Safety and Tolerability of MEDI-551 in Patients With Relapsing Forms of Multiple Sclerosis: Results From a Phase 1 Randomised, Placebo-Controlled, Escalating Intravenous and Subcutaneous Dose Study

Abstract
Background: CD19 blockade is a promising new target in the pathophysiology of multiple sclerosis (MS). MEDI-551, a fully humanised, afucosylated IgG1κ monoclonal antibody, binds to and depletes CD19+B cells.

Objectives: Assess safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity of ascending intravenous (IV) and subcutaneous (SC) doses of MEDI-551 in studies with matching IVs.

Methods: In the phase 1 (NCT01356478) study, patients were randomised 3:1 to receive MEDI-551 at doses of 30, 100, or 600 mg IV, or 100 or 300 mg SC, on days 1 and 15. On days 1 and 15 prior to each dose, patients received premedication to reduce risk of possible infusion-related reactions (IRRs) and infusion site reactions (ISRs). In a total of 134 patients, blood was collected periodically for PK, PD, and antidrug antibodies (ADAs).

Results: In total, 28 patients were randomised; 27 (MEDI-551, 20; PBO, 7) completed treatment. The most common IRRs were of grade 1 or 2 severity. In the IV cohort, 9/15 patients receiving MEDI-551 IV (60%) had B-cell depletion in an in-vitro assay, which occurred between days 2 and 15. The median EDSS score did not change in either treatment group (MEDI-551, 30, 100, or 600 mg IV, or 100 or 300 mg SC, on days 1 and 15). The mean number of new or newly enlarging T2 lesions vs placebo was 0.1 (0.30) in the MEDI-551 group vs 1.1 (1.35) in the placebo group.

Conclusions: MEDI-551 was shown to be safe and tolerable in patients with relapsing forms of MS; PK, PD, and ADA results met the study criteria. Higher doses caused longer B-cell depletion. Most related AEs seen only with MEDI-551 were B-cell counts was observed for all MEDI-551 dose groups. The mean drug half-life was 16 days.

Objectives
- The primary objective was to evaluate the safety and tolerability of escalating intravenous (IV) and subcutaneous (SC) doses of MEDI-551 in adult patients with relapsing forms of MS.
- Secondary objectives included evaluations of pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity.

Methods
- Eligible patients were 18-65 years of age with - Relapsing MS by McDonald 2010 criteria
  - At least 1 relapse in the prior 2 years
  - Expanded Disability Status Scale (EDSS) score of 4.5 or less
  - Normal baseline B-cell count
  - LDH within 2 standard deviations of the mean

- Intravenous (IV) and subcutaneous (SC) doses of MEDI-551 led to dose-dependent B-cell depletion.
- The kinetics of B-cell repletion were dose dependent
- The median EDSS score did not change in either treatment group
- Higher MEDI-551 doses caused longer B-cell depletion
- Most related AEs seen only with MEDI-551 were B-cell counts was observed for all MEDI-551 dose groups.
- The mean drug half-life was 16 days.