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PRESENTATION #693

# Renal and cardiac responses in a phase 1/2 study of AT-02, a novel pan-amyloid depleter IgG fusion protein for the treatment of patients with AL amyloidosis

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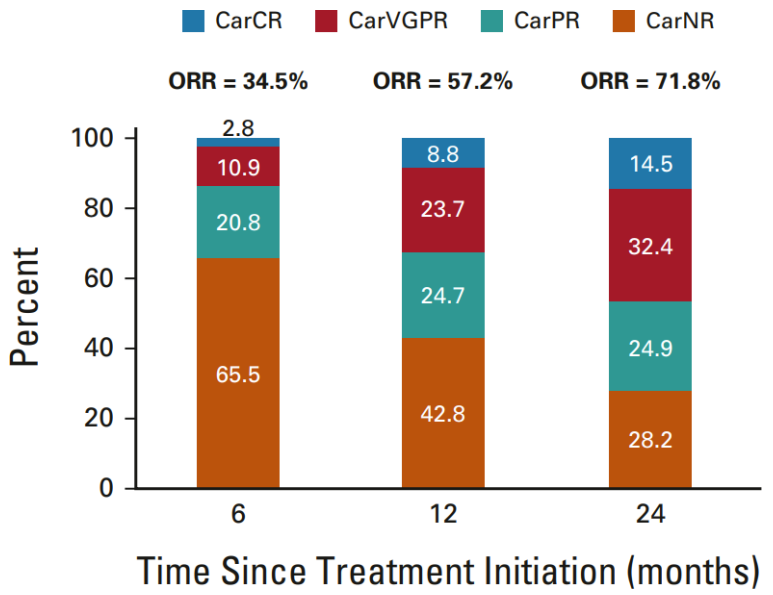
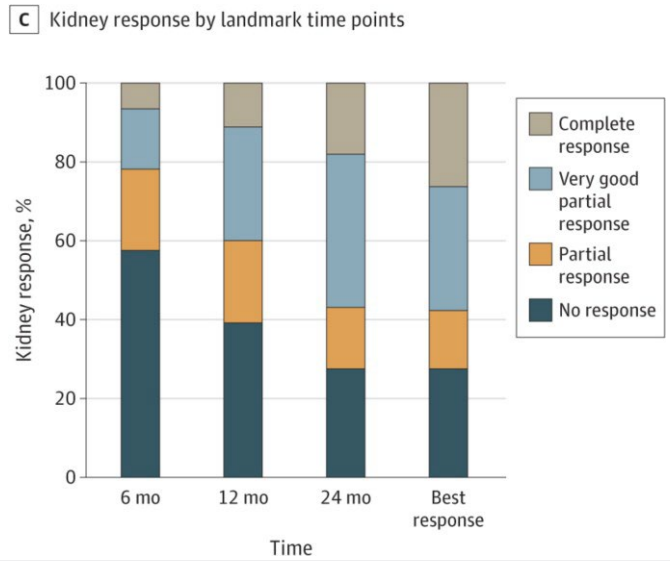
# Unmet Needs in AL Amyloidosis

- Significant advances in plasma cells-targeted therapies
  - Organ dysfunction remains a major challenge in AL amyloidosis
  - Recent trials of fibril depleters in newly diagnosed cardiac AL patients were not successful
- There are currently no therapies to address organ dysfunction in patients with AL amyloidosis who achieved favorable hematological remission (CR/VGPR)
  - Cardiac and renal organ involvement are common, and drive morbidity and mortality
  - A minority of patients achieve complete organ response






Muchtar et al. JCO 2022, Muchtar et al. JAMA Onc 2024

# Change In eGFR At 24-Months In Relation to Renal Response At That Time Point

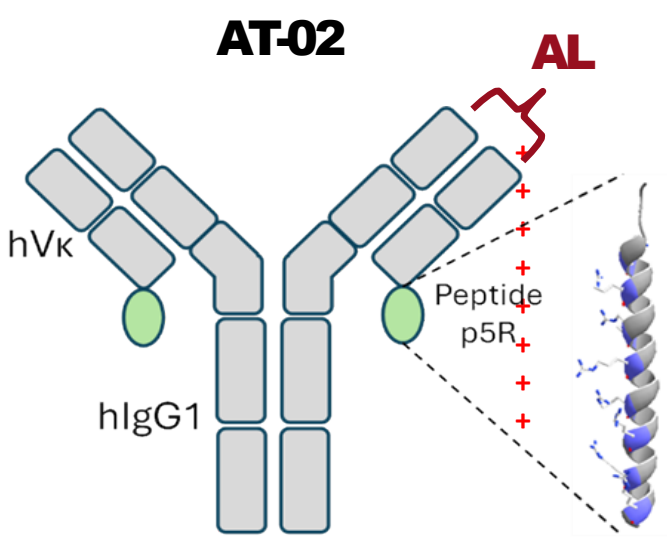
| | Change in eGFR from baseline at 24-months |
|---|---|
| Renal CR | -5 |
| Renal VGPR | -4 |
| Renal PR | -4 |
| Renal NR | -9 |

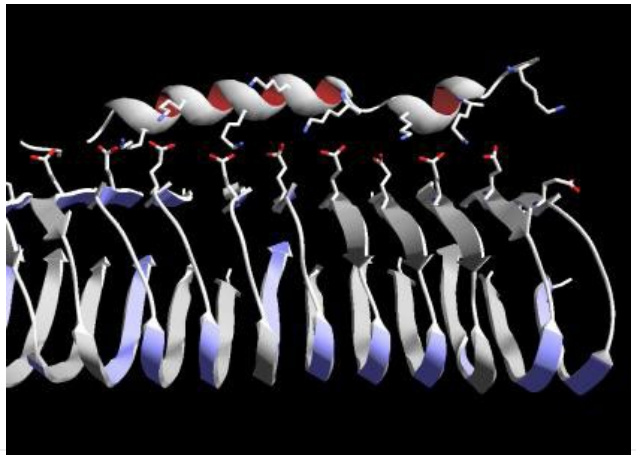


Mukhtar et al. ARC FDA Forum 2025

# AT-02 is a Pan-Amyloid Fusion Protein designed to deplete Amyloid

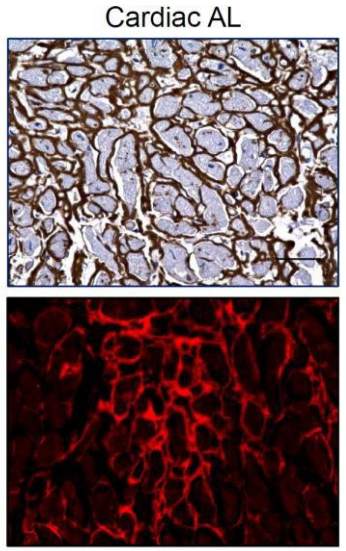
- High affinity binding to amyloid fibrils and hyper-sulfated glycoaminoglycans (GAGs) through P5R
- CDR domain binds misfolded λ and κ light chains and AL fibrils
- Opsonization of amyloid through enhancing phagocytosis and inducing complement fixation (Via FcγR mediated interaction).



