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GSK, Fondazione Telethon and Ospedale San Raffaele announce EU regulatory submission for gene therapy to treat rare disease ADA-SCID

GSK, Fondazione Telethon (Telethon) and Ospedale San Raffaele (OSR) today announced the submission of a marketing application to the European Medicines Agency (EMA) for a gene therapy (GSK2696273) to treat patients with a rare disease, adenosine deaminase severe combined immunodeficiency syndrome (ADA-SCID), for whom no suitable human leukocyte antigen (HLA)-matched related stem cell donor is available.

ADA-SCID is an ultra rare disease in which patients cannot make lymphocytes (a type of white blood cell) and, as a result, have a severely deficient immune system. An estimated 14 children in Europe are born each year with the condition. A faulty gene inherited from both parents stops production of an essential protein called adenosine deaminase (ADA), which is particularly important for the formation of lymphocytes and a functioning immune system. Children born with ADA-SCID have an impaired ability to fight off everyday infections resulting in severe and life-threatening illness. They rarely survive beyond 1-2 years unless immune function is restored.

Patients with ADA-SCID initially take antibiotics and antifungal treatments to help protect themselves from serious infections, but most require a bone marrow transplant from a matched donor. However, the effectiveness of these transplants is highly dependent upon how close the match is between donor and patient. If no suitable donors are available, gene therapy, if approved, will provide another option.

Treatment with the investigational gene therapy begins with removal of cells from a patient's bone marrow. Haematopoietic progenitor and stem cells are then purified from the bone marrow and over the course of a few days a modified virus, or vector, is used to insert one or more functional copies of the ADA gene into a proportion of those cells. When the gene-corrected cells are reintroduced to the patient and successful engraftment has taken place, the cells begin producing the ADA protein, thus restoring the patient's ability to make lymphocytes which can then fight off infections. Using the patient's own cells avoids the risk of immune-incompatibility, which is a common and life threatening complication associated with bone marrow transplant.

GSK2696273 is an investigational gene therapy which is not approved for use anywhere in the world.

The European Marketing Application is based on results from 18 children treated with the investigational gene therapy, twelve of whom were enrolled in a pivotal clinical trial conducted at San Raffaele Telethon Institute for Gene Therapy (TIGET). The first child was treated over thirteen years ago and all patients are alive today. Three of the eighteen patients required either long term (>3 month) enzyme replacement therapy or follow up bone marrow transplant. No significant tolerability events considered related to the gene therapy or leukemic events have been reported to date. Plans to publish data supporting the regulatory filing in a scientific peer-reviewed journal are in progress.



The marketing application follows on from a strategic alliance formed in 2010 between GSK, OSR and Telethon. The alliance takes forward over 15 years of research performed at TIGET – one of the pioneers that successfully brought *ex vivo* gene therapy from pre-clinical studies to the treatment of patients. Since in-licensing the ADA-SCID gene therapy development programme in 2010, GSK – working with the biotechnology company MolMed S.p.A - optimised, characterised and validated both the vector and cell manufacturing methods. GSK also led regulatory plans, with support from TIGET investigators, to develop a marketing application by following standards described in the European Union for Advanced Therapy Medicinal Products. If approved, the gene therapy will first be made available at OSR in Milan, Italy with GSK as the marketing authorisation holder.

ADA-SCID is the lead programme under the GSK/OSR/Telethon collaboration. Under the terms of the agreement, GSK has exclusive options to develop six further applications of *ex vivo* stem cell therapy, using the gene transfer technology developed by TIGET scientists. GSK has already exercised its option to develop two further programmes in rare diseases called metachromatic leukodystrophy (MLD) and Wiskott-Aldrich syndrome (WAS), which are both currently in clinical trials.

Comments from collaborators:

Patrick Vallance, President of Pharmaceuticals R&D at GSK, said: “I am very pleased that we are now at a stage to file for approval of this gene therapy for ADA-SCID – a devastating rare disease which drastically limits and shortens patients’ lives. Development of this therapy would not have been possible without the immense support of the ADA-SCID patients’ families and the work of so many pioneering scientists who have worked in this cutting edge area of medicine for decades. We are privileged to take forward this submission.

“We believe this marks a significant milestone, showing the potential of gene therapy as an important additional modality for tackling the underlying cause of serious diseases.”

Francesca Pasinelli, General Manager at Fondazione Telethon, said: “The alliance with GSK was key to our strategy to bring all the relevant actors together to produce viable therapies for rare genetic diseases. We are now moving from the breakthrough results of gene therapy developed at TIGET to, if approved, bringing available treatments for ADA-SCID patients in need. This is an important step toward the fulfilment of that vision and our promise to charitable donors supporting our work.”

Nicola Bedin, CEO of San Raffaele Research Hospital, said: “We are very satisfied with this extraordinary result gained thanks to the effective and innovative cooperation between three first-class institutes. San Raffaele research hospital pioneered investing in gene therapy and we are proud of the scientific results we have obtained. Once again, the union of basic research, clinical research and medical practice, which is the characteristic feature of San Raffaele’s organisational model, proves successful. We hope that this gene therapy will be approved and made available as soon as possible so that people can benefit from it”.

