood neutrophil counts may be consistent with PTC124 activity. Statistically significant reductions in blood neutrophil counts were observed in both the U.S. and Israeli studies. Furthermore, improvements in circulating levels of liver enzymes in the blood were seen in both trials, supporting the hypotheses that PTC124 would offer systemic benefits to patients with multiorgan compromise due to cystic fibrosis. Trends toward improved pulmonary function and body weight were also observed in patients participating in the Phase 2a program. Although a formal symptom assessment was not a component of the Phase 2a program, a number of patients described decreased sputum volume and thickness, decreased frequency and severity of coughing, and a better sense of well-being during PTC124 therapy. PTC124 was well tolerated, resulting in excellent compliance with the treatment regimen.

The pharmacokinetic data from adult patients in the interim analysis indicated that PTC124 was readily absorbed from the gastrointestinal tract. The desired blood levels were achieved and maintained at the first and fourteenth days of both the lower-dose and higher-dose treatment regimens.

PTC124 was generally well-tolerated among the forty-two patients included in the studies. No serious drug-related adverse events were reported. All adverse events that were potentially drug-related were mild or moderate in severity. There were no safety concerns identified in patients' physical examinations, vital sign measurements, or electrocardiograms. We did not observe any serious changes in laboratory safety tests. There were no dosing interruptions or trial discontinuations due to toxicity. Treatment compliance was very good, with patients taking more than 95% of the intended total drug treatment at both the lower and higher dose levels.

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15. Q: **Are any results of the Duchenne muscular dystrophy Phase 2a trials available?**

A: In May of 2007, we presented positive preliminary data from a Phase 2a clinical trial of PTC124 in patients with Duchenne muscular dystrophy due to a nonsense mutation. This Phase 2a multi-site, open-label, dose-ranging clinical trial has evaluated muscle dystrophin expression in patients with nonsense-mutation-mediated Duchenne muscular dystrophy. Blood levels of muscle-derived creatine kinase have been measured as assessments of muscle integrity. PTC124 safety, compliance, and pharmacokinetics are also being evaluated.

The Phase 2a clinical trial has been conducted at three sites in the United States: Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; and the University of Utah, Salt Lake City, Utah. In the study, patients have received 28 days of PTC124 treatment at one of three dose levels. All clinical trial participants are boys with a nonsense mutation in the dystrophin gene, substantially elevated serum creatine kinase levels, and symptoms associated with Duchenne muscular dystrophy. The analysis presented includes data from 26 patients with Duchenne muscular dystrophy who received PTC124 at the low-dose and medium-dose levels. Completion of analysis of data from a higher dose level is ongoing.

The primary endpoint of the trial has been the proportion of patients having an increase in dystrophin expression in muscle during 28 days of treatment with PTC124. Pre- and post-treatment muscle biopsies were available from all 26 patients for analysis. In vitro treatment of patient muscle cells with PTC124 showed evidence of a dose-dependent increase in dystrophin expression in all of the evaluable patients. Preliminary review of the data indicates that, at both dose levels evaluated in this analysis, approximately half of the patients demonstrated visible improvement in the staining for muscle dystrophin in vivo. Overall, four of the six, or 67 percent, of patients treated at the lower dose level and 10 of the 20, or 50 percent, of patients treated at the medium dose level demonstrated an increase in the expression of dystrophin post-treatment.

Additionally, statistically significant reductions in the concentrations of muscle-derived creatine kinase levels in the blood were observed during PTC124 treatment. Several parents and teachers reported that boys participating in the study had improvements in terms of greater activity level and increased endurance during treatment. Individual subjects at both dose levels demonstrated some improvements in upper and lower muscle strength; however, in the overall analysis the magnitude of change was not statistically significant.
PTC124 was generally well tolerated among the 26 patients included in the study. Adverse events were infrequent, mild to moderate in severity, and did not result in therapy interruptions or discontinuations. There were no safety concerns based on physical examinations, vital sign measurements, electrocardiograms, or laboratory parameters. Compliance with PTC124 treatment was excellent (greater than 98%) at both dose levels.

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16. Q: **Were there any side effects from PTC124 in the clinical studies?**

A:

PTC124 is being dosed based on patient body weight (i.e., milligrams

of drug per kilograms of patient body weight). Some healthy volunteers in Phase 1 trials received very high single doses of the drug (150 or 200 mg/kg) that are above those expected to be given for therapeutic purposes. The Phase 1 subjects experienced transient effects of nausea, vomiting, diarrhea, headache, and dizziness. These effects were mild and disappeared rapidly (generally within minutes to hours). Further evaluation of the safety of the drug in healthy volunteers receiving treatment for up to 14 days at doses up to 50 mg/kg twice-per-day revealed no symptomatic drug-related adverse events at any dose level. Modest elevations of liver enzymes were observed in some subjects. These elevated enzyme levels did not require cessation of PTC124 administration, and enzyme levels typically returned to normal after completion of the treatment phase.

PTC124 was generally well-tolerated among the forty-two patients included in the Phase 2a cystic fibrosis studies. No serious drug-related adverse events were reported. All adverse events that were potentially drug-related were mild or moderate in severity. There were no safety concerns identified in patients' physical examinations, vital sign measurements, or electrocardiograms. We did not observe any serious changes in laboratory safety tests. There were no dosing interruptions or trial discontinuations due to toxicity. Treatment compliance was very good, with patients taking more than 95% of the intended total drug treatment at both the lower and higher dose levels.

PTC124 was generally well tolerated among the 26 patients included in the Phase 2a Duchenne muscular dystrophy study. Adverse events were infrequent, mild to moderate in severity, and did not result in therapy interruptions or discontinuations. There were no safety concerns based on physical examinations, vital sign measurements, electrocardiograms or laboratory parameters. Compliance with PTC124 treatment was excellent (greater than 98%) at both dose levels.

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17. Q: Do the preliminary results mean that the drug is beneficial and safe for patients?

A: We believe the data are consistent with our hypothesis that treatment with PTC124 can restore the production and function of CFTR in some patients with cystic fibrosis and of dystrophin in some patients with Duchenne muscular dystrophy when these disorders are caused by a nonsense mutation. We feel that the improvements in clinical parameters observed in these studies are encouraging and the safety results show that the drug is well tolerated over two to four weeks of treatment in children and in adult patients. However, these results are preliminary and were obtained from a small number of patients. In order to improve certainty about these results, we must finalize the ongoing studies and the full analyses of all data. In order to determine whether PTC124 treatment will lead to long-term clinical benefit and be safe for patients, we will need to perform additional studies of longer duration.

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18. Q: What are the next steps in the clinical development of PTC124?

A: Our early analysis of the preliminary data from the cystic fibrosis and Duchenne muscular dystrophy studies is encouraging. However, full analyses are still ongoing. Once the final Phase 2a results are available and regulatory authorities concur, PTC hopes to advance PTC124 into Phase 2b/Phase 3 studies in patients with cystic fibrosis and Duchenne muscular dystrophy due to nonsense mutations. We are also assessing additional genetic disorders that are characterized by nonsense mutations to determine whether to initiate clinical trials of PTC124 for the treatment of those diseases.

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19. Q: Since the Phase 2a data are positive, will Phase 2b/Phase 3 trials still be necessary?

A: The Phase 2a trials are not designed to assess the efficacy of PTC124 or to compare the efficacy to other therapies. Because they are short in duration, they also cannot examine the safety of longer-term administration of PTC124. The Phase 2a studies form the basis for the development of longer-term Phase 2b/Phase 3 trials. We expect that conduct of Phase 2b/Phase 3 clinical trials will be required to

evaluate the efficacy and long-term safety of PTC124 and to support registration of the drug with regulatory authorities. We expect that primary endpoints for future trials in cystic fibrosis would include clinical measures of lung function and that primary endpoints for future trials in Duchenne muscular dystrophy would include clinical measures of muscle integrity or endurance.

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20. Q: Is an expanded-access program planned for PTC124?

A: At this time, an expanded access program would be premature. Although the early data in cystic fibrosis and Duchenne muscular dystrophy are promising, the results are very preliminary, and were obtained from a small number of patients receiving PTC124 for a short period of time. Conduct of an expanded access program at this time might result in unacceptable risks for patients and might jeopardize the development of PTC124 so that it cannot become available for all patients who might benefit if its efficacy and safety are eventually proven.

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21. Q: Will Phase 2b/Phase 3 studies be conducted internationally?

A: Based on the results of the evolving Phase 2a data and data from the long-term safety studies in animals, we are in discussions with investigators, patient advocacy organizations, regulatory authorities, and potential collaborators regarding the conduct of additional trials in several regions of the world.

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22. Q: What is the best way for patients and families to ensure that they are informed about how to participate in the clinical studies?

A: Once a clinical trial is initiated, important information is made available at www.clinicaltrials.gov. PTC sends updates via email about our trials and other news about PTC. To join the mailing list, visit the "Contact Us" portion of our website (www.ptcbio.com/contact_form). We also recommend that patients work closely with their treating physician and genetic counselor, as well as communicating with patient advocacy groups, in order to understand their options.

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23. Q: How can I learn more about PTC124 and the science behind it, including the preclinical studies?

A: There are a few sources for this information. We recommend you visit our website (www.ptcbio.com), which has an extensive section on PTC124. Additionally, in May 2007 the journal Nature featured an article on PTC124. You can read this article online at www.ptcbio.com.

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24. Q: Where can I find additional information?

A: Additional details about PTC124 clinical trials can be found on www.clinicaltrials.gov and by contacting Ms. Diane Goetz, Director, Patient and Professional Advocacy at PTC Therapeutics (908-222-7000 ext.9256, PatientInfo@ptcbio.com).

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RESOURCES FOR PATIENTS AND FAMILIES*:

Association Francaise Contre Les Myopathies (AFM)
www.afm-france.org

Cystic Fibrosis Foundation (CFF)
www.cff.org

European Organization for Rare Disorders (EURORDIS)
www.eurordis.org

FDA Clinical Trials Website
www.clinicaltrials.gov

EXHIBIT H

Giving patients a say: how to work with patient advocacy groups

Anne-Laure Winkler & David Finegold

Working with patient advocacy groups poses many challenges to entrepreneurs, but the benefits can be substantial. Here, we examine the relationship between biotech PTC Therapeutics and Parent Project Muscular Dystrophy to highlight some key factors for success in such partnerships.

When a child is diagnosed with a terminal disease, parents will try almost anything to help. One direction in which they are increasingly channeling their efforts is to use their own money to fund early-stage research at companies. But what are the pros and cons for entrepreneurs of working with investors who have such a desperate need to find treatments? We looked at one such collaboration, Project Catalyst, which is a partnership between Parent Project Muscular Dystrophy (PPMD), a group of around 3,000 parents and relatives, 50 of which each contributed at least $25,000 for research, and South Plainfield, New Jersey–based PTC Therapeutics. Based on our study of this successful collaboration, we offer tips for working effectively with patient groups and disease-oriented foundations.

Genesis of the collaboration

PTC Therapeutics was co-founded by Stuart Peltz in 1998 to commercialize his research on post-transcriptional control processes. PTC's first program was to discover a drug to treat disorders that occur as a consequence of nonsense mutations. After years of R&D on small molecules with the capacity to suppress premature polypeptide chain termination at nonsense mutations, PTC applied a set of criteria, including current knowledge of disease, strength of patient groups and the status of genotyping to choose two initial indications for its lead drug, PTC124: cystic fibrosis (CF) and Duchenne muscular dystrophy (DMD).

