Phase 1/2 Study of Safety and Pharmacokinetics of BION-1301 Targeting APRIL, a Proliferation–Inducing Ligand, in Adults with Relapsed or Refractory Multiple Myeloma

**BACKGROUND**

- BION-1301 is a first-in-class, fully human monoclonal antibody directed against a proliferation-inducing ligand (APRIL) for treatment of relapsed/refractory multiple myeloma (MM).

- APRIL is secreted by cells in the bone marrow niche and binds to BCMA (B-cell maturation antigen) and TACI (transmembrane activator and CAML interactor) expressed on human MM cells to drive their proliferation and survival.

- APRIL induces resistance to doxetasmel, nelarabine, and bortezomib, and other standard-of-care drugs in subpopulations of regulatory T cells and B cells.

- In patients with MM, serum APRIL levels are elevated and associated with promotion of malignancy, chemoresistance, and immune resistance.

Figure 1. BION-1301 Unique Epitope Mapped to Receptor Binding Sites

**Figure 2. BION-1301 and Its Parental Mouse Antibody hAPRIL.01A Binding to APRIL and Blocking of APRIL Binding to BCMA or TACI**

**OBJECTIVES**

The objective of this Phase 1/2 first-in-human study is to determine the recommended phase 2 dose (RP2D) of BION-1301 by evaluating the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and clinical activity of BION-1301 administered as an intravenous infusion alone or with low dose dexamethasone (DEX) and to inform future development of clinical studies for patients with MM.

**CLINICAL STUDY DESIGN**

- **This is an open-label, multicenter, Phase 1/2 clinical study for subjects with relapsed or refractory MM whose disease has progressed after at least 3 prior systemic therapies.**

- **Phase 1**
  - Cohort 1: Dose Escalation Design starting as a 50 mg BION-1301 IV infusion as a 2 hour infusion (3 hours for doses ≥ 200 mg).
  - Dose escalation is to proceed in subsequent cohorts until the RP2D is identified.

- **The maximum administered dose will not exceed 2700 mg**

- **Dose limiting toxicity (DLT)** will be an increase in any 2 of the following:
  - Serum M-protein ≥ 5 g/dL.
  - Serum M-protein: ≥ 2.2 mg/dL at any timepoint.
  - Serum Free Light Chain (FLC) assay: involved FLC level ≥ 10 mg/dL provided serum FLC ratio is abnormal.

- **In cases where SPEP is unreliable, serum quantitative immunoglobulin (qIgA) ≥ 750 mg/dL is acceptable.**

- **Phase 2 (Dose Confirmation) portion of the study to receive open label treatment:**
  - Cohort 6: 1350 mg weekly dosing.

- **Additional cohorts will be enrolled to evaluate weekly dosing for up to 8 weeks, followed by Q2W dosing until disease progression or unacceptable toxicity.**

**ENDPOINTS**

- **Phase 1 endpoints include**
  - Incidence of dose-limiting toxicities, treatment-emergent adverse events (TEAEs), and changes in safety parameters
  - PK parameters based on BION-1301 serum levels following a single dose and a multiple dose regimen
  - Change from baseline in soluble APRIL
  - Relative reduction in serum and urine M-protein levels defined as the maximum percent reduction from baseline.

- **Phase 2 endpoints include**
  - Objective response rate based on International Myeloma Working Group (IMWG) uniform response criteria of stringent complete response, complete response, very good partial response, or partial response.
  - Progression-free survival defined as time from first dose of study drug to date of progression or death due to any cause.
  - Overall survival defined as the time from first dose of study drug to date of death due to any cause.
  - Incidence of TEAEs, changes in safety parameters, and unacceptable toxicities.

**KEY INCLUSION CRITERIA**

- Male or female, age ≥ 18 years
-Confirmed diagnosis of MM per IMWG criteria
- Measurable disease as defined in 1 of the following:
  - Serum M-protein ≥ 5 g/dL.
  - Serum M-protein: ≥ 2.2 mg/dL at any timepoint.
  - Serum Free Light Chain (FLC) assay: involved FLC level ≥ 10 mg/dL provided serum FLC ratio is abnormal.

**KEY EXCLUSION CRITERIA**

- Monoclonal gammopathy of undetermined significance (MGUS), emmygmmma.

- Waldenstrom’s macroglobulinemia, or IgM myeloma

- Active chronic or latent bacterial or fungal infection

- Active hepatitis or active or controlled HIV infection

- 4 Prior treatment directed to B-Cell Activating Factor (BAFF; BLyS), B-Cell Maturation Antibody (BCMA), TACI, or TACI-Related DCC4 (TACI) (BAFF antagonist

- Inclusion of APRIL or BION-1301 licensed to or distributed by Aduro Biotech, Inc.

**CONCLUSIONS**

- BION-1301 has the potential to address the need for improved efficacy in relapsed or refractory multiple myeloma.

- BION-1301’s phase 1/2 phase study results will inform future development of a phase 2 clinical study.