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 that 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 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 will initiate the first patient

studies in children and young adults with Duchenne muscular dystrophy and cystic fibrosis, and 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) and by Ambry Genetics (http://www.ambrygen.com) to confirm the diagnosis of a nonsense mutation.

12. 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 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.

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

A: Some healthy volunteers receiving very high single doses of the drug (150 or 200 mg/kg) that are above those that are expected to be given for therapeutic purposes have 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 that there were no symptomatic drug-related adverse events at any dose level. Minor, reversible laboratory changes were noted in some of the subjects.

14. Q. Where will the studies involving patients be conducted?

A: The study centers are primarily 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 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. A Phase 2 cystic fibrosis study is also being conducted in Israel, at the Hadassah Medical Center, Jerusalem.

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.

Contact information regarding these sites can be obtained through PTC (please see answer to Question 26).

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

A: For the Phase 2 studies in cystic fibrosis, the University of Alabama at Birmingham is currently recruiting patients. We expect additional sites to start recruitment in the next few weeks, pending approval by the appropriate review committees in each potential clinical site.

Additional details can be found on www.clinicaltrials.gov and you can continue to monitor this website for updated information on initiation of recruitment in new study sites.

For the Phase 2 studies in Duchenne muscular dystrophy, the study protocol and other required documents have been submitted to the review committees at each potential clinical trial site. We are currently waiting for review of these documents and obtaining approvals for initiation of the study. Once sites are ready to start patient recruitment, information will be posted on www.clinicaltrials.gov. We estimate that sites will be ready to start enrollment for the Phase 2 study in Duchenne muscular dystrophy within October/November of 2005.

16. **Q. What are the goals of the Phase 2 studies in Duchenne muscular dystrophy and cystic fibrosis?**
A: The main 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 CFTR (in cystic fibrosis) or dystrophin (in Duchenne muscular dystrophy).

17. **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.

18. **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 ≥18 years.
- Body weight ≥40 kg.
- Adequate lung function (FEV1 ≥40% of predicted and oxygen saturation ≥ 92% on room air).
- Normal liver and kidney function.
- Willingness to avoid pregnancy (if a woman) or avoid impregnating a woman (if a man) during the study drug administration and follow-up periods.
- No systemic gentamicin treatment for ≥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.

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 ≥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 ≥3 months.
- No systemic gentamicin treatment for ≥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 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 cystic fibrosis, enrollment of patients who are ≥18 years of age may help to optimize compliance with study procedures like TEPD. Dornase alfa and inhaled tobramycin are permitted in the study given their established place in CF supportive care. Pregnancy testing in female patients and restrictions on eligibility relating to reproductive potential, pregnancy, and lactation are important because PTC124 is a new chemical entity and its effects on

fertility, pregnancy, and breastfeeding will not be fully known. While conventional supportive therapies will be permitted, efforts will be made to avoid use of concomitant medications that might confound interpretation of study results. In particular, if medically appropriate, investigators may substitute other antibiotics for aminoglycosides in patients who require treatment for CF exacerbations.

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 reproduction 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 ≥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.

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

A. PTC124 will be administered over a total of 28 days. Patients will be treated 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.

22. 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. 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.

23. 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.

24. **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 cystic fibrosis or Duchenne muscular dystrophy as well as with investigators at the study sites (please see Question 26). 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 also see Questions 10, 11, 14, and 15.

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. Is there someone at PTC I can contact for additional information?**
A: Please 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:

FDA Clinical Trials Website - www.clinicaltrials.gov

Muscular Dystrophy Association - www.mda.org

Parent Project Muscular Dystrophy (PPMD) - www.parentprojectmd.org

AFM (French Association against Muscular Disorders) - www.afm-france.org

Cystic Fibrosis Foundation (CFF) - www.cff.org

Vaincre La Mucoviscidose (French Cystic Fibrosis Association) - www.vaincrelamuco.org

National Organization for Rare Disorders (NORD) - www.rarediseases.org

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