Survival Benefit of Birtamimab in Mayo Stage IV AL Amyloidosis in the Phase 3 VITAL Study Consistent After Adjustment for Key Baseline Variables

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There Is an Urgent Need for Therapies That Improve Survival in Patients With Advanced AL Amyloidosis

- **Amyloid light chain (AL) amyloidosis is a rare, progressive, and typically fatal disorder caused by an underlying plasma cell dyscrasia**
- **Misfolded kappa (κ) and lambda (λ) immunoglobulin light chain proteins[1,2] form aggregates that can cause cellular toxicity and form amyloid fibrils that deposit in tissues, causing organ dysfunction that is the hallmark of advanced AL amyloidosis[3]**
- **Using the validated 2012 Mayo Clinic Staging System, Stage IV patients have the highest risk for early death (median survival from diagnosis of 5.8 months)[4]**

Survival by Mayo 2012 Stage

N=810 patients with AL amyloidosis[4]

Mayo 2012 Stage	Median OS, Months (95% CI)	5-Year Survival Rate (%)
I	94.1 (64–154)	59
II	40.3 (24–59)	42
III	14.0 (11–18)	20
IV	**5.8 (5–7)**	**14**

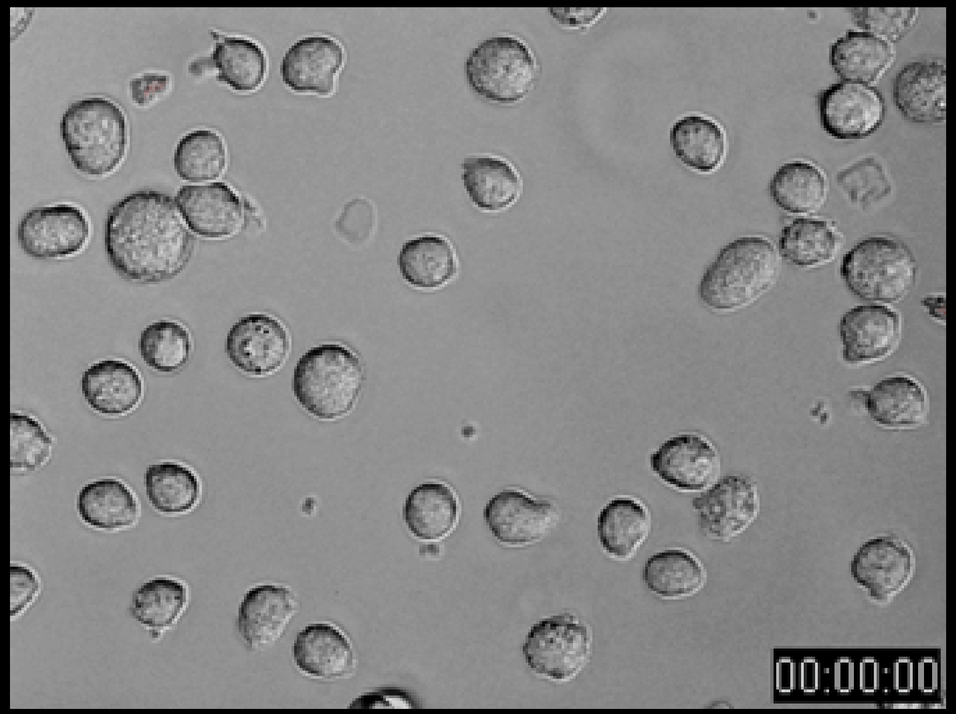
Current treatments target plasma cells to decrease production of immunoglobulin light chains and have not yet demonstrated a survival benefit in patients with advanced AL amyloidosis[5–7]

CI, confidence interval; OS, overall survival.