Alessandro Aiuti, Clinical Research Coordinator at TIGET, said: “This is an important landmark for clinicians, researchers and all the staff at TIGET who have been working side by side with GSK towards approval of this gene therapy. In the past years we have witnessed how a single infusion of gene modified stem cells has changed the lives of these children and their families. If authorised, we will be ready to offer gene therapy at our center to ADA-SCID patients in need from Europe and other countries.”

Notes to editors:

About ADA-SCID

ADA-SCID, one form of Severe Combined Immune Deficiency (SCID), is an autosomal recessive inherited disorder whereby affected children inherit two mutated genes, one from each parent. ADA-SCID is usually diagnosed within six months of birth due to recurrent infections and failure to thrive.

Bone marrow transplant from a matched related donor is currently the best treatment option. However, the majority of patients (approximately 70-80%) do not have access to a matched related donor so they receive bone marrow cells from unrelated donors. Survival rates for ADA-SCID patients receiving bone marrow from unrelated donors is <70% and this is the group of patients for whom it is proposed gene therapy should be used. New Born Screening (NBC) programmes are increasingly being implemented following the recognition that early diagnosis and treatment leads to markedly improved outcomes for patients.

About the gene therapy (GSK2696273)

Replacing faulty stem cells has been practised for more than 40 years, in the form of donor haematopoietic stem cell (HSC) transplants (bone marrow transplants). However, such transplants rely on stem cells taken from an immune matched, or closely related, donor. As immune (or HLA) matching is never perfect, immune incompatibility can cause rejection and graft versus host diseases, is a common life threatening side effect that requires management with potent immunosuppressant medicines which in themselves increase the risk of infection.

GSK2696273 is an autologous *ex vivo* stem cell gene therapy. Treatment with autologous cell gene therapy means that the cell donor and recipient is the same person. The HSCs of the patient (typically children) are harvested from the bone marrow in a hospital setting and then taken to a cell processing facility where they undergo a tightly controlled manufacturing process. Under this laboratory setting (“*ex-vivo*”), a retrovirus (based upon the Moloney Murine Leukaemia Virus MoMLV) is used to enter cells and insert the corrected gene. This step is known as transduction. The gene-corrected cells are then re-introduced to the patient via an intravenous infusion. This procedure takes about 1 week. In order to improve the engraftment of the gene-modified cells in the patient’s bone marrow, patients are also pre-treated with low dose busulfan (a chemotherapy). Recovery from busulfan can take 2 months, during which time the patient remains in hospital.

About Clinical Results

A total of 18 children (median age 1.7 years) have been treated with the gene therapy in two pilot studies (n=3), a pivotal phase I/II clinical study (n=12) and a named patient, early access program (n=3).

Results from the pivotal study in 12 children demonstrated the efficacy of GSK2696273. A 100% survival rate was observed for all children after an average of 7 year follow-up (the longest follow-up in the first treated patient was 11.5 years). Intervention-free survival in this pivotal population (defined as survival without the need for long-term (>3 month) re-introduction of enzyme replacement therapy, or bone marrow transplant) was 92%.

Results from an integrated analysis of all 18 children supported the safety profile of GSK2696273. As expected for this disease, all children reported infection adverse events. The three most frequent being upper respiratory tract infection, gastroenteritis, and rhinitis. Anaemia and neutropenia were reported with the highest incidence shortly after gene therapy and are, therefore, thought to be related to busulfan conditioning (chemotherapy). Throughout follow-up, events that may be related to immune reconstitution (autoimmunity and atopy) were reported. No significant tolerability events considered related to GSK2696273 or leukemic events have been reported to date.

Interim results were presented by MP Cicalese and colleagues at the European Society for Immunodeficiencies (ESID) meeting in November 2014.

GSK – one of the world’s leading research-based pharmaceutical and healthcare companies – is committed to improving the quality of human life by enabling people to do more, feel better and live longer. For further information please visit www.gsk.com.

Fondazione Telethon – is a major biomedical charity in Italy, whose mission is to advance biomedical research towards the cure of rare genetic diseases. For further information please visit www.telethon.it/en/about-us.



San Raffaele -Telethon Institute for Gene Therapy (TIGET)

Settled in Milan, Italy, the San Raffaele-Telethon Institute for Gene Therapy (TIGET) is a joint venture between the San Raffaele Hospital and Scientific Institute and the Telethon Foundation established in 1995 to perform research on gene transfer and cell transplantation and translate its results into clinical applications of gene and cell therapies for different genetic diseases. For more information, please visit the Institute website, <http://www.tiget.it/>.

Ospedale San Raffale - Since 2012 San Raffaele University and research Hospital is part of San Donato Hospital Group, which is with 18 hospitals, 5000 beds, 4000 physicians and 4 million patients per year, the leading hospital group in Italy. We are a private provider of an essential public service. For further information please visit: www.grupposandonato.it

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Cautionary statement regarding forward-looking statements

GSK cautions investors that any forward-looking statements or projections made by GSK, including those made in this announcement, are subject to risks and uncertainties that may cause actual results to differ materially from those projected. Such factors include, but are not limited to, those described under Item 3.D 'Risk factors' in the company's Annual Report on Form 20-F for 2014.

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