

## FREQUENTLY ASKED QUESTIONS

### ABOUT PTC THERAPEUTICS, INC. AND PTC124

**1. Q: What does the ‘PTC’ in PTC Therapeutics stand for?**

**A:** PTC stands for “Post-Transcriptional Control.” Post-transcriptional control mechanisms constitute all regulatory events that take place after an RNA molecule is made (i.e., after the transcription process). These include the translation (decoding) of the RNA molecule to synthesize a specific protein. There are multiple regulatory events in the translation of RNA and these events have a direct effect on how much protein is produced. Overproduction or underproduction of critical proteins can be involved in many disease processes. Our approach is to discover and develop small molecule drugs that inhibit or enhance protein production through modulation of post-transcriptional control mechanisms.

**2. Q: What post-transcriptional processes are targeted?**

**A:** The main regulatory points in post-transcriptional control include:

- 1) pre-messenger RNA (mRNA) processing;
- 2) mRNA transport out of the cell nucleus;
- 3) control of mRNA translation; and,
- 4) control of mRNA degradation.

All of these processes are necessary for the regulated expression of proteins necessary for health, and all represent opportunities for therapeutic intervention through PTC’s technologies and expertise.

**3. Q: Do you only target RNA?**

**A:** No, post-transcriptional events involve both proteins and RNA that interact in precise and specific ways. We discover and develop compounds that work by interacting with RNA, protein, or RNA-protein complexes.

**4. Q: Are you an antisense or an RNAi company?**

**A:** No, our approach is focused on discovering and developing small molecule drugs, which use the traditional chemistry methods developed and refined by the pharmaceutical industry. Our compounds possess favorable pharmaceutical properties for formulation, manufacturing, and patient acceptability (for example, oral bioavailability).

In contrast, antisense and RNAi technologies rely on the delivery of large RNA-like molecules that inhibit protein production. Antisense and RNAi technologies inactivate a target gene and can only down-regulate gene expression. Our approach has the advantage of identifying small molecules can either up- or down-regulate gene expression by modulating post-transcriptional control mechanisms, greatly expanding the drug discovery opportunity to modulate protein production in cells to treat diseases.

## PTC124

**5. 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. Such a mutation is a single-point 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 truncated protein that is too short to perform its necessary function.

Nonsense mutations are the basis for approximately 5-15% of the individual cases of most inherited diseases, including muscular dystrophy, cystic fibrosis, hemophilia, neurofibromatosis, retinitis pigmentosa, bullous skin diseases, lysosomal storage diseases, and a variety of other genetic disorders.

PTC124 belongs to a new class of small molecules discovered by PTC Therapeutics. PTC124 allows ribosomes to bypass the nonsense mutations (the premature stop signals) in mRNA and continue the translation process to make a full-length and functional protein.

**6. 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 into 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.

Development of PTC124 (currently in clinical trials) offers a unique approach to the treatment of genetic disorders, coupling a specific type of genetic defect with a small molecule drug that has the potential to overcome that genetic defect. By addressing the underlying cause of the disease, it is anticipated that PTC124 might decrease dependence on palliative interventions and ameliorate the debilitation and mortality in patients with genetic disorders due to nonsense mutations. Because PTC124 is a small molecule drug that can be taken by mouth, it does not suffer from the delivery challenges that have limited gene therapy or the high costs and complex delivery of enzyme replacement therapy. This approach offers advantages because it builds on experience with existing drugs that are widely used clinically; relies on traditional, practical-to-deliver, small molecule pharmacology; does not alter the endogenous patient genome; and does not necessitate the delivery of foreign genetic material or viruses.

**7. 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 in an individual patient. We plan to initiate the first

patient studies in children and young adults with Duchenne muscular dystrophy and cystic fibrosis, but hope eventually to expand development to multiple genetic disorders. We are continuing our preclinical research in order to assess the potential clinical utility of PTC124 in other genetic disorders.

**8. 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:** PTC has carefully analyzed this issue in specificity studies in tissue culture systems and in animal models. These studies have demonstrated that PTC124 specifically acts to allow ribosomes to read through nonsense mutations (premature stop codons) but does not induce the ribosomes to read through normal stop codons near the end of the mRNA. Dose levels of PTC124 that are substantially higher than those required to induce premature stop codon read-through have been well tolerated and show no evidence of read-through of normal stop codons in animals. As part of the Phase 1 clinical studies, special tests were performed that revealed no evidence of undesirable, nonspecific readthrough of normal stop codons in humans.

