Background Interleukin-21 (IL-21) is a pleiotropic cytokine. Both IL-21 and the IL-21 receptor (IL-21R) have been shown to be upregulated in systemic lupus erythematosus (SLE). BOS161721, a humanized monoclonal immunoglobulin (IgG1) that binds to and neutralizes IL-21. It is currently in development for the treatment of SLE. The primary objective of this trial was to assess safety and tolerability of single intravenous (i.v.) and subcutaneous (s.c.) doses of BOS161721 in healthy volunteers (HV).

Methods A phase 1, randomized, single-center, placebo-controlled, double-blind, single-dose-escalation trial was conducted in male and female HV (n=61) aged 18–55 years. Subjects were randomized in a 3:1 ratio (BOS161721: placebo) and received either a single SC dose of BOS161721 (1#, 3, 10, 22#, 30, 60, 120, or 240 mg, #=i.v. administration) or placebo. Key safety parameters included adverse events (AEs), injection-site reactions and detection of neutralizing antibodies (nAbs) against BOS161721. Pharmacokinetic (PK) and pharmacodynamic (PD) parameters included pStat3 levels and expression levels of IL-21 gene signature in blood.

Results A total of 39 treatment emergent AEs were reported in 47 subjects (83%). The most commonly reported related AE was influenza-like illness (6.4%). No dose dependency was detected for AEs. One serious AE (fatal pulmonary embolism) was reported 127 days post dosing in a subject exposed to 240 mg SC of BOS161721; it was evaluated as not related to the study drug by the investigator. No nAbs were detected. No clinically relevant changes in laboratory parameters, vital signs or ECG were observed. Dose-linearity PK was observed with SC administration and Tmax occurred at approximately 6 days posts dose, indicating no evidence of target mediated clearance. The mean terminal elimination half-life of BOS161721 was estimated to be 80 days at the highest dose of 240 mg. Notably, a dose dependent decrease was observed for the pSTAT3 parameter indicating complete neutralization of IL-21 signaling at doses of 60 mg and greater.

Conclusions BOS161721 was safe and well tolerated in HV. Dose-linear PK of BOS161721 was demonstrated in HV. Importantly, BOS161721 potently suppressed IL-21 induced signaling which demonstrates the expected biologic and potential clinical activity of BOS161721. A phase 1b study is currently ongoing in patients with SLE.

Funding Source(s): Boston Pharmaceuticals