Sometime shortly after, H. Lee Sweeney, chair of the University of Pennsylvania School of Medicine's department of physiology, introduced the PTC management team to representatives of PPMD, a grassroots organization focused on finding treatments for DMD. Sweeney had built independent relationships as a scientific advisor to PTC and a scientific director for PPMD and brought the two together when he felt the time was right. For PPMD's founder Patricia Furlong, who lost two sons at the ages of 15 and 17 to DMD, "it was like a dream come true." Not only did PTC124 offer a potential lifetime therapy for some individuals with DMD, but also the company's technology could be used to develop other novel treatments. DMD is a progressive muscle disorder that causes the loss of both muscle function and independence. Because the DMD gene is found on the 'x' chromosome, the disorder manifests primarily in boys. PTC124 addressed only a small subpopulation of DMD patients, those with specific nonsense mutations; however, the majority of DMD patients have other types of mutations. PTC's senior vice president of corporate development, Cláudia Hirawat, relates what happened next. "Pat [Furlong] said, 'I'm so glad that you're working for 15% of the boys [with nonsense mutations], but that's just not good enough. I've got 85% of the boys we've got to do something for. We know you have this technology and we want you to do this.'"

In 2003, PPMD formed Project Catalyst to support PTC's screen of five targets relevant to all boys and young men with DMD, in the hopes that at least one of these would yield a clinical candidate (according to industry averages for attrition). To fund the work, PPMD pledged to raise $1 million from parents, and PTC contributed with its internal resources. Unexpectedly, four of the five targets yielded positive results. That posed a dilemma for the partners: each target represented a different, complementary approach to treating DMD, yet the costs of pursuing all four targets would be substantial—an estimated $1.7 million for hit-to-lead efforts and $15 million for lead optimization. It was at this point that the partners applied to the US National Institutes of Health (NIH) for funding, which in July 2007 awarded the research collaboration between Sweeney and PTC a grant of $15.4 million (see **Box 1**).

Benefits of partnership

This partnership has benefited both sides in many ways (**Table 1**). Most important for PTC, the deal secured additional funds for risky, early-stage research, typically the most difficult to fund. This enabled PTC to expand its pipeline without diluting the company's ownership. This type of financing is becoming more popular with life science companies. US disease foundations are slated to invest $75 million in company drug development in 2007, a tenfold increase from 2000 (ref. 1).

PPMD is also a powerful force in the education of policy makers. When patient advocacy groups trust a corporate partner, they can be a strong voice for more government resources and more rapid US Food and Drug Administration (FDA) drug approval. Parents with sick children carry an intense emotional weight and even small patient groups can be very effective advocates. Furlong worked with a lawyer member of the organization to help pass the MD-Care Act in 2001 that mandates that the NIH promote research for muscular dystrophy.

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Box 1 The NINDS program for translational research in neurological diseases

Recent progress in disease mechanisms offers unparalleled opportunities for treatment of neurological disorders. Five years ago, the National Institute of Neurological Disorders and Stroke (NINDS) committed to reduce the burden of disease through an integrated program for identification and preclinical testing of new therapies (*Nat. Neurosci.* 5, 1029–1030, 2002). Facilitation of applications and progress by NINDS staff, special review environments and milestone-driven funding plans are key elements of this program.

In November 2005, NINDS partnered with the National Institute of Arthritis and Musculoskeletal and Skin Diseases to launch initiatives specifically for muscular dystrophy in association with the existing NINDS translational research program. As John Porter, a program director at NINDS, explains, this program for muscular dystrophy supports both academic and corporate researchers for preclinical development of drug and biologic therapies. The program currently funds a broad range of therapeutic strategies, from drugs that mitigate progression of the disease to gene modification or gene therapy approaches that may cure the disorder. Partnering is the key to success in translational research. Porter states that "the collaboration between patient groups, companies, academia and government, exemplified in the recent award to Lee Sweeney and PTC Therapeutics, may be the best way to go for a rare disease." More information on the NINDS support for translational research in muscular dystrophy can be found at http://www.ninds.nih.gov/funding/research/translational/index.htm.

Another benefit is the insight patient groups can provide. Working with patient groups in the drug discovery stage enables a company to gain a much deeper understanding of the disease and can have a major impact on how it markets its drugs. In the case of Project Catalyst, input from parents and patient groups was invaluable in shaping the DMD research program, even before it reached the clinic. Working with disease foundations can yield similar, nonmonetary benefits. For example, by virtue of reviewing 800 academic and industry grants a year, the Michael J. Fox Foundation for Parkinson's Research understands where the science is, and "what's hot, what's tired," says Sohini Chowdhury, the foundation's associate director of research programs.

PTC always understood that patient groups offered a bridge to researchers, clinicians and patients. Access is critical in rare diseases, where only a handful of medical experts may focus on a specific disease, and patient groups will naturally build close relationships with these specialists. "As a company, you need to work with those scientists and you need the blessing of the patient organization to do so," observes Abbey Meyers, founder of the National Organization for Rare Diseases.

Finally, working with PPMD in Project Catalyst and interacting with individuals with the disease has helped instill a sense of urgency in researchers at PTC—the employees at PTC are exposed to both DMD patients and their parents on a regular basis. PTC scientists Ellen Welch and Sergey Paushkin say that they "never feel more motivated" then after their contact with the DMD community. Likewise for Sweeney, this type of applied research offers the chance to "do something that might change someone's life. You feel you're doing something for these families, for these kids, for society." This kind of commitment helps sustain efforts during the inevitable setbacks in the long drug development process.

For PPMD, the partnership also gets the parents closer to their main objective: finding new treatments for their sons. By targeting its resources at the hard-to-fund translational phase of research (between government funding for basic science and later-stage clinical trials where startups can often identify a large partner to fund), even a small group like PPMD was able to have a significant influence on PTC's choice of development priorities. And through collaborations with drug companies, patient groups can educate their members on the latest scientific and clinical progress in their disease area and the development process itself. Companies also offer a set of general business and organizational capabilities that can provide support for patient groups, many of which rely heavily on volunteers. PTC has offered its patient groups access to experts and to the development of materials and help in increasing their public exposure (see **Box 2**).

Table 1 Benefits of company–patient group partnerships

Benefit	To company	To patient group
Financial	Increased access to funding, which can often stimulate other sources of financing	Money directly employed in finding treatments; broad exposure and successful efforts often lead to additional funding in area
Public and political profile	Advocacy power useful for interactions with FDA and other regulators	Group recognized as contributor to search for new treatments
Advice and expertise	Increased access to patients, investigators and thought leaders	Receive information and nonfinancial support from companies
Research	Increased scientific knowledge in areas of commercial interest	Increased scientific knowledge of disease
Products	Opportunities to expand indications and markets for products that were previously unanticipated	Increased likelihood of products in disease areas of interest
Motivation	Human element inspires scientists to overcome challenges of drug R&D	Empowers patients to feel they are directly contributing to search for a treatment.

Partnership issues and their management

A company should strive to have a cohesive strategy for managing its relationship with each patient group. According to Mark Krueger, a leader in this field whose consulting company advises companies in their relationships with patient advocacy groups, this should include a clear definition of milestones, appropriate financial management and appointment of a single contact person. Project Catalyst established a milestone-based approach, which clarifies what each party is to contribute in resources, to expect in outputs, and when. Project spending and dedicated staff are carefully monitored, and regular meetings enable the partners to track progress and keep members focused. PTC has gone so far as to establish a patient and professional advocacy group to communicate with PPMD and the other patient groups it works with, such as the Muscular Dystrophy Association in Tucson, Arizona; the Spinal Muscular Atrophy Foundation in New York; Fight SMA in Richmond, Virginia; and the Cystic Fibrosis Foundation in Bethesda, Maryland.

Regarding money, foundations and parent groups can structure their funding to companies in many ways: from no-strings-attached grants, to interest-free loans, to equity or

venture capital-like investments. The social venture capital approach offers clear benefits (that is, increasing accountability by holding companies to clear milestones and providing a potential return that can be reinvested in the search for future treatments). But it can also raise issues: funders may be perceived to be too closely tied to a single company and not objective in evaluating all proposals, whereas companies may be less interested in giving up significant royalties or equity to pursue small-market indications. In the case of Project Catalyst, although the funding is a grant, it is treated with all the rigor and accountability of an investment. For a research foundation like the Michael J. Fox Foundation, which has a wider spectrum of corporate partnerships, it tailors the type of investment to the level of involvement and stage of research. It says it views its grants as investments, but it is not in the business of getting returns. It simply wants research to go faster.

In their zeal to pursue a research program or to keep their business going, companies may overstate the potential of a new technology. Desperate to treat patients, PPMD fell victim to this early in its history when it bought into the potential for a quick cure through gene therapy. As an advisor, Sweeney views it as his job to ask the hard questions of companies or scientists who may be too optimistic when making presentations at patient meetings. Although PTC is eager to find a treatment for DMD, the company stays cautious in its communication with PPMD and its stakeholders

Although there are many advantages to having an expert intermediary like Sweeney work closely with patient groups and the companies they fund, there are also inherent potential conflicts of interest built into that dual role. Sweeney says that the potential conflicts arise because he's trying to look after the best interests of both sides, and at times it is not possible to do something that is of maximum benefit to everyone. Without NIH funding, Sweeney would have needed to advise PPMD to fund the target that was as disease specific as possible, leaving the company to use its own money to do things of more value to the company. When these conflicts of interest cannot be avoided, the best bet is to fully disclose potential conflicts and to have clearly defined guidelines for resolving them.

PTC and PPMD were fortunate that the promising results of their initial research led to the NIH grant, because without that substantial funding, they might have been forced to make difficult choices about which of the badly needed complementary approaches they could afford to fund. As their experience (and that of other industry projects funded by disease foundations) suggests, it is vital that the partners plan early for what will happen at later stages in the pipeline. What strategies will they use to fund subsequent stages of development? And what will happen if a company is unable to or chooses not to continue with the development program? In the latter case, funders sometime retain the rights to take the potential treatment elsewhere for development.

Box 2 Illustration of the benefits for the larger company: Genzyme

As Elliot Hillback, senior vice president of corporate affairs for Genzyme of Cambridge, Massachusetts, notes, "strong relationships between companies and patient groups can be formed more easily and are likely to be stronger in disease areas where there is a chronic condition, which lasts a long time and the outcomes are somewhat predictable, such as with genetic diseases and multiple sclerosis. There's an evolving course of action, and you can build long-term relationships with those [patient] groups and work on long-term treatments and hopefully eventually a cure."

Genzyme had to figure out a sustainable business model to treat very small patient populations with their orphan drugs, while also developing ways to work with the health care systems in areas of the world where there is no support for the treatment of a rare disorder. Genzyme's collaborative efforts worldwide with patient groups in the lysosomal storage disorder area have helped. As a result, Genzyme's internal patient advocacy group based in Cambridge has grown from one to five dedicated members to build relationships in different regions in the world across different diseases. It has created a global patient guidance document that helps clarify expectations for employees working with patient groups around the world.

Patients and Genzyme also work on access to therapy and reimbursement. Hillback says his company seeks to align with patients in helping all the parties in the health care system understand the disease and therapy as accurately as possible so that doctors will be full partners in optimizing the patient's care and the drug will be reimbursed in an appropriate way.

But perhaps the greatest benefit comes during difficult periods. When Genzyme faced a supply shortage of its drug, Myozyme (alglucosidase alfa) for Pompe disease, the company was very forthcoming and worked closely with patients to obtain the best possible outcome, with some patients willing to skip a dose periodically to try to ensure the company could treat everyone, says Hillback.

Key success factors

Several factors determine the success or failure of a partnership with patient advocacy groups (Table 2).

Early start to partnership. Working with patient groups in the drug discovery stage enables the company to gain a much deeper level of understanding of the disease and can have a strong impact on how a company markets its drugs. "Companies are going to realize that they need to collaborate with patient groups earlier, that this is an investment in the relationship and that it has a very deep commercial impact later on," says Hirawat, adding, "When you can marry patient advocacy with later marketing effort, you can see a significant payoff because you are viewing the patients as your customers, and as such they are important stakeholders and the best source of information."

