AFFIRM-AL STUDY

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Protocol NEOD001-301

STUDY OVERVIEW

The AFFIRM-AL Study is a clinical research study evaluating an investigational drug called birtamimab for adults who are newly diagnosed with AL amyloidosis and in Mayo Stage IV.

TARGET POPULATION

Adults age 18+ who are newly diagnosed with AL amyloidosis, are in Mayo Stage IV and are treatment-naïve.

NUMBER IN TRIAL

Looking for 150 patients spread out over sites in North America, Europe, Israel, Asia and Australia.

KEY OBJECTIVES

Primary:

- To evaluate the efficacy of birtamimab plus standard of care compared to placebo plus standard of care when administered intravenously in Mayo Stage IV subjects with AL amyloidosis by assessing time to all-cause mortality.

Secondary:

- To evaluate birtamimab plus standard of care compared to placebo plus standard of care on the following:
  - Change from baseline to Month 9 in the 6-Minute Walk Test (6MWT) distance.
  - Change from baseline to Month 9 in health-related quality of life using the Short Form-36 questionnaire Version 2 (SF-36v2).

INCLUSION CRITERIA

Subjects must meet ***all*** of the following criteria:

1. Aged ≥18 years and legal age of consent according to local regulations.
2. Newly diagnosed and AL amyloidosis treatment-naïve.
3. Bone marrow demonstrating clonal plasma cells.
4. Confirmed diagnosis of AL amyloidosis by the following:
   - Histochemical diagnosis of amyloidosis determined by polarizing light microscopy of green birefringent material in Congo red-stained tissue specimens **OR** characteristic electron microscopy appearance.

   AND

   - Confirmatory immunohistochemistry **OR** mass spectroscopy of AL amyloidosis.
5. If the subject meets any of the following:
   - Is black or of African American descent.
   - Is over 75 years of age with concurrent monoclonal gammopathy.
   - Has a history of familial amyloidosis and has concurrent monoclonal gammopathy.

INCLUSION CRITERIA CONTINUED

AND

- No tissue is available for typing and the subject has echocardiographic evidence of amyloidosis and biopsy-proven amyloidosis with a monoclonal gammopathy, then subject must have gene sequencing consistent with transthyretin (TTR) wild type (i.e., no TTR mutation present) AND must score 0 in technetium-99m-3,3-diphosphono-1,2 propanodicarboxylic acid, hydroxymethylenediphosphonate or pyrophosphate scintigraphy.

6. Cardiac involvement as defined by ***all*** of the following:
   - Past documented or presently noted clinical signs and symptoms supportive of a diagnosis of heart failure in the setting of a confirmed diagnosis of AL amyloidosis in the absence of an alternative explanation for heart failure.
   - Either an endomyocardial biopsy demonstrating AL amyloidosis or an echocardiogram demonstrating a mean left ventricular wall thickness at diastole >12 mm in the absence of other causes (e.g., severe hypertension, aortic stenosis), which would adequately explain the degree of wall thickening.

INCLUSION CRITERIA CONTINUED

7. Confirmed Mayo Stage IV as defined by:
   - NT-proBNP ≥1800 pg/mL and
   - Troponin-T ≥0.025 ng/mL (mcg/L) or high sensitivity cardiac troponin T≥40 ng/L and
   - dFLC ≥18 mg/dL
8. Planned first-line chemotherapy contains bortezomib administered subcutaneously weekly.
9. Adequate bone marrow reserve, hepatic function and renal function, as demonstrated by:
   - Absolute neutrophil count ≥1.0 × 10^9/L
   - Platelet count ≥75 × 10^9/L
   - Hemoglobin ≥9 g/dL
   - Total bilirubin ≤2 × the upper limit of normal (ULN)(***except*** for subjects with Gilbert's syndrome, in which case direct bilirubin ≤2 × ULN)
   - Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase ≤3 × ULN
   - Alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase ≤3 × ULN
   - Alkaline phosphatase (ALP) ≤5 × ULN (***except*** for subjects with hepatomegaly and isozymes specific to liver, rather than bone)
   - Estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m^2 as estimated by the Chronic Kidney Disease Epidemiology Collaboration equation

INCLUSION CRITERIA CONTINUED

10. Seated systolic blood pressure (BP) 90 to 180 mmHg.
11. Distance walked during each Screening 6MWT is ≥30 meters and ≤550 meters.
12. Women of childbearing potential (WOCBP) must have 2 negative pregnancy tests during Screening, the second within 24 hours prior to the first administration of study drug and must agree to use highly effective physician-approved contraception from Screening to 90 days following the last study drug administration.
13. Male subjects must be surgically sterile or must agree to use highly effective physician-approved contraception from Screening to 90 days following the last study drug administration.
14. Ability to understand and willingness to sign an Informed Consent Form prior to initiation of any study procedures.

