# Birtamimab in Patients with Mayo Stage IV AL Amyloidosis: Rationale for Confirmatory AFFIRM-AL Phase 3 Study

GERTZ, MORIE A.[1]; SANCHORAWALA, VAISHALI[2]; WECHALEKAR, ASHUTOSH[3]; ANDO, YUKIO[4]; KOH, YOUNGIL[5]; NIE, CHRISTIE[6]; JIN, YUYING[6]; CONRAD, ANSGAR[6]; KASTRITIS, EFSTATHIOS[7]; ON BEHALF OF THE AFFIRM-AL STUDY INVESTIGATORS

*[1]Division of Hematology, Department of Internal Medicine, Mayo Clinic, Rochester, MN, USA; [2]Amyloidosis Center, Boston University School of Medicine, Boston Medical Center, Boston, MA, USA; [3]Royal Free Hospital School of Medicine, University College London Medical School, London, United Kingdom; [4]Nagasaki International University, Nagasaki, Japan; [5]Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea, Republic of (South); [6]Prothena Biosciences Inc, South San Francisco, CA, USA; [7]Department of Clinical Therapeutics, Alexandra Hospital, Medical School, National & Kapodistrian University of Athens, Athens, Greece*

**Background:** Amyloid light chain (AL) amyloidosis--a progressive disorder caused by misfolded light chains produced by plasma cells--is associated with high mortality, poor quality of life, and increased healthcare costs, particularly in newly diagnosed patients with advanced disease (Mayo 2012 Stage IV, median overall survival <6 months). Birtamimab is a monoclonal antibody designed to neutralize circulating soluble and deplete deposited insoluble amyloid, by promoting phagocytic clearance. In 2018, the Phase 3 VITAL study in newly diagnosed, treatment-naive patients was terminated based on a futility analysis of the primary endpoint (time to all-cause mortality [ACM] or time to cardiac hospitalization >90 days after first study drug infusion); the final hazard ratio (HR) numerically favored birtamimab + standard of care (SOC) over placebo + SOC (0.835 [95% CI: 0.5799, 1.2011]; p=0.330). Post hoc analysis of ACM over 9 months revealed a substantial survival benefit (HR=0.413 [95% CI: 0.191, 0.895]; p=0.025) in patients at high risk for early death (Mayo 2012 Stage IV), for which no approved treatments exist. Post hoc analyses of secondary endpoints in this subgroup indicated meaningful improvements in health-related quality of life (assessed with 36-Item Short Form Health Survey version 2; SF-36v2) and 6-minute walk test (6MWT) distance with birtamimab + SOC (p<0.05) at 9 months. In the overall study, the most commonly reported treatment-emergent adverse events (fatigue, nausea, peripheral edema, constipation and diarrhea) were similar in both treatment groups.

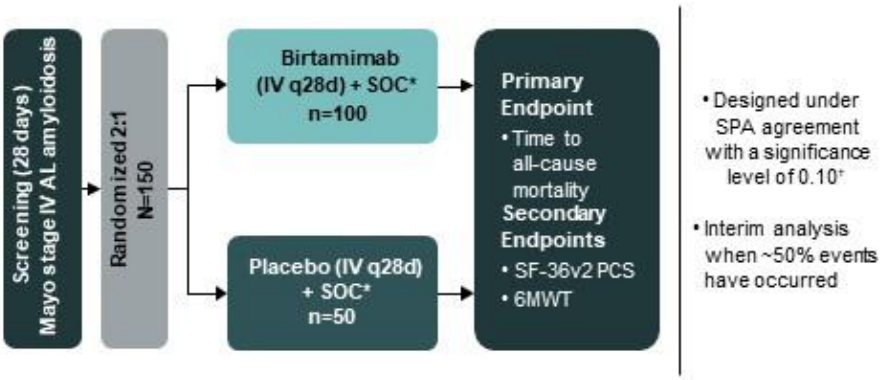
**Objective:** The Phase 3, double-blind, placebo-controlled AFFIRM-AL study (NCT04973137) will enroll up to 150 Mayo Stage IV patients with newly diagnosed, untreated AL amyloidosis and is designed to confirm the survival benefit observed in the VITAL study in patients with Mayo 2012 Stage IV AL amyloidosis.

**Material & Methods:** Patients will be randomized (2:1) to 24 mg/kg intravenous birtamimab or placebo every 28 days. Both arms will receive concomitant SOC chemotherapy with a first-line bortezomib-containing regimen; at the discretion of the investigator, initiation of daratumumab (D) at randomization is allowed (Figure 1). Patients will be stratified at randomization based on their 6MWT distance (<300 vs ≥300 meters) and initiation of D. The primary efficacy endpoint is time to ACM. Secondary endpoints are change from baseline to month 9 in the physical component summary of the SF-36v2 and 6MWT distance. Given the >50% reduction in the risk of ACM observed in the post hoc analysis of VITAL for patients with Mayo Stage IV disease, the AFFIRM-AL study is designed to confirm this effect of birtamimab, at a significance level of 0.10 under a Special Protocol Assessment (SPA) with the U.S. Food and Drug Administration (FDA).

**Results:** Approximately 130 global sites are planned; site initiation and patient randomization are ongoing.

**Summary & Conclusion:** Treatments that improve survival in AL amyloidosis are needed for patients with advanced cardiac involvement, as median overall survival for patients with Mayo 2012 Stage IV disease is <6 months. The AFFIRM-AL study is designed to confirm the >50% reduction in the risk of ACM observed in the VITAL study in patients with Mayo 2012 Stage IV AL amyloidosis.

**Figure 1.** AFFIRM-AL Global Study Design




*Initiation of daratumumab at randomization is allowed at the discretion of the investigator

†A p ≤0.10 will indicate that the result is statistically significant

6MWT, 6-Minute Walk Test; IV, intravenous; NT-proBNP, N-terminal pro hormone B-type natriuretic peptide; q28d, infusion once every 28 days; SF-36v2 PCS, Short-Form 36 version 2 Physical Component Score; SOC, standard of care; SPA, United States Food and Drug Administration Special Protocol Assessment

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