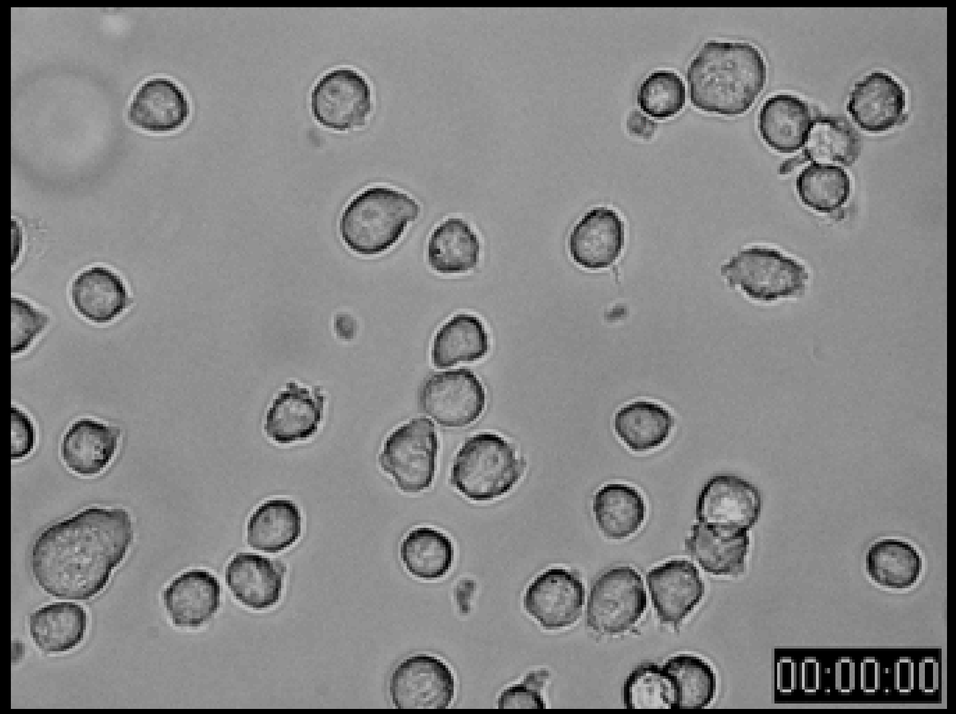
1. Bayliss M, et al. *Orphanet J Rare Dis*. 2017;12:1-10; 2. Renz M, et al. *Amyloid*. 2016;23:168-177; 3. Merlini G, et al. *Nat Rev Dis Primers*. 2018;4:38; 4. Kumar S, et al. *J Clin Oncol*. 2012;30:989-995; 5. Muchtar E, et al. *Mayo Clin Proc*. 2021;96:1546-1577; 6. Staron A, et al. *Blood Cancer J*. 2021;11:139; 7. Kastritis E, et al. *N Engl J Med*. 2021;385:46–58.

Birtamimab Is an Investigational Humanized IgG1 mAb that Directly Binds To a Conserved Epitope on Both κ and λ Immunoglobulin Light Chain Isoforms[1]

Isotype Control mAb[2]



m-Birtamimab[2]*



Birtamimab:

- **neutralizes and disaggregates circulating soluble, toxic light chain aggregates[1]**
- **depletes insoluble AL amyloid deposits by inducing macrophages to clear amyloid via phagocytosis[1,3†]**

*m-Birtamimab is the murine form of birtamimab (2A4); †Phagocytosis shown here in a human macrophage cell line [THP-1]).
AL, light chain; mAb, monoclonal antibody.

1. Renz M, et al. *Amyloid*. 2016;23:168-177; 2. Prothena, Data on File; 3. Wall JS, et al. *PLoS One*. 2012;7:e52686.

VITAL: Phase 3 Multicenter, Double-Blind, Placebo-Controlled RCT in Newly Diagnosed Treatment-Naïve AL Amyloidosis Patients[1,2]

THE VITAL AMYLOIDOSIS STUDY

Key Inclusion Criteria
- ≥18 years old
- Confirmed diagnosis of AL amyloidosis
- Newly diagnosed and treatment naïve
- Cardiac involvement
  - NT-proBNP ≥650 pg/mL and ≤8500 pg/mL

Key Exclusion Criteria
- Non-AL amyloidosis or MM
- NT-proBNP >8500 pg/mL
- Plans to undergo ASCT or receipt of prior anti-PCD therapy

Screening → 1:1 Randomization (N=260)

