

DECLINE IN SLOW VITAL CAPACITY PREDICTS RESPIRATORY INSUFFICIENCY, USE OF ASSISTED VENTILATION, TRACHEOSTOMY, OR DEATH

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BACKGROUND

- Death and disability in ALS are strongly related to respiratory failure often assessed in the clinic by measuring vital capacity
- Vital capacity, either Forced Vital Capacity (FVC) or Slow Vital Capacity (SVC), is an important outcome measure for ALS clinical trials
- Tirasemtiv*, a selective fast skeletal muscle troponin activator, evaluated in a phase 2b clinical trial in patients with ALS (BENEFIT-ALS), showed a statistically significant reduction of the decline in percent predicted SVC over 12 weeks compared to patients receiving placebo

OBJECTIVES

- To investigate the natural history of SVC decline
- To determine what variables impact SVC
- To determine how changes in SVC predict function and other clinically meaningful events

METHODS

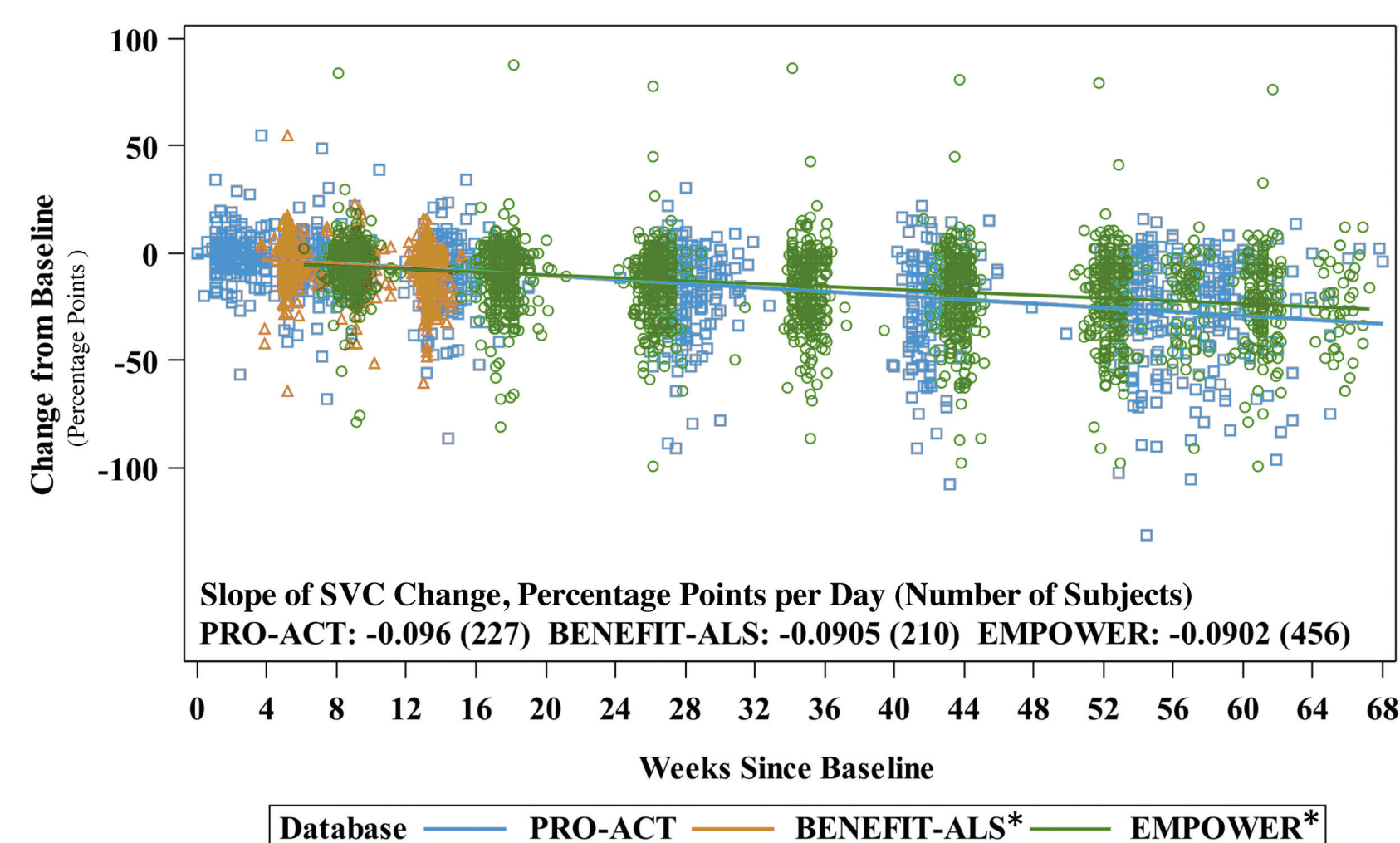
- We queried data from the placebo group in the dexpropimexole phase 3 clinical trial, EMPOWER, one of the largest clinical trials conducted in ALS with 943 patients enrolled (Cudkovic *et al.*, 2013)
- In EMPOWER, patients were assessed for at least one year, with regular measurements of SVC, Sniff Nasal Inspiratory Pressure (SNIP), ALS Functional Rating Scale-Revised (ALSFRS-R), and quantitative strength measurements using hand held dynamometry (HHD). Time to respiratory failure, defined as tracheostomy with permanent assisted ventilation or use of non-invasive ventilation for ≥ 22 hours per day for ≥ 10 consecutive days and survival, was also collected