**P5 Peptide**

**Fibril**




Biotinyl-AT02

Congo red



Wall, J.S., *et al.* The antibody-peptide fusion protein, AT-02, is an effective opsonin with pan-amyloid reactivity. *npj Drug Discov.* 2, 18 (2025).

# AT- 02 Ph 1/2 Study

- The Phase 1/2 was a 3-part study to characterize safety and initial evaluation of efficacy
  - Single Dose in HVs and in patients with systemic amyloidosis: n=4 AL amyloidosis patients
  - Multiple dose for 4 weeks in patients with systemic amyloidosis n=15 AL amyloidosis patients
  - Extension trial with dosing up to 48 weeks in patients with cardiac amyloidosis
- Amyloidosis eligibility criteria for AL patients in extension trial
  - Previously achieved hematologic CR or VGPR
  - NT-proBNP >650 and <8500 pg/ml and cardiac ECV $\geq$40% by CMR
- Extension Dose Cohorts
  - Group 1: 2500 mg q4w (n=5 AL) / Group 2: 2500 mg q2w (n=9 AL)
- Measures Assessed for this exploratory efficacy analysis
  - Serum and urine biomarkers
  - 6MWT and KCCQ

This analysis focuses on AL Amyloidosis patients who entered the extension study

# Baseline Demographics – AL Participants in the OLE

| Characteristic | Dosing Regimen | | Total (N=14) |
|---|---|---|---|
| | 2500 mg Q4W (N=5) | 2500 mg Q2W (N=9) | |
| White Race | 5 (100%) | 9 (100%) | 14 (100%) |
| Male Sex | 4 (80%) | 8 (89%) | 12 (86%) |
| Age (years, mean (SD) | 67.0 (10.20) | 62.2 (10.70) | 63.9 (10.40) |
| Lambda Free Light Chain | 2 (40%) | 7 (78%) | 9 (64%) |
| Complete response | 3 (60%) | 2 (22%) | 5 (36%) |
| AL Disease Duration (yrs, mean (SD))* | 2.1 (1.48) | 3.2 (2.02) | 2.7 (1.83) |



Data Extract: 12SEP2025

# Baseline Characteristics – AL Participants in the OLE

| Characteristics Median (Q1, Q3) | Dosing Regimen | | Total (N=14) |
|---|---|---|---|
| | 2500 mg Q4W (N=5) | 2500 mg Q2W (N=9) | |
| 6MWD(m) | 382.5 (300.0, 397.0) | 382.0 (336.1, 416.0) | 382.3 (309.0, 411.3) |
| KCCQ-23 OS | 84.4 (80.7, 85.4) | 62.8 (57.0, 64.1) | 67.2 (58.7, 84.0) |
| NT-proBNP (ng/L) | 741 (709, 1147) | 853 (814, 1135) | 849 (741, 1147) |
| hsTnT (ng/L) | 22.0 (20.0, 25.0) | 30.0 (20.0, 32.0) | 25.5 (20.0, 31.8) |
| eGFR (mL/min/1.73m^2) | 87.7 (72.0, 91.1) | 61.3 (51.6, 84.6) | 68.7 (54.3, 90.3) |
| Creatinine (mg/dL) | 0.92 (0.92, 0.96) | 1.17 (0.98, 1.27) | 1.02 (0.92, 1.24) |
| BUN (mg/dL) | 16.9 (12.9, 20.5) | 21.0 (18.0, 35.0) | 20.8 (17.2, 26.4) |



Data Extract: 12SEP2025

# Organ Response Evaluable

Renal
(UACR >300 mg/g or eGFR < 90mL/min/1.73 $m^2$)

2500 mg q4w
3/5 (60%)

2500 mg q2w
7/9 (78%)

Cardiac
(NT-proBNP >650 pg/mL)

2500 mg q4w
4/5 (80%)

2500 mg q2w
8/9 (89%)

Efficacy Outcomes (n=10)
eGFR improvement
Proteinuria improvement

Efficacy Outcomes at Week 24 (n=9*)
NT-proBNP
6MWT
KCCQ-OS

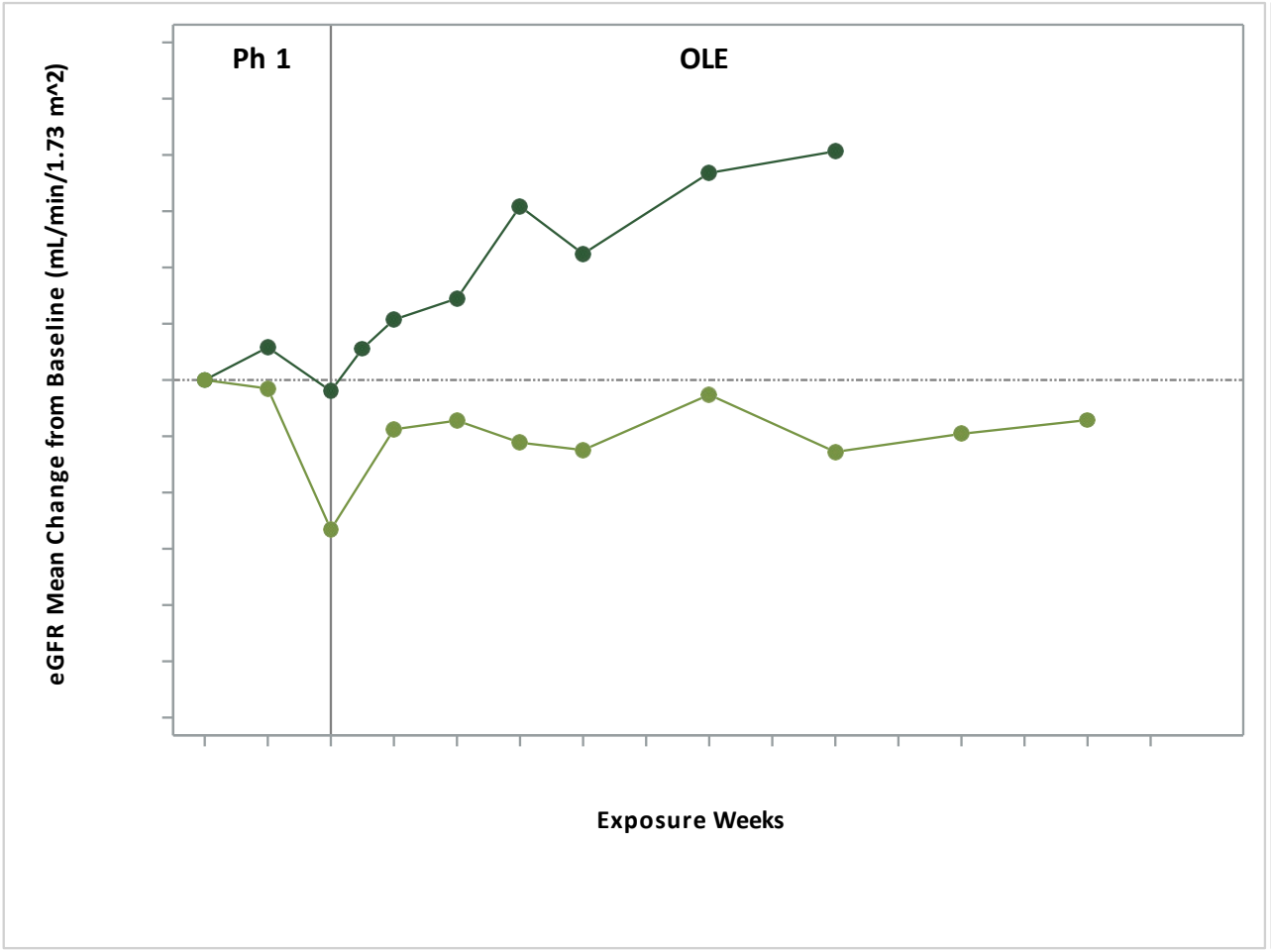
One evaluable organ: 36%
Two evaluable organs: 57%