Supportive top management. The bond between the partners is likely to be stronger if the leaders of the company have signaled that it is a business priority and an activity to which they personally devote energy. PTC's business leaders, Peltz and Hirawat, regularly participate in the meetings with PPMD.

Table 2 Factors and working strategies in successful collaborations

Factors for success	How to tackle issues
Early start to partnership	Plan the partnership
Supportive top management	Choose the right form of funding
Open and honest communication	Manage expectations
Shared goals and empathy	Perceive potential conflict of interests
Trusted intermediaries	Plan for success
Strong commitment to overcoming roadblocks	

Open and honest communication. A strong collaboration starts with frank dialog and mutual respect. "We keep the communication lines open; issues arise when people are not in the loop," notes Peltz. The relationship has actually helped enhance the company's communication strategy. Although it is necessary for biotech companies to be optimistic about the future, they also have to be cautious about what they communicate—according to PTC's Hirawat, this approach helps the company manage the expectations of both patients and other stakeholders.

Shared goals and empathy. Sometimes when working with patient advocacy groups, companies can end up viewing the patients only as funders or customers. That is a mistake. Krueger notes, "PTC teaches us that treating groups with respect, as equal partners, is essential." From the start, PTC approached its collaboration with PPMD by trying to understand the needs of its partner. The key from the patients' perspective is that the company listens to their input and incorporates it into decisions. In fact, Kimberly Galberaith, PPMD's executive vice president, says her group isn't "used to people talking to us as if we know anything." In Project Catalyst, though, everyone works together—the patient group, the company and the investigators. Once a drug is approved, then a fourth player enters the dialog: the payer.

Trusted intermediaries. Finding the right people to connect with in organizations is critical for a collaboration's success. Sweeney emphasizes, "It's all about personalities, about trust. I thought [a potential relationship with PPMD] would be a natural fit with some companies, but there was no fit with the people."

In Project Catalyst, Sweeney's own personal interest and the role he has played in bringing PTC and PPMD together have proved vital to creating a strong partnership. Although Sweeney's dedication to both sides may be unusual, Krueger notes that the existence of committed, caring top-level scientific advisors is a key bridge between patients and companies in many other disease areas.

Strong commitment to overcoming roadblocks. The people and organizations involved in these collaborations are deeply committed to successful outcomes. The strongest test to commitment is revealed in the efforts and creativity the partners invest to overcome obstacles. Committed partners tend to deviate from the norm of business as usual. To progress as far as it has, PTC has also had to pioneer new funding strategies, approaching patient organizations that didn't typically partner with industry before, such as the Muscular Dystrophy Association. And it had to be willing to commit a high percentage of its resources to multiple treatments for DMD, a rare disease that is currently considered untreatable.

Conclusions

Partnerships between biotech companies and patient groups offer an opportunity for win-win collaborations: biotech companies can get much needed funding, valuable information and support for their research, development and commercialization efforts, whereas patients are likely to get the new treatments they seek more quickly than through funding of academic research.

1. Gambrill, S. Venture philanthropy is on the rise. *Thomson CenterWatch, Clinical Trials Today.* <http://www.clinicaltrialstoday.com/centerwatch_clinical_tria/2007/08/venture-philant.html> (6 August 2007)

EXHIBIT I

Muscular Dystrophy Leading the Duchenne muscular dystrophy community

FOR IMMEDIATE RELEASE
Contact: Nick Manetto 202.312.7499/nick.manetto@bakerd.com

NIH Awards Multi-Million Dollar Translational Research Grant to Further Pursuit of Duchenne Treatments

Funding Builds Upon PPMD Investment & Advocacy

WASHINGTON (July 11, 2007) - The National Institutes of Health (NIH) has awarded a significant $15.4 million translational research grant that will build on and advance promising efforts aimed at developing treatments and therapies for Duchenne and Becker Muscular Dystrophy.

The five-year award, to biopharmaceutical company PTC Therapeutics, Inc. and the University of Pennsylvania School of Medicine, will enable the recipients to build upon the research groundwork laid nearly four years ago by Parent Project Muscular Dystrophy and PTC through their joint Project Catalyst initiative.

"This is absolutely outstanding news," said PPMD Founding President and CEO Pat Furlong. "For years, PPMD and our many supporters in Congress have been working with the NIH to advance translational research projects like these, and this success is clear evidence that the tireless work of all - especially our researchers, supporter and advocates - is paying off."

To date, PPMD's Project Catalyst has raised $3 million dollars, funding that has supported research into a number of promising projects and advanced the work to the level worthy of funding from the NIH, the world's premier medical research organization.

PPMD advocates and our champions in Congress have played a critical role in the process by advocating for and securing increased NIH funding for Duchenne research, and for encouraging Congress to prioritize translational projects within this funding.

"As I've said so many times in the past, our impassioned and growing corps of advocates makes the difference. By partnering with their lawmakers to take action to advance the Duchenne Translational agenda, they've been able to sustain NIH funding for critical initiatives during a very tight budget period," Furlong said.

"When a group of parents began this journey many years ago, we envisioned a day when such a significant NIH award would be possible. Today, that vision has materialized and led us one important step forward in our mission to conquer Duchenne."

EXHIBIT J

PDA

View Full Version : Minnesota mom becomes 'heat-seeking missile' for MD funds

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Minnesota mom becomes 'heat-seeking missile' for MD funds
Todd Milbourn
Star TribuneÂ*Published May 22, 2002WASHINGTON, D.C. --

Until they heard from Cheri Gunvalson, many members of Congress didn't know much about the form of muscular dystrophy that afflicts her son, Jacob.

"They just had no clue it was the number one genetic killer of children worldwide . . . and that there's no treatment," said Gunvalson, a registered nurse from Gonvick, Minn.

Gunvalson says she phoned 430 congressional offices and met with dozens of legislators face to face and, when President Bush signed a bill last December, won a nearly two-fold increase in federal research dollars for muscular dystrophy.

And she's still at it.

Gunvalson and advocates for those with Duchenne muscular dystrophy are now pushing for $10 million for the Centers for Disease Control and Prevention to collect more data on the disease. Last week she was at the University of Minnesota, meeting with scientists to discuss research progress. Under the law, three major research centers will be established, and the university hopes to play a part.

At her urging, Minnesota Democrats Sen. Paul Wellstone and Rep. Collin Peterson sponsored the legislation, which is the only comprehensive, disease-specific bill that Bush has signed. "It was the ultimate grassroots," Wellstone said. "I mean, this mother did all this with a computer and a phone in a farmhouse in northern Minnesota, and probably in a flannel nightgown."

Artist and jokester

Jacob is a lot like other 10-year-olds growing up in rural Minnesota. But Duchenne, the most common form of muscular dystrophy, is gradually weakening his muscles. Jacob is still able to walk short distances. Many boys with the disease -- it affects one in every 3,500 boys -- are in a wheelchair by his age.

Its early signs include difficulty climbing stairs and a wobbly gait, which usually appear between ages 3 and 5. The disease eventually progresses to the heart and lungs, before killing the victim, usually before age 21.

Jacob enjoys watching TV, playing video games and riding go-karts around the neighborhood. He's shy around people he doesn't know, but around the house he's the family prankster, his mom said.

"When I open my fridge, I sometimes find a rubber mouse," she said. His mom describes him as a gifted artist who works in several mediums.

"I do all animals because it's boring drawing scenery and other stuff," Jacob said.

Jacob has a brother, Ben, 13, and a sister, Kelsey, 7. On the two days a week that she doesn't work, Gunvalson will drop her kids off at the bus stop, then log on to the computer and pick up the phone. She said she tries to balance her time working on Duchenne with the needs of her kids and her husband, John. "Some mothers golf, some mothers have horses -- well their mother has a computer," she says.

David Mesick of Eden Prairie, a board member of Parent Project Muscular Dystrophy, said Gunvalson was the "fireplug" that helped turn the bill into law.
Joel Wood, a top insurance industry lobbyist in Washington, whose son James has Duchenne, calls Gunvalson, a "heat-seeking missile."

"She works a special magic. She can connect on both a substantive and emotional level," said Wood, who worked with Gunvalson on the bill. Gunvalson explains her success this way: "I never give up, and I'm always polite."

Gunvalson and Wood, a Republican, said the Minnesota Democrats' advocacy and ability to work across the aisle were crucial. Wood said that Wellstone's familiarity with the National Institutes of Health (NIH) and advocacy on other health issues made him a key ally. Wellstone is a member of the Senate Health, Education, Labor and Pensions Committee.

Duchenne affects males, with rare exceptions. The disease is usually inherited, though a third of the cases are spontaneous mutations.

After Jacob's muscular dystrophy was diagnosed, Gunvalson said, she was outraged to find that there was sparse federal funding for Duchenne research. "The way the research was going I didn't believe it would get here in time for my son without federal involvement," she said.

'On the verge'

In fiscal year 2001, $14.3 million of the NIH's $17 billion budget was devoted to muscular dystrophy, including about $9 million for Duchenne research, Wellstone's office said. The Congressional Budget Office estimated that the law would increase funding for muscular dystrophy research by $54 million over the next four years.

Although the Muscular Dystrophy Association has raised tens of millions of dollars annually through its Labor Day telethon, hosted by Jerry Lewis, it generally doesn't advocate for federal dollars.

Mesick said that because of the visibility and success of the MDA telethons, there is a perception that enough is being done for the disease. Parent Project was established in 1994 to push for federal support to find treatments and a cure.

Researchers are exploring possible gene therapies and are using stem cells to regenerate some muscles in laboratory tests. "We are on the verge of making meaningful progress in the treatment of [Duchenne] for the first time in history," said Dr. Lee Sweeney, a muscle biology expert at the University of Pennsylvania.

Said Gunvalson: "It's not a question of whether, but when this disease will be conquered. As soon as there's a medicine, we'll be on the first airplane to get it. We're just keeping him as healthy as possible until that time."

EXHIBIT K

Answers 03/20/1990

TREATMENT IND UPDATE

The following may be used to answer inquiries about FDA's "treatment IND" program:

Under the FDA treatment IND (investigational new drug) regulations enacted in 1987, drugs that are in controlled clinical trials can be provided outside these trials to treat patients with serious or immediately life-threatening diseases for which no comparable or satisfactory alternate therapy exists.

Certain safeguards must be observed, including requirements:

-- That the patient is fully informed of the risks and expressly consents.

-- That the drug is not promoted or otherwise "commercialized," though drug companies can charge patients to recover the cost of the drug's manufacture, research, development and handling.

-- That clinical trials are underway and continue unimpeded, and the sponsor of the drug actively pursues marketing approval of the drug with "due diligence."

FDA has approved 18 drugs for use under its treatment IND program.

-MORE-

The most recent approval, baclofen for infusion into the spinal canal (intrathecal infusion) using the Medtronic SynchroMed Infusion System, was approved for those multiple sclerosis and spinal cord injury patients with severe and chronic spasticity who cannot tolerate or do not respond to oral baclofen. The drug has been available in an oral form for treating spasticity for 12 years. But about 20,000 patients who suffer painful chronic spasticity either do not experience sufficient benefit from the oral preparation or suffer unacceptable side effects.

One study has indicated that intrathecal baclofen can have a dramatic clinical effect in some patients who had not responded to oral baclofen.

The SynchroMed Infusion System, an infusion pump containing baclofen, is placed beneath the skin in the patient's abdomen. It can be programmed via radio signals to dispense the drug through a small catheter inserted into the spinal canal. The device is refilled every four to eight weeks by injection with a hypodermic needle through the skin and a self-sealing rubber cover on the pump.

