



# Analysis of Disease Progression in Patients with Transthyretin Cardiac Amyloidosis

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# Study of Disease Progression in Transthyretin Cardiac Amyloidosis: Multi-center Retrospective Analysis

## Goal

- Characterize disease severity and rate of progression in a multinational population of wild type ATTR cardiac amyloidosis (ATTRwt), also referred to as senile systemic amyloidosis (SSA), and compare with data in familial amyloidotic cardiomyopathy (FAC)

## Methods

- Demographics, overall survival collected retrospectively in 2 countries with 2 study investigators:
  - National Amyloidosis Centre (NAC), London, UK: ATTRwt (N=207), FAC (N=88)
  - Columbia University, New York, NY, USA: ATTRwt (N=48), FAC (N=49)
- Single site data collected retrospectively for:
  - Serial 6 minute walk distance (6-MWD): NAC, ATTRwt (N=153), FAC (N=39)
  - Hospitalizations: Columbia, ATTRwt (N=48), FAC (N=49)
- Statistical analysis
  - Time-to-events estimated using Kaplan-Meier method and 95% CIs for medians were obtained using Brookmeyer-Crowley methodology
  - Longitudinal changes in 6-MWD were summarized using descriptive statistics. Analyses considered distance walked = 0 m for patients deemed by investigator too unwell to walk at a given follow-up visit.
  - For analysis 6 month intervals were chosen to maximize the number of subjects with data at each time point after the initial visit (i.e. baseline)

# Disease Progression in Transthyretin Amyloidosis: Published Prospective and Retrospective Studies

Prospective study	TRACS <sup>1</sup>		Connors et. al. <sup>2</sup>			
	Yes	No	Yes	No	No	No
TTR Genotype	N=18 Wild Type	N=11 V122I	N=82 Wild Type	N=35 V122I	N=48 T60A	N=13 S77Y
Median Survival from diagnosis, months	43.0	25.6	46	41	59	62
Median time to first CV hospitalization, months	42.1	26.3	NA	NA	NA	NA
6-MWD; mean change from baseline at 12 months, month(SD)	N=10 -24.9 (73.4)	N=4 -91.1 (43.9)	NA	NA	NA	NA
6-MWD; mean change from baseline at 18 months, months (SD)	N=7 -43.9 (99.4)	N=3 -117.5 (75.2)	NA	NA	NA	NA

