LUMC

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your reference
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Geachte mevrouw/meneer,

In 2009 hebben wij vergunning gekregen om een gentherapie studie uit te voeren met genetisch gemodificeerde *Lactococcus lactis*. Tot op heden hebben wij geen patiënten in deze studie geincludeerd en het is ook niet meer te voorzien dat er patiënten geincludeerd zullen worden. Dat is ook de reden waarom het formulier "Beschrijving van voorgenomen werkzaamheden" niet is ingestuurd. Omdat wij vanuit de beschikking verplicht zijn om een jaarverslag in te dienen sturen wij u dit hierbij toe.

Ik hoop u hiermee voldoende te hebben geïnformeerd.

Met vriendelijke groet,

G. van Willigen PhD
Environmentalsafety Officer

Attachments: Report performed activities 2009

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Report performed activities

1. General information
   1.1. Permit number IM 08-004
   1.2. 2009

2. Description of activities
   2.1. This phase 2A trial is to evaluate the safety, tolerability, pharmocodynamics and efficacy of AG011, a human IL-10 producing Lactococcus lactis in subjects with moderately active ulcerative colitis. This Phase 2a clinical trial constitutes the next step of a global clinical development program, intended to lead to a new therapeutic strategy for the treatment of IBD.

   2.2. Crohn's disease (CD) and ulcerative colitis (UC) are the two major forms of IBD. Their exact aetiology is not fully understood. CD can affect any part of the gastrointestinal (GI) tract from mouth to anus.
   While there is no known medical or surgical cure for CD, UC can be cured by surgical removal of the entire colon. Standard care for IBD are a number of medical treatments aimed at inducing and maintaining clinical remission. Administration of recombinant hIL-10 is one such possible treatment.
   The main biological functions of hIL-10 include limiting and terminating inflammatory responses and regulating the proliferation of several immune cells. It has been proposed that hIL-10 plays a key role in modulating the immune response.
   Recombinant hIL-10 has been produced and tested in clinical trials for different indications, including rheumatoid arthritis, IBD, psoriasis, organ transplantation, and chronic hepatitis C.
   Systemic hIL-10 treatment of CD and UC patients is not very effective in inducing clinical remission and can be associated with considerable side effects. These side effects are partly due to the fact that high systemic hIL-10 concentrations induce the proinflammatory cytokine interferon-gamma (IFN-gamma).
   The concept of rebalancing the intestinal immune response with hIL-10 remains very compelling. Studies in experimental models have already shown that topical treatment with hIL-10 is highly effective in either preventing or improving disease.
   ActoGeniX is developing living, non-pathogenic *L. lactis* strains for local delivery of therapeutics in the gut. This approach would reduce the need for high systemic doses of biopharmaceuticals by topical and active delivery of these biological drugs to the GI tract. The micro-organisms pass through the GI tract within a few days after oral administration

   2.3. AG011is the *L. lactis* MG1363 strain carrying a human interleukin 10 (hIL10) expression cassette is stably cloned in the bacterial genome. For the construction of the GMO the plasmid pAGX0037 carrying the hIL10 expression cassette flanked by sequences of the thymidylate synthase gene (thyA) is cloned. By double homologous recombination between the plasmid and chromosomal DNA of L. lactis the hIL10 is stably incorporated into the genome replacing the thyA gene.
   Expression of the secretion sequence SSup45 and the synthetic hIL10 gene are regulated by a bacterial promoter derived from *L. Lactis* MG1363, the host organism used in this study. The plasmid used for the genetic modification is completely absent in the genetically modified *L. lactis.*
   Due to deletion of the thyA gene, coding for the enzyme needed for thymidine production, the genetically modified *L. lactis* is dependent on thymine or thymidine *in the growth* medium. Absence of thymine or thymidine is toxic for bacteria and results in to thymineless death.

3. Results
   In 2009 no patients were included in the study. No GMO has been received by the LUMC