STATISTICAL METHODS

- All 469 patients randomized to placebo in the EMPOWER clinical trial were included with a maximum duration of follow-up of 1.5 years
- Slope of decline in SVC was estimated using a repeated measures mixed model and adjusting for baseline SVC
- Pearson Product Moment correlation coefficient (r) was used to evaluate the strength of association between the decline in SVC and other continuous clinical outcomes variables
- Cox proportional hazards regression was used to model the time to clinical event variables from the Month 6 visit to the end of the follow-up period using the slope of SVC change from baseline to the Month 6 visit as an explanatory variable, adjusting for baseline riluzole use and ALSFRS-R score
- The respiratory clinical outcomes included the earlier of time to death or:
 - time to decline in any of the three questions of the respiration subdomain of ALSFRS-R
 - time to the first onset of respiratory insufficiency
 - time to tracheostomy
- All cause mortality was evaluated as well

RESULTS

FIGURE 1: RATE OF DECLINE IN SVC IS SIMILAR IN THREE LARGE DATA SETS



* From the placebo arms of BENEFIT-ALS and EMPOWER

RESULTS (CONTD.)

FALL IN SVC BY SUBGROUP

Age

Age Group	Number of Observations	Slope (percentage points/day)	95% CI of Slope	P-value
<50	641	-0.075	-0.091, -0.059	0.005*
50-65	1164	-0.086	-0.096, -0.076	0.007**
>65	532	-0.120	-0.142, -0.097	---

* <50 compared to >65
 ** 50-65 compared to >65

Sex

Group	Number of Observations	Slope (percentage points/day)	95% CI of Slope	P-value
Male	1541	-0.086	-0.0973, -0.075	0.5605*
Female	796	-0.098	-0.111, -0.086	---

* Male compared to Female

Riluzole Use

Riluzole Use	Number of Observations	Slope (percentage points/day)	95% CI of Slope	P-value
No	517	-0.102	-0.122, -0.081	0.2547*
Yes	1820	-0.088	-0.097, -0.079	---

* No Riluzole compared with Riluzole

Baseline SVC

Group	Number of Observations	Slope (percentage points/day)	95% CI of Slope	P-value
<65%	93	-0.073	-0.137, -0.008	0.1796*
65-75%	295	-0.094	-0.118, -0.069	0.0940**
>75%	1949	-0.090	-0.099, -0.081	---

* <65% compared to >75%
 ** 65-75% compared to >75%

Site of ALS Onset

ALS Onset Site	Number of Observations	Slope (percentage points/day)	95% CI of Slope	P-value
Bulbar	477	-0.104	-0.125, -0.083	0.059*
Other	1860	-0.086	-0.094, -0.077	---

* Bulbar compared to Other

RESULTS (CONTD.)

FALL IN SVC BY SUBGROUP (CONTD.)

Baseline ALSFRS-R

Group	Number of Observations	Slope (percentage points/day)	95% CI of Slope	P-value
≤ 39	1095	-0.102	-0.113, -0.091	0.0001*
>39	1242	-0.076	-0.088, -0.064	---