6-MWD: 6 minute walk distance; NA; not available

1. Ruberg et al., Am Heart J. 2012; 2. Connors et al., Amyloid. 2011

# Demographics

## All Patients

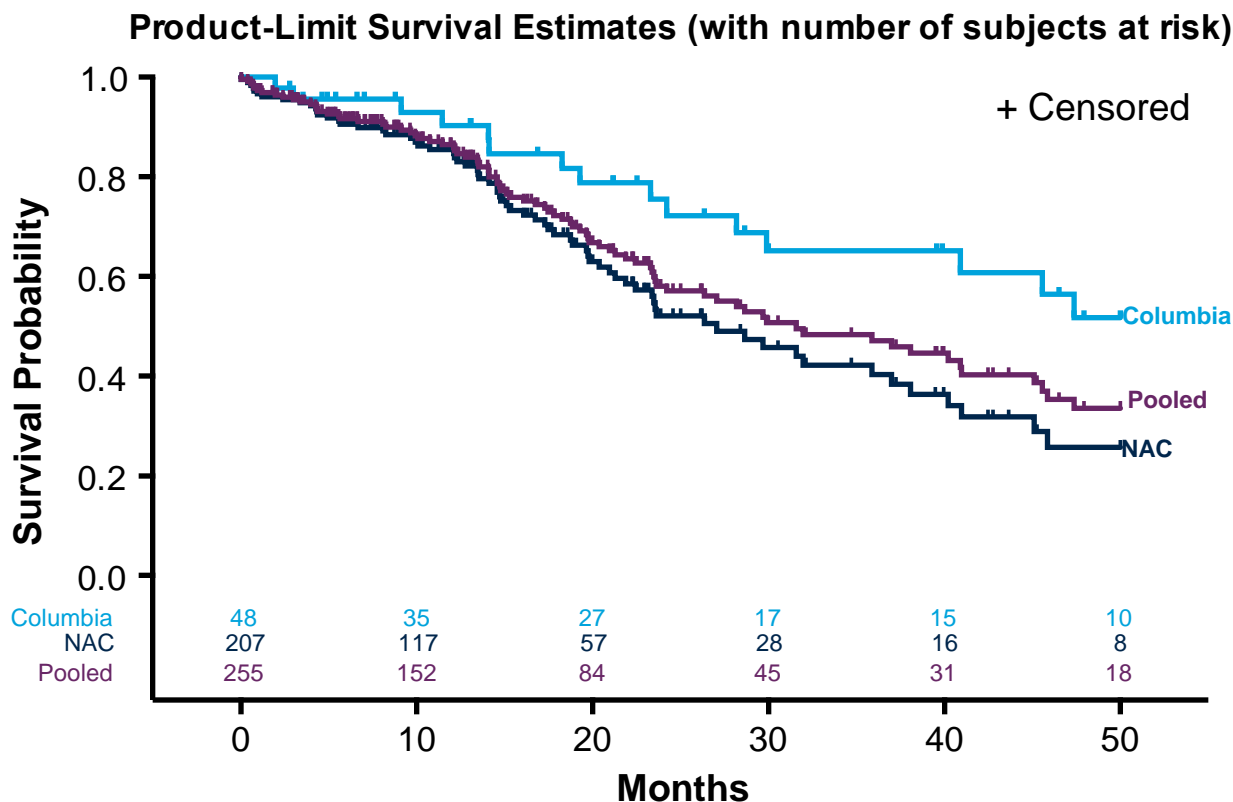
	ATTRwt		FAC		ATTRwt	FAC
	NAC (N=207)	Columbia (N=48)	NAC (N=88)	Columbia (N=49)	Total Pooled (N=255)	Total Pooled (N=137)
<b>Mutation, n (%)</b>						
V122I	0	0	88 (100)	29 (59)	0	117 (85)
T60A	0	0	0	10 (20)	0	10 (7)
V30M	0	0	0	2 (4)	0	2 (1)
Wild Type	207 (100)	48 (100)	0	0	255 (100)	0
Other types	0	0	0	8 (16)	0	8 (6)
<b>Median Age (yrs)</b> [min, max]	77 [56,90]	77 [66,89]	76 [57,88]	66 [41,84]	77 [56,90]	72 [41, 88]
<b>Males, n (%)</b>	192 (93)	45 (94)	70 (80)	39 (80)	237 (93)	109 (80)
<b>Baseline NYHA Class, n (%)</b>	N=161	N=47	N=75	N=49	N=208	N=124
I	28 (14)	1 (2)	6 (7)	7 (14)	29 (14)	13 (10)
II	93 (45)	28 (61)	38 (43)	11 (22)	121 (58)	49 (40)
III	39 (19)	16 (33)	30 (34)	23 (47)	55 (26)	53 (43)
IV	1 (<1)	2 (4)	1 (1)	8 (16)	3 (1)	9 (7)
<b>Stabilizer Use, n (%)</b>	12 (6)	18 (38)	2 (3)	10 (20)	30 (12)	12 (9)