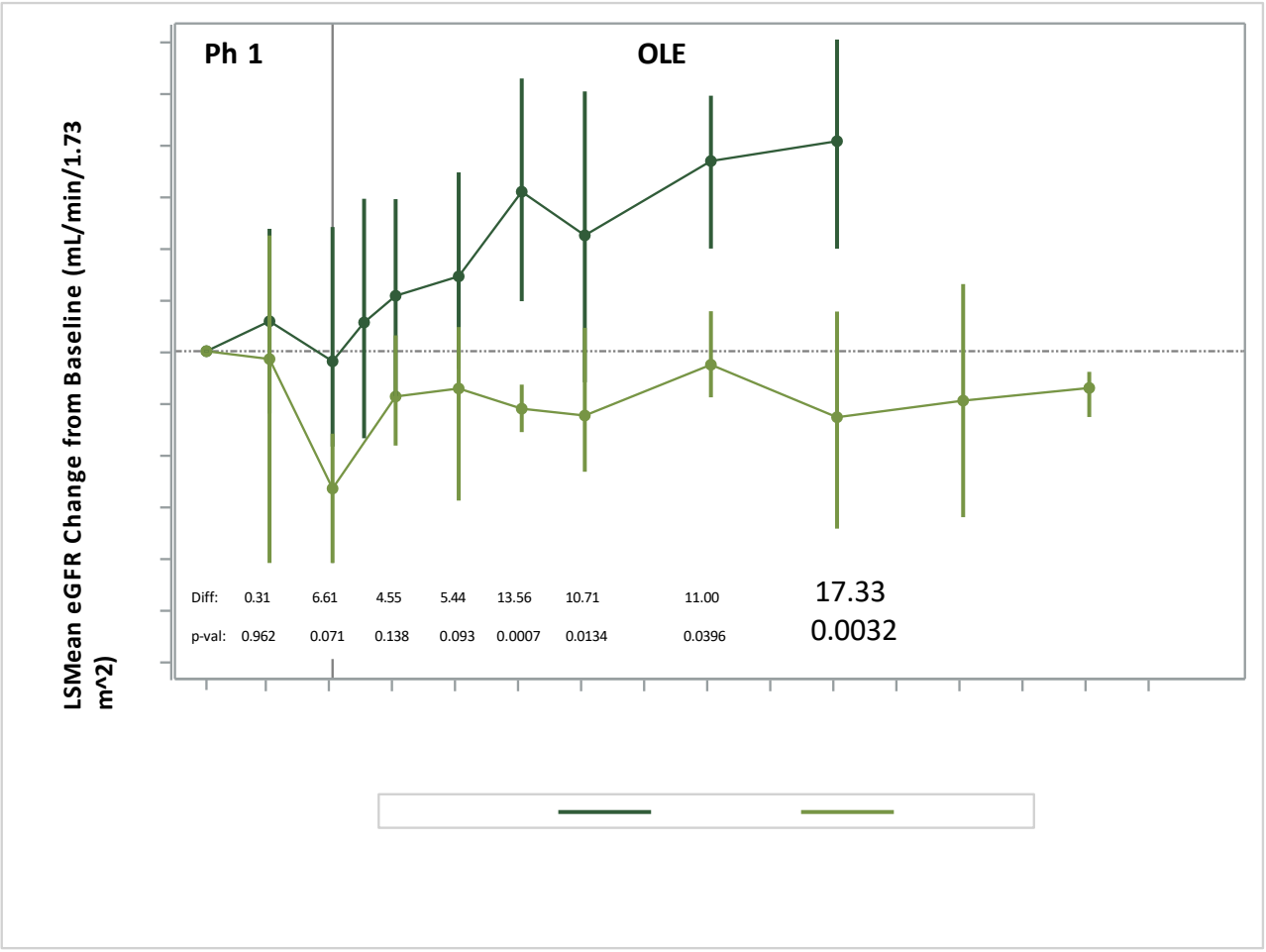
* 3 participants did not have Week 24 assessments due to death or missing visit

