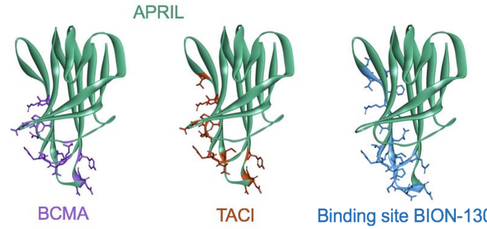
Phase 1/2 Study of Safety and Pharmacokinetics of BION-1301 Targeting APRIL, a Proliferation-Inducing Ligand, in Adults with Relapsed or Refractory Multiple Myeloma

Parameswaran Hari[1], Anastasios Raptis[2], James Berenson[3], Alexander Spira[4], Ajay Nooka[5], Maria Chaudhry[6], Nitya Nair[7], Hamid Namini[7], Jackie Walling[7], Deb Chapman[7], William Bensinger[8]
[1]Medical College of Wisconsin, Milwaukee, WI; [2]University of Pittsburgh School of Medicine, Pittsburgh, PA; [3]The Institute for Myeloma & Bone Cancer Research, West Hollywood, CA; [4]Inova Fairfax Hospital, Fairfax, VA; [5]Emory University School of Medicine, Atlanta, GA; [6]The Ohio State University Comprehensive Cancer Center, Columbus, OH; [7]Aduro Biotech, Inc., Berkeley, CA; [8]Swedish Cancer Institute, Seattle, WA

BACKGROUND

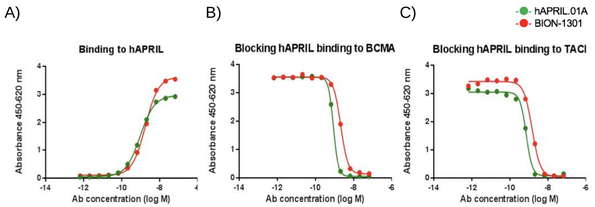
- BION-1301 is a first in class humanized monoclonal antibody directed against a proliferation-inducing ligand (APRIL) for treatment of relapsed/refractory multiple myeloma (MM)
- APRIL secreted by cells in the bone marrow niche binds to BCMA (B-Cell maturation antigen) and TACI (transmembrane activator and CAML interactor) expressed on human MM cells to drive their proliferation and survival[1]
- APRIL induces resistance to dexamethasone, lenalidomide, bortezomib, and other standard-of-care drugs[1] and drives expansion of regulatory T cells and B cells[2]
- In patients with MM, serum APRIL levels are elevated and associated with promotion of malignancy, chemo- and immune-resistance

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



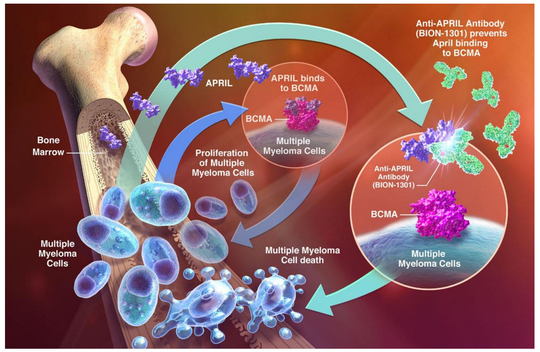
BION-1301 (blue) shares its APRIL binding site with that of both receptors BCMA (purple) and TACI (orange)

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



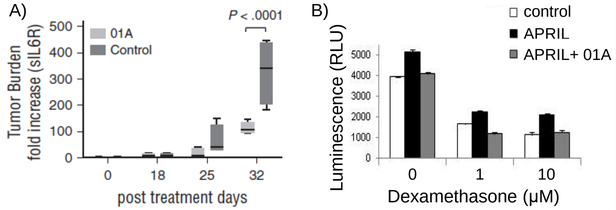
- FLAG-APRIL was captured using anti-FLAG antibodies and binding of BION-1301 was detected
- EC50 was calculated in which the average value of 3 independent experiments was 0.29 ± 0.05 nM (A)
- ELISA plates were coated with BCMA or TACI and BION-1301 was preincubated with recombinant FLAG-APRIL and added to the plates
- Binding of FLAG-APRIL was detected using anti-FLAG antibodies. Blocking potency (IC50) was 1.61 ± 0.78 nM BCMA (B) and 1.29 ± 0.89 nM TACI (C) respectively

Figure 3. Mode of Action of BION-1301



BION-1301 blocks APRIL from binding to BCMA and TACI, leading to inhibition of MM cell proliferation and survival, and enhancement of MM sensitivity to other treatments[2]

Figure 4[1]. hAPRIL.01A (01A) Blocks MM Cell Growth in a SCID-hu Mouse Model of Human MM and Inhibits APRIL-Induced Protection from Dexamethasone



A) Tumor burden, as monitored by soluble IL-6R in murine blood, was significantly decreased following 4 weeks of 01A treatment compared with vehicle control treatment (P<.0001 at day 32, n=4 each group) indicating that 01A is cytotoxic against MM cells in the BM microenvironment in vivo