# Baseline Characteristics

## All Patients

	ATTRwt		FAC		ATTRwt	FAC
	NAC (N=207)	Columbia (N=48)	NAC (N=88)	Columbia (N=49)	Total Pooled (N=255)	Total Pooled (N=137)
<b>BMI (kg/m<sup>2</sup>)</b> Median [min, max]	N=176 <b>26.4</b> [18.1, 39.5]	N=48 <b>26.4</b> [20.6, 46.3]	N=73 <b>25.7</b> [15.9, 38.5]	N=49 <b>25.3</b> [19.3, 36.6]	N=224 <b>26.4</b> [18.1, 46.3]	N=122 <b>26.0</b> [15.9, 38.5]
<b>eGFR (mL/min/1.73m<sup>2</sup>)</b> Median [min, max]	N=184 <b>56.0</b> [10, 100]	N=46 <b>51.5</b> [19.3, 114.7]	N=76 <b>51.5</b> [20, 90]	N=47 <b>54.7</b> [20, 115]	N=230 <b>54.0</b> [10, 115]	N=123 <b>55.3</b> [20, 115]
<b>Troponin T (ng/mL)</b> Median [min, max]	N=158 <b>0.1</b> [0.01, 0.34]	N=35 <b>0.1</b> [0.01, 2.6]	N=61 <b>0.07</b> [0.01, 0.04]	N=39 <b>0.1</b> [0.02, 2.7]	N=193 <b>0.1</b> [0.01, 2.6]	N=100 <b>0.15</b> [0.01, 2.7]
<b>NT-proBNP (ng/L)</b> Median [min, max]	N=191 <b>3104</b> [271, 27603]	NA	N=78 <b>3560</b> [491, 31198]	NA	NA	NA
<b>BNP (ng/L)</b> Median [min, max]	NA	N=40 <b>537</b> [77, 2570]	NA	N=43 <b>728</b> [15, 2910.5]	NA	NA
<b>LVEF (%)</b> Median [min, max]	N=146 <b>47</b> [22, 70]	N=35 <b>49</b> [20, 85]	N=81 <b>41</b> [25, 64]	N=39 <b>31</b> [15, 65]	N=181 <b>47</b> [20, 85]	N=120 <b>40</b> [15, 65]
<b>IVS thickness (cm)</b> Median [min, max]	N=207 <b>1.7</b> [1.0, 2.7]	N=34 <b>1.8</b> [1.0, 2.7]	N=88 <b>1.7</b> [1.0, 2.2]	N=35 <b>1.7</b> [0.8, 2.8]	N=241 <b>1.7</b> [1.0, 2.7]	N=123 <b>1.7</b> [0.8, 2.8]

# Survival: ATTRwt



Group	N	Deaths	Censored	Median Survival* (months) (95% CI)
Columbia	48	15	33	Not Reached (30.0, Not Reached)
NAC	207	69	138	27.1 (21.9, 37.0)
Pooled	255	84	171	31.6 (23.6, 41.0)