# AL Phase 1/2 Study Renal Evaluable Data: eGFR and UACR

# eGFR: Mean Change From Baseline by Dose

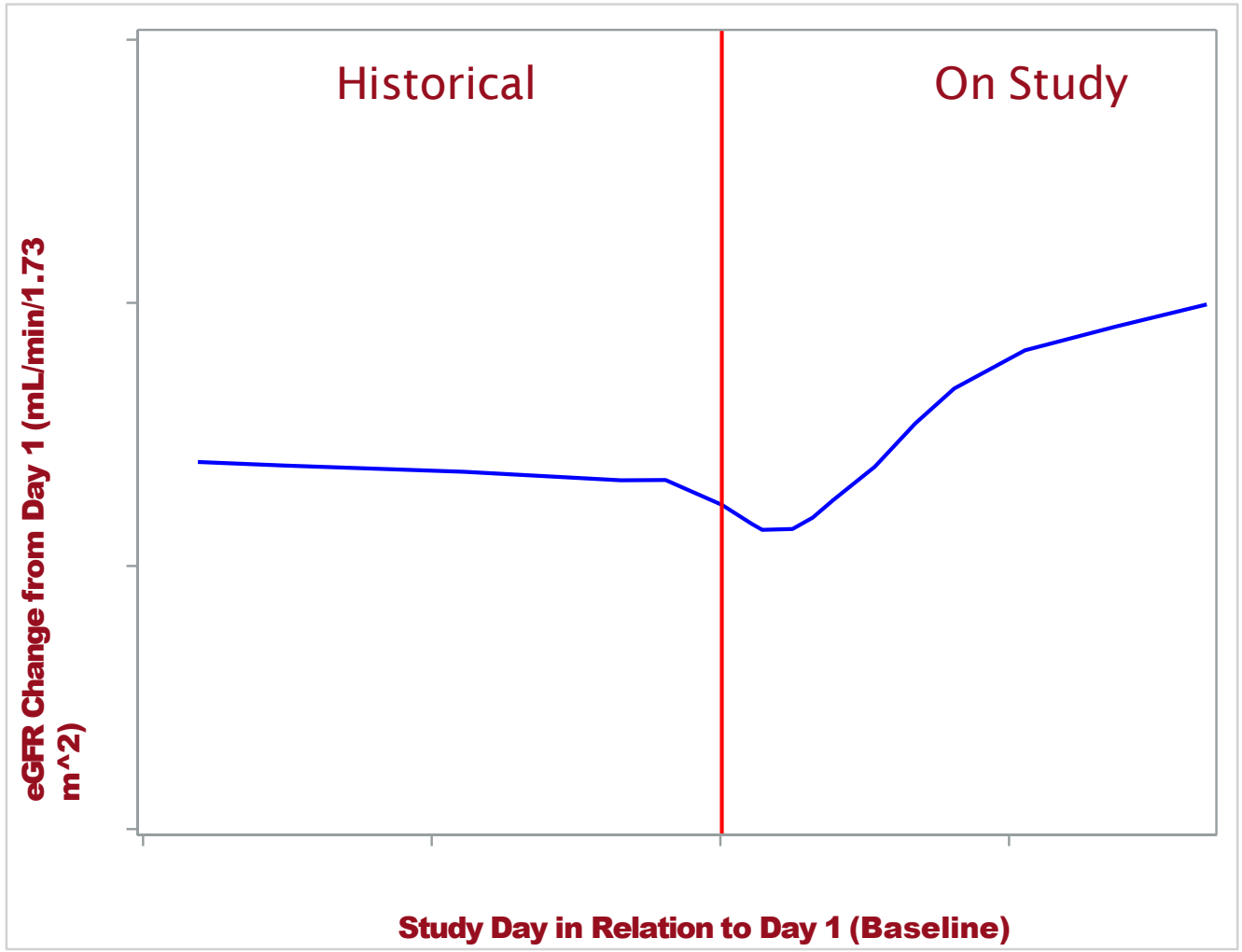
## AL Renal Evaluable Participants (eGFR <90 mL/min/1.73m$^2$)

