Title:

Safety and feasibility of a tolerogenic dendritic cell-based treatment for multiple sclerosis (MS): a comparison of intranodal and intradermal cell administration in two phase I clinical trials

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Introduction: Most disease-modifying treatments for multiple sclerosis (MS) give rise to side-effects, ranging from mild to severe. Hence, an unmet need for treatments that combine excellent safety and high efficacy remains. Antigen-specific tolerization with autologous tolerogenic dendritic cells (tolDC) is a promising approach to meet this need.

Objectives: We assess the safety and feasibility of the therapeutic use of autologous tolDC in a well-defined population of MS patients in two single-center clinical trials, comparing intradermal (i.d., MS-tolDC, NCT02618902) and intranodal (i.n., TOLERVIT-MS, NCT02903537) administration.

Methods: Autologous monocytes are extracted via a leukapheresis procedure and cultured, stimulated and loaded with 7 myelin-derived antigens (MBP_{13-32}, $MBP_{111-129}$, $MBP_{154-170}$, $PLP_{139-154}$, MOG_{1-20}, MOG_{35-55} and MBP_{83-99}) and frozen, compliant with good manufacturing practice (GMP). According to a best-of-five design, six administrations at consecutive intervals are planned in 3 cohorts receiving incremental doses of tolDC. The number of adverse events (AE) and relapses,

neurological disability and magnetic resonance imaging (MRI) endpoints are evaluated to assess safety.

Results: Until September 12, 2018, 15 patients have been screened, of which 4 have been included in the clinical trial with i.d. administration of tolDC and 6 in the clinical trial with i.n. administration. Six patients received the investigational product and are currently in the treatment and safety follow-up phase. Four of the treated patients were diagnosed with relapsing remitting MS (1 male and 3 female) and two with primary progressive MS. The age ranged between 30 and 43 years and the baseline EDSS between 1.5 and 6.0. To date, no serious adverse events have been reported. Most adverse events were considered to be treatment unrelated, except for mild-moderate local reactions seen at the injection site. Two patients experienced a mild MS relapse (not meeting protocol defined criteria for confirmed MS relapse).

Conclusions: The interim results of the first dose cohort do not show an important safety signal to date. Further treatment and follow-up of patients is ongoing.

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Trial registration: Both studies are registered at clinicaltrials.gov: NCT02618902 and NCT02903537 (EudraCT numbers: 2015-002975-16 and 2015-003541-26, respectively).

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