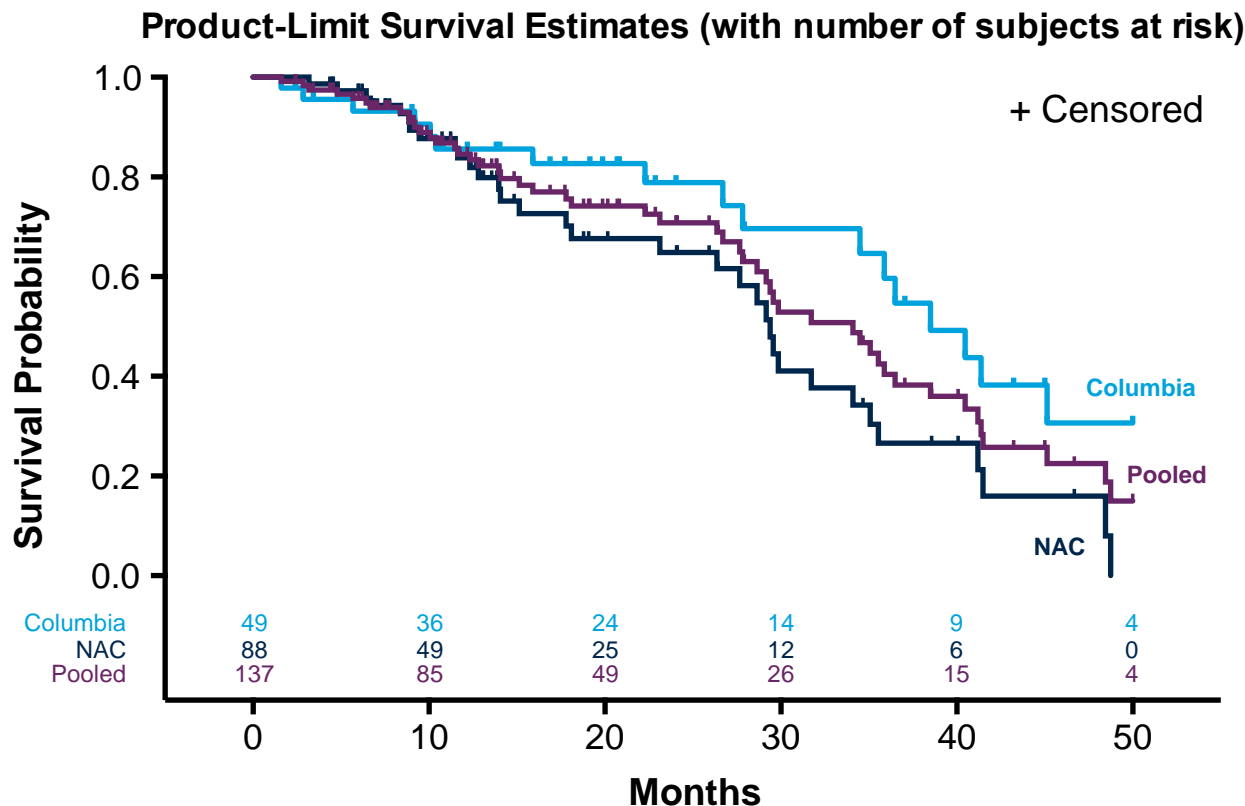
\*Time since first visit

Note: Median follow-up from first visit:

Columbia = 22 months (range 1 – 50)

NAC = 9 months (range 0 – 50)

# Survival: FAC



Group	N	Deaths	Censored	Median Survival* (months) (95% CI)