* ≤ 39 compared to >39

SVC CORRELATES WEAKLY WITH SNIP AND INDIVIDUAL RESPIRATORY ITEMS OF ALSFRS-R

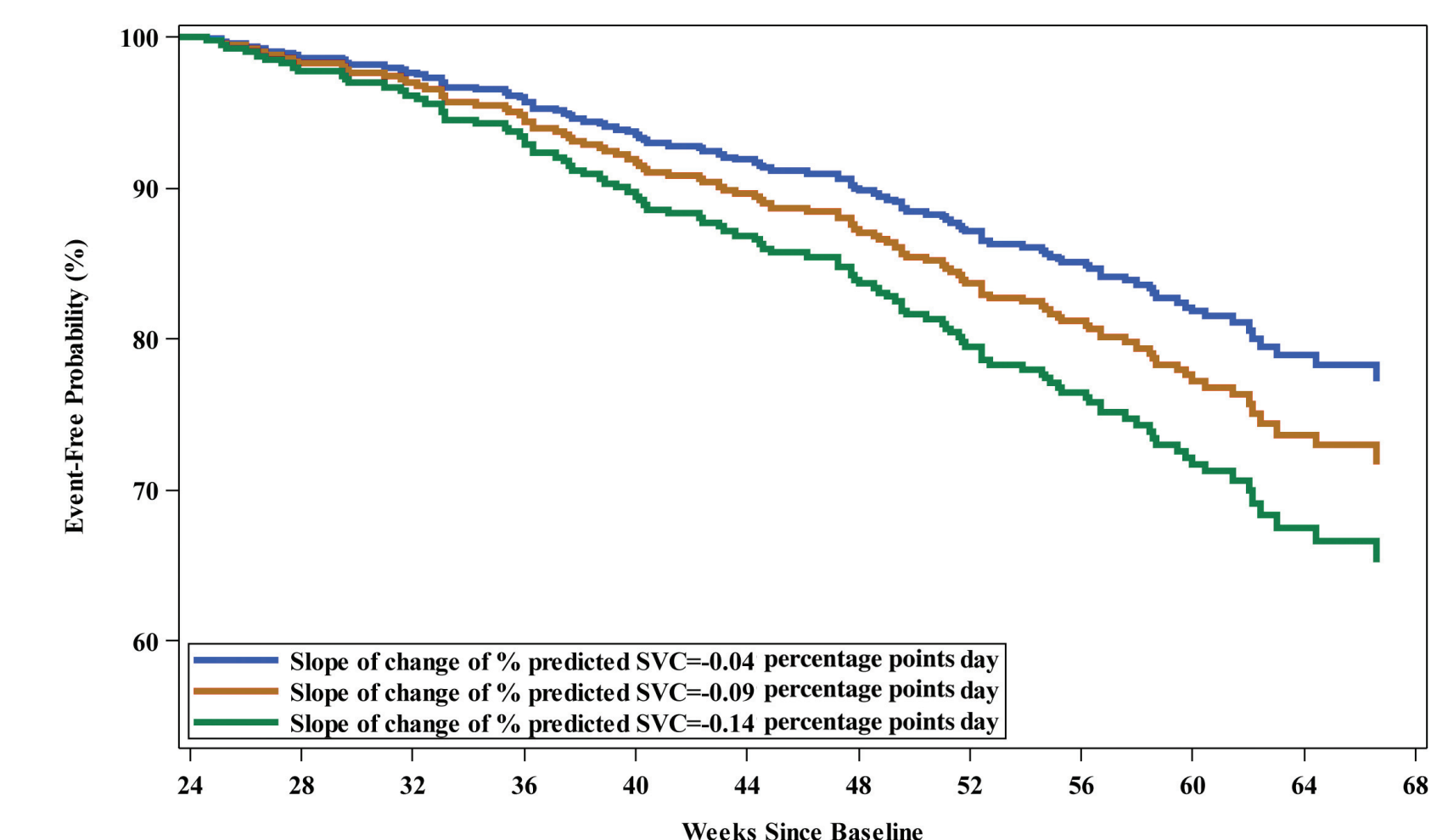
Pearson Correlation Coefficients*	Change from Baseline in SNIP	Change from Baseline in ALSFRS-R Dyspnea	Change from Baseline in ALSFRS-R Orthopnea	Change from Baseline in ALSFRS-R Respiratory Insufficiency
	0.33	0.23	0.26	0.28

RELATIONSHIP OF SVC TO THE RISK OF OTHER CLINICALLY MEANINGFUL EVENTS AND MEASURES IN ALS

A decrease in percent predicted SVC decline by 0.05%/day predicts**:	Risk Reduction
Decline in respiratory domain of the ALSFRS-R or death	19%
First onset of respiratory insufficiency or death	22%
First occurrence of tracheostomy or death	23%
Death at any time after month 6	23%

* Based on a Cox proportional hazards regression to model time to clinical events
 ** P<0.0001 in all cases

FIGURE 2: PROBABILITY OF RESPIRATORY FAILURE-FREE SURVIVAL PREDICTED BY SLOPE OF SVC CHANGE*



Note: Based on a Cox proportional hazards regression to model time to clinical events
 * P<0.0001

CONCLUSIONS

- The rate of decline of SVC in ALS is consistent among the three data sets evaluated
- From the EMPOWER data set, age and baseline ALSFRS-R had a significant inter-action with rate of decline of SVC
- The change in SVC explained a minority of the variability in the respiratory items of the ALSFRS-R and SNIP
- The change in SVC strongly predicts meaningful clinical events, including respiratory failure or death in ALS