Although there has been significant benefit from intrathecal baclofen in some patients, overall exposure of patients is small to date, and there is need for caution and careful patient monitoring. At least one death not explained by any other cause has occurred with the intrathecal infusion of baclofen. The informed consent obtained from patients in the treatment IND will make note of this, and FDA will require that doctors using the device call each patient under their care every week for at least the first six months of treatment and that the treatment IND sponsor call each doctor each week to ascertain the status of all patients.

-MORE-

Physicians treating patients with severe spasticity who have failed oral antispastic medications can contact Medtronic Inc. at 800-328-0810 or 612-572-5000 for detailed information about enrollment in the treatment protocol and the drug's distribution.

A list of previously approved treatment IND's and their status follows.

TREATMENT IND LIST

Drug: Cytomegalovirus immune globulin (CMV-IG)
Treatment IND Granted: October 1987
Indication: Prevention of cytomegalovirus infections in renal transplant

patients.
Sponsor: Comonwealth of Massachusetts, Department of Public Health.
Market Approval Date: Not yet approved.

Drug: Ifosfamide & Mesna
Treatment IND Granted: December 1987
Indication: Germ cell carcinoma.
Sponsor: National Cancer Institute.
Market Approval Date: December 31, 1988.

Drug: Trimetrexate
Treatment IND Granted: February 1988
Indication: AIDS patients with Pneumocystis carinii pneumonia who are intolerant to standard forms of therapy.
Sponsor: National Institute of Allergy and Infectious Diseases.
Market Approval Date: Not yet approved.

Drug: Anafranil (clomipramine HCl)
Treatment IND Granted: June 1988
Indication: Severe cases of Obsessive Compulsive Disorder.
Sponsor: Ciba-Geigy.
Market Approval Date: December 29, 1989.

Drug: Eldepryl (selegiline HCl)
Treatment IND Granted: June 1988
Indication: Severe Parkinson's Disease.
Sponsor: Somerset Pharmaceuticals.
Market Approval Date: June 5, 1989.

Drug: Pentostatin
Treatment IND Granted: July 1988
Indication: Hairy cell leukemia refractory to alpha interferon.
Sponsor: National Cancer Institute.
Market Approval Date: Not yet approved.

-MORE-

Drug: Teniposide
Treatment IND Granted: October 1988
Indication: Relapsed or refractory acute lymphoblastic leukemia.
Sponsor: National Cancer Institute.
Market Approval Date: Not yet approved.

Drug: Ganciclovir
Treatment IND Granted: November 1988
Indication: CMV retinitis in AIDS patients.
Sponsor: National Institute of Allergy and Infectious Diseases.
Market Approval Date: June 23, 1989.

Drug: Pentamidine Isethionate Aerosol
Treatment IND Granted: February 1989
Indication: Prevention of Pneumocystis carinii penumonia (PCP) in AIDS patients who have recovered from an episode of PCP.
Sponsor: LyphoMed.
Market Approval Date: June 15, 1989.

Drug: Levamisole hydrochloride
Treatment IND Granted: May 1989
Indication: For use (with 5-fluorouracil) as an adjuvant treatment for Dukes C adenocarcinoma of the colon.
Sponsor: National Cancer Institute.
Market Approval Date: Not yet approved.

Drug: Erythropoietin (EPO)
Treatment IND Granted: June 1989

Indication: Treatment of AZT related anemia in HIV positive patients.
Sponsor: Ortho.
Market Approval Date: Not yet approved.

Drug: Exosurf (synthetic pulmonary surfactant)
Treatment IND Granted: July 1989
Indication: Prophylactic treatment of newborns likely to develop respiratory distress syndrome and rescue treatment of newborns with confirmed RDS.
Sponsor: Burroughs Wellcome.
Market Approval Date: Not yet approved.

Drug: 2'3' dideoxyinosine (ddI)
Treatment IND Granted: September 1989
Indication: Treatment of AIDS patients intolerant to AZT.
Sponsor: Bristol Myers.
Market Approval Date: Not yet approved.

Drug: Survanta (bovine pulmonary surfactant)
Treatment IND Granted: October 1989
Indication: Prevention and treatment of respiratory distress syndrome in premature infants.
Sponsor: Ross Labs.
Market Approval Date: Not yet approved.

-MORE-

Drug: zidovudine
Treatment IND Granted: October 1989
Indication: Treatment of children under the age of 13 who have AIDS or are suffering from symptoms of advanced infection with the AIDS virus.
Sponsor: Burroughs Wellcome.
Market Approval Date: Not yet approved.

Drug: mannose terminated beta-glucocerebrosidase
Treatment IND Granted: November 1989
Indication: Treatment of patients with chronic Gaucher's disease.
Sponsor: Genzyme Corporation.
Market Approval Date: Not yet approved.

Drug: fludarabine phosphate
Treatment IND Granted: November 1989
Indication: Chronic Lymphocytic Leukemia
Sponsor: National Cancer Institute
Market Approval Date: Not yet approved.

EXHIBIT L

Dear Mrs. Gunvalson,

I am writing in response to your inquiry concerning the possible availability of PTC 124 under a single patient IND to treat your son, Jacob, for Duchenne Muscular Dystrophy. I am sorry to hear of your son's progressive difficulties despite his current therapy with gentamycin.

As you know, a new potential therapy such as PTC 124 is ideally first given to patients as part of a clinical trial. From your inquiry, I understand that your son did not meet the inclusion criteria for the clinical trial now in progress for the treatment of Duchenne muscular dystrophy. In my opinion, the best option for your son would be to request a protocol exception. If approved by the sponsor, a protocol exception allows some patients who are ineligible to participate in a study to be treated with the investigational drug under the existing study IND at one of the study centers participating in the trial. Thus, the new therapy is given under the supervision of a study investigator who has had at least some experience with this new therapy and who will be informed by the sponsor of the ongoing clinical experience of the other study investigators conducting the trial of the new therapy. The dose and length of treatment allowable would depend on safety information currently available and would not exceed those allowable under the study protocol.

The alternative to the protocol exception would be the single patient IND which also requires the approval of the sponsor. In general, the FDA is supportive of a physician's filing a single patient IND to allow treatment with an investigational drug of a patient with a serious illness when no alternative effective therapy exists, when clinical studies of the drug are ongoing, and when a sponsor agrees to provide the drug. The length of treatment allowable under the single patient IND would again depend on the safety information currently available.

The physician who would propose to treat your son under either the protocol exception mechanism or the single patient IND mechanism should contact Katherine Needleman, the Consumer Safety Officer in our Division who is responsible for PTC 124. She will work with the physician to explain and assist in the process. Ms Needleman's maybe contacted by email katherine.needleman@fda.hhs.gov or by phone 301-796-1125.

An explanation of the single patient IND is posted on the FDA internet public website (http://www.fda.gov/ola/2001/compassionateuse0620.html) and may be useful in your understanding this type of IND. It also briefly discusses protocol exception mechanism.

The following excerpts from this explanation are specifically relevant to your request:

Background

We are very much aware of the impact FDA's processes and decisions have on the public we serve. Under the Federal Food, Drug, and Cosmetic (FD&C) Act and related statutes, the Government has a vitally important role in helping to ensure that the marketed medical products upon which patients and their health care practitioners rely are shown to be both safe and effective. Just as important, we have critical responsibilities in helping to ensure that the use of investigational drugs is carried out safely, and that the limitations of current information on the drug are conveyed to the patient. We are particularly aware that even before a drug is approved for marketing, there may be enough information to support varying degrees of treatment use for people with serious illness when there is no effective treatment available. In various ways, FDA has attempted to make it possible for investigational drugs to be available in these situations, but availability must bear a relation to how much information we have. The safeguards provided by FDA's activities are particularly important for our most vulnerable citizens, those who are seriously ill.

We understand that patients and their family members are often unfamiliar with FDA's legal and regulatory responsibilities. Often they are unaware that FDA cannot compel a company to supply an individual patient with an investigational drug outside of its planned clinical trials. The manufacturer or sponsor makes the final decision to provide an experimental drug or therapy to a patient. The sponsor may consider many factors, including the amount of information available about the drug, the amount of drug available, and how best to use its resources to optimize development of the drug for marketing. This maximizes the availability of the drug to patients who can benefit from it. In some cases, the sponsor is unwilling to provide the product outside of clinical trials, especially relatively early in drug development. Patients are sometimes confused or angered by this situation and misinterpret the company's unwillingness to provide the product as an FDA action.

FDA may not allow treatment uses because of safety concerns. Generally, however, if a physician makes a request for treatment use of an experimental drug, in a patient for whom no effective therapy exists, and there is an ongoing study of the drug and a sponsor agrees to provide the product, FDA does not object to the treatment use.

There have been cases in which treatment use has been considered appropriate, despite relatively little evidence supporting the usefulness of the drug for the particular indication. Generally, when there was no effective alternative drug or treatment for the particular condition and there was sufficient information about safety, treatment use can be justified. Physicians may always contact FDA to propose such a use for a specific patient when they believe circumstances warrant this use. . . .

Protocol Exception/Exemptions

In cases where a patient cannot be enrolled in an existing protocol because of some factor that makes the patient ineligible to participate in the study, research sponsors or investigators often can make a protocol exception to treat such a patient. The data from that patient would not be part of the report of the original study. Usually such special exceptions arise in the same institutions that are conducting the original study, where investigators are familiar with the drug.

Access to Investigational New Products

The ideal way for a patient to receive a promising but unproven drug is as a participant in a controlled clinical trial. Such trials provide appropriate patient protections and potential benefits (for example, IRB review, informed consent, free product or treatment, and FDA review of pre-clinical data and the protocols for the clinical trials) and maximize the gathering of useful information about the product, potentially benefiting the entire patient population. It is not possible, however, for all patients who might benefit from the drug to enroll in controlled clinical trials.

FDA believes that it is appropriate to make certain promising, but not yet approved, products available to patients with serious and life-threatening illnesses who lack alternative treatment. This should be done in a way that does not interfere with recruitment to the clinical trials needed to support the effectiveness and safety of the drug.

I hope that this information is helpful to you and to your son.

EXHIBIT M

To: Wirsz, Emil
Subject: Re: PTC Therapeutics Announces Encouraging Preliminary Phase 2 Results of PTC124 in Duchenne Muscular Dystrophy

Hi,
I think the fact they got dystrophin expression in all is great! The next ph 2a (higher dose due to the kids metabolizes it faster than they thought and they need to get to the peak concentration)boys like Jacob and wheelchair bound may qualify. It will be for 1 month. Then hopefully longer.

When will you be coming to the states for your work as this would be a great time.

Cheri

---- Original Message ----
From: Wirsz, Emil
To: cgunval@gvtel.com
Sent: Saturday, October 28, 2006 10:52 AM
Subject: FW: PTC Therapeutics Announces Encouraging Preliminary Phase 2 Results of PTC124 in Duchenne Muscular Dystrophy

Hi Cheri,

you got this message for sure too.
I am just checking to see what news you have:
- do you have more details ?
- did the drug work well ?
- any news when Ph III will start ?
- any luck with compassionate ?

Emil

From: PTC_Therapeutics [mailto:PTC_Therapeutics@ptcbio.com]
Sent: Saturday, October 21, 2006 8:00 PM
To: undisclosed-recipients
Subject: PTC Therapeutics Announces Encouraging Preliminary Phase 2 Results of PTC124 in Duchenne Muscular Dystrophy

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FOR IMMEDIATE RELEASE

PTC THERAPEUTICS ANNOUNCES ENCOURAGING PRELIMINARY PHASE 2 RESULTS OF PTC124 IN DUCHENNE MUSCULAR DYSTROPHY

SOUTH PLAINFIELD, NJ – October 21, 2006 - PTC Therapeutics, Inc. (PTC), a biopharmaceutical company focused on the discovery and development of small-molecule drugs targeting post-transcriptional control processes, today announced encouraging data from a Phase 2

clinical trial of PTC124 in patients with Duchenne muscular dystrophy (DMD) due to a nonsense mutation. The results imply pharmacological activity based on preliminary data that suggest increases in dystrophin in muscle biopsies in a number of patients and statistically significant improvements in muscle enzymes in serum. The preliminary data were presented today at the PPUK 4th International DMD Conference in London, England.