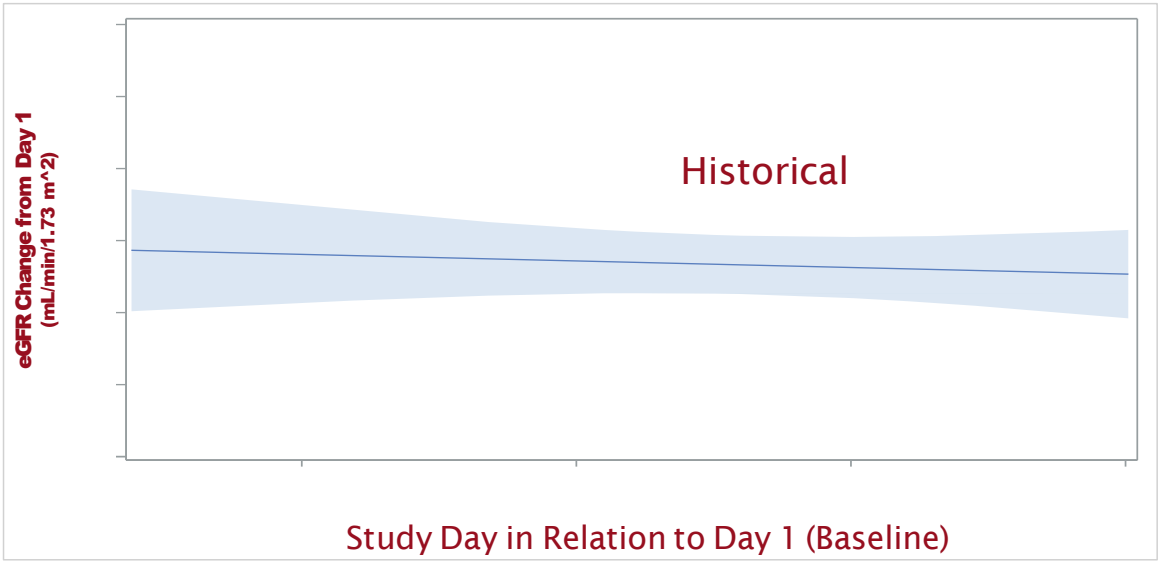


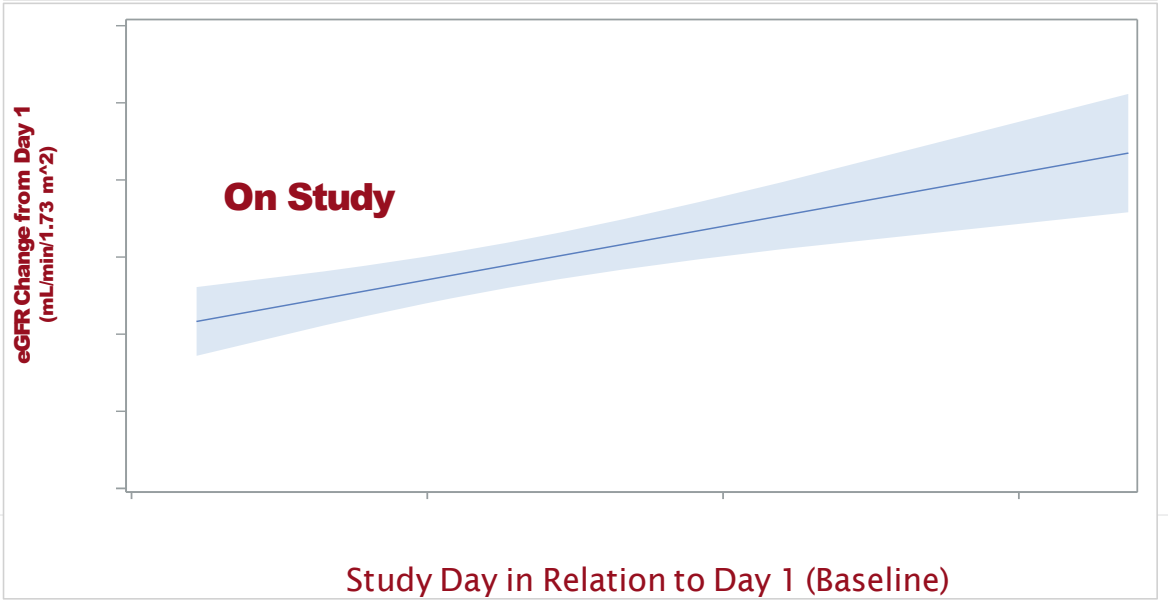



# eGFR: Change from Day 1 in Participants with Historical Data

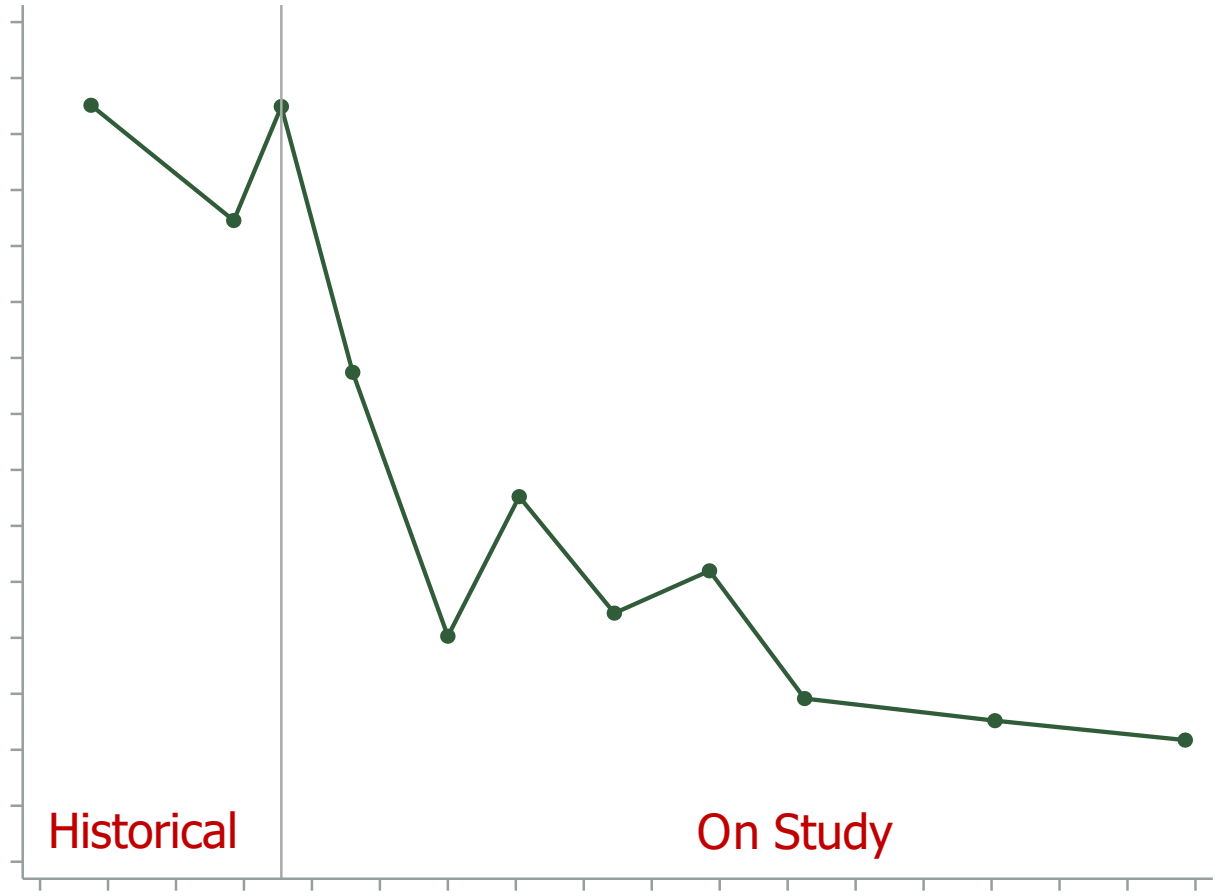
## (5 AL Renal Participants in high dose group with historical data)



# Participant 1002-1014: Single patient with significant proteinuria at baseline




- 51 year-old male
- AL kappa (renal/cardiac) diagnosed in 2023 (1 year prior to enrollment), treated with DaraCyBorD.
- On maintenance daratumumab in CR

| Analyte | Baseline | Week 24 |
|---|---|---|
| κ FLC (mg/L) | 8.9 | 8.5 |
| λ FLC (mg/L) | 6.0 | 6.7 |
| eGFR (mL/min/1.73m^2) | 85 | 105 |
| BUN (mg/dL) | 21 | 19 |
| Uric Acid (mg/dL) | 6.5 | 5.3 |
| NT-proBNP (ng/L) | 814 | 499 |
| hs Troponin T (ng/L) | 20 | 13 |