Columbia	49	17	32	38.5 (34.5, Not Reached)
NAC	88	33	55	29.4 (26.4, 35.1)
Pooled	137	50	87	34.1 (28.6, 38.5)

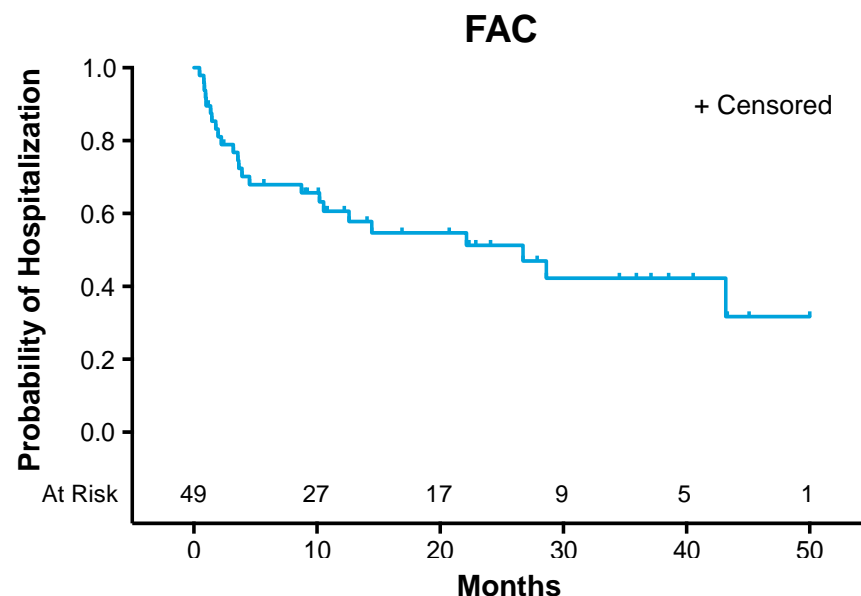
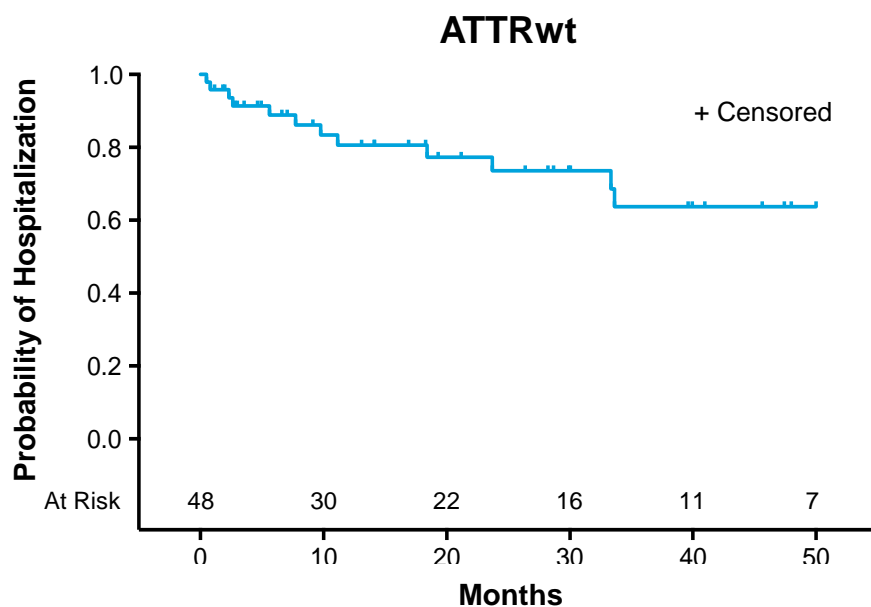
\*\*Time from first visit to death