"These results are the first example of an oral therapy addressing the underlying cause of DMD by restoring dystrophin production," said Dr. Richard Finkel, Director of the Neuromuscular Program, Children's Hospital of Philadelphia, PA, one of the trial's lead investigators. "There are limited therapeutic options for patients living with DMD, and these data strongly indicate PTC124 warrants further clinical investigation in this patient population, which has a great unmet medical need."

Langdon Miller, M.D., Chief Medical Officer, PTC, stated, "These preliminary results in patients with DMD provide confirmation of proof of concept that PTC124 can induce ribosomal readthrough of nonsense mutations as an approach to treating genetic disorders. Given that PTC124 was very well-tolerated and activity was observed at lower-than-expected plasma concentrations, we are amending this trial to evaluate higher dose levels and the potential to further increase dystrophin expression."

"In the first half of 2007, we expect to present the final data set from this Phase 2 clinical trial and meet with regulatory authorities to determine the next steps for further clinical development of PTC124. Following these discussions, we hope to initiate longer-term clinical trials for PTC124 in 2007," said Dr. Miller.

Patients with DMD lack dystrophin, a protein that is critical to the structural stability of muscle fibers. This Phase 2 multi-site, open-label, dose-ranging clinical trial is evaluating muscle dystrophin expression in patients with nonsense-mutation-mediated DMD. Blood levels of muscle-derived creatine kinase are being measured as assessments of muscle integrity. PTC124 safety, compliance, and pharmacokinetics are also being evaluated.

Patients included in the interim analysis were enrolled at three clinical sites in the United States: Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; and the University of Utah, Salt Lake City, Utah. In the study, patients received 28 days of PTC124 treatment at one of two dose levels. All patients were boys with a nonsense mutation in the dystrophin gene, substantially elevated serum creatine kinase, and symptoms associated with DMD.

Assessment of the *in vitro* effects of PTC124 on dystrophin expression showed dose-dependent

production of full-length dystrophin in myocytes obtained from multiple study subjects; these data suggest the potential for response across a range of early to late nonsense mutations within the dystrophin gene. Evaluation of the *in vivo* effects of PTC124 over the 28-day treatment course suggest an increase in dystrophin expression in muscle biopsies in a number of the boys participating in the trial, although quantitative analysis is not yet complete. Statistically significant reductions in the concentrations of muscle-derived creatine kinase levels in the blood were observed during PTC124 treatment. Although no formal questionnaire was used to collect data on changes in DMD-related symptoms, several parents and teachers reported that boys participating in the study had improvements in terms of greater activity level and increased endurance during treatment.

PTC124 was well tolerated among the 26 patients included in the study. Potentially drug-related adverse events were infrequent, mild to moderate in severity, did not result in therapy interruptions or discontinuations, and were reversible. There were no safety concerns based on physical examinations, vital sign measurements, electrocardiograms, or laboratory parameters. Compliance was excellent at both dose levels.

"These preliminary results are very encouraging and add to the growing body of clinical evidence supporting the potential of PTC124 as a treatment for genetic disorders due to a nonsense mutation," said Stuart W. Peltz, Ph.D., President and Chief Executive Officer of PTC Therapeutics. "The findings in the DMD trials are consistent with the results observed in Phase 2 clinical trials of PTC124 in patients with cystic fibrosis. We intend to extend this concept into other nonsense-mediated genetic disorders."

ABOUT DUCHENNE MUSCULAR DYSTROPHY

Duchenne muscular dystrophy (DMD) is a progressive muscle disorder that causes the loss of both muscle function and independence. DMD is perhaps the most prevalent of the muscular dystrophies and is the most common lethal genetic disorder diagnosed during childhood today. Each year, approximately 20,000 children worldwide are born with DMD (one of every 3,500 male children). More information regarding DMD is available through the Muscular Dystrophy Association (www.mdausa.org) and the Parent Project Muscular Dystrophy (www.parentprojectmd.org).

ABOUT PTC124

PTC124 is an orally delivered product candidate in Phase 2 clinical development for the treatment of genetic disorders due to nonsense mutations. Nonsense mutations are single-point alterations in the genetic code that prematurely halt the translation process, producing a shortened, non-functional protein. PTC124 has demonstrated activity in preclinical genetic disease models harboring nonsense mutations allowing the restoration of the production of full-length, functional proteins. In Phase 1 clinical trials, PTC124 was generally well tolerated, achieved target plasma concentrations that have

been associated with activity in preclinical models, and did not induce ribosomal readthrough of normal stop codons. PTC is currently conducting Phase 2 clinical trials of PTC124 in nonsense-mutation-mediated cystic fibrosis (CF) and Duchenne muscular dystrophy (DMD).

It is estimated that 10% of the cases of CF and 13% of the cases of DMD are due to nonsense mutations. PTC believes that PTC124 is potentially applicable to a broad range of other genetic disorders in which a nonsense mutation is the cause of the disease. The FDA has granted PTC124 Fast-Track designations and Orphan Drug designations for the treatment of CF and DMD due to nonsense mutations. PTC124 has also been granted orphan drug status for the treatment of CF and DMD by the Committee for Orphan Medicinal Products (COMP) of the European Medicines Agency (EMEA). PTC124's development is supported by grants from the Muscular Dystrophy Association (MDA), Cystic Fibrosis Foundation Therapeutics, Inc. (CFFT), Parent Project Muscular Dystrophy (PPMD), FDA's Office of Orphan Products Development (OOPD), and by General Clinical Research Center grants from the National Center for Research Resources (NCRR).

ABOUT PTC THERAPEUTICS, INC.

PTC is a biopharmaceutical company focused on the discovery and development of orally administered, proprietary small-molecule drugs that target post-transcriptional control processes. Post-transcriptional control processes regulate the rate and timing of protein production and are of central importance to proper cellular function. PTC has assembled proprietary technologies and extensive knowledge of post-transcriptional control processes that it applies in its drug discovery and development activities. PTC's current pipeline of clinical and preclinical product candidates addresses multiple indications, including genetic disorders, oncology, and infectious diseases.

FOR MORE INFORMATION:

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PATIENTS, PATIENTS' FAMILIES, INVESTIGATORS AND PATIENT ORGANIZATIONS

Kerri Donnelly
PTC Therapeutics, Inc.
(908) 222-7000, x112
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EXHIBIT N

Patient Name: Gunvalson, Jacob #1535
MR No.: 01360556
Date of Birth: 10-5-91
Age: 15 yrs., 7 mos.
Insurance Status: Blue Cross and Blue Shield
Initial Visit: 5-30-07
Current Visit: 5-30-07
Accompanied by: parents

John Parkin, M.D.
MeritCare Clinic
Bemidji North
1705 Ann Street, NW
Bemidji, MN 56601
Phone: 218-333-5000
Fax: 218-333-4728

Dear Dr. Parkin:

Thank you for having us see Jacob in consultation for a comprehensive evaluation of his Duchenne Muscular Dystrophy in particular with concerns for recent loss of ambulation. We had the pleasure of seeing Jacob along with parents in our Neuromuscular Comprehensive Care Center/MDA Clinic on 5-30-07/

ASSESSMENT:

- Duchenne Muscular Dystrophy (nonsense mutation exon 5)
- Functional Activity Level: 6
- Loss of independent ambulation at age 15 ½ .
- Steroid therapy from age 8 years with initial Prednisone, followed by daily Deflazacort from age 9 (about 6 years)
- Growth failure and pubertal delays with delayed bone age of 9 years, for chronologic age of 15-years, 7-months
- Bone osteoporosis with DEXA scores corrected for bone age of about -2 for lumbar spine and on Fosamax for a few years.
- Spine x-rays – no evidence of compression fractures
- Vitamin D deficiency - 25 Hydroxy Vitamin D level of 18.9
- Elevated random urine calcium / creatinine ratio of 0.5 (maybe as a result of low creatinine)
- Decreased fasting glucose insulin ration of 3.4 and concern for insulin resistance
- Asymptomatic cataracts from age 11 years
- Anxiety – on Xanax p.r.n.
- Cardiac – sinus tachycardia 6 months ago, on beta blocker and Losartan
- Spine – 11 degree scoliosis
- MRI muscles in lower extremities with complete fatty replacement in the thighs, moderate fatty replacement in the legs without T2 signals of inflammation / edema
- IV gentamicin therapy for nonsense mutation for the last 3 years from 2004 with side effect of bilateral high tone hearing loss at 8,000 Hz for the past year (preserved renal function on GFR study)

CHIEF COMPLAINT: Loss of ambulation 2 months prior to visit and interest in "braced ambulation."

CURRENT MEDICATIONS: Losartan 50 mg daily; Metoprolol 25 mg daily; Vitamin D 1000 IU/daily; Fosamax 70 mg weekly; Deflazacort 36 mg q.a.m. daily; calcium 500 mg b.i.d. MiraLax 34 g p.r.n.; Gentamicin 386 mg IV 3 times/week; Saline flush port; Juven 1 packet b.i.d.; Xanax 0.25 mg p.r.n.; Tylenol #3 1-2 q. 4h p.r.n.; multivitamin tab 1 daily.

ALLERGIES: None.

HISTORY OF PRESENT ILLNESS:
History was obtained from parents as well as from review of Jacob's previous medical records. Please allow me to summarize Jacob's history for my records.

Gross Motor Function: Jacob is a charming 15-year, 7-month-old right-handed Caucasian young man with Duchenne Muscular Dystrophy diagnosed at the age of 6 years. When Jacob was 2-3 years old, parents had concerns that he was walking and running differently. (running like a 'washing machine'). Per Mom, Jacob did not have a Gower's Maneuver until he was age 5-6 years of age. He did not have calf hypertrophy. Jacob was unable to jump at that time. He could go up steps with alternate feet at times, but usually went up one foot at a time with hand holding onto railings. Jacob had a right gastrocnemius muscle biopsy on 1-13-98. Per Dr. Stephen Smith's report, (light microscopy showed early onset muscular dystrophy). Immunohistochemistry with dystrophin monoclonal antibodies 1,2 and 3 showed reduced immunoreactivity over the sarcolemma with dystrophin 1, representing the mid rod domain. There was no immunoreactivity with dystrophin 3 and minimal immunoreactivity over several fibers with dystrophin 2, representing the C terminus. With this, Dr. Stephen Smith reported ("presence of reduced dystrophin immunoreactivity is compatible with Becker dystrophinopathy"). Jacob had mutational studies done under a research study by Dr. Jerry Mendell at Ohio State in October 2000. The research study found a nonsense (stop codon mutation) in exon 5.

Jacob was treated with corticosteroid therapy from age 8. He first started high dose Prednisone on the weekend schedule. Per Mom, he got weaker with increased falls and was changed 2 weeks later to Prednisone 10-days-on and 10-days-off. However, he still experienced falls and was changed after 2 months to daily Prednisone. This lasted a couple of months and was changed to daily Deflazacort as Jacob had unacceptable behavioral side effects with Prednisone. He was aggressive and was having fights at school. Hence, Jacob has been on daily Deflazacort at 0.9 mg/kg/day since the age of 9 years. Over time, the dose of Deflazacort had been increased to the current 36 mg q.a.m. (for about 2 years). Jacob experienced decreased falls, walked better, and could jump with great effort after doing daily steroids. However, his motor function declined in 2004, and Mom started Jacob on intravenous gentamicin therapy to treat DMD with stop codon mutation. Jacob was initially on IV (through a port) 7.5 mg/kg of gentamicin per day. The dose was gradually increased to 10 mg/kg/day. However, with concerns for nephrotoxicity and the development of high tone deafness, Jacob has been having some drug holidays with gentamicin, getting a total 386 mg/dose only x3 week. Per Mom, Jacob gets drug holidays of 4-5 days to a week's break every 2-3 months. Per Mom, Jacob reports decreased energy when not on gentamicin therapy.