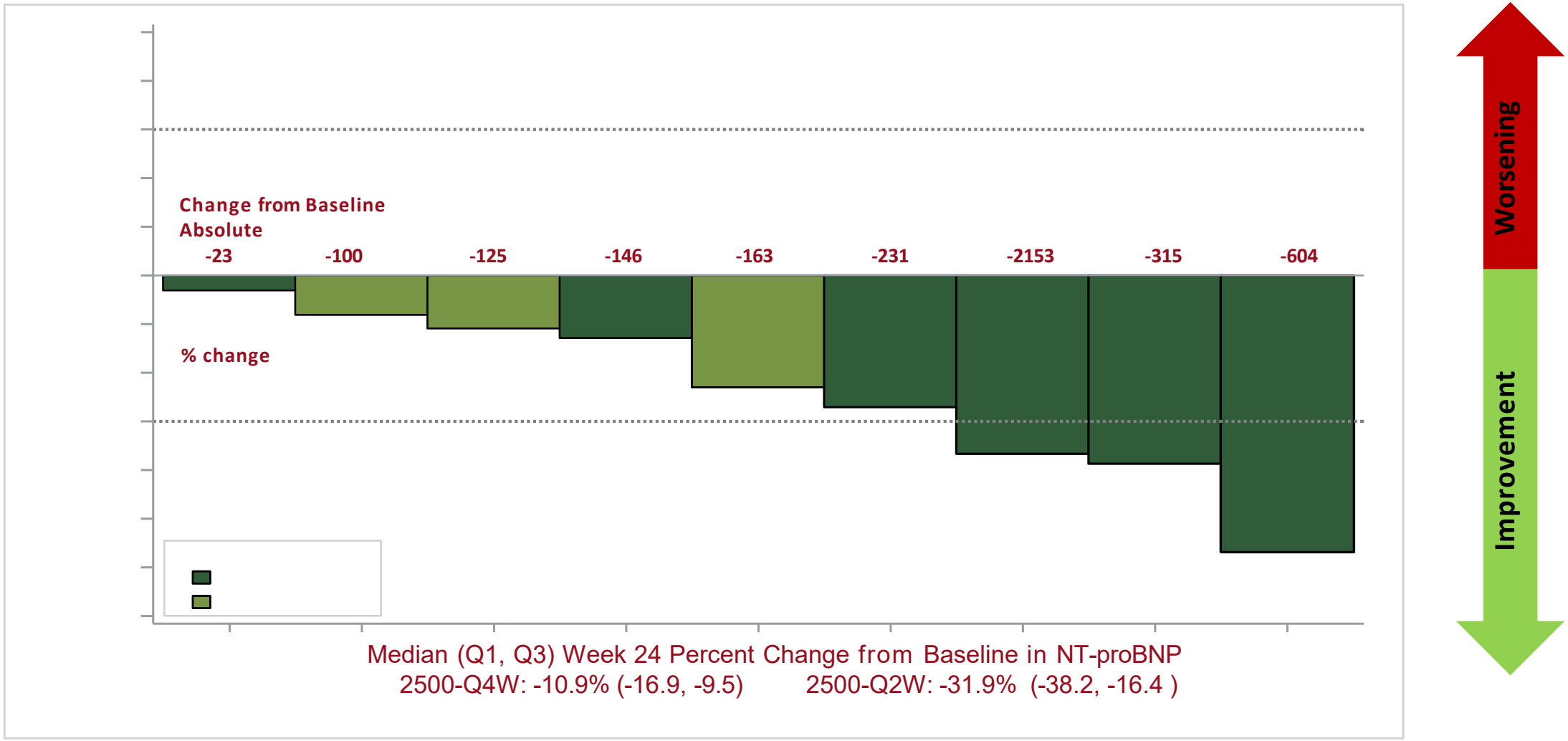


Data extract 12SEP2025

# AL Phase 1/2 Study: Cardiac Evaluable Data

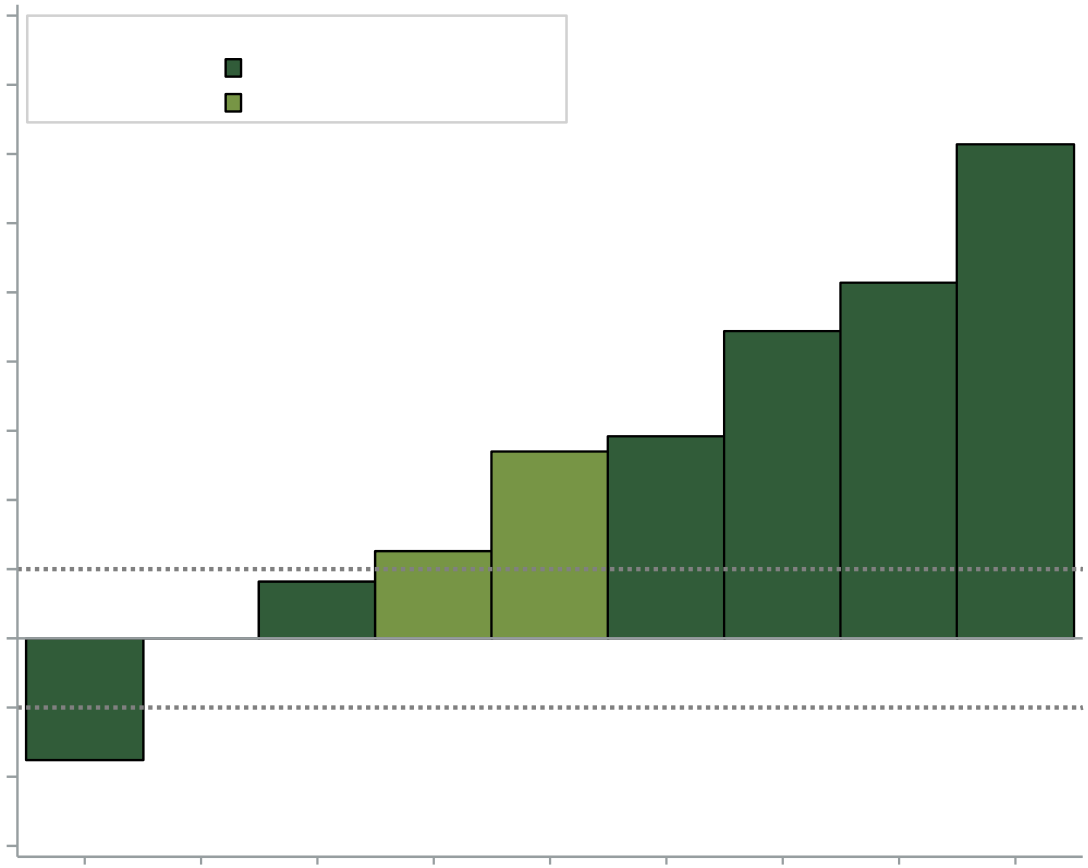
# Percent Change from Baseline NT-proBNP (Week 24)

## Part 3 Cardiac Evaluable AL Participants in the OLE



# Part 3 Cardiac Evaluable AL Participants in the OLE (Week 24)

## KCCQ-23

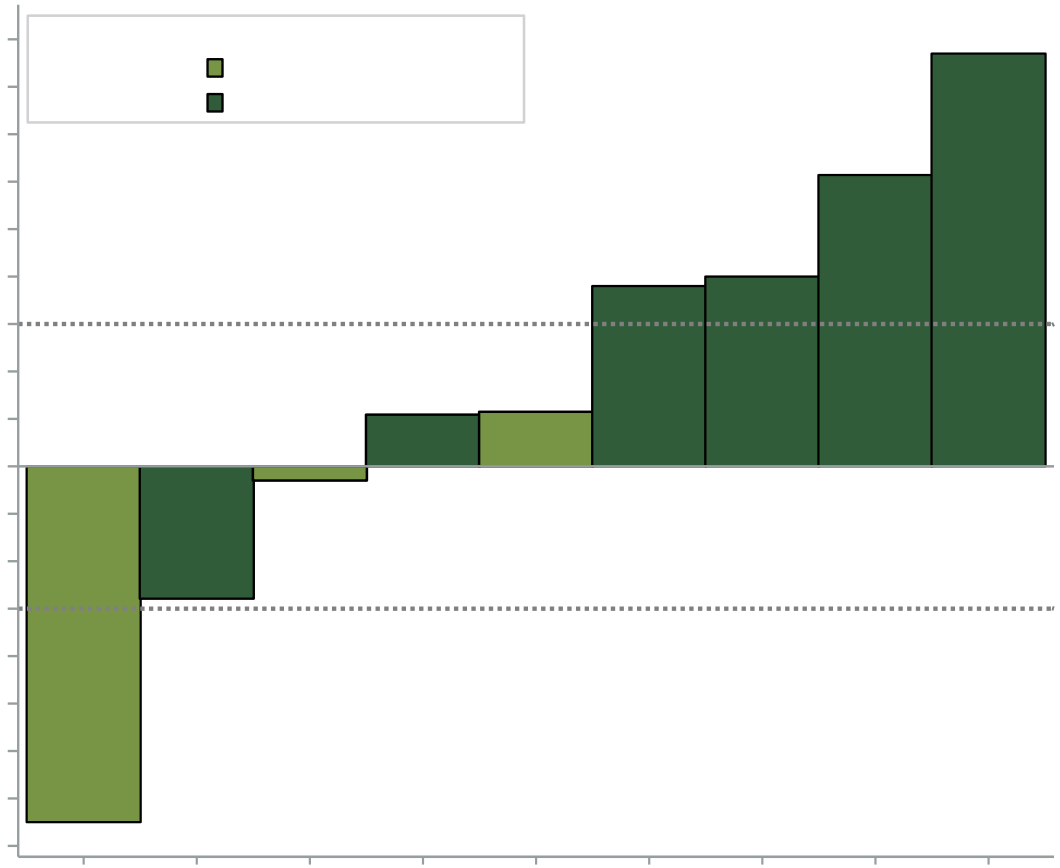


Median (Q1, Q3) Week 24 Change from Baseline in KCCQ-OS
2500-Q4W: 6.3 (3.2, 9.9) 2500-Q2W: 18.4 (6.7, 24.8)

