A PHASE 1B SINGLE ARM OPEN-LABEL STUDY OF BUDOPRUTUG, AN ANTI-CD19 MONOCLONAL ANTIBODY WITH ENHANCED ADCC, IN PRIMARY MEMBRANOUS NEPHROPATHY (PMN)

Frank Cortazar,MD[1]; William Bonificio,PhD[2]; Naveen Daryani, PharmD[2]; Stephen B. Thomas, PhD[2]

[1]NewYork Nephrology, Vasculitis and Glomerular Center, Albany, NY, USA; [2]Climb Bio, Inc (formerly Tenet Medicines)

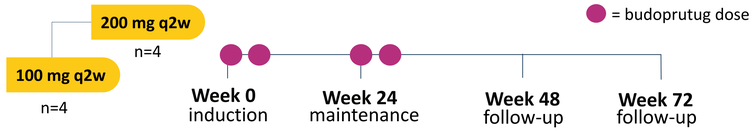
BACKGROUND

- Primary membranous nephropathy (pMN) is characterized by a histologic pattern of injury caused by autoantibodies directed against podocyte antigens.
  - If left untreated, progressive loss of renal function occurs, leading to kidney failure in ~60% of patients within 10 years.
  - Degree of proteinuria has been correlated with long-term outcomes and, thus, complete remission (CR) of proteinuria is an established surrogate marker for disease control and progression.
- Approximately 70% of cases of pMN are caused by autoantibodies directed against the phospholipase A2 receptor (PLA2R), with the remaining cases caused by autoantibodies against other glomeruli antigens.
- Targeting B lymphocytes with anti-CD20 monoclonal antibodies or cyclophosphamide and steroids are effective therapies for pMN, but these fail to induce CR in most patients and can be associated with treatment-related toxicity.
- Budoprutug is a monoclonal antibody (mAb) bioengineered with a low-fucosylated Fc region for enhanced antibody-dependent cell cytotoxicity (ADCC). It targets the CD19 epitope expressed on maturing B-cells from pro-B-cells through peripheral, tissue resident plasmablasts and plasma cells.
- Budoprutug targets a broader spectrum of B cells and progenitors compared with anti-CD20 mAbs, which may translate into improved efficacy in the management of autoantibody-mediated diseases, including pMN.
- Here, we present the results of a Phase 1b study of budoprutug in patients with pMN.

METHODS

Study Design

This was a phase 1b, open label, dose escalation study of the safety and pharmacodynamics of budoprutug in adult patients with pMN conducted at 4 sites in the United States (NCT04652570). All patients provided informed consent.



Key Enrollment Criteria

- Eligible patients had primary MN with a history of nephrotic syndrome, received maximally tolerated therapy with a renin-angiotensin system inhibitor for 6 months, and had a urine protein to creatinine ratio (UPCR) of > 2 g/g on two measurements during screening.

Treatment

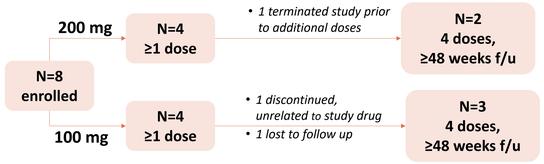
- Patients were administered doses of budoprutug, 100 or 200 mg IV, on days 1 and 15, and then 6 months later on days 169 and 183.

Endpoints

- The primary safety endpoint was the incidence of treatment-emergent adverse events (TEAEs).
- Secondary safety endpoints included dose-limiting toxicities (DLTs) and change from baseline in clinical laboratory assessments, ECGs, vital signs, and physical examinations.
- Secondary efficacy objectives included B-cell levels, anti-phospholipase A2 receptor (anti-PLA2R) antibody (Ab) levels, and changes in proteinuria.
- Efficacy analysis was restricted to patients with ≥48 weeks of follow-up.