**9. 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. However, PTC124 is a new chemical entity completely unrelated to gentamicin and has no antibiotic properties. PTC124 has been specifically designed to bypass nonsense mutations as a potential treatment for genetic disorders. Gentamicin, while a good antibiotic, has been shown not to be very potent at nonsense mutation read-through, is delivered intravenously, and can have serious side effects, including kidney damage and hearing loss. By contrast, PTC124 has been shown to be very potent in reading through nonsense mutations in preclinical studies, is an oral drug, and appears to be tolerated in animal pharmacological and toxicology testing and in Phase 1 clinical studies in healthy volunteers.

**10. Q: If patients are interested in knowing whether a nonsense mutation is the cause of their disease, what should they do?**

**A:** Gene sequencing can determine if a patient has the disease because of a nonsense mutation. This is one of the first examples 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 physicians 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 special expertise in studying patients with a particular disease. 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 patients with cystic fibrosis, full-length gene sequencing is available through Ambry Genetics (<http://www.ambrygen.com>).

**11. Q. How will PTC Therapeutics identify patients with nonsense mutations?**

**A:** For the clinical trials in Duchenne muscular dystrophy and cystic fibrosis, PTC Therapeutics will employ the tests offered by the University of Utah ([http://www.genome.utah.edu/DMD/clinical\\_test.shtml](http://www.genome.utah.edu/DMD/clinical_test.shtml)) and by Ambry Genetics (<http://www.ambrygen.com>) to confirm the diagnosis of a nonsense mutation.

**12. Q: What are the next regulatory steps for PTC124?**

**A:** The first step in clinical development of a compound is the submission of an Investigational New Drug Application (IND) to the Food and Drug Administration (FDA). Because PTC124 may potentially treat multiple diseases, in February 2004 we met with the FDA to discuss the path of development for PTC124, in what is called a pre-IND meeting. This was a meeting involving multiple divisions of the FDA. Based on input from the FDA, an IND was then filed with the Division of Pulmonary and Allergy Drug Products; this IND allowed the commencement of Phase 1 trials and will support Phase 2 and 3 studies in patients with cystic fibrosis. Now that the Phase 1 trials in healthy volunteers are complete, an additional IND will be submitted to the Division of Neuropharmacology Drug Products to support Phase 2 and 3 studies in Duchenne muscular dystrophy.

**13. Q: What are the next steps toward initiating Phase 2 trials of PTC124?**

**A:** For the Phase 2 studies in both Duchenne muscular dystrophy and cystic fibrosis, PTC is now submitting the protocols and other related documents to the FDA and to appropriate review committees at each of the potential clinical trial sites. Review of these documents typically takes 4-12 weeks from the time they are received. If the protocols are approved, and assuming the relevant INDs are in effect, PTC will list details relating to the trials on [www.clinicaltrials.gov](http://www.clinicaltrials.gov). We hope to start enrollment in the cystic fibrosis Phase 2 program in August 2005 and enrollment in the Duchenne muscular dystrophy Phase 2 program in September 2005.

**14. Q. Why have the Phase 1 trials been conducted in healthy volunteers?**

**A:** The Phase 1 trials have been conducted in healthy volunteers to rapidly characterize the general safety pharmacokinetics, palatability, and effects of food on PTC124 absorption. These data have allowed development of a dosing regimen for the planned Phase 2 studies in Duchenne muscular dystrophy and cystic fibrosis. Because PTC124 potentially has applicability across multiple genetic disorders, we also hope to use the information from the Phase 1 studies as the foundation for studying its safety and efficacy in other indications.

**15. Q. Have there been any side effects from PTC124 in the healthy volunteer studies?**

**A:** Patients receiving very high single doses of the drug (generally above those that are expected to be given for therapeutic purposes) have experienced transient effects of nausea (without vomiting) and headache. These effects were mild and disappeared rapidly (generally within minutes to hours). Further evaluation of the safety of the drug in patients receiving treatment for up to 14 days at doses up to 50 mg/kg twice-per-day also revealed that there were no symptomatic drug-related adverse events at any dose level. Minor, reversible laboratory changes were noted in some of the subjects.

**16. Q. When is PTC going to begin recruiting patients for the Phase 2 trials?**

**A:** Pending concurrence by the FDA with the plans for Phase 2 trials, we hope to begin patient accrual by the third quarter of 2005.