B) MM cells were incubated for 4 days with dexamethasone in the presence of APRIL with or without anti-APRIL (01A, 10 μg/ml), and assayed by [3H]thymidine uptake. In a dose-dependent manner, anti-APRIL (01A) significantly blocked APRIL-induced protection against dexamethasone induced MM 3+3 cell death

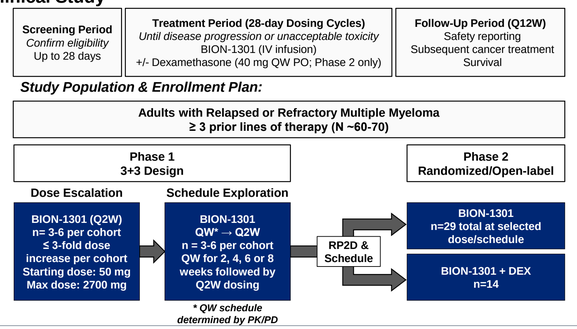
OBJECTIVES

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 (IV) 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, first-in-human, 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 (3+3 Dose Escalation design) dosing started as a 50 mg BION-1301 IV infusion
- Dose escalation is to proceed in successive cohorts until the RP2D is identified
- The maximum administered dose will not exceed 2700 mg
- During initial dose escalation, the dosing interval is once every two weeks (Q2W) as a 2-hour infusion (3 hours for doses ≥2000 mg)
- Additional cohorts will be enrolled to evaluate weekly dosing for up to 8 weeks, followed by Q2W dosing with the same or a lower dose
- Once an RP2D and schedule are identified, subjects will be randomized in the Phase 2 (Dose Confirmation) portion of the study to receive open-label BION-1301 alone or BION-1301 with low dose DEX at the assigned dose and schedule until disease progression or unacceptable toxicity

Figure 5. First-in-human, Open-Label, Multicenter, 3+3 Phase 1/2 Clinical Study



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 after repeated dosing*
  - 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 first tumor 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

* Also a Phase 2 Endpoint

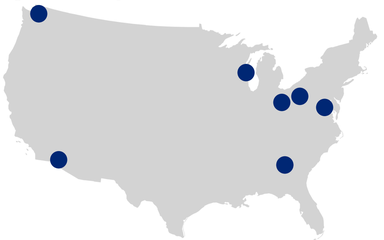
KEY INCLUSION CRITERIA

1. Male or female, aged ≥ 18 years
2. Confirmed diagnosis of MM per IMWG criteria
3. Measurable disease as defined by ≥1 of the following:
   - Serum M-protein ≥ 0.5 g/dL
   - Urine M-protein ≥ 200 mg/24 hours
   - 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 (0.75 g/dL) is acceptable
4. Relapsed or refractory[3] to 3 or more different prior lines of therapy for MM, including IMiDs, PIs, chemotherapies, or monoclonal antibodies, and not a candidate for, or intolerant to established therapy known to provide clinical benefit
   - Relapse defined as progression of disease after an initial response (minimal response or better) to previous treatment, more than 60 days after cessation of treatment
   - Refractory disease defined as < 25% reduction in M-protein or progression of disease during treatment or within 60 days after cessation of treatment
5. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 – 1

KEY EXCLUSION CRITERIA

1. Monoclonal gammopathy of undetermined significance (MGUS), smoldering myeloma, Waldenstrom's macroglobulinemia, or IgM myeloma
2. Active plasma cell leukemia (> 2.0 × 10^9/L circulating plasma cells by standard differential)
3. POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes)
4. Prior treatment directed to B-cell Activating Factor (BAFF; BLyS), B-cell Maturation Antigen (BCMA;TNFSF17) or Transmembrane Activator and CAML interactor (TACI; TNFSF13B), including antibodies or BCMA- or TACI-directed Chimeric Antigen Receptor (CAR)-T cell therapy

Figure 6. Study Site Locations



7 Study Sites Open to Recruitment

- Seattle, WA
- Milwaukee, WI
- Pittsburgh, PA
- Columbus, OH
- Fairfax, VA
- West Hollywood, CA
- Atlanta, GA

As of March 4, 2019, 21 patients have been dosed in 6 cohorts

- Cohorts 1-5, given doses Q2W between 50-2700 mg, have completed the dose limiting toxicity evaluation period without dose limiting toxicities (DLTs)
- Patients enrolled in Cohort 6 (1350 mg weekly dosing) are being observed for the DLT evaluation period
- Enrollment in the phase 1 dose-escalation study has been completed

CONCLUSIONS

- BION-1301 has the potential to address the need for improved efficacy in relapsed or refractory multiple myeloma patients
- BION-1301's phase 1 study results will inform future development of a phase 2 clinical study

References:
1. Tai *et al.* Blood. 2016.
2. Tai *et al.* Leukemia. 2018.
3. Rajkumar *et al.* Lancet Oncol. 2011.

Acknowledgments:
We would like to thank all of investigators and their teams for their participation in this study. Writing support was provided by Xelay Acumen Group, Inc., and funded by Aduro Biotech, Inc.