

Marianna Fontana,¹ Julian D. Gillmore,¹ Joseph Selvanayagam,² Dariusz Korczyk,³ Olga Motorna,⁴ Graham Hillis,⁵ James L. Hare,⁶ Mazen Hanna,⁷ Brian Drachman,⁸ Ahmad Masri,⁹ Brett W. Sperry,¹⁰ Vasvi Singh,¹¹ Joban Vaishnav,¹² Jonathan S. Wall,¹³ Claire Sherman,¹⁴ Gregory Bell,¹⁴ Matthew Meldorf¹⁴

¹University College London, Royal Free Hospital, London, United Kingdom; ²Flinders Medical Centre, Bedford Park, SA, Australia; ³Princess Alexandra Hospital, Box Hill, VIC, Australia; ³Princess Alexandra Hospital, Box Hill, VIC, Australia; ³Princess Alexandra, OH, USA; ⁸University of Pennsylvania, Philadelphia, PA, USA; ¹⁴Attralus, Inc, Burlingame, CA, USA; ¹³University of Tennessee Graduate School of Medicine, Knoxville, TN, USA; ¹⁴Attralus, Inc, Burlingame, CA, USA ¹⁵University of Tennessee Graduate School of Medicine, Knoxville, TN, USA; ¹⁴Attralus, Inc, Burlingame, CA, USA ¹⁴

Systemic Amyloidosis

- Systemic amyloidosis is a group of progressive, debilitating, and often fatal diseases,¹ with a median life expectancy of 2 to 5 years in patients with cardiac involvement²
- There are approximately 17 different types of systemic amyloid diseases, each caused by a specific precursor protein that deposits in the extracellular space as amyloid fibrils³
- Deposition of insoluble amyloid fibrils in organs such as the heart, kidneys, liver, and nerves leads to organ dysfunction and is associated with significant morbidity and mortality⁴
- Current therapies target the precursor protein slowing disease progression, but do not directly address the underlying amyloid deposits²

AT-02: A Humanized IgG1-Peptide Fusion with Pan-Amyloid Reactivity

- AT-02 is a humanized IgG1 monoclonal antibody with an amyloid binding peptide genetically fused to the light chain, mediating pan-amyloid binding to trigger macrophage-mediated phagocytosis (**Figure 1**)
- The pan-amyloid reactive peptide p5R is fused to the C-terminal of the light chain
- Peptide p5R binds the ubiquitous hypersulfated glycosaminoglycans and fibrils in amyloid via electrostatic interactions
- AT-02 was designed to be capable of:
- Binding to all types of amyloid deposits with high potency
- Opsonizing the deposits and promoting macrophage-mediated amyloid clearance
- Binding complement to enhance phagocytosis of amyloid

Figure 1. AT-02 Structure



- AT-02 demonstrated potent binding to AL and ATTR amyloid extracts, with <0.5 nM binding (EC50)
- When injected intravenously, AT-02 colocalized with AL amyloid in the heart of a murine model of AL λ 6 amyloidosis
- AT-02 enhanced macrophage-mediated phagocytosis of AL and ATTR amyloid extracts *in vitro* and *in vivo* using a murine model of human AL amyloidoma (Figure 2 and Figure 3)
- Opsonization of human AL amyloid with AT-02 expedited clearance of the mass *in vivo*
- AT-02 treatment caused significant reductions of cardiac, renal, and hepatic amyloid in a transgenic mouse model of aggressive AA amyloidosis (**Figure 4**)

Amyloid In Vitro

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Phase 2 Clinical Trial Design of AT-02 Phase 2 Open-Label Extension Study in Systemic Amyloidosis

Summary of Pre-clinical Results



150

Concentration (nM)

250

Figure 2. AT-02 Promotes Phagocytosis of ATTR and AL

Figure 3. AT-02 Promotes Phagocytosis of Amyloid *In Vivo*



Figure 4. AT-02 Reduced Amyloid Deposition in an AA mouse model



50

Phase 2 Extension Study

Objectives

- The primary objective is to assess the safety and tolerability of AT-02 in patients with systemic amyloidosis
- The secondary objectives include assessment of pharmacokinetics, immunogenicity, and clinical activity of AT-02

Participants

 The AT-02 phase 2 open-label extension trial will enroll patients ≥18 years old with systemic amyloidosis, who have completed the SAD or MD portion of the phase 1 trial

Figure 5. Study Design



*ECHO and CMR read and analyzed by centralized core labs

Conclusions

- AT-02 is a novel antibody-peptide fusion protein designed as a pan-amyloid clearing therapeutic
- In pre-clinical studies AT-02 bound diverse types of amyloid and amyloid-like fibrils with high potency (EC50 <0.5 nM) and caused significant reduction of cardiac, renal and hepatic amyloid
- AT-02 is currently in phase 1/2 clinical trials and could represent a novel therapeutic agent for the removal of systemic amyloid deposits of diverse types

Abbreviations

6-MWT, Six Minute Walk Test Distance; AA, amyloid A; AApoAI, Apo AI amyloidosis; AApoAIV, Apo AIV amyloidosis; AL, amyloid light-chain; ATTR, transthyretin amyloid; CMR, cardiac magnetic resonance; CR, complete response; EC50, half-maximal effective concentration; ECHO, echocardiogram; ECV, extracellular volume; IgG1, immunoglobulin G1; KCCQ-23, Kansas City Cardiomyopathy Questionnaire-23; MD, multiple dose; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association; SAD, single ascending dose; TEAE, treatment-emergent adverse event ; VGPR, very good partial response.

References

- 1. Muchtar E et al. *J Intern Med*. 2021;289:268-292.
- 2. Kittleson MM et al. *J Am Coll Cardiol*. 2023;81(11):1076-1126. 3. Benson MD et al. *Amyloid*. 2018;25:215-219.
- 4. Castano A et al. *Heart Fail Rev.* 2015;20:163-178



• Patients from the MD portion of the phase 1 study must have AL, ATTR, AApoAI, or AApoAIV amyloidosis, with evidence of amyloid by CMR and elevated NT-proBNP levels

Study Design

- The study design is presented in **Figure 5**
- Primary endpoints include incidence, frequency, and severity of TEAEs and change from baseline in clinical laboratory results
- Secondary endpoints include change from baseline in extracellular volume by CMR, measures of structure and function using CMR and echocardiography, NT-proBNP and troponin levels, NYHA functional classification, KCCQ-23, and 6-MWT

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Disclosures

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