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

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BACKGROUND

- Amyloid light chain (AL) amyloidosis is a rare, progressive, and typically fatal disorder caused by the extracellular deposition of misfolded immunoglobulin light chains (amyloid) in organs and tissue[1,2]
  - Cardiac impairment and multi-organ damage are key predictors of reduced survival and poor disease outcomes in AL amyloidosis[1]
- The mortality risk for newly diagnosed, treatment-naive patients can be categorized using the validated Mayo Clinic Staging System, a prognostic classification system for mortality risk in newly diagnosed patients with AL amyloidosis (**Table 1**)[3]
  - Mayo stages range from I to IV, with Stage IV patients having the highest risk for early mortality
  - An urgent need remains for treatments that improve survival in patients at high risk for early mortality

Table 1. Mayo Staging Criteria: A Prognostic Risk Classification System[3]

Stratification for Mayo Staging Criteria		
Test	**Value**	**Score**
NT-proBNP	<1800 pg/mL	0
	≥1800 pg/mL	1
Troponin-T[a]	<0.03 ng/mL	0
	≥0.03 ng/mL	1
dFLC	<18 mg/dL	0
	≥18 mg/dL	1

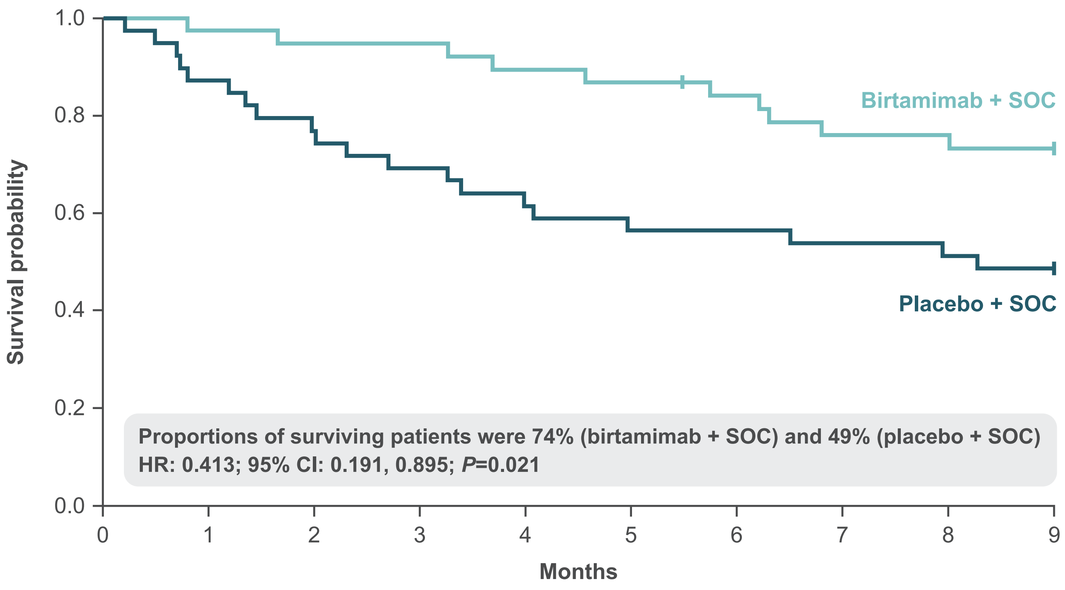
Total Score:
0 = Mayo Stage I
1 = Mayo Stage II
2 = Mayo Stage III
3 = Mayo Stage IV

[a]Modified from the value of 0.025 ng/mL cited in Kumar et al., to 0.03 ng/mL, which is the lowest validated determination for this commercially available test.

dFLC, differential free light chain; NT-proBNP, N-terminal pro-brain natriuretic peptide

- Birtamimab is an investigational fully humanized IgG1 monoclonal antibody designed to neutralize circulating soluble and deplete organ-deposited insoluble amyloid, by promoting phagocytic clearance[2,4]
- The Phase 3 VITAL study (NCT02312206) was terminated based on a futility analysis of the composite primary endpoint (time to all-cause mortality [ACM] or time to cardiac hospitalization ≥91 days after first study drug infusion)
  - The final hazard ratio (HR) numerically favored birtamimab + standard of care (SOC) over placebo + SOC (HR: 0.826; 95% confidence interval [CI]: 0.574, 1.189; log-rank *P*=0.303)
- Post hoc analysis of ACM over 9 months revealed a pronounced survival benefit (HR: 0.413; 95% CI: 0.191, 0.895; log-rank *P*=0.021) in patients at high risk for early mortality (Mayo Stage IV) (**Figure 1**)
  - Proportions of surviving patients were 74% (birtamimab + SOC) and 49% (placebo + SOC)

Figure 1. VITAL Study of Birtamimab in AL Amyloidosis: All-Cause Mortality, Mayo Stage IV (N=77), 9 Months



All-cause mortality regardless of prior cardiac hospitalization.