Birtamimab
(24 mg/kg IV) + SoC*
n=130

Infusion every 28 days for 42 months

Placebo
(normal saline IV) + SoC*
n=130

End of study/early treatment discontinuation visit† → Open-label extension study

Interim futility analysis performed in April 2018 resulted in early study termination

Stratification criteria:
- 6MWT (<300 m vs ≥300 m)
- Mayo Stage (I/II vs III/IV)
- Renal Stage (I vs II/III)

Primary endpoint:
Time to all-cause mortality (ACM) or cardiac hospitalization (CH)

Key secondary endpoints:
- Change from baseline to month 9 in 6MWT distance
- Change from baseline to month 9 in the SF-36v2 PCS

Safety

Post hoc analyses:
- Time to ACM in Mayo Stage IV patients at month 9‡
- Sensitivity analyses of time to ACM in Mayo Stage IV patients adjusted for baseline characteristics

The primary composite endpoint of time to ACM or CH in the overall population (n=260) favored birtamimab over placebo, but the difference was not statistically significant (HR=0.826 [95% CI: 0.574, 1.189]; log-rank *P*=0.303)

*SoC at the time of the study; †28–35 days after last dose; ‡Censoring at month 9 was based on observed median overall survival in placebo arm (8.3 months) and for consistency with secondary endpoints.
6MWT, 6-minute walk test; AL, light chain; ASCT, autologous stem call transplant; CI, confidence interval; ECG, electrocardiogram; HR, hazard ratio; IV, intravenous; MM, multiple myeloma; NT-proBNP, N-terminal pro-brain natriuretic peptide; PCD, plasma cell-directed; RCT, randomized controlled trial; SF-36v2 PCS, Short Form-36 Version 2 Physical Component Score; SoC, standard of care.

1. Gertz M, et al. *Blood*. 2019;134:3166 [Abstract and Poster]; 2. VITAL Study; NCT02312206. Accessed October 2022. https://clinicaltrials.gov/ct2/show/NCT02312206.

VITAL Patient Demographics Were Balanced Between Treatment Arms

	All Patients (N=260)		Mayo Stage IV Patients (n=77)	
	Birtamimab + SoC (n=130)	Placebo + SoC (n=130)	Birtamimab + SoC (n=38)	Placebo + SoC (n=39)
Age, years, median (Q1, Q3)	64.2 (57.6, 70.9)	62.6 (57.0, 69.3)	63.6 (55.7, 69.8)	63.7 (57.0, 68.4)
Male, n (%)	82 (63.1)	90 (69.2)	25 (65.8)	28 (71.8)
Ethnicity, n (%)				
Hispanic or Latino	2 (1.5)	2 (1.5)	0	0
Not Hispanic or Latino	116 (89.2)	122 (93.8)	34 (89.5)	36 (92.3)
Not provided or unknown	12 (9.2)	6 (4.6)	4 (10.5)	3 (7.7)
Race, n (%)				
White	118 (90.8)	120 (92.3)	36 (94.7)	36 (92.3)
Black or African American	9 (6.9)	3 (2.3)	2 (5.3)	2 (5.1)
Asian	2 (1.5)	2 (1.5)	0	0
Other	1 (0.8)	5 (3.8)	0	1 (2.6)

QX, quartile *X*; SoC, standard of care.

VITAL Patient Baseline Disease Characteristics Were Balanced Between Treatment Arms