Note: Median follow-up from first visit:

Columbia = 18 months (range 0 – 50)

NAC = 9 months (range 0 – 47)

# Time to First CV Hospitalization

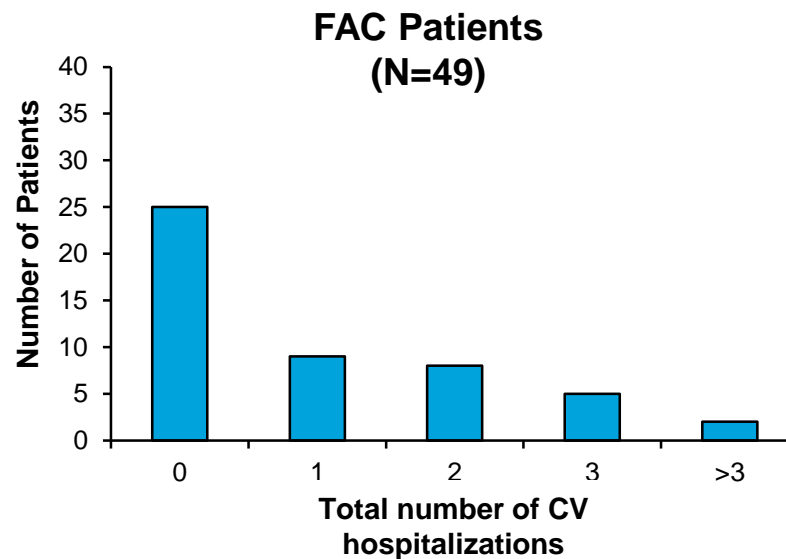
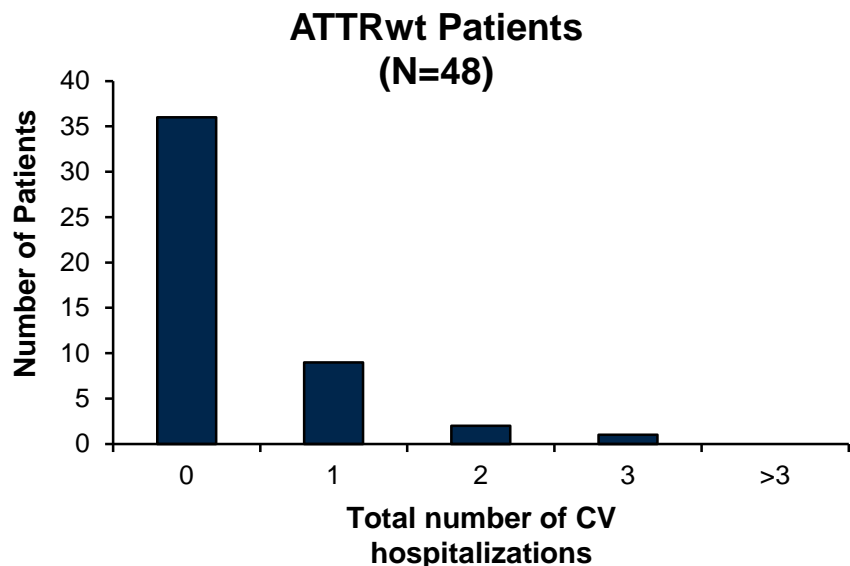


