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**Title:** Safety, immunogenicity and pharmacokinetics (PK) of a 120 mg/kg/week dose of alpha$_1$-proteinase inhibitor in alpha$_1$-antitrypsin deficiency

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**Body:** Background: The approved dose of alpha$_1$-proteinase inhibitor (alpha$_1$-PI) for treating alpha$_1$-antitrypsin deficiency (AATD) is 60 mg/kg/week intravenously (IV). Although this dose aims to increase serum alpha$_1$-PI levels above a proposed “protective” threshold (11mM), it is still below the normal range in healthy subjects. We report the safety, tolerability, and PK parameters of 120 mg/kg/week IV alpha$_1$-PI (Prolastin®-C). Methods: In this double-blind crossover study, 30 symptomatic AATD patients were randomly assigned to 60 or 120 mg/kg/week IV Prolastin®-C for 8 weeks, and then changed to the alternate dose after a 2-week washout period. Adverse events (AEs) were recorded, plasma was tested for anti-drug antibodies (ADA) and PK parameters of alpha$_1$-PI were measured. In addition, a neutralizing antibody ELISA was developed and validated for potential characterization of ADAs. Results: The higher dose was well tolerated by all subjects and the frequency of AEs did not appear to be dose-dependent. Exacerbation of COPD was the most frequent AE, consistent with the subjects’ diagnoses. Mean steady-state trough serum alpha$_1$-PI concentration after the 120 mg/kg weekly dose was higher than that after the 60 mg/kg dose (27.7μM and 17.3μM, respectively). Plasma samples tested negative for anti-Prolastin®-C antibodies with a screening/confirmatory ELISA assay. Conclusions: The 120 mg/kg/week dose of Prolastin®-C was well tolerated, did not result in an immunogenicity response and achieved favorable physiologic alpha$_1$-PI serum levels. Assessment of the clinical efficacy of this higher dose on the symptoms and progression of AATD is warranted.