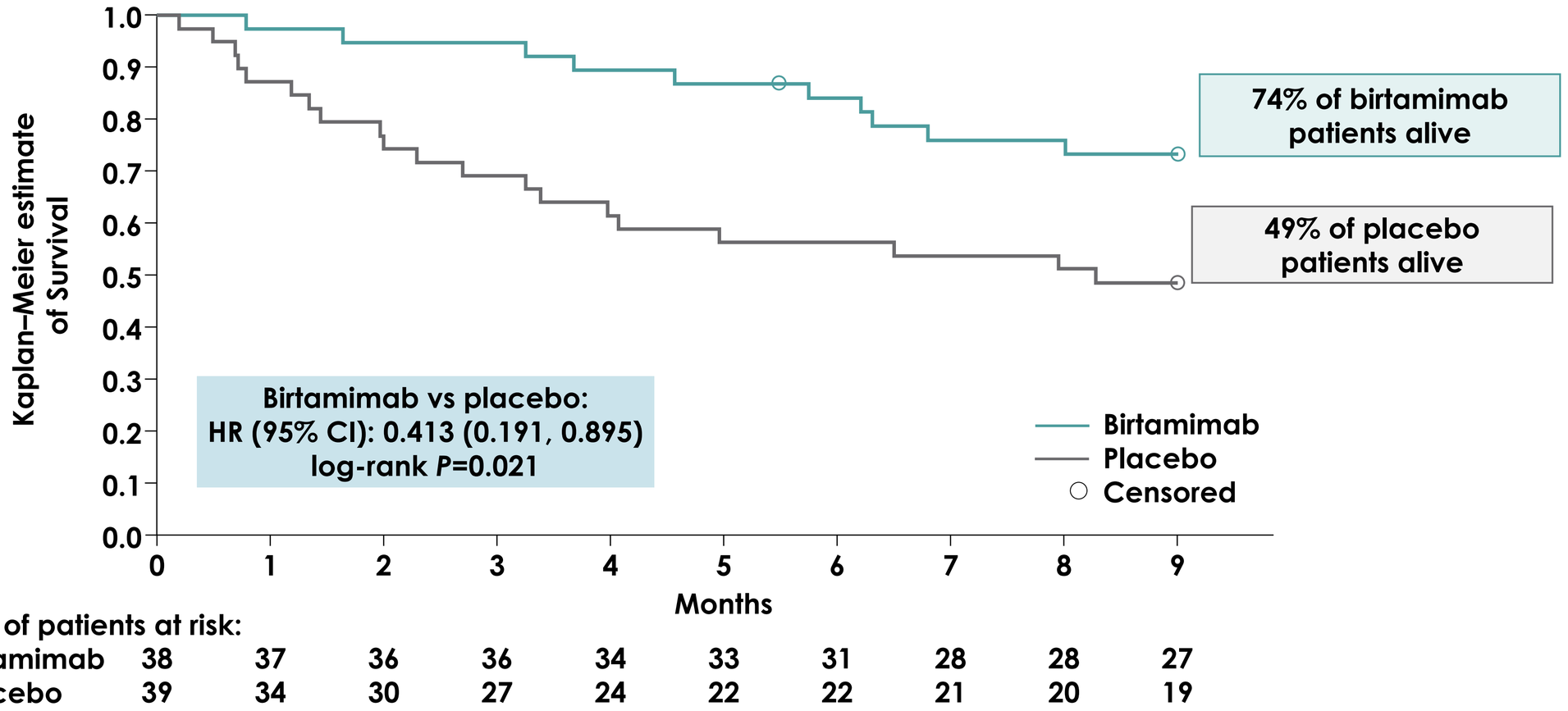
	All Patients (N=260)		Mayo Stage IV Patients (n=77)	
	Birtamimab + SoC (n=130)	Placebo + SoC (n=130)	Birtamimab + SoC (n=38)	Placebo + SoC (n=39)
Duration since AL amyloidosis diagnosis, months, median (Q1, Q3)	1.31 (0.92, 1.87)	1.48 (0.95, 2.17)	1.15 (0.69, 1.58)	1.45 (0.89, 1.81)
Number of derived involved organs at baseline, median (Q1, Q3)	2.0 (1.0, 2.0)	2.0 (1.0, 2.0)	1.5 (1.0, 2.0)	2.0 (1.0, 2.0)
Screening NT-proBNP, pg/mL, median (Q1, Q3)	3146.2 (1650.0, 5173.0)	3183.7 (1910.0, 5551.0)	5141.3 (3228.0, 5939.4)	5415.0 (4054.0, 8073.0)
Screening troponin-T,* ng/mL, median (Q1,Q3)	0.03 (0.02, 0.06)	0.02 (0.02, 0.08)	0.05 (0.04, 0.09)	0.09 (0.06, 0.13)
Baseline dFLC,† mg/dL, median (Q1, Q3)	26.31 (13.83, 53.05)	38.18 (18.00, 63.06)	44.44 (25.13, 56.17)	57.42 (35.52, 106.28)
Mayo Stage, n (%)				
I	11 (8.5)	10 (7.7)	N/A	N/A
II	34 (26.2)	28 (21.5)	N/A	N/A
III	47 (36.2)	53 (40.8)	N/A	N/A
IV	38 (29.2)	39 (30.0)	38 (100)	39 (100)