AL, amyloid light chain; CI, confidence interval; HR, hazard ratio; SOC, standard of care (hematologic-directed chemotherapy)

- Of the 260 patients enrolled in the VITAL study, 29.6% were characterized as Mayo Stage IV at baseline. These patients had a median age of 64 years and were primarily white (93.5%) and male (68.8%) (**Table 2**)
  - The survival benefit of birtamimab in the Mayo Stage IV subgroup was consistent after adjustment for key baseline variables, including demographic factors (age, sex, race, ethnicity), clinical characteristics (age at diagnosis, duration since diagnosis, New York Heart Association class, 6-Minute Walk Test [6MWT] distance) and laboratory parameters (N-terminal pro-brain natriuretic peptide [NT-proBNP], differential free light chain [dFLC], free light chain [FLC], troponin-T)

Table 2. VITAL Study Demographics and Key Baseline Characteristics for Mayo Stage IV Patients

	Birtamimab + SOC (n=38)	Placebo + SOC (n=39)	Total (N=77)
Age (years), median (Q1, Q3)	63.6 (55.7, 69.8)	63.7 (57.0, 68.4)	63.7 (56.9, 68.6)
Sex, n (%)			
Male	25 (65.8)	28 (71.8)	53 (68.8)
Female	13 (34.2)	11 (28.2)	24 (31.2)
Race, n (%)			
Black or African American	2 (5.3)	2 (5.1)	4 (5.2)
White	36 (94.7)	36 (92.3)	72 (93.5)
Other	0	1 (2.6)	1 (1.3)
Ethnicity, n (%)			
Not Hispanic or Latino	34 (89.5)	36 (92.3)	70 (90.9)
Not provided or unknown	4 (10.5)	3 (7.7)	7 (9.1)
Screening NT-proBNP, n (%)			
≥1800 pg/mL	38 (100)	39 (100)	77 (100)
dFLC ratio, median (Q1, Q3)[a]	44.44 (25.13, 56.17)	57.42 (35.52, 106.28)	49.56 (29.49, 72.05)
FLC ratio, median (Q1, Q3)	0.05 (0.02, 0.08)	0.05 (0.03, 11.14)	0.05 (0.03, 0.10)

[a]Baseline dFLC is only calculated for subjects with an abnormal baseline FLC ratio (Kappa/Lambda <0.26 or >1.65) and is defined as the difference between involved and uninvolved free light chains.

dFLC, differential free light chain; NT-proBNP, N-terminal pro-brain natriuretic peptide; FLC, free light chain; Q1, 25th percentile; Q3, 75th percentile; SOC, standard of care

- Multiple monthly infusions of birtamimab (24 mg/kg) were safe and well tolerated in the VITAL study (**Table 3**)
  - The six most commonly reported treatment-emergent adverse events in the birtamimab group (fatigue, nausea, peripheral edema, constipation, diarrhea, and dyspnea) occurred at generally similar rates in the placebo group

Table 3. VITAL Study Safety Summary for Mayo Stage IV Patients

Number (%) of subjects reporting at least 1 of the following:	Birtamimab + SOC (n=38), n (%)	Placebo + SOC (n=39), n (%)
TEAE	38 (100)	39 (100)
TEAE considered related to study drug	12 (31.6)	10 (25.6)
TEAE grade ≥3	30 (78.9)	35 (89.7)
TEAE grade ≥3 considered related to study drug	1 (2.6)	4 (10.3)
Related TEAE leading to death	0	0

SOC, standard of care; TEAE, treatment-emergent adverse event

PURPOSE

- This global, multicenter, double-blind, placebo-controlled, 2:1 randomized, time-to-event confirmatory Phase 3 study compares birtamimab plus SOC with placebo plus SOC in patients with newly diagnosed, treatment-naive AL amyloidosis categorized as Mayo Stage IV (ClinicalTrials.gov identifier: NCT04973137)
- AFFIRM-AL was designed in consultation with the US Food and Drug Administration under a Special Protocol Assessment (SPA)

STUDY ENDPOINTS

Endpoints

- Primary endpoint
  - Time to ACM, defined as time from the first dose of study drug until death
- Secondary endpoints
  - Physical Component Summary (PCS) score of the Short Form-36, version 2 (SF-36v2), defined as the change from baseline to month 9 in health-related quality of life (HRQoL) using the SF-36v2
  - 6MWT distance, defined as the change from baseline to month 9 in the 6MWT distance in meters

PATIENT ELIGIBILITY

Figure 2. AFFIRM-AL Trial Eligibility Criteria

Key Inclusion Criteria

- Aged ≥18 years
- Newly diagnosed and AL amyloidosis; treatment naive with cardiac involvement
- Confirmed Mayo Stage IV disease as defined by:
  - NT-proBNP ≥1800 pg/mL and
  - Troponin-T ≥0.03 ng/mL and
  - dFLC ≥18 mg/dL
- Planned first-line chemotherapy contains bortezomib administered subcutaneously weekly