**17. Q. Where will the studies involving patients be conducted?**

**A:** Study centers will primarily be university hospitals selected for their expertise in performing specialized clinical trials in Duchenne muscular dystrophy or cystic fibrosis. Initial studies will be performed in the United States and may also be conducted internationally. In the US, the proposed sites for the Phase 2 Duchenne muscular dystrophy trial are the Children's Hospital of Philadelphia, Philadelphia, PA; Cincinnati Children's Hospital Medical Center, Cincinnati, OH; and, the University of Utah, Salt Lake City, UT. The proposed sites for the Phase 2 cystic fibrosis study are University of Alabama, Birmingham, AL; the Johns Hopkins Hospital, Baltimore, MD; Rainbow Babies' and Children's Hospital, Cleveland, OH; and Denver Children's Hospital, Denver, CO.

**18. Q. Will PTC cover the expenses of the travel and hotel fees involved with the clinical studies?**

**A:** PTC will be covering the expenses of the PTC124 medication and the testing that will be required as part of the study. In addition, the company will work with investigators, the recruiting sites, and other organizations to assist families in meeting the travel and housing expenses associated with study participation.

**19. Q. What are the entry criteria for the Phase 2 clinical trials in Duchenne muscular dystrophy?**

**A:** In general, patients must meet all of the following conditions to be eligible for enrollment to the Phase 2 Duchenne muscular dystrophy study:

- Diagnosis of Duchenne muscular dystrophy based on standard physical signs of the disease, increased serum creatine kinase (CK), and absence of dystrophin on a muscle biopsy.
- Presence of a nonsense mutation in the dystrophin gene as confirmed by the University of Utah, Salt Lake City, UT.
- Ability to ambulate.
- Male sex.
- Age  $\geq 5$  years.
- Normal liver and kidney function.
- If a sexually active patient, willingness to avoid impregnating a woman during the study drug administration and follow-up periods.
- No steroid therapy or stability of steroid therapy for  $\geq 3$  months.
- No systemic gentamicin treatment for  $\geq 3$  months prior to study treatment.
- Willingness to comply with study procedures.

- Ability and willingness to provide informed consent/assent.

Other, more specific entry criteria will also apply. Final patient eligibility must be determined by the treating physician at the study site. Until final approvals and regulatory authorizations are received, these criteria remain subject to review and possible revision.

**20. Q. What are the entry criteria for the Phase 2 clinical trials in cystic fibrosis?**

**A:** In general, patients must meet all of the following conditions to be eligible for enrollment to the Phase 2 cystic fibrosis study:

- Diagnosis of cystic fibrosis based on documented evidence of a conclusively abnormal sweat test.
- Abnormal chloride secretion as measured by nasal transepithelial potential difference (TEPD).
- Presence of a nonsense mutation in one of the alleles of the *cftr* gene as confirmed by Ambry Genetics, Costa Mesa, CA.
- Age  $\geq 18$  years.
- Body weight  $\geq 40$  kg.
- Adequate lung function (FEV1  $\geq 40\%$  of predicted and oxygen saturation  $\geq 92\%$  on room air).
- Normal liver and kidney function.
- Willingness to avoid pregnancy (if a women) or avoid impregnating a women (if a man) during the study drug administration and follow-up periods.
- No systemic gentamicin treatment for  $\geq 14$  days prior to study treatment.
- Willingness to comply with study procedures.
- Ability and willingness to provide informed consent.

Other, more specific entry criteria will also apply. Final patient eligibility must be determined by the treating physician at the study site. Until final approvals and regulatory authorizations are received, these criteria remain subject to review and possible revision.

**21. Q. What are the reasons for the entry criteria?**

**A.** The subject entry criteria are designed to limit enrollment to subjects who clearly have nonsense-mutation-mediated Duchenne muscular dystrophy or cystic fibrosis based on clinical, laboratory, and genetic findings but are sufficiently well (both in terms of the disease and in terms of concomitant illness) so as to be able to safely participate in study procedures and provide interpretable results. In Duchenne muscular dystrophy, study of children is important given the early onset of the disease in childhood. Study of ambulatory patients with Duchenne muscular dystrophy permits full evaluation of both dystrophin production and muscle function; later studies can potentially include patients who are nonambulatory. While not a risk for most subjects likely to be enrolled to this study, restriction on eligibility relating to reproductive potential in any subjects known to be sexually active is important because PTC124 is a new chemical entity and its effects on fertility have not been fully characterized.

Given that corticosteroids are commonly used in the treatment of Duchenne muscular dystrophy and are unlikely to confound the assessment of the primary outcome measure, enrollment of subjects receiving corticosteroids is permitted. Since alteration in serum CK levels or muscle function tests are known to occur over 1 to 2 months following changes in corticosteroid administration, it is mandatory that the doses and schedule of these medications be kept constant for  $\geq 3$  months prior to entry into the study in order to avoid misinterpretation of these study endpoints. While conventional supportive therapies will be permitted, efforts will be made to avoid use of concomitant medications (i.e., aminoglycosides) that might confound interpretation of study results.

**22. Q. How often, how long and at what doses will a patient need to take PTC124 in the Phase 2 trials?**

**A** Pending concurrence from the FDA, PTC124 will be administered over a total of 28 days. Patients will be treated daily at either a lower dose level (i.e., 4-, 4-, and 8-mg/kg) 3 times per day within 30 minutes after a meal at 6-, 6-, and 12-hour intervals (e.g., ~7:00 AM after breakfast, ~1:00 PM after lunch, and ~7:00 PM after dinner) or at a higher dose level (i.e., 10-, 10-, and 20-mg/kg) 3 times per day with food at the same 6-, 6-, and 12-hour intervals.

**23. Q. Why is the duration of the Phase 2 study limited to 28 days?**

**A.** Phase 2 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. Our goal with PTC124 in Phase 2 is to determine that the drug specifically allows for readthrough of nonsense mutations and leads to synthesis of full-length, active dystrophin (in Duchenne muscular dystrophy) or CFTR (in cystic fibrosis). The duration of the Phase 2 studies is based on knowledge that PTC124 was safe for at least 28 days in animals.

The Phase 2 studies form the basis for the development of Phase 3 trials, which focus on determining efficacy (also known as clinical benefit) and longer-term safety of a new drug. Prior to performing the Phase 3 studies, longer-term studies in animals will be necessary. It is anticipated that patients who show evidence of PTC124-mediated activity in Phase 2 are likely to be able to participate in the longer-term Phase 3 studies.

**24. Q. In what form will PTC124 be provided to patients?**

**A:** In the Phase 2 studies the drug powder will be mixed with water to form a milky, white suspension with a vanilla flavor. PTC124 will be 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.

**25. Q. Is PTC developing PTC124 on its own or does it have plans to form partnerships in the development of the drug (in the US, in Europe or Japan)?**

**A:** PTC is currently developing the drug on its own, with support and guidance from multiple investigators and patient advocacy groups. We may seek partnerships or assistance from other companies in the future.

**26. Q. What is the best way for patients and families to ensure that they will be able to participate in the Phase 2 studies?**

**A:** Patients and families may wish to discuss the potential for study participation with the physician primarily involved in the patient's care for Duchenne muscular dystrophy or cystic fibrosis. We at PTC are happy to answer any specific questions, but also recommend that patients work closely with their treating physician and genetic counselor, as well as communicating with patient advocacy groups. Please find in the appendix section a list of resources (please also see Question 12).

**27. Q. Is there someone at PTC I can contact for additional information?**

**A:** You can contact Ms. Kerri Donnelly, Senior Associate, Corporate Development, at PTC Therapeutics (kdonnelly@ptcbio.com; 908-222-7000, x112).

### **A FEW IMPORTANT RESOURCES FOR PATIENTS AND FAMILIES:**

**Food and Drug Administration (FDA)** - [www.fda.gov](http://www.fda.gov)

**Clinical Trials** website sponsored and maintained by the FDA - [www.clinicaltrials.gov](http://www.clinicaltrials.gov)

**Muscular Dystrophy Association** - [www.mda.org](http://www.mda.org)

**Parent Project Muscular Dystrophy (PPMD)** - [www.parentprojectmd.org](http://www.parentprojectmd.org)

**AFM** (French Association against Muscular Disorders) - [www.afm-france.org](http://www.afm-france.org)

**Cystic Fibrosis Foundation (CFF)** - [www.cff.org](http://www.cff.org)

**Vaincre La Mucoviscidose** (French Cystic Fibrosis Association) - [www.vaincrelamuco.org](http://www.vaincrelamuco.org)

**National Organization for Rare Disorders (NORD)** - [www.rarediseases.org](http://www.rarediseases.org)

**European Organization for Rare Disorders (EURORDIS)** - [www.eurordis.org](http://www.eurordis.org)