*Mayo Stage criteria for troponin-T levels were modified from a value of 0.025 ng/mL cited in Kumar et al[1] to 0.03ng/mL, the lowest validated determination for the commercially available test; †Baseline dFLC is calculated only for patients with an abnormal baseline FLC ratio (kappa/lambda <0.26 or >1.65) and is defined as the difference between involved and uninvolved FLCs.

AL, light chain; dFLC, difference between involved minus uninvolved serum free light chains; N/A, not applicable; NT-proBNP, N-terminal pro-brain natriuretic peptide; Q*X*, quartile *X*; SoC, standard of care.

1. Kumar S, et al. *J Clin Oncol*. 2012;30:989-995.

Post Hoc Analyses in Mayo Stage IV Patients (n=77) Showed Significant Improvement in ACM With Birtamimab at Month 9*

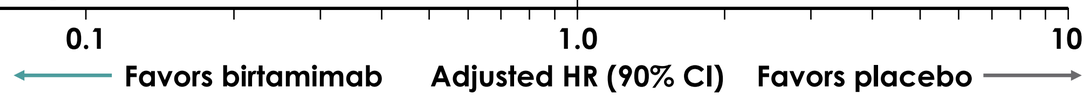


Survival curves separated early between the two treatment arms; at month 9, 74% of Mayo Stage IV patients treated with birtamimab and 49% of those given placebo survived

*The 9-month time point was chosen based on median overall survival in the placebo arm of 8.3 months and to align with secondary endpoints which looked at change from baseline at month 9.
ACM, all-cause mortality; CI, confidence interval; HR, hazard ratio.

Sensitivity Analyses of Birtamimab Survival Benefit at Month 9 in Mayo Stage IV Patients (n=77) Confirmed Robustness of Post Hoc Result

Baseline Variable	Adjusted HR (90% CI)
Age	0.414 (0.216, 0.792)
Sex	0.415 (0.216, 0.796)
Race	0.399 (0.208, 0.765)
Ethnicity	0.419 (0.218, 0.804)
Age at diagnosis	0.414 (0.216, 0.792)
Duration since diagnosis (months)	0.420 (0.215, 0.820)
NT-proBNP	0.460 (0.238, 0.889)
dFLC	0.465 (0.243, 0.889)
FLC	0.410 (0.213, 0.788)
NYHA class	0.381 (0.194, 0.750)
Troponin-T	0.422 (0.220, 0.812)
6MWT distance	0.336 (0.173, 0.651)