Diagnosis	Time to First CV Hospitalization*	
	# (%) of Patients with $\geq 1$ CV Hospitalization	Median (95% CI)
ATTRwt (n=46)	12 (25)	Not Reached (33.7, Not Reached)
FAC (n=49)	24 (49)	26.7 months (10.2, Not Reached)

Available data from Columbia group; CV designation non-adjudicated; only reflects hospitalizations at study site



# Frequency of CV Hospitalizations



No. of CV hospitalizations:	ATTRwt N (%)	FAC N (%)
0	36 (75)	25 (51)
1	9 (19)	9 (18)
2	2 (4)	8 (16)
3	1 (2)	5 (10)
>3	0	2 (4)
Total	48	49

Available data from Columbia group; CV designation non-adjudicated; only reflects hospitalizations at study site

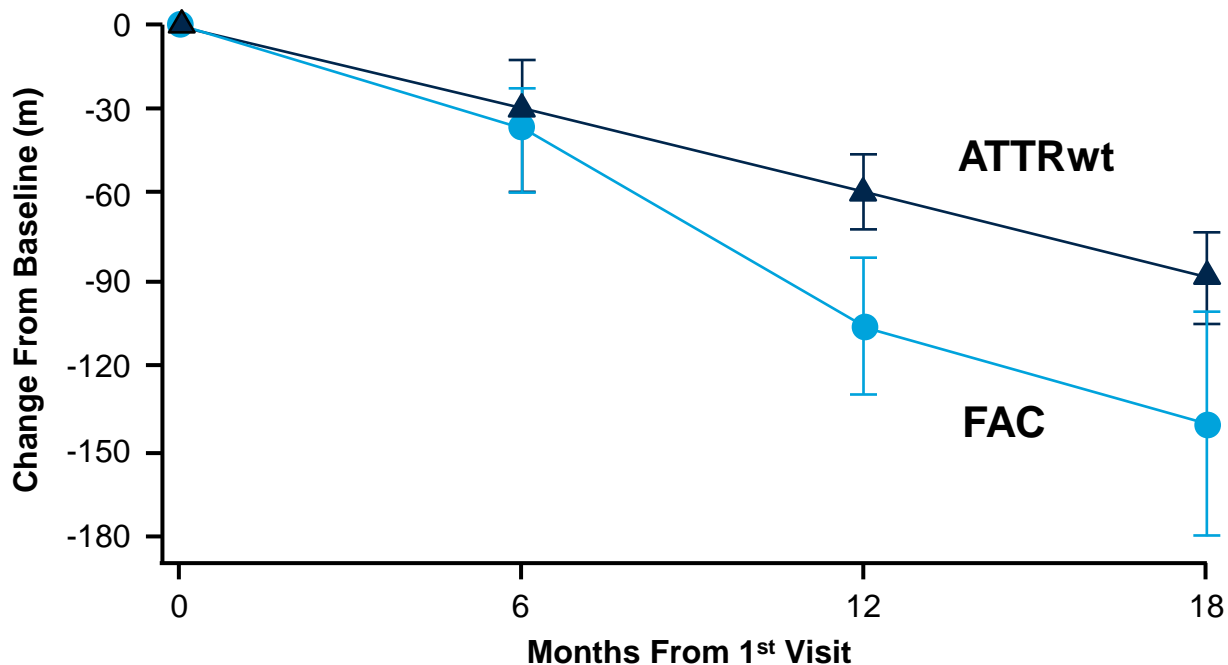
# Patients in 6-MWD Analysis

## Demographics and Baseline Characteristics

Characteristics	ATTRwt with 6-MWD Data (n=153*)	FAC with 6-MWD Data (n=39*)
Genotype, n (%)		
V122I	NA	39 (100)
Wild type	153 (100)	NA
Age (yrs)	N=146	N=37
Median	76 yrs.	76 yrs.
[min, max]	[59, 89]	[60, 87]
Baseline NYHA Class, n (%)	N=130	N=32
I	12 (9)	1 (3)
II	85 (65)	19 (59)
III	32 (25)	12 (38)
IV	1 (<1)	0
Baseline ECOG PS, n (%)	N=130	N=33
1	11 (8)	15 (45)
2	72 (55)	15 (45)
3	42 (32)	3 (9)
4	5 (4)	0 (0)
Stabilizer Use, n (%)	18 (12)	9 (23)
Baseline NTpro-BNP (ng/L)	N=141	N=34
Median	2883	3015
[min, max]	[118, 31003]	[440, 9818]
Baseline IVSD diastole (cm)	N=136	N=33
Median	1.7	1.7
[min, max]	[1.0, 2.3]	[1.0, 2.0]

\*Note: All patients from NAC. FAC group includes 21 additional patients who were not part of the n=88 NAC dataset analyzed for survival. ATTRwt group includes 80 additional patients who were not part of the n=207 NAC dataset analyzed for survival.

# Change in 6-MWD Over 18 Months



Visit		Actual Value (meters)		Change From Baseline (meters)		Percentage Change from Baseline (%)	
		ATTRwt	FAC	ATTRwt	FAC	ATTRwt	FAC
<b>Baseline</b> ATTRwt, N=153 FAC, N=39	<b>Mean (+/- SEM) Range</b>	<b>313 (10)</b> 16, 570	<b>281 (20)</b> 46, 485	NA	NA	NA	NA
<b>Month 6</b> ATTRwt, N=125 FAC, N=32	<b>Mean (+/- SEM) Range</b>	<b>276 (13)</b> 0, 553	<b>233 (25)</b> 0, 465	<b>-30 (7)</b> -345, 136	<b>-36 (23)</b> -426, 209	<b>-12 (4)</b> -100, 202	<b>-6 (12)</b> -100, 261
<b>Month 12</b> ATTRwt, N=88 FAC, N=27	<b>Mean (+/- SEM) Range</b>	<b>281 (16)</b> 0, 552	<b>178 (24)</b> 0, 432	<b>-59 (13)</b> -506, 152	<b>-106 (24)</b> -449, 32	<b>-17 (4)</b> -100, 77	<b>-34 (7)</b> -100, 15
<b>Month 18</b> ATTRwt, N=55 FAC, N=16	<b>Mean (+/- SEM) Range</b>	<b>237 (21)</b> 0, 549	<b>158 (35)</b> 0, 421	<b>-89 (16)</b> -422, 168	<b>-140 (39)</b> -485, 80	<b>-31, (6)</b> -100, 68	<b>-46 (12)</b> -100, 50

# Summary

- Poor survival is observed in both ATTRwt and FAC
- Clear decline in 6-MWD in both ATTRwt and FAC patients with mild-moderate heart failure over an 18-month period
- The observed decrease in 6-MWD was, on average, less pronounced in ATTRwt than in FAC over 18 months, suggesting the possibility of slower functional decline in ATTRwt
  - Mean decline of 59 m at 12 months and 89 m at 18 months compared to baseline in ATTRwt was less than the 106 m and 140 m mean decline compared to baseline at 12 and 18 months, respectively, observed in FAC patients

# Acknowledgments

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**Thank You**