June 7, 1996
PCNS # 43
Cephalon

Myotrophin® for the Treatment of Amyotrophic Lateral Sclerosis

Agenda

Deborah F. Geliñas, M.D.

- AALS scale is a reliable measure of disease progression
- Disease progression varies between patients

William F. Graney, M.D.

- Body of evidence supporting