Jacob was ambulating at home with holding on for support till about 2 months ago. He was unable to stand or walk following a "presumed spine compression fracture" in March 2007 after falling one night in the bathroom. Jacob and parents are keen to explore the potential of long leg braces "for braced ambulation". Jacob swims everyday and he will be getting a stander.

REVIEW OF SYSTEMS : Overall health is reported to be good.

Cardiac: Jacob had problems with increased heart rate and tachycardia 6 months ago. He was said to have a normal echocardiogram. Jacob had been on prophylactic lisinopril for the past 1 ½ years. The episode of tachycardia 6 months ago led to an increased dose of lisinopril and use of a beta blocker. (metoprolol) Lisinopril was subsequently switched to losartan in February 2007.

Pulmonary: Jacob had normal PFT's ordered by your office. He plays the trumpet and Mom touches base with Pediatric Pulmonologist Dr. Jonathan Finder at Pittsburgh Children's. Jacob is said to sleep well.

Nutrition/Bone Health: Jacob enjoys food but the family has been counting his calories. He had his 1st fracture (spine fracture) two months ago. Jacob had been on Fosamax for a few years. He currently is on Fosamax 70 mg once a week, Vitamin D 1000 IU/day and calcium supplements.

Vision: Jacob has cataracts associated with daily Deflazacort therapy. Cataracts were diagnosed 4 years ago. He has glasses for vision 20/30 and 20/40. He has annual eye checks.

Hearing: Jacob has high tone deafness at 8,000 Hz associated with gentamicin therapy. High tone deafness was

diagnosed a year ago.

Psycho-social/School: Jacob takes Xanax 0.25 mg p.r.n. for anxiety with flying and elevators. Jacob is coping well with his disabilities and his hobbies include sports and the NFL.

GI: Jacob using MiraLax and Colace for constipation.

Renal: Jacob has no previous nephrology evaluations. He will be seeing Dr. Elizabeth Jackson and had a GFR study at this visit.

Endocrine: Height has dropped from the 50th percentile to less than 3rd percentile after age 9. Weight has increased from the 10th percentile to the 25th-50th percentile, age 12-13 years. Jacob has no facial hair or signs of puberty.

There are no other complaints or concerns.

ANTENATAL HISTORY: Unremarkable.

BIRTH HISTORY: 38-week normal vaginal delivery with a birthweight of 7-pounds, 15 ½ ounces. Apgar scores were 7 and 9 and there were no perinatal problems.

DEVELOPMENTAL HISTORY: Gross motor milestones were normal except for independent walking at about the age of 15 months. Fine motor and language skills were age appropriate. Jacob is an 'A' student.

FAMILY HISTORY: There is family history of Duchenne Muscular Dystrophy. Per Mom, she tested negative for the mutation at the City of Hope lab about 5 years ago. An 18-year-old brother, Ben, is very athletic and will be entering college. Sister Kelsey, age 12, tested negative for the mutation.

PHYSICAL EXAMINATION:
Height: 4' 6.5 inches (20 cm below 3rd percentile) **Weight: 42.9 kg** (below 3rd percentile)
Heart Rate: 97/ min **Blood Pressure:** 115/72
Segmental Arm Span: (usually greater than height by 2-3 inches) measured at 149.5 cm, which is about 7 cm below 3rd percentile

GENERAL EXAMINATION: Jacob was looking well; he had no cushingoid facies. He was quite well nourished. He had no facial hair. Heart and lungs were clear, abdomen was soft and his spine was straight. There was some tenderness over the low back.

NEUROLOGICAL EXAMINATION: Mental status was appropriate. Jacob was alert, articulate and very pleasant. Cranial nerve exam was normal. On motor exam, Jacob had tight pronators with decreased range of forearm supination and tight long finger flexors with a mild Biethem's sign. He had no muscle hypertrophy. There were no significant hip flexor or knee flexor contractures. (< 5 degrees). Ankle dorsiflexion was up to neutral bilaterally with L-sitting. Jacob was able to hold his neck up against gravity to the plane of the body in the supine position. He got up from supine to sitting with forward truncal flexion with hand support on the bed. I elicited grade 3+ strength for shoulder abduction and grade 3 strength for elbow flexion. Hip flexors were grade 2 (Jacob was able to elevate them against gravity only by turning his body to the side). Jacob had active quadriceps extension bilaterally through a range of 60 to 75 degrees when seated over the edge of the table. Jacob could stand with a lot of support and very prominent lumbar lordosis only when we stabilized his knees in extension and supported his body weight at the ischia.

IMPRESSION : Although Jacob has been labeled as a Becker Muscular Dystrophy, he clearly has the clinical phenotype of a patient with Duchenne Muscular Dystrophy with regards to his presentation and the profile of his declining motor function to the loss of independent ambulation at age 15 ½ with steroid therapy. Moreover, the immunocytochemical staining reported in Jacob's biopsy is only that of reduced staining with the rod domain, i.e. dystrophin I with no minimal staining for dystrophin II and III. Apparently, no quantitation of dystrophin was

done with Western blot or immunoblotting studies. Such immunocytochemical staining has been seen in our clinic patients with Duchenne Muscular Dystrophy. MRI muscle done at this visit (severe fatty replacement of muscles) and DEXA studies (44% fat mass) are also consistent with a diagnosis of Duchenne Muscular Dystrophy.

The age at loss of ambulation at 15 ½ is quite consistent with DMD patients treated with daily steroids. The benefit of additional IV gentamicin therapy at this point in time does not seem to outweigh the risks of (otoxicity and concern for renal compromise with continued therapy). Jacob seems to be a good candidate for intensive rehab into ischial weight bearing long leg braces.

Jacob has significant side effects associated with chronic steroid therapy: osteoporosis, asymptomatic cataracts, growth failure, pubertal delays and insulin resistance. His Vitamin D deficiency is also going to negatively affect his bone health further. His function can be optimized when appropriate interventions for these complications.

DIAGNOSTIC PLANS / EVALUATIONS:

Cardiac: 5-31-07 Dr. Linda Cripe. Cardiac MRI 5-31-07: normal study except for mild diastolic dysfunction.

Pulmonary: 5-31-07 Dr. Narong Simakajornboon. PFT 5-30-07: forced vital capacity of 2.48 L (109% predicted) MIP 95, MEP 86, cough peak flow 200 L/min.

MRI of thighs and legs showed diffused essentially complete fatty replacement of the muscles of the thighs with some sparing of the sartorius gracilis and semitendinosis muscles. Muscle volume in the lower leg was far better preserved with moderate fatty infiltration with some sparing of the medial head of the gastrocnemius and popliteals muscles. There were no increased signals seen on two waited sequences to indicate active inflammation or edema.

Monitoring Labs: renal panel: sodium 139, C02 30, creatinine low 0.2, calcium 9.7, phosphorus 4.8, CPK 3367, AST 119, ALT 158, alkaline phosphatase low 62 (range 65 – 525). TSH 0.9, Total T4 10.1, free T4 2.3, IGF-1 591.2 (range 358 – 870), IGFbp-3 normal 5.1, 25 Hydroxy Vitamin D low at 18.9, Total CoQ10 , CoQ10 %reduced. Random urine calcium / creatinine ratio 0.5, random calcium 23.5, random creatinine 46, FSH 7.8, LH 4.2, testosterone low at 12, serum amino acids normal, random urine calcium 23.5, random urine creatinine 46, calcium/creatine ratio 0.5, zinc level 836 normal (range 670 – 1240), creatine level 2.1

Bone Health: X-ray bone age: chronological age 15-years, 7-months; estimated bone age: delayed at 9 - years, Spine X-rays: no compression fractures. 11 degrees left sided scoliosis. Dexa studies L/S Spine z-score: -3.5 (when corrected for bone age of 9 years, it is about -2)
Distal Femur: R1 (uncorrected for bone age) -4.6, R2 -4.5, R3 -3.5 **%Body Fat: 44.2 Whole Body Z-score:** -3.2

Nephrology Evaluation: Dr. Elizabeth Jackson on 5-29-07. Renal ultrasound on 5-30-07: normal kidneys with no nephrocalcinosis. GFR studies with (TC-99M-DTP 149 ml/min/1.75 square meters) preserved renal function.

Audiology: testing on 5-29-07. Moderate to severe hearing loss at 8,000 Hz

THERAPEUTIC PLANS:

1. Jacob was evaluated by Orthotist, Ted Ryder, and PT, Amy Meyer. We felt Jacob is a good candidate for ischial weight bearing KAFO's to enable him to ambulate with long leg braces. Mr. Ryder made the cast for Jacob's braces and he will return in a couple of weeks for intensive rehabilitation to relearn how to stand and walk with these braces.
2. With the growth failure and insulin resistance, Jacob will also be evaluated by Dr. Meilan Rutter following a growth hormone skin test upon his return.
3. Dietician, Kirans Rao, will meet the family upon Jacob's return to discuss dietary modifications, especially in view of the concern for insulin resistance. Mom will be getting a dietary recall to enable Kirans to work on the interventions.

4. Jacob will continue on his Deflazacort 36 mg q.a.m.
5. Jacob will need to have a 24-hour urine calcium study before we increase his Vitamin D and calcium supplements to treat his Vitamin D deficiency.
6. Although Jacob still has preserved renal function, he already has otoxicity from the gentamicin therapy. With the decline in Jacob's motor function, and my concern for the lack of efficacy for gentamicin therapy at this point in time, I discussed with Mom the option of discontinuing gentamicin especially in the light of up coming PTC-124 clinical trials. Mom is reluctant to discontinue gentamicin at this point in time as she feels that Jacob reports less energy when off gentamicin and she perceives lower CK level on gentamicin. However, she is open to checking CK level without gentamicin therapy and consider discontinuing if there is no difference without gentamicin.

FOLLOW-UP:

- **To return in mid June for intensive Rehab for KAFO's, growth hormone skin test and Endocrine evaluation in the near future.**
- **Clinic follow-up will be 3 months after acquisition and rehab into KAFO's.**

I personally took a history, examined this patient, reviewed the medical notes and test reports from parents. I formulated the treatment plan.

Face to face time spent on counseling family / caregivers concerning the diagnosis, problems, progress, care and research advances: 80 min. Total consult time: 120 min.

Thank you for allowing us to participate in the care of this patient.

Sincerely,

Brenda Wong, M.D.
Child Neurologist
Associate Professor of Pediatrics and Neurology
Neuromuscular Comprehensive Care Center

BW/do
Date Transcribed: 6-11-07

Mr.& Mrs. Gunvalson
11617 506th Street
Gonvick, MN 56644

Kirana Rao
Nutritionist
CCHMC ML 5043

Amy Meyer, PT (to pass to Rehab Attending on service)
Physical Therapy
CCHMC ML 4007

Meilan Runer, M.D.
Endocrine
CCHMC ML 7012

Concierge
CCHMC ML 9014

Elizabeth Jackson, M.D.
Nephrology
CCHMC ML 7022

EXHIBIT O

-----Original Message-----
From: Cheri Gunvalson [mailto:cgunval@gvtel.com]
Sent: Monday, October 22, 2007 1:41 PM
To: Hirawat, Claudia
Subject: RE: trial criteria

Hi,
How are you doing? I heard your husband has left PTC. Please wish him well! It is a big loss to PTC and the boys!