Improvement

Worsening

## 6MWD



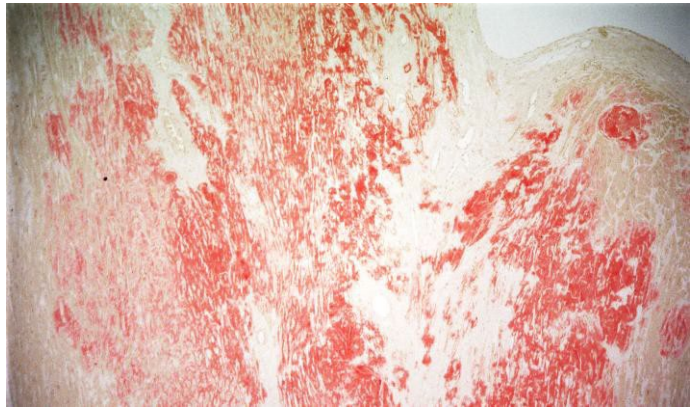
Median (Q1, Q3) Week 24 Change from Baseline in 6MWD
2500-Q4W: -3.0 (-39.0, 4.3) 2500-Q2W: 39.0 (16.7, 56.1)

Note: 3 participants did not have w24 efficacy assessments

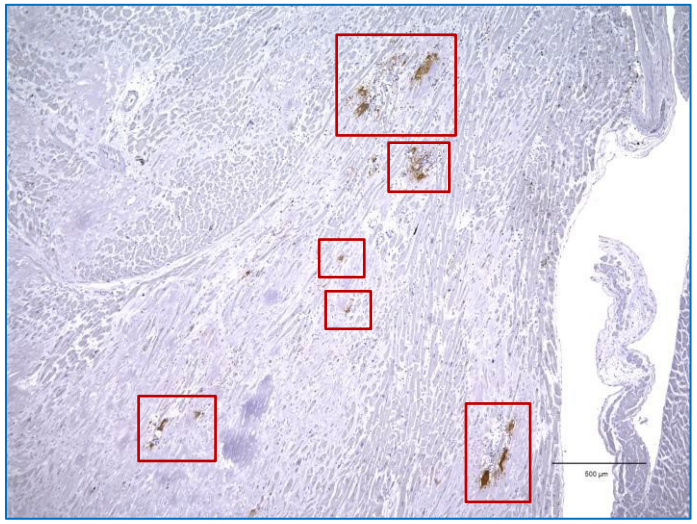
# Evidence of Target Engagement -Histology and PET imaging

# Cardiac Histology from an ATTR-CM Participant Treated with AT-02

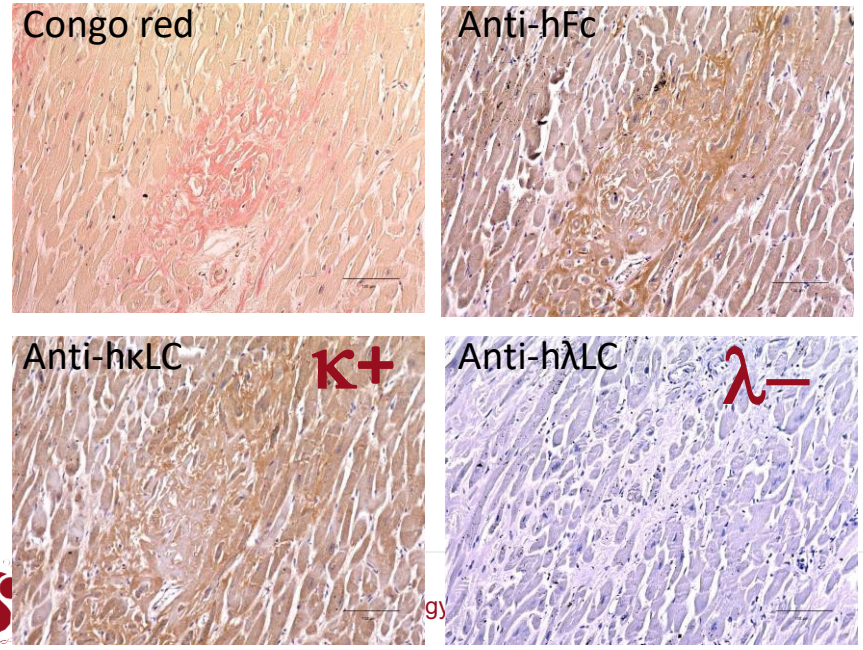
## Cardiac ATTR -Congo red (brightfield; 4x)

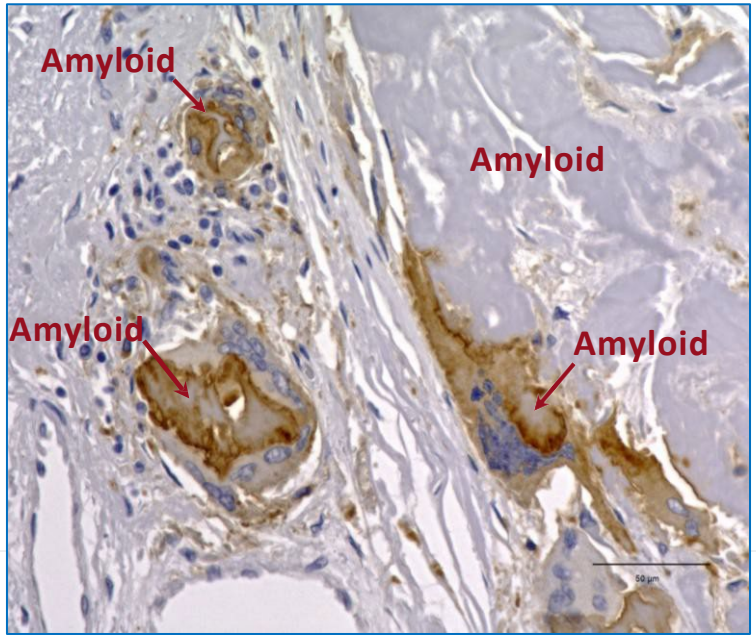


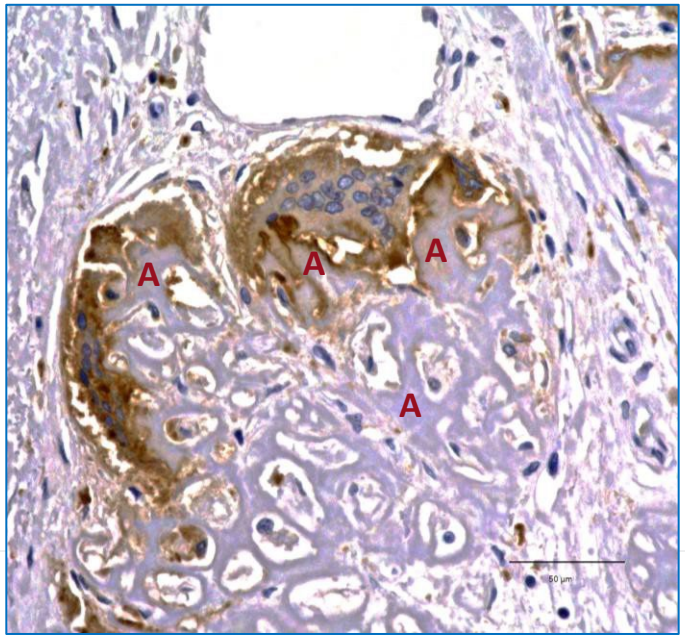
## Clusters of CD68-positive giant cells (4x)