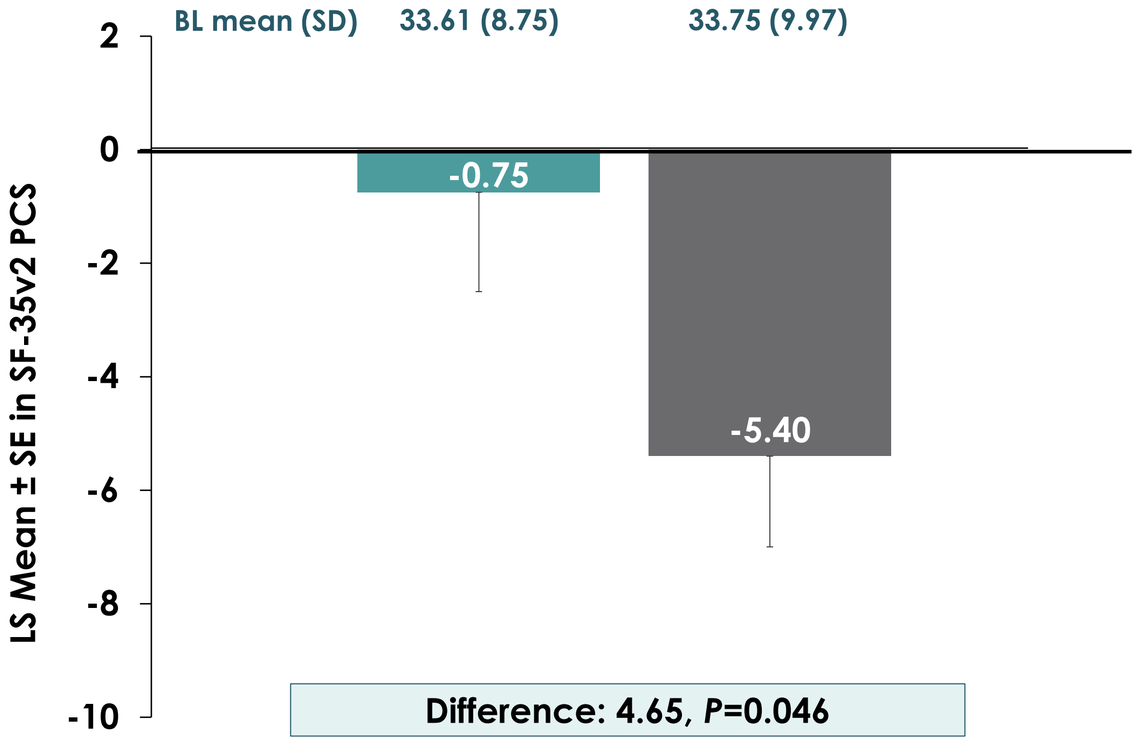
After adjustment for key baseline demographic, clinical, and laboratory variables, the adjusted HRs for ACM at month 9 ranged from 0.336 to 0.465, with all upper bounds of the 90% CI <1.0

Semi-parametric Cox regression model with randomization strata (Renal Stage, 6MWT distance) was used with each baseline variable added separately to assess impact on overall survival. All adjudicated deaths prior to month 9 were included in analysis.

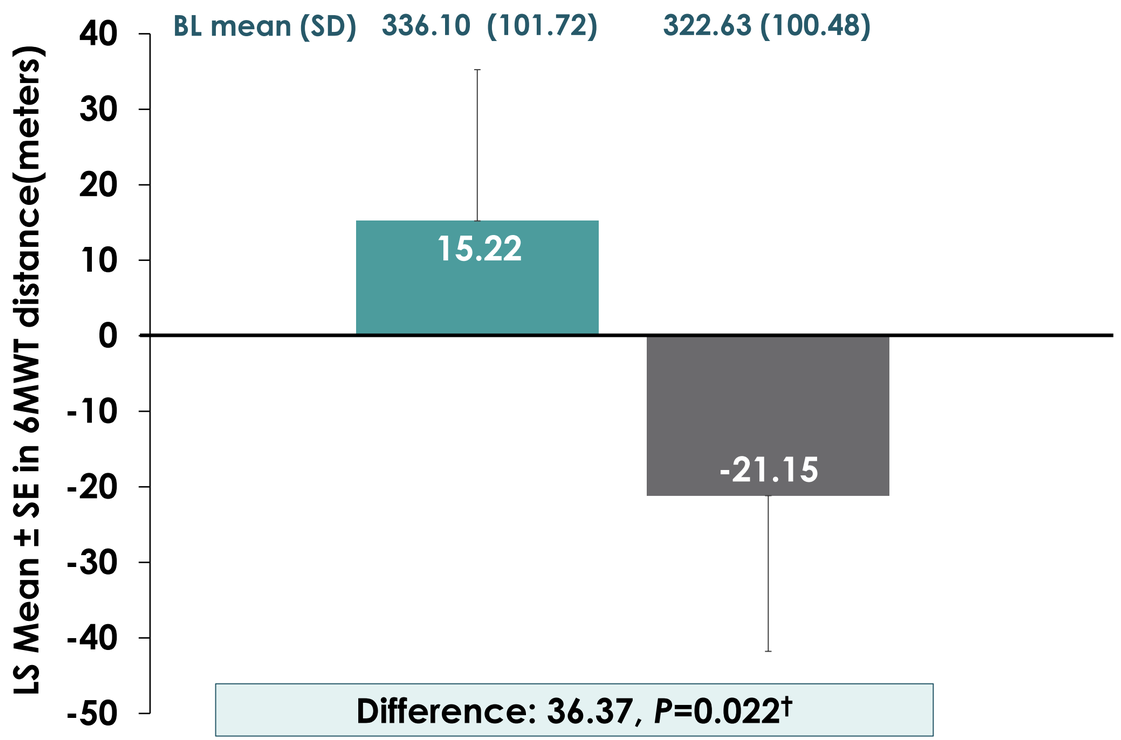
6MWT, 6-minute walk test; ACM, all-cause mortality; CI, confidence interval; dFLC, difference between involved minus uninvolved serum free light chains; FLC, free light chain; HR, hazard ratio; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association.

