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

**A:** Nonsense mutations are a type of mutation that causes genetic disorders by affecting the amount of the protein produced in the body. 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 cystic fibrosis, muscular dystrophy, 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 offers a unique approach to the treatment of genetic disorders, coupling testing for a specific type of genetic defect with a small molecule drug that has the potential to safely correct the disease manifestations associated with that genetic defect. By providing a definitive therapy, 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 cystic fibrosis and Duchenne muscular dystrophy, 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. 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. This specificity has also been demonstrated in preclinical toxicology studies in animals; dose levels of PTC124 that are substantially higher than those required to induce premature stop codon read-through have been well tolerated in animals, with no evidence of adverse events that appear to be attributable to read-through of normal stop codons.

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 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 well tolerated in animal pharmacological and toxicology testing.

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 specialty laboratory, sometimes at a university hospital that has special expertise in studying patients with a particular disease. For patients with cystic fibrosis, full-length gene sequencing is available through Ambry Genetics.
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).

11. Q. How will PTC Therapeutics identify patients with nonsense mutations?
   A: For the clinical trials in cystic fibrosis and Duchenne muscular dystrophy, PTC Therapeutics will employ the tests offered by Ambry Genetics (http://www.ambrygen.com) and by the University of Utah (http://www.genome.utah.edu/DMD/clinical_test.shtml) to confirm the diagnosis of a nonsense mutation.

12. Q: What are the next steps for PTC124?
   A: We are currently enrolling healthy volunteer subjects to Phase 1 clinical trials. Phase 2 trials in cystic fibrosis and Duchenne muscular dystrophy are planned to begin in the first half of 2005.

13. Q. Why are Phase 1 trials being conducted in healthy volunteers?
   A: The Phase 1 trials are being conducted in healthy volunteers to rapidly characterize the general safety and oral absorption of PTC124. Because PTC124 potentially has applicability across multiple genetic disorders, we hope to use the information from the Phase 1 studies as the foundation for studying its safety and efficacy in cystic fibrosis, Duchenne muscular dystrophy, and other indications.

   Rapid evaluation of the safety, pharmacokinetics, palatability, and affects of food on drug absorption in healthy volunteers also permits us to design more definitive Phase 2 studies evaluating the activity of the drug in patients.

14. Q. Where are the Phase 1 studies being conducted?
   A: The Phase 1 studies are being performed at SFBC International in Miami, Florida. SFBC has a specialized clinical trials unit that has long experience in the conduct of Phase 1 clinical studies.

15. Q. Where will the Phase 2 and 3 studies be conducted?
   A: While final site selection for the Phase 2 and 3 studies has not been performed, Phase 2/3 study centers will primarily be university hospitals selected for their expertise in performing specialized clinical trials in cystic fibrosis or Duchenne muscular dystrophy. Initial studies will be performed in the United States and may also be conducted internationally.

16. Q. What types of patients will be eligible for the clinical trials in cystic fibrosis and Duchenne muscular dystrophy?
   A: In general, patients will be children and young adults with clear evidence of disease based on appropriate clinical, laboratory, and genetic tests. Genetic testing will be required to confirm that the patient has the disease because of a nonsense mutation. It will be important that patients are able to take PTC124 during the required periods and that certain type of medications (primarily gentamicin-like
drugs) be avoided during the study. Patients will need to be capable of participating in the testing procedures required to determine whether PTC124 is working. Patients must also be able to undergo blood tests for pharmacokinetics and for safety and must be able to describe whether they are having any side effects that might be related to study medication. Specific eligibility details will be finalized working in conjunction with clinical investigators, regulatory authorities, and patients and parents.

17. Q. How often will a patient need to take PTC124 in the clinical trials?
   A: The frequency of drug administration required to maintain active drug concentrations circulating in the bloodstream will be determined from the pharmacokinetic data acquired in the Phase 1 studies. From these data, it will be possible to determine if it is best to give the drug once, twice, or three times per day. Data from the healthy volunteer study program will also provide information regarding how food may alter the absorption of the drug, so that the best timing of drug administration relative to meals can be understood.

18. Q. What doses of PTC124 will patients get?
   A: Information derived from the Phase 1, healthy-volunteer studies will help guide us in selecting doses that are appropriate for the Phase 2 studies in patients. However, further evaluation of the dose range may be important in patients and therefore it is likely that a range of doses will be tested in the Phase 2 trials. An attempt will be made to ensure that each participating patient receives doses high enough to safely provide the chance to demonstrate activity in reading through the nonsense mutation.

19. Q. How long will patients need to take PTC124?
   A: In the Phase 2 trials, intermittent treatment with PTC124 is planned over several months. In the Phase 3 studies, continuous therapy with PTC124 for at least six months is being considered. The final duration of therapy will be worked out in conjunction with the regulatory authorities.

20. Q. In what form will PTC124 be provided to patients?
   A: In the Phase 1 studies in health volunteers, the drug powder is mixed with water to form a milky, white suspension. The healthy volunteers are being asked to describe the taste of the drug on a specific questionnaire, so that it will be possible to understand whether there are taste characteristics that we would want to change in order to make the drug as palatable as possible for children participating in Phase 2 and 3 trials. It is possible that PTC124 for these later studies will be provided as a powder in a sachet (like a sugar packet) that will be suspended with water or juice and, as in the Phase 1 formulation, 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.
21. 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. However, we may seek partnerships or assistance from other companies and from patient advocacy organizations.

22. Q.  Is there someone I can contact for additional information?
   A: You can send additional inquiries to Ms. Kerri Donnelly, Senior Associate, Corporate Development at PTC Therapeutics (kdonnelly@ptcbio.com) 908-222-7000, x112.