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FIRST-EVER TREATMENT FOR RARE CHILDHOOD AGING DISEASE SHOWS IMPROVEMENT IN ALL TRIAL PARTICIPANTS

Drug Originally Developed for Cancer Proves Effective for Children with Progeria

BOSTON, MA (September 24, 2012) – Results of the first-ever clinical drug trial for children with Progeria, a rare, fatal "rapid-aging" disease, demonstrate the efficacy of a farnesyltransferase inhibitor (FTI), a drug originally developed to treat cancer. The clinical trial results, completed only six years after scientists identified the cause of Progeria, included significant improvements in weight gain, bone structure and, most importantly, the cardiovascular system, according to The Progeria Research Foundation (PRF) and Boston Children's Hospital. The study results were published today in *Proceedings of the National Academy of Sciences* (Epub ahead of print).

Progeria, also known as Hutchinson-Gilford Progeria Syndrome (HGPS), is a rare, fatal genetic disease characterized by an appearance of accelerated aging in children. All children with Progeria die of the same heart disease that affects millions of normal aging adults (atherosclerosis), but instead of occurring at 60 or 70 years of age, these children may suffer heart attacks and strokes as early as age 5 years, with the average age of death at 13 years.

"To discover that some aspects of damage to the blood vessels in Progeria can not only be slowed by the FTI called lonafarnib, but even partially reversed within just 2.5 years of treatment is a tremendous breakthrough, because cardiovascular disease is the ultimate cause of death in children with Progeria," said Leslie Gordon, M.D., Ph.D., lead author of the study, medical director for PRF, and mother of a child with Progeria. In addition, Dr. Gordon is a staff scientist at Boston Children's Hospital and Harvard Medical School, and associate professor at Hasbro Children's Hospital and Alpert Medical School of Brown University.

Results Yield Improvements in One or More Study Measures for All Children

Twenty-eight children from sixteen countries participated in the two-and-a-half year drug trial, representing 75 percent of known Progeria cases worldwide at the time the trial began. Of those, 26 are children with the classic form of Progeria. The children traveled to Boston every four months to receive comprehensive medical testing through Boston Children's Hospital's Clinical and Translational Study Unit.

Treatment consisted of the FTI lonafarnib, supplied by Merck & Co., given to children orally, twice-a-day over the course of the study, under the supervision of principal investigator Mark Kieran, M.D., Ph.D., director of pediatric medical neuro-oncology at the Dana-Farber/Children's Hospital Cancer Center.

The research team, which included specialists at Boston Children's Hospital, Brigham & Women's Hospital and Dana-Farber Cancer Institute, evaluated the children's rate of weight gain compared to their pre-

therapy rate as the primary outcome because children with Progeria experience severe failure to thrive, and have a consistent, very slow linear rate of weight gain over time. Researchers also examined arterial stiffness (a predictor of heart attack and stroke in the general population), bone density and rigidity (indicators of osteoporosis). Every child completing the study showed improvement in an ability to gain additional weight, increased flexibility of blood vessels or improved bone structure.

Results included improvement in one or more of the following areas:

- **Weight:** One in three children demonstrated a greater than 50 percent increase in annual rate of weight gain or switched from weight loss to weight gain, due to increased muscle and bone mass.
- **Bone Structure:** On average, skeletal rigidity (which was highly abnormal at trial initiation) improved to normal levels after FTI treatment.
- **Cardiovascular:** Arterial stiffness, strongly associated with atherosclerosis in the general aging population, decreased by 35 percent. Vessel wall density also improved with treatment.

Following the 2003 discovery of the gene that causes Progeria, researchers identified FTIs as a potential drug treatment for Progeria. Children with Progeria have a genetic mutation that leads to the production of the protein progerin, which is responsible for Progeria. Progerin blocks normal cell function and part of its toxic effect on the body is caused by a molecule called a "farnesyl group," which attaches to the progerin protein. FTIs act by blocking the attachment of the farnesyl group onto progerin.

"In the early stages of planning for this clinical trial, we realized that my team's experience using FTIs to treat children with brain cancer could bring together PRF's preclinical research efforts and the expertise we needed to study the drug in children with Progeria," said Kieran, the study's senior author and associate professor of Pediatrics at Harvard Medical School. "The premise behind studying this drug was that by stopping the attachment of the farnesyl group onto progerin in children with Progeria, progerin may be inactivated, reducing some effects of the disease."