## Multinucleated CD68-positive giant cells associated with amyloid (40x)



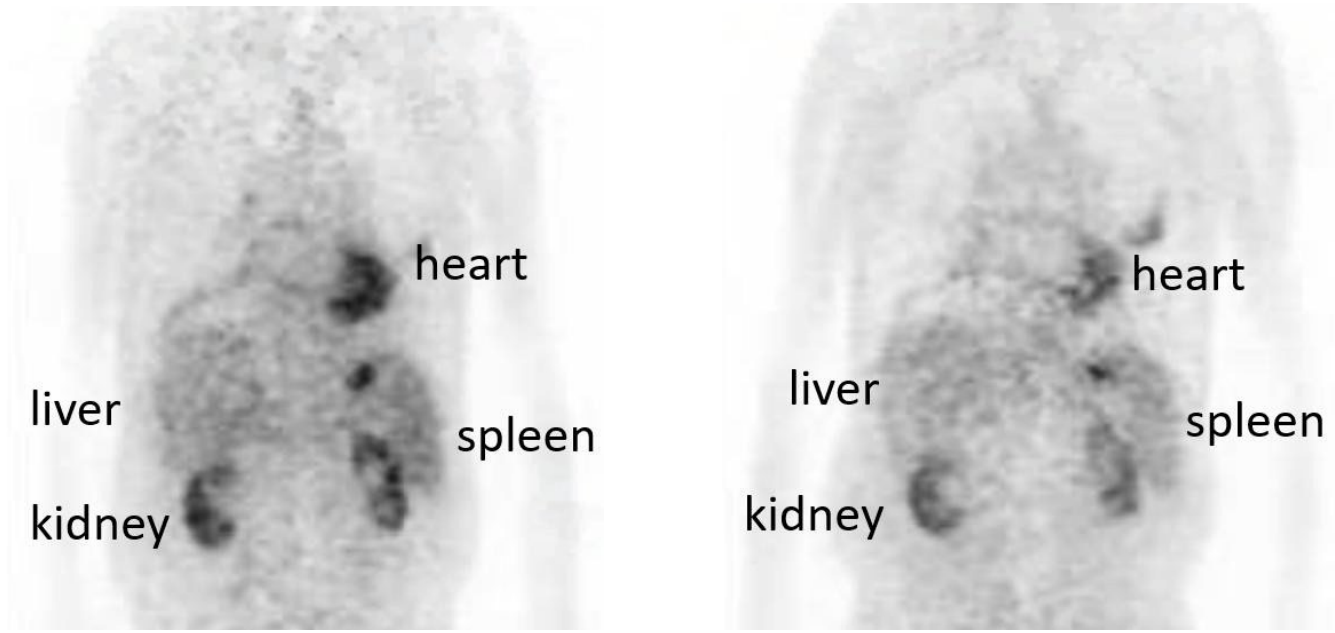
# Reductions in AT-01 Uptake in Heart, Kidney, Liver and Spleen Post AT-02

## 1002-1011: 74 yo male, ALk/CR, NYHA Class Ⅱ treated with AT-02 2500 mg q2w

1 Month Pre AT-02
14JUN2024

→

5 Months Post Start of AT-02
16DEC2024




| Standardized Uptake Value (SUVmean) | | | Biomarkers |
|---|---|---|---|
| LV Septum | 9.3 | 8.0 (-14%) | NT-proBNP (-47%) |
| Liver | 4.5 | 3.8 (-16%) | ALP (-6%) |
| Spleen | 5.4 | 3.8 (-30%) | |
| R Kidney | 7.4 | 6.1 (-19%) | eGFR (+12 ml/min) |
| L Kidney | 7.3 | 5.7 (-22%) | |

| Analyte | Baseline | OLE Week 24 |
|---|---|---|
| κ FLC | 20.9 | 17 |
| λ FLC | 20.1 | 18.8 |
| eGFR | 62 | 74 |
| BUN | 48 | 29 |
| Na | 126 | 136 |
| Uric Acid | 10.3 | 7.5 |
| NT-proBNP | 5872 | 3719 |
| TnT | 75 | 69 |

| Endpoint | Baseline | OLE Week 24 |
|---|---|---|
| 6MWD (m) | 169.5 | 141.6 |
| KCCQ-OS | 57.0 | 79.2 |

Significant improvement in symptoms, reduction in torsemide dose (60 mg BID to 20 mg daily), no metolazone, and resolution of chronic hyponatremia.

# AT-02 Safety and Tolerability

| Safety Summary – Participants with | 2500 mg Q4W (N=5) | 2500 mg Q2W (N=9) | Total (N=14) |
|---|---|---|---|
| Any AE | 5 (100%) | 7 (78%) | 12 (86%) |
| Any Drug-Related AE | 1 (20%) | 4 (44%) | 5 (36%) |
| Any SAE | 2 (40%) | 2 (22%) | 4 (29%) |
| Any Death | 1 (20%) | 1 (11%) | 2 (14%) |

- All drug-related AEs are Infusion related reaction (IRRs) and none were reported as SAEs
- Deaths
  - -Motor vehicle accident resulting in death (Q4W)
  - -Cardiac arrest resulting in death deemed not drug related (Q2W)



Data Extract: 12SEP2025

# Summary

- In patients with AL amyloidosis who achieved CR/VGPR, AT02:
  - Generally safe and tolerated, with IRRs as the only identified risk, mitigated by a premedication plan.
  - Improvements were observed in known surrogates of AL burden of disease, including NT-proBNP, 6MWT, KCCQ and eGFR.
  - Improvements in eGFR were observed in AL patients (l or k) few years after their ≥ VGPR hematologic response.
- Preliminary evidence of target engagement observed through activation of multinucleated CD68-positive giant cell and reduction of uptake on novel AT-01 PET imaging
- Expansion renal cohort recruitment is underway. Patients with impaired eGFR and/or proteinuria will receive 2500 mg of AT02 bi-weekly for 24 weeks.
- These data support the progression to a phase III trial in patients with AL amyloidosis who achieved CR/VGPR and continue to show signs of renal and/or cardiac organ dysfunction.