(PB4504) PHASE 1 STUDY TO EVALUATE SUBCUTANEOUS BUDOPRUTUG, A LOW-FUCOSYLATED ANTI-CD19 MAB, IN HEALTHY VOLUNTEERS, AS A POTENTIAL TREATMENT FOR IMMUNE-MEDIATED DISEASES WITH ADMINISTRATION OPTIONALITY

Topic: 38. Novel technologies, techniques and digital analytical tools in hematology

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Background

Budoprutug (TNT119) is an anti-CD19 mAb bioengineered with picomolar binding affinity for CD19 and a low-fucosylated Fc region for enhanced antibody-dependent cell cytotoxicity. CD19 is expressed from the early pro-B stage through maturation and differentiation to plasmablasts and on subsets of plasma cells, providing the potential for budoprutug to provide deep and sustained depletion of pathogenic B cells, including autoantibody-producing cells. Intravenous (IV) budoprutug was previously evaluated in two Phase 1 studies, one of which was a study of advanced CD19+ indolent B-cell lymphoma or chronic lymphocytic leukemia (CRUKD/12/003). It is currently being evaluated in several studies in immune-mediated diseases, including a Phase 1b/2a study in immune thrombocytopenia (NCT07043946). A low viscosity, high concentration (>175 mg/mL) formulation of budoprutug was developed to enable a subcutaneous (SC) administration, which could provide route-of-administration optionality. In non-human primates, SC budoprutug demonstrated high bioavailability without safety or local tolerability concerns.

Aims

To assess the safety, pharmacokinetics (PK) and pharmacodynamics (PD) of SC budoprutug in adult healthy volunteers (HV) and to assess feasibility for clinical trials in immune-mediated diseases.

Methods

This was a Phase 1, randomized, double-blind, placebo-controlled, single-ascending-dose study (NCT07090655) in HV. Primary endpoints included incidence and severity of treatment-emergent adverse events and incidence of infusion/injection-related reactions (IRRs). Secondary and exploratory endpoints included PK parameters, bioavailability, B-cell counts, and serum immunoglobulin levels. Participants received SC budoprutug (3 mg or 6 mg), IV budoprutug (6 mg), or placebo. SC cohorts were randomized 6:2 (active:placebo); IV cohort was randomized 12:2. Doses were selected to produce measurable but submaximal B-cell depletion (<50% predicted). Acetaminophen/paracetamol and diphenhydramine were given as pre-medications. Pts were followed for 8 weeks.

Results

The study enrolled a total of 30 pts (SC 3mg, n=6; SC 6mg, n=6; IV 6mg, n=12; placebo, n=6). Safety profiles were comparable between SC and IV groups. IRRs occurred in 0/6, 3/6, 4/12, and 0/6 pts in the SC 3mg, SC 6mg, IV 6mg, and placebo groups, respectively. All were Grade 1 except a single Grade 2 postural hypotension (IV group), and all resolved within 48 hours. No injection/infusion-site reactions were observed. PK interpretation for SC doses was limited as most of the concentrations were below the limit of quantification; however robust PD effects were observed. All active groups demonstrated rapid B-cell depletion, reaching approximately 85% reduction from baseline (Figure 1). B-cell depletion was similar between SC and IV administration, suggesting adequate systemic exposure to achieve robust PD activity. Higher baseline natural killer (NK) cell counts were associated with greater depth of CD20+ B-cell depletion.

Summary/Conclusion

To our knowledge, these are the first presented data of a B-cell depleting anti-CD19 mAb in HV. SC budoprutug showed robust effects on B-cell depletion with similar tolerability to matched-dose IV budoprutug, despite being studied at doses predicted to produce modest impact on B cells. The comparable PD between routes supports the feasibility of SC administration and provides flexibility for continued development in immune-mediated diseases.

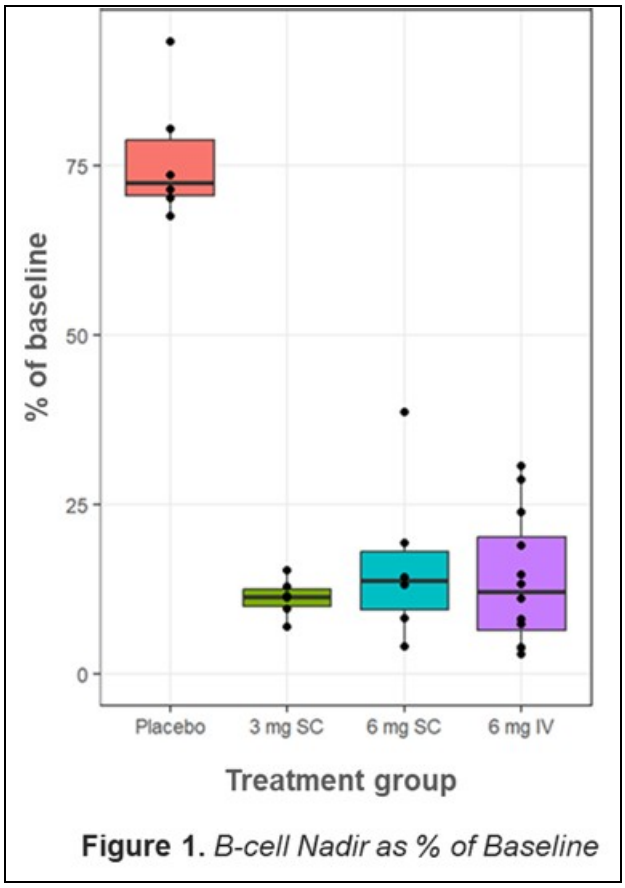

Figure 1. *B-cell Nadir as % of Baseline*