"PRF provides a model for disease research organizations, and is a good example of successful translational research, moving from gene discovery to clinical treatment at an unprecedented pace," added Dr. Kieran.

Since PRF's founding in 1999, the organization and its scientific partners have identified the genetic mutation that causes the disease, funded preclinical research and funded clinical trials. A second clinical trial, funded by the National Institutes of Health and PRF, is currently underway and more trials are expected to follow.

"The partnership between The Progeria Research Foundation, the research team and these courageous families was essential for success," said Dr. Gordon. "It required identifying children and their home doctors from around the globe, obtaining the essential pre-trial clinical information, transporting families to and from Boston, supplying translators both inside and outside of the hospital setting, and putting together a multidisciplinary clinical team to assess treatment effects. But it was all worth it, and I believe we have set in motion a blueprint for successful treatment trials for children with Progeria and for other rare diseases."

"The results of this study provide our family with excitement and hope for Megan's future," said Sandy Nighbor, mother of Megan, a 12-year-old child who participated in the clinical trial. "We're grateful to The Progeria Research Foundation and all of the doctors for their commitment to helping my daughter and all children with Progeria."

Progeria Linked to Normal Aging Process

Previous research shows that progerin is also produced in the general population and increases in the body with age. A number of studies successfully linked progerin with normal aging, including a causal link between progerin and genetic instability, specifically telomere dysfunction in the aging process. Researchers plan to continue researching the effect of FTIs, which may help scientists learn more about cardiovascular disease that affects millions, as well as the normal aging process.

"One of the main reasons we achieved breakthrough results in this first trial is because of the tremendous supporters who provided funding, and helped get us one step closer to achieving our ultimate goal – a cure for Progeria," said Audrey Gordon, Executive Director of PRF. "Every donation makes a difference. With continued support, we will fund research that will not only allow children with Progeria around the world to live long and healthy lives, but may also advance our understanding of the normal aging process that affects us all."

About The Progeria Research Foundation (PRF)

The Progeria Research Foundation (PRF) was established in 1999 to find the cause, treatment and cure for Progeria – a rapid aging disease that causes children to die from heart disease or stroke at an average age of 13 years. In the past 13 years, research conducted in partnership with PRF has identified the gene that causes Progeria and possible treatments. PRF funded and coordinated this first-ever Progeria clinical trial. PRF is currently funding a clinical trial in which children with Progeria receive FTI plus two additional medications to slow the progression of Progeria. PRF continues to identify more children who can benefit from the programs and services that it provides while helping advance research towards treatment and cure. To learn more about Progeria and what you can do to help, please visit www.progeriaresearch.org.

About Boston Children's Hospital

Boston Children's Hospital is home to the world's largest research enterprise based at a pediatric medical center, where its discoveries have benefited both children and adults since 1869. More than 1,100 scientists, including nine members of the National Academy of Sciences, 11 members of the Institute of Medicine and nine members of the Howard Hughes Medical Institute comprise Boston Children's research community. Founded as a 20-bed hospital for children, Boston Children's today is a 395 bed comprehensive center for pediatric and adolescent health care grounded in the values of excellence in patient care and sensitivity to the complex needs and diversity of children and families. Boston Children's also is the primary pediatric teaching affiliate of Harvard Medical School. For more information about research and clinical innovation at Boston Children's, visit: http://vectorblog.org/.

About the Dana-Farber/Children's Hospital Cancer Center

Dana-Farber/Children's Hospital Cancer Center (DF/CHCC) combines the strengths of Dana-Farber Cancer Institute, a world-class cancer institute, and Boston Children's Hospital, an internationally known pediatric hospital. For over 60 years, these two Harvard Medical School affiliates have provided comprehensive care for children and adolescents with cancer. Committed to conducting research to better understand and treat childhood cancers, DF/CHCC is the Pediatric Oncology Experimental Therapeutics Investigator Consortium's (POETIC) only Phase I Clinical Trial site in New England, and is home to one of the world's most sophisticated and accomplished Pediatric Stem Cell Transplantation centers. DF/CHCC also offers comprehensive transitional and long-term survivorship programs to childhood cancer survivors of all ages.

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