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Oral Presentations

OR01

Safety and clinical benefit of lentiviral haematopoietic stem and progenitor cell gene therapy in 23 patients with Wiskott-Aldrich Syndrome with up to 10.5 years of follow-up

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Allogeneic haematopoietic stem cell transplantation (HSCT) can be curative for Wiskott-Aldrich Syndrome (WAS). However, despite outcome improvements, HSCT is still limited by donor availability and higher risk of complications in older subjects. Gene therapy (GT) is being studied as an alternative treatment. Between 2010 and 2020, 23 WAS patients were treated with OTL-103, as part of phase I/II (n = 8) or III (n = 6) clinical trials or Expanded Access Program (EAP) (n = 9), at a median age of 3.1 years (range: 1.0-35.1). OTL-103 is an investigational autologous haematopoietic stem and progenitor cell (HSPC) GT composed of $CD34^+$ HSPCs transduced *ex vivo* with a self-inactivating lentiviral vector encoding human *WAS* cDNA under endogenous promoter control. Seventeen subjects received fresh OTL-103, while six received its cryopreserved formulation. Before OTL-103, subjects received rituximab and reduced-intensity conditioning. At data cut, median follow-up was 3.6 years (range: 0.4-10.5). All were alive, except one EAP subject who died early post-GT due to pre-existing neurological condition deterioration. To date, no signs of insertional mutagenesis or GT-related adverse events have been observed. Efficacy analysis performed in trials' subjects confirmed sustained engraftment of gene-corrected cells, leading to substantial increase of WASP expression in lymphocytes and platelets. This resulted in ameliorated T-cell functionality and platelet count, with marked reduction of severe infections and moderate/severe bleedings. Antimicrobial and bleeding prophylaxis was stopped. Eczema improved and clinical autoimmunity resolved. Our data suggest that lentiviral GT is well tolerated and leads to sustained clinical benefit, underlying its potential as an alternative therapeutic option for WAS.

OR02

Experience of genome editing patient haematopoietic stem cells to treat X-linked Agammaglobulinemia

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CRISPR/Cas technology has improved in recent years and human trials of this technology have been reported in cell-based cancer therapies and monogenic disorders. For patients with

Advanced Therapy Medicinal Products (ATMPs) is a European classification of medicinal products based on genes, cells and tissues that have been specifically regulated in the European Union (EU) from 2007. Their manufacturing (i.e. their production) raises specific challenges for ensuring quality and complying with regulatory requirements in order to obtain manufacturing and marketing authorizations. For this reason, detailed guidelines on Good Manufacturing Practices specific to ATMPs have been adopted by the European Commission, and have been enforceable since 2017. They are distinct from other guidelines on GMP applicable to other kinds of biological medicinal products. Separate GMP guidelines, covering manufacture of biological active substances and medicinal products for human use including biological active substances were revised in June 2018 with the objective of preventing overlaps in scope with the ATMP GMP guidelines. Our hypothesis is that the biological nature that commonly characterizes ATMPs and biologicals may give rise to significant similarities in the manufacturing aspects as addressed by the respective guidelines. Through a comparative textual analysis of the GMP guidelines for biological medicinal products and ATMPs, this poster will highlight the key areas of similarities and differences. This analysis reveals why we have two different texts and whether they are based on substantial differences regarding production between ATMPs and other types of biological medicinal products.

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Specific guidelines requirements for clinical trials with Advanced Therapy Medicinal Products in the European Union

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Advanced Therapy Medicinal Products (ATMPs), a European legal classification of medicinal products based on genes, cells and tissues, raise specific issues in the context of clinical trials. In comparison to more traditional medicinal products, ATMPs have been subject to specific regulatory provisions in the European Union (EU) since Regulation (EC) n°1394/2007. Yet for the clinical trials with ATMPs, the general regime laid out in Regulation 536/2014 on clinical trials (which came into effect on 31 January 2022) applies, together with the ICH E6 Guidelines on Good Clinical Practice (GCP). For clinical trials conducted in the EU, compliance with GCP is mandatory. The European Commission has also adopted and published 2019 Guidelines on GCP specific to ATMPs, as required by Article 4 of Regulation (EC) n°1394/2007 on ATMPs. These guidelines both adapt the ICH guidelines to ATMPs' characteristics and provide additional measures that have been considered necessary. However, they are not exhaustive as they explain only some specificities of ATMPs and they remain complementary to the general rules. After having analysed these documents, we will highlight the specificity of requirements for investigational ATMPs in order to reveal the specific challenges they are addressing and why these challenges warrant separate regulation in order to obtain clinical trials' authorisation for investigational ATMPs.

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Pre-clinical safety evaluation for mRNA-vaccine development in mouse model

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Messenger RNA (mRNA) vaccine has emerged as an attractive agent for prevention of infectious disease and anti-cancer therapy. However, there is a fatal risk that the safety evaluation for mRNA vaccine have not been fully studied yet. In this study, we evaluated the safety of four type of COVID-19 S-protein targeting mRNA vaccines with different compositions (C2/LNP90, C2LNP128, C3LNP90 and C3LNP128). Theses vaccines were intramuscularly injected to 6-wk old male and female ICR mice with twice at an interval of 2 wks. The necropsy was carried out on 2 days or 14 days after secondary injection. The results showed that the body weight was decreased for 2days after the first injection in C2/LNP128 and C3/LNP128-injected mice, but it was almost recovered at 7day post injection (dpi). At 2 dpi after secondary injection, the endpoint blood analysis of demonstrated that C2/LNP128 and C3/LNP128 decreased the number of lymphocytes, monocytes and reticulocytes carrying the abnormal level of liver function indicator such as albumin, AST, ALT and total protein. Additionally, C2/LNP128 decreased the number of platelet and C3LNP128 decreased the number of red blood cells, respectably. Spleen and inguinal lymph node were enlarged in all experimental group. Notably, C2/LNP128 and C3/LNP128 induced severe edema in injection site, femoris muscle. At 14 dpi after secondary injection, the toxicity that was observed at 2 dpi after secondary injection was recovered. These results suggest that the potential side effects of mRNA vaccines must be systematically evaluated with multiple aspect of toxicology.

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Optimisation of lentiviral vectors for gene therapy of pulmonary fibrosis

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