Key Exclusion Criteria

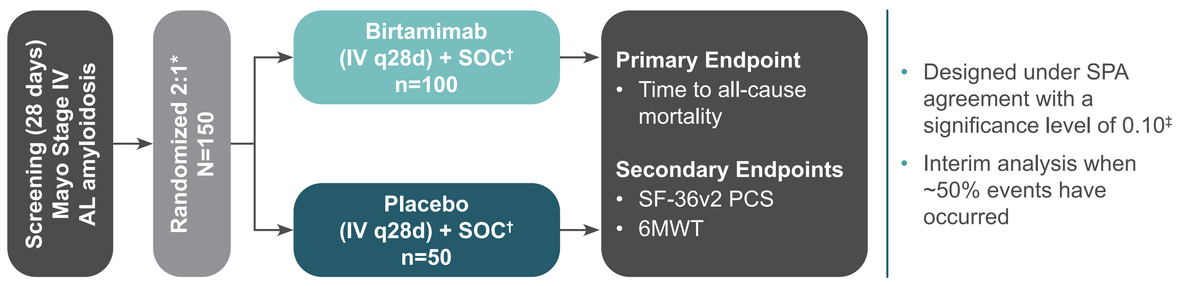
- Non-AL amyloidosis
- NT-proBNP >8500 pg/mL
- Meets the IMWG definition of multiple myeloma
- Eligible for and plans to undergo ASCT or organ transplant during the study
- Myocardial infarction, uncontrolled angina, severe uncontrolled ventricular arrhythmias, or ECG evidence of acute ischemia within 6 months prior to study drug administration
- Selected prior treatments*

*Prior treatment with plasma cell-directed chemotherapy, birtamimab, daratumumab, 11-1F4, anti-serum amyloid P antibody, doxycycline for amyloid, or other investigational treatment directed at amyloid.

AL, amyloid light chain; ASCT, autologous stem cell transplant; dFLC, differential free light chain; ECG, electrocardiogram; IMWG, International Myeloma Working Group; NT-proBNP, N-terminal pro-brain natriuretic peptide

STUDY DESIGN

Figure 3. AFFIRM-AL Global Study Design



- Designed under SPA agreement with a significance level of 0.10‡
- Interim analysis when ~50% events have occurred

*Initiation of daratumumab at randomization is allowed at the discretion of the investigator. Randomization is stratified based on patients' 6MWT distance (<300 vs ≥300 meters) and initiation of daratumumab.
†The initial first-line chemotherapy regimen must include bortezomib.
‡A *P*≤0.10 will indicate that the result is statistically significant.

AL, amyloid light chain; 6MWT, 6-Minute Walk Test; IV, intravenous; NT-proBNP, N-terminal pro-brain 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

STUDY ASSESSMENTS AND STATISTICAL CONSIDERATIONS

- Routine screening assessments will be performed at baseline and patients who enroll will remain on study until completion, which will occur when a predefined number of primary endpoint events (ACM) have been reached
  - An interim analysis will be conducted when ~50% of the events have occurred
  - All patients will be followed until the last primary endpoint event has occurred
- Safety will be routinely monitored by assessing vital signs, 12-lead electrocardiograms, routine laboratory assessments, frequency and severity of adverse events, and immunogenicity
  - Adverse events will be graded by National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0
- Primary analysis of ACM-free survival is event driven; the estimated overall study duration is approximately 30 months, including the screening, enrollment, and treatment periods
- With a planned sample size of N=150, the trial provides sufficient power for the primary endpoint of time to ACM
  - Using the O'Brien-Fleming group sequential methodology, the overall significance level of 0.10 will be divided between the interim and final analyses
- An independent data monitoring committee (DMC) will review data on a regular basis at selected intervals to ensure that birtamimab is safe and well tolerated
  - The DMC will also evaluate the results of the interim analysis and determine if the trial can be stopped early for overwhelming efficacy

CONCLUSIONS

- Birtamimab is the only investigational therapeutic that has shown a significant survival benefit in Mayo Stage IV AL amyloidosis patients post hoc in a placebo-controlled study
- AFFIRM-AL is a confirmatory Phase 3 global study of birtamimab in Mayo Stage IV AL amyloidosis patients
- Site initiations and patient randomization are ongoing
  - Approximately 150 patients may be enrolled in the study (100 and 50 patients in the birtamimab and placebo arms, respectively)
- Approximately 100 global sites are planned for this study
- Enrollment is planned for sites in:
  - Austria, Belgium, Czechia, Denmark, France, Germany, Greece, Hungary, Ireland, Israel, Italy, Netherlands, Poland, Portugal, Spain, Turkey, United Kingdom
  - Australia, Japan, Republic of Korea (South Korea), Taiwan
  - Canada, United States

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AUTHOR DISCLOSURES
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