Is there any news you can share?

Warm regards!

cheri

---- Original Message ----
From: chirawat@ptcbio.com
To: cgunval@gvtel.com, dgoetz@ptcbio.com
Subject: RE: trial criteria
Date: Wed, 10 Oct 2007 04:37:42 -0400

>Hi Cheri,
>
>I am glad Diane got back to you, I am in London on business.
>
>Hope all is well. Thank you for the cards and photos. I was in NY
>last week and had a slice of pizza, I was thinking of Jacob telling
>me this is the one thing he wanted to do in NY. It was wonderful, but
>I hope I can convince him next time that there are lots of other cool
>things to do and try too!
>
>Now that we have a marketing team (Theresa Natalicchio has joined us
>from Pfizer), Diane and her team will report to her, heading up the
>patient advocacy function at PTC. I will focus on business
>development, my other PTC role, which has been very busy.
>
>Of course I remain a patient advocate, and will continue to be very
>active with PPMD.
>
>Hope to see you soon,
>
>Cláudia
>
>THIS ELECTRONIC MAIL MESSAGE AND ANY ATTACHMENT IS CONFIDENTIAL AND
>MAY CONTAIN PRIVILEGED INFORMATION INTENDED ONLY FOR USE OF THE
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>helppro@ptcbio.com to notify us of the error, and delete the original
>message and any attachments. The views or opinions presented in this
>message are solely those of the author and do not necessarily
>represent those of PTC Therapeutics. Thank you.
>
>-----Original Message-----
>From: Cheri Gunvalson [mailto:cgunval@gvtel.com]
>Sent: Tuesday, October 09, 2007 6:29 PM
>To: Goetz, Diane; Hirawat, Claudia

EXHIBIT P

----- Original Message -----
From: "Hirawat, Claudia " <chirawat@ptcbio.com>
To: "Cheri Gunvalson" <cgunval@qvtel.com>
Sent: Thursday, October 25, 2007 12:20 PM
Subject: RE: trial criteria

Hi Cheri,

Sorry to be slow to respond, I was traveling.

Yes, Samit has joined Novartis in the oncology group (which is his background). As you know, Leone Atkinson has joined PTC a few months ago to run the PTC124 DMD program, and I believe they will hire a pulmonologist to run the CF portion. So while we will sure miss working with him, I think the team is in good shape. Samit was deeply touched by your visit to our home. We both marveled at your parenting skills and your energy! You are one amazing family and I do hope you will visit us again!

But Samit is not free from the boys, oh no, we are keeping the boys! Samit continues to consult to PTC and to help think of other potential treatment avenues for DMD. He is also advising on other lines of research targeting DMD.

A little summary of what is going on here at PTC: now that we have hired Theresa Natalicchio as head of marketing (please read into the optimism behind his hire!), we are transferring the patient advocacy function to that group. This means the Diane and Lindsay now report into the marketing group. I will now continue to focus my efforts on the business development part of my job. Diane and Lindsay have extensive experience in this area and I will continue to work closely with them, but they are the best source of information for you going forward. Diane's email is dgoetz@ptcbio.com and Lindsay's is lrosen@ptcbio.com. They have a shared email box that ensures all emails are answered quickly, so the best place to write to is patientinfo@ptcbio.com.

As far as the current status, my understanding is that we are in the final stretch of our discussions with the FDA and hopefully will have a more specific plan for next steps eminently, with the goal of initiating the next round of studies in the next couple of months as planned. Fingers and toes are crossed.

Once we get this plan in place, it will be a good time to talk in more detail of what the next steps

can mean for Jacob. We will keep you posted and please stay in touch.

You have all the official contacts, but please know I have all this photos of Jacob seating right here in front of me, and consider all the Gunvalson's my personal friends, so please call and write to me ANYTIME!

A big hug to the whole gang,

Cláudia

EXHIBIT Q

From: Cheri Gunvalson [mailto:cgunval@gvtel.com]
Sent: Sunday, December 30, 2007 3:32 PM
To: Goetz, Diane
Subject: 124 2a extension

Diane,

I have tried to explain the situation for Jacob's MD and was wondering if you could clarify. In November when I asked you if PTC would release the drug for expanded access and you said no to expanded access but yes he would get the drug in a different mannor. Then we had the call with Claudia that many things were still up in the air. Could you please clarify whre Jacob is at in regards to PTC 124? Also is it possible for Jacob to be protocal exception that Dr Russle Katz wrote to me about in 2006 for the 2a trial?

Thank you,

Cheri

EXHIBIT R

>>>Original Message -----
From: Goetz, Diane
To: Cheri Gunvalson
Sent: Sunday, December 30, 2007 5:22 PM
Subject: [Spam] RE: 124 2a extension

Hi, Cheri-

We are trying to figure out whether it would be possible for Jacob and other boys who do not qualify for the 2b study to participate in another study. We won't be able to determine that until we have a better idea of what the 2a extension study will be. As we have recently announced, we are close to initiating the Phase 2b study. We have begun to plan for the extension study but we cannot move ahead with that until the 2b study is launched. That is about as specific as I can be at this point.

As for your second question, I'm sorry but I can't answer that until I talk to the clinical team about the exact definition and implications of the term "protocol exception," as it is not one with which I am familiar. It sounds to me like another way of saying "single patient IND," which we have already discussed and which I have explained would not be possible philosophically or practically. I could be wrong about this definition, so I want to be sure I understand the term. I will try to discuss it this coming week but I don't know what people's schedules are so I can't give you a time when I will have an answer. I will try my best to get an answer by Friday.

Best,
Diane

Diane M Goetz
Director of Patient and Professional Advocacy
PTC Therapeutics
100 Corporate Court
South Plainfield, NJ 07080
Tel: 908 912-9256 *PLEASE NOTE NEW DIRECT LINE*
Fax: 908 222-7231
Mobile: 908 251-0837
dgoetz@ptcbio.com
www.ptcbio.com

.15 p.m.

EXHIBIT S

From: Cheri Gunvalson [mailto:cgunval@gvtel.com]
Sent: Tuesday, January 01, 2008 12:14 PM
To: Goetz, Diane
Subject: Re: [Spam] RE: 124 2a extension

Dear Diane,
My understanding from Dr Katz's email is a protocol exception is that Jacob could be in the 2a trial as a protocal exception ie an exception to the protocal. It is my understanding the FDA wants saftey data on the drug in as many patients as possible in a controlled setting such as the 2a trial so they can evaluate more fully the saftey of the drug. Especially in cases like this when it is a rare subgruop. So it is win win for the FDA to gather more saftey data and for the patient. It is my understanding the FDA is trying to get drug companies to use this avenue more. David Banks from the FDA told me some time ago that he believed that Dr Katz would consider an expidited review of our case for a protocal exception.

Sincerely,

Cheri

EXHIBIT T

From: Goetz, Diane
To: Cheri Gunvalson
Sent: Friday, January 04, 2008 11:56 AM
Subject: RE: [Spam] RE: 124 2a extension

Dear Cheri,
I was reading the *Wall Street Journal* on the way to work today and there was an ad for a book called *The Power of a Positive No*. One of the blurbs on this book was written by Jim Collins (author of *Good To Great*), who said, "Ury [the author] teaches us how to say NO - with grace and effect - so that we might create an even better YES." I haven't read the book so I'm not sure how to say no to a protocol exception with grace and effect, but I can definitely tell you we're saying no because we're trying to create an even better yes. When it's all over you'll understand exactly what I mean and why, but we're not there yet. I know it's hard for you but please hold tight. The best path forward is still very much on the agenda here.
Best,

Diane

Diane M Goetz
Director of Patient and Professional Advocacy
PTC Therapeutics
100 Corporate Court
South Plainfield, NJ 07080
Tel: 908 912-9256 *PLEASE NOTE NEW DIRECT LINE*
Fax: 908 222-7231
Mobile: 908 251-0837
dgoetz@ptcbio.com
www.ptcbio.com

EXHIBIT U

From: "Goetz, Diane" <dgoetz@ptcbio.com>
To: "Taylor, Bettilou (Appropriations)" <Bettilou_Taylor@appro.senate.gov>
Cc: "Cheri Gunvalson" <cgunval@gvtel.com>
Sent: Friday, January 25, 2008 6:20 PM
Subject: RE: Jacob

Dear Bettilou,

It's nice to hear from you again. Happy New Year to you, too. I'm sorry for the long delay in responding to you.

As you might imagine, it is very difficult to do right by all the patients who could potentially benefit from PTC124, and there are many opinions about the best way to accomplish that. One thing we all agree on: the best thing for all the boys is to get PTC124 approved and to market as quickly as possible. That is, and must be, our primary goal.

PTC has not changed its position on trying to find the best way to involve Jacob and other boys in similar circumstances in our studies. It continues to be a priority for us.

I hope you will support us, as I know Cheri does, in our mission to make PTC124 available, as expeditiously as possible, to all boys who could potentially benefit from it.

Best,
Diane

Diane M Goetz
Director of Patient and Professional Advocacy
PTC Therapeutics
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Fax: 908 222-7231
Mobile: 908 251-0837
dgoetz@ptcbio.com
www.ptcbio.com

-----Original Message-----
From: Taylor, Bettilou (Appropriations)
[mailto:Bettilou_Taylor@appro.senate.gov]
Sent: Monday, January 14, 2008 2:59 PM
To: Goetz, Diane

Subject: Jacob

Diane -- I read with much regret -- you e-mail to Cheri. I know that these decisions are difficult ones -- can you tell me why you won't grant a protocol exception for Jacob?

I also would like to know why Cheri thought that Jacob was going to get the drug -- she had called all of her friends and was so excited that PTC finally decided to let him have the drug and then the let down that it was not going to happen.

I understand from my discussions with the FDA that they are encouraging companies to grant exceptions to provide as much info as possible about the side effects from the drug to a variety of patients.

I know that this is difficult for all involved -- but I am trying to understand. As you can imagine when the Senators get involved -- they want to know all of the ins and outs of the issue.

Thanks again for taking time to be so kind to us during our visit. Hope you have a wonderful New Year.

BLT

EXHIBIT V

PTC News

PTC News 2007 Archive

PTC News 2006 Archive

PTC News 2005 Archive

Upcoming Events

PTC News

4/23/2008 PTC Therapeutics Announces Initiation of Phase 2b Registration-Directed Clinical Trial of PTC124 ir Duchenne/Becker Muscular Dystrophy

2/4/2008 PTC Therapeutics Announces Publicatior of Preclinical Data in *PNAS*

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PTC THERAPEUTICS ANNOUNCES INITIATION OF PHASE 2B REGISTRATION-DIRECTED CLINICAL TRIAL OF PTC124 IN DUCHENNE/BECKER MUSCULAR DYSTROPHY

First Registration Study of an Investigational Drug for Duchenne/Becker Muscular Dystrophy

SOUTH PLAINFIELD, NJ – April 23, 2008 - PTC Therapeutics, Inc. (PTC), today announced the initiation o an international pivotal trial of PTC124 in patients with Duchenne/Becker muscular dystrophy (DMD/BMD) due to a nonsense mutation. The primary objective of this registration-directed Phase 2b trial is to demonstrate the efficacy of PTC124 as measured by improvements in the walking ability of patients with this progressive genetic disease.

"DMD/BMD is a disorder with a significant need for better treatment options, and we are very encouraged by the promising results we have seen to date with PTC124," said Brenda Wong, M.D., Associate Professor of Pediatrics and Neurology, Cincinnati Children's Hospital Medical Center, Cincinnati, who was involved in the Phase 2a study and is one of the trial's lead investigators. "We believe that the safety profile of PTC124 and activity we have seen in the Phase 2a studies clearly support the initiation of this longer-term, registration-directed efficacy and safety study. We are very pleased to be a part of this groundbreaking trial."