RESULTS

PATIENT DISPOSITION



8 patients were enrolled on study, all of whom received at least one dose of budoprutug. 3 patients discontinued or were lost to follow-up. Patients who completed treatment and had at least 48 weeks of follow-up constitute the efficacy population (N=5)

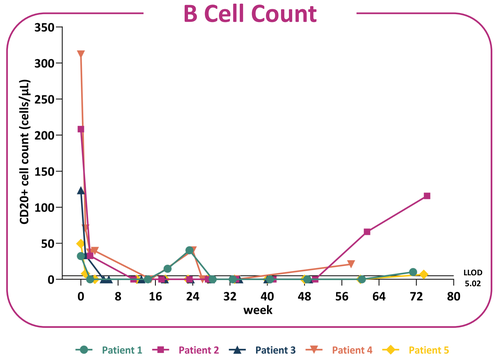
DEMOGRAPHICS & DISEASE CHARACTERISTICS

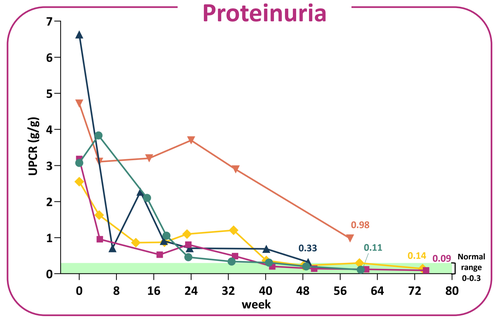
- The study enrolled a population of patients consistent with moderate to severe disease. Demographics are presented for the efficacy population (N=5).
- Median age was 55 (range, 35-64) years. All patients were male.
- Duration of disease at baseline: 2 – 13 years.
- Mean (SD) B cell (CD20+ cell) count at baseline: 145.08 ± 116.36 cells/µL. Mean (SD) anti-PLA2R autoantibodies at baseline in 3 patients who were PLA2R positive: 70.57 ± 15.61 RU/mL.
- Mean (SD) UPCR at baseline: 4.03 ± 1.66 g/g.

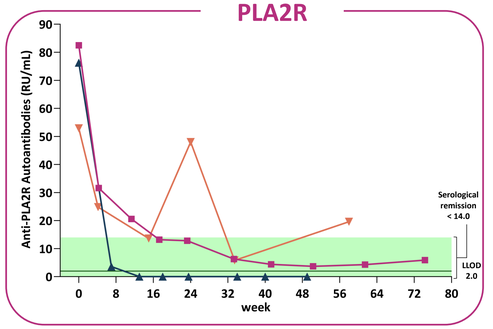
SAFETY

- There were no deaths on study.
- 4 patients reported infections on study: 3 cases of COVID-19 and 1 case of bacterial pneumonia.
- There were 3 SAEs (grade 3 bacterial pneumonia, grade 4 rhabdomyolysis, and grade 3 chronic obstructive pulmonary disease), none of which were considered to be related to budoprutug by the investigator, and all of which resolved with treatment or observation.
- No dose limiting toxicities (DLTs) were observed and there were no study discontinuations due to adverse events.

EFFICACY







- Budoprutug administration was associated with resolution of proteinuria and immunological remission.
- All patients had full depletion of B-cells by week 12, and 3 patients maintained depletion of B-cells for ≥48 weeks.
- Two patients did have B-cell recovery between weeks 12 and 24, however these patients were durably depleted upon additional dosing at week 24.
- 3 patients who were PLA2R positive at baseline had a serological remission with PLA2R antibodies <14 RU/mL.
- All 5 patients achieved partial or complete remission (CR) of proteinuria. 3 patients achieved CR of proteinuria.
- The two patients with 72 weeks of follow up both maintained CRs.

CONCLUSIONS

- **This phase 1b study of budoprutug in pMN enrolled a population of patients consistent with moderate to severe disease. In the efficacy analysis population, the duration of disease ranged from 2 to 13 years, all patients had complications of disease and in the 3 of 5 patients who were PLA2R antibody positive, baseline titers were > 50 RU/mL**
- **Budoprutug was observed to be generally well-tolerated; no drug-related Grade ≥3 AEs or SAEs were reported.**
- **Treatment of patients with primary MN with 4 doses of budoprutug 100 mg or 200 mg resulted in high rates of serologic and clinical remission, including normalization of proteinuria.**
- **These results suggest that budoprutug may offer an opportunity to induce remission of MN in patients with moderate to severe disease.**
- **Larger studies are needed to further evaluate the efficacy of budoprutug in pMN.**

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