In Mayo Stage IV Patients, Birtamimab Was Associated With Less Deterioration in Quality of Life and Improved 6MWT Distance At Month 9

SF-36v2 PCS Change from Baseline at Month 9*



6MWT Distance Change from Baseline at Month 9*



Birtamimab + SoC (n=38) Placebo + SoC (n=39)

*Estimates of the LS mean and SE for each treatment group were estimated using an MMRM methodology including fixed effects for treatment group, categorical time point (all postbaseline visits), treatment group by visit interaction, stratification factors (Renal Stage: I, II/III; baseline 6MWT distance: <300 meters, ≥300 meters), the associated baseline value as a covariate, and a compound symmetry covariance structure to model the within-patient errors; †6MWT distance values were ranked from worst (lowest distance) to best (highest distance) performance per a 7-step ranking algorithm and *P*-values are based on a rank ANCOVA.
6MWT, 6-minute walk test; LS, least squares; MMRM, mixed-effect model for repeated measures; SF-36v2 PCS, Short Form-36 Version 2 Physical Component Score; SD, standard deviation; SE, standard error; SoC, standard of care.

Multiple Intravenous Infusions of Birtamimab Were Generally Safe and Well Tolerated Overall and in Mayo Stage IV Patients

Similar or Lower Rates of Treatment-Related TEAEs With Birtamimab Versus Placebo

n (%)	All Patients (N=260)		Mayo Stage IV Patients (n=77)	
	Birtamimab + SoC (n=130)	Placebo + SoC (n=130)	Birtamimab + SoC (n=38)	Placebo + SoC (n=39)
Patients reporting ≥1 of the following:				
Treatment-related TEAE	41 (31.5)	50 (38.5)	12 (31.6)	10 (25.6)
Treatment-related TEAE grade ≥3	6 (4.6)	12 (9.2)	1 (2.6)	4 (10.3)
Treatment-related serious TEAE	4 (3.1)	5 (3.8)	1 (2.6)	1 (2.6)
TEAE leading to study drug withdrawal	6 (4.6)	14 (10.8)	3 (7.9)	2 (5.1)
Treatment-related TEAE leading to death	0	0	0	0

- The four most common TEAEs* among Mayo Stage IV patients in the birtamimab and placebo arms were peripheral edema (55.3% vs 48.7%), constipation (42.1% vs 33.3%), nausea (42.1% vs 30.8%), and dyspnea (42.1% vs 30.8%)
- In the overall population, infusion-associated TEAEs† occurred in 5 (3.8%) patients in the birtamimab arm and 3 (2.3%) in the placebo arm; all were mild or moderate and began on day 1, except one grade 3 event that occurred in a birtamimab-treated patient on day 226 and resolved on the same day
- In Mayo Stage IV patients, infusion-associated TEAEs were reported in 3 patients in the birtamimab arm and included dyspnea (n=1), chest discomfort (n=1), and hypoxia concurring with an infusion-related reaction (n=1)

*Most common in the birtamimab arm; †Infusion-associated TEAEs as assessed by the investigator.
SoC, standard of care; TEAE, treatment-emergent adverse event.

VITAL Conclusions in Mayo Stage IV Patients

- **Post hoc analysis of Mayo Stage IV patients showed a significant improvement in time to all-cause mortality at month 9**
  - **At month 9, 74% of patients treated with birtamimab survived versus 49% of those given placebo**
- **The survival benefit of birtamimab in VITAL was consistent across all key baseline variables in Mayo Stage IV patients, reinforcing the strength of the survival data in these patients at high risk of early mortality**
- **Treatment with birtamimab in Mayo Stage IV patients was also associated with significantly less deterioration in QoL and improved cardiac functioning***
- **Birtamimab was generally safe and well tolerated in the overall patient population and in Mayo Stage IV patients in this study**

*Per 6MWT.
6MWT, 6-minute walk test; QoL, quality of life; SF-36 v2 PCS, Short Form-36 Version 2 Physical Component Score.

Birtamimab Summary and Future Directions

- **Birtamimab is an investigational antibody with a humanized amino acid sequence[1]**
- **Birtamimab selectively binds both circulating κ and λ isoforms of soluble light chain aggregates and insoluble AL amyloid deposits[2]**
- **Birtamimab half-life (13–16 days[2]) allows once-monthly IV dosing with 1-hour infusion**
- **Safety data from >300 patients with AL amyloidosis indicates birtamimab administered in clinical trials to date was well tolerated[1]**
- **Potential survival benefit observed with birtamimab in Mayo Stage IV patients in post hoc analysis of VITAL with HR=0.413 (*P*=0.021) at month 9**

AFFIRM-AL

Confirmatory Phase 3 global RCT of birtamimab in newly diagnosed, treatment-naïve patients with Mayo Stage IV AL amyloidosis (NCT04973137)[3] is active and enrolling

✓ **Study design under SPA with the FDA; primary endpoint all-cause mortality with *P*≤0.1**

✓ **2:1 randomization to birtamimab + SoC versus placebo + SoC**

For more information about AFFIRM-AL, please scan to visit the study website

AL, light chain; FDA, Food and Drug Administration; HR, hazard ratio; SoC, standard of care; SPA, Special Protocol Agreement.

1. Gertz MA, et al. *J Clin Oncol*. 2016;34:1097-1103; 2. Renz M, et al. *Amyloid*. 2016;23:168-177; 3. AFFIRM-AL Amyloidosis Study; NCT04973137. Accessed October 2022. https://clinicaltrials.gov/ct2/show/NCT04973137.

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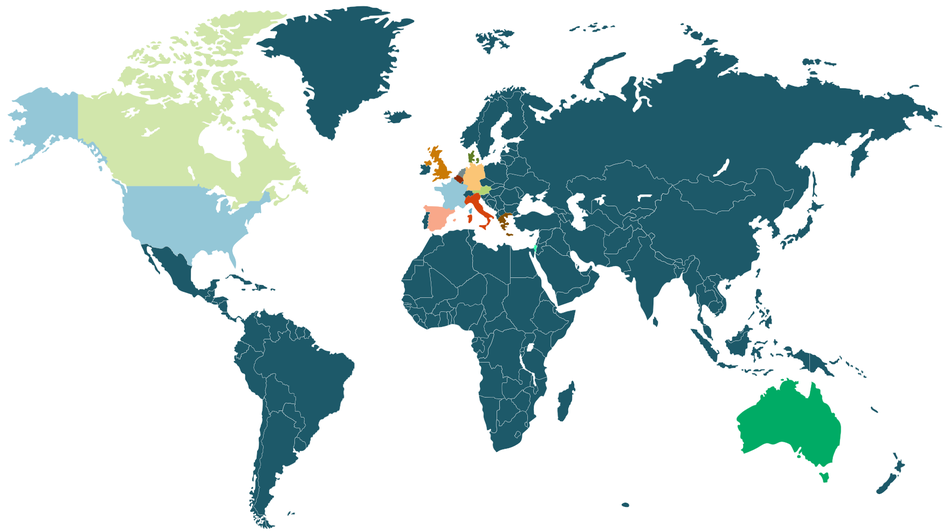

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