Patients with DMD and BMD are boys and young men who lack dystrophin, a protein that is critical to the structural stability of muscle fibers. Patients develop progressive muscle weakness that leads to loss of ambulation, wheelchair dependency, and eventual decline in respiratory and cardiac function. It is estimated that one in 10 DMD patients are likely to have a Becker presentation, a milder form of the disease that is associated with later manifestation of symptoms. In essence, DMD and BMD represent a continuum of the same disease.

PTC124 is a novel, orally delivered drug in development for the treatment of patients with genetic disorders due to a nonsense mutation, a type of mutation found in approximately 13% of patients with DMD. In this double-blind study, patients will be randomized to receive placebo, or one of two dose levels of PTC124, three times per day. Eligible patients will be boys with nonsense-mutation-mediated DMD/BMD who are at least 5 years of age and are able to walk at least 75 meters or approximately 80 yards in six minutes. PTC expects to
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enroll a total of 165 patients at approximately 35 investigational sites; all study subjects will undergo 48 weeks of blinded treatment. Thereafter, all participants, including those who have been receiving placebo, will be eligible to enroll in an open-label PTC124 extension study.

The primary outcome measure is the total distance walked during a 6-minute walk test, a test of ambulation that has now been standardized for boys with DMD/BMD through a collaboration with noted investigator, Craig McDonald, M.D., at University of California at Davis. Other outcome measures in the Phase 2b study will evaluate activity at home, muscle and heart function, strength, cognitive ability, muscle integrity, and muscle dystrophin expression. Safety parameters, compliance, and PTC124 blood levels also will be monitored.

"We are very pleased to announce the initiation of the Phase 2b trial for PTC124 in boys with DMD/BMD," said Langdon Miller, M.D., Chief Medical Officer of PTC. "We applaud the patients, parents, and clinicians who have committed themselves to this effort. The design of this trial reflects our ongoing collaboration with the advocacy community, investigators at leading neuromuscular centers, and the U.S. and European regulatory agencies. We hope that PTC124 will soon offer a treatment that addresses the underlying cause of the disease for patients with nonsense-mediated DMD/BMD and that the development of PTC124 will set the stage for improving therapeutic options in this disabling and life-threatening disorder."

Stuart W. Peltz, Ph.D., President and Chief Executive Officer of PTC Therapeutics added, "Initiation of the Phase 2b trial is an important milestone for PTC. The trial builds on the results we have achieved to date in DMD and cystic fibrosis (CF) and constitutes a major step forward in establishing the potential for PTC124 as a paradigm shift in the treatment of genetic disorders. Our future plans for PTC124 include the initiation of longer-term studies in CF, as well as additional proof-of-concept studies in other indications."

ABOUT DUCHENNE AND BECKER MUSCULAR DYSTROPHY

Duchenne and Becker muscular dystrophy (DMD/BMD) are progressive muscle disorders that cause the loss of both muscle function and independence. DMD/BMD is perhaps the most prevalent of the muscular dystrophies and is the most common lethal genetic disorder diagnosed during childhood today. Each year, approximately 20,000 children worldwide are born with DMD (one of every 3,500 male children). It is estimated that one in 10 DMD patients are likely to have a Becker presentation, a milder form of the disease that is associated with later manifestation of symptoms. In essence, DMD and BMD represent a continuum of the same disease. More information regarding DMD and BMD is available through the Muscular Dystrophy Association (www.mdausa.org), the Parent Project Muscular Dystrophy (www.parentprojectmd.org), and the Association Française contre les Myopathies (www.afm-france.org).

ABOUT PTC124

PTC124 is an orally delivered investigational new drug in Phase 2 clinical development for the treatment of genetic disorders due to nonsense mutations. Nonsense mutations are single-point alterations in the genetic code that prematurely halt the translation process, producing a shortened, non-functional protein. PTC124 has restored production of full-length, functional proteins in preclinical genetic disease models harboring nonsense mutations. In Phase 1 clinical trials, PTC124 was generally well tolerated, achieved target plasma concentrations that

have been associated with activity in preclinical models and did not induce ribosomal read through of normal stop codons. PTC124 has demonstrated pharmacodynamic proof of concept in Phase 2a clinical trials in nonsense-mutation-mediated Duchenne muscular dystrophy (DMD) and cystic fibrosis (CF).

It is estimated that 13% of the cases of DMD and 10% of the cases of CF are due to nonsense mutations. PTC believes that PTC124 is potentially applicable to a broad range of other genetic disorders in which a nonsense mutation is the cause of the disease. The FDA has granted PTC124 Subpart E designation for expedited development, evaluation, and marketing and has granted Orphan Drug designations for the treatment of CF and DMD due to nonsense mutations. PTC124 has also been granted orphan drug status for the treatment of CF and DMD by the European Commission. PTC124's development has been supported by grants from the Muscular Dystrophy Association (MDA), Cystic Fibrosis Foundation Therapeutics, Inc. (CFFT), Parent Project Muscular Dystrophy (PPMD), FDA's Office of Orphan Products Development (OOPD) and by General Clinical Research Center grants from the National Center for Research Resources (NCRR). For additional information on the PTC124 clinical trial, please visit www.clinicialtrials.gov and search using the keyword: PTC124.

ABOUT PTC THERAPEUTICS, INC.
PTC is a biopharmaceutical company focused on the discovery, development and commercialization of orally administered, proprietary, small-molecule drugs that target post-transcriptional control processes. Post-transcriptional control processes regulate the rate and timing of protein production and are of central importance to proper cellular function. PTC's internally-discovered pipeline addresses multiple therapeutic areas, including genetic disorders, oncology and infectious diseases. In addition, PTC has developed proprietary technologies and extensive knowledge of post-transcriptional control processes that it applies in its drug discovery and development activities, including the Gene Expression Modulation by Small-molecules (GEMS) technology platform, which has been the basis for collaborations with leading pharmaceutical and biotechnology companies such as Pfizer, Celgene, CV Therapeutics and Schering-Plough. For more information, visit the company's website, www.ptcbio.com.
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PTC THERAPEUTICS ANNOUNCES PUBLICATION OF PRECLINICAL DATA IN *PNAS*

Data Show PTC124 Addresses Underlying Cause of Genetic Disorders and Restores Protein Function in Cystic Fibrosis Model

South Plainfield, N.J., February 4, 2008 — PTC Therapeutics, Inc. today announced the publication of new preclinical data in the February 12, 2008 edition of the Proceedings of the National Academy of Sciences (PNAS), which show that PTC124, a novel drug designed to bypass nonsense mutations, was active in a preclinical model of cystic fibrosis (CF). These results support and add to research published last year in the journal Nature, which demonstrated the activity of PTC124 in a preclinical model of Duchenne muscular dystrophy (DMD). PTC124 has demonstrated pharmacodynamic proof of concept in Phase 2a clinical trials in nonsense-mutation-mediated CF and DMD.

PTC has catalogued over 2,400 distinct genetic disorders where nonsense mutations are the cause of the disease in a significant percentage of patients. Nonsense mutations

inactivate gene function and are known to cause anywhere from five to 70 percent of the individual cases of most inherited diseases, such as cystic fibrosis (10%) and Hurler's syndrome (70%).

"The preclinical and clinical data on PTC124 support our hope that this drug will be an important disease-modifying therapy for cystic fibrosis," said Robert J. Beall, Ph.D., President and CEO of the Cystic Fibrosis Foundation. "This is an exciting potential new treatment for patients afflicted with nonsense-mutation-mediated CF. We look forward to the next stage of clinical development to demonstrate the benefits of this promising new investigational drug."

As with the DMD data published in Nature, the results published in PNAS further demonstrate that PTC124 targets genetic mutations in a completely new way. PTC124 functions by overcoming the premature stop signal and reading through the complete genetic instructions, resulting in the restoration of a full-length, functional protein. Patients with CF lack the CFTR protein, a chloride channel that maintains proper hydration of epithelial cells in the lung, pancreas, and liver. The data in PNAS demonstrate that PTC124 allows CFTR to be made in cells in which it was previously absent, to be delivered to the proper cellular location, and to induce chloride channel function. Collectively, these results indicate that this new approach may ultimately be applicable to a subset of patients across a large number of genetic disorders.

The paper entitled, "PTC124 is an orally bioavailable compound that promotes suppression of the human CFTR-G542X nonsense allele in a CF mouse model," will be available in an advanced online publication of PNAS during the week of February 4, 2008 (http://www.pnas.org/papbyrecent.shtml). This publication is the result of collaborative efforts between the University of Alabama at Birmingham and PTC Therapeutics.

"These preclinical data further demonstrate the potential applicability of the PTC124 mechanism of action to multiple genetic disorders," said Stuart W. Peltz, Ph.D., President and Chief Executive Officer of PTC Therapeutics. "We look forward to further evaluating PTC124 in registration-directed clinical trials in both CF and DMD this year, as well as in studies in additional genetic disorders in the future."

About PTC124

PTC124 is an orally delivered investigational new drug in Phase 2 clinical development for the treatment of genetic disorders due to nonsense mutations. Nonsense mutations are single-point alterations in the genetic code that prematurely halt the translation process, producing a shortened, non-functional protein. PTC124 has restored production of full-length, functional proteins in preclinical genetic disease models harboring nonsense mutations. In Phase 1 clinical trials, PTC124 was generally well tolerated, achieved target plasma concentrations that have been associated with activity in preclinical models and did not induce ribosomal read through of normal stop codons. PTC124 has demonstrated pharmacodynamic proof of concept in Phase 2a clinical trials in nonsense-mutation-mediated cystic fibrosis (CF) and Duchenne muscular dystrophy (DMD).

It is estimated that 10% of the cases of CF and 13% of the cases of DMD are due to nonsense mutations. PTC believes that PTC124 is potentially applicable to a broad

range of other genetic disorders in which a nonsense mutation is the cause of the disease. The FDA has granted PTC124 Subpart E designation for expedited development, evaluation and marketing and has granted Orphan Drug designations for the treatment of CF and DMD due to nonsense mutations. PTC124 has also been granted orphan drug status for the treatment of CF and DMD by the European Commission. PTC124's development has been supported by grants from the Muscular Dystrophy Association (MDA), Cystic Fibrosis Foundation Therapeutics, Inc. (CFFT), Parent Project Muscular Dystrophy (PPMD), FDA's Office of Orphan Products Development (OOPD) and by General Clinical Research Center grants from the National Center for Research Resources (NCRR).

About the Cystic Fibrosis Foundation
The Cystic Fibrosis Foundation is the leading organization devoted to curing and controlling cystic fibrosis. Headquartered in Bethesda, Md., the Foundation funds CF research, has 80 chapter and branch offices, and supports and accredits a nationwide network of 115 CF care centers, which provide vital treatments and other CF resources to patients and families. For more information, visit www.cff.org.

About PTC Therapeutics, Inc.
PTC is a biopharmaceutical company focused on the discovery, development and commercialization of orally administered, proprietary, small-molecule drugs that target post-transcriptional control processes. Post-transcriptional control processes regulate the rate and timing of protein production and are of central importance to proper cellular function. PTC's internally-discovered pipeline addresses multiple therapeutic areas, including genetic disorders, oncology and infectious diseases. In addition, PTC has developed proprietary technologies and extensive knowledge of post-transcriptional control processes that it applies in its drug discovery and development activities, including the Gene Expression Modulation by Small-molecules (GEMS) technology platform, which has been the basis for collaborations with leading pharmaceutical and biotechnology companies such as Pfizer, Celgene, CV Therapeutics and Schering-Plough. For more information, visit the company's website, www.ptcbio.com.

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