EXCLUSION CRITERIA

Subjects must meet ***none*** of the following criteria:

1. Non-AL amyloidosis.
2. NT-proBNP >8500 pg/mL.
3. Meets the International Myeloma Working Group (IMWG) definition of multiple myeloma, ***except*** for malignancy biomarker of involved/and uninvolved serum free light chain ratio ≥100.
4. Subject is eligible for ***and*** plans to undergo ASCT or organ transplant during the study.
5. Symptomatic orthostatic hypotension that in the medical judgment of the Investigator would interfere with the subject's ability to safely receive treatment or complete study assessments.
6. Myocardial infarction, uncontrolled angina, severe uncontrolled ventricular arrhythmias, or ECG evidence of acute ischemia, within 6 months prior to the Month 1-Day 1 Visit.
7. Severe valvular stenosis (e.g., aortic or mitral stenosis with a valve area <1.0 cm^2) or severe congenital heart disease.

EXCLUSION CRITERIA

8. ECG evidence of acute ischemia or active conduction system abnormalities ***with the exception*** of any of the following:
   - First degree AV-block
   - Second degree AV-block Type 1 (Mobitz Type 1/ Wenckebach type)
   - Right or left bundle branch block
   - Atrial fibrillation with a controlled ventricular rate (uncontrolled [>110 bpm] ventricular rate is not allowed [determined by an average of 3 beats in Lead II or 3 representative beats if Lead II is not representative of the overall ECG])
9. Peripheral neuropathy assessed as National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Grade 2 with pain, Grade 3 or Grade 4.
10. Subject is receiving oral or intravenous antibiotics, antifungals, or antivirals within 1 week of Month 1-Day 1 with the exception of prophylactic oral agents.
11. Prior treatment with hematopoietic growth factors, transfusions of blood or blood products within 1 week of Month 1-Day 1.
12. Prior radiotherapy within 4 weeks of Month 1-Day 1.
13. Major surgery within 4 weeks of Month 1-Day 1 or planned major surgery during the study.

EXCLUSION CRITERIA

14. Active malignancy ***with the exception*** of any of the following:
    - Adequately treated cutaneous basal cell carcinoma, squamous cell carcinoma or in situ cervical cancer.
    - Adequately treated Stage I cancer from which the subject is currently in remission and has been in remission for 2 years.
    - Low-risk prostate cancer with Gleason score <7, prostate-specific antigen <10 ng/mL, and a stage of cancer at most cT2a, cN0, and CM0.
    - Any other cancer from which the subject has been disease-free for ≥2 years.
15. History of severe allergy to any of the components of birtamimab such as histidine/L histidine hydrochloride monohydrate, trehalose dehydrate or polysorbate 20, or history of Grade ≥3 infusion-related AEs or hypersensitivity to another monoclonal antibody, or known hypersensitivity to diphenhydramine (or an equivalent H1 antihistamine) or acetaminophen (or its equivalent, paracetamol)
16. Known unresolved or active HIV, hepatitis B, hepatitis C, or SARS-CoV-2 infection.
17. 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.

EXCLUSION CRITERIA

18. Treatment with another investigational agent within 30 days of Month 1-Day 1.
19. Women who are pregnant or lactating.
20. Any condition which could interfere with, or the treatment for which might interfere with, the conduct of the study or which would, in the opinion of the Investigator, unacceptably increase the subject's risk by participating in the study.
21. Subject is under legal custodianship.
22. History of epilepsy or seizure disorder ***with the exception of*** childhood febrile seizures.
23. Waldenström's macroglobulinemia and/or immunoglobulin M monoclonal gammopathy.

For a complete list of inclusion/exclusion criteria with references, please refer to the most recent version of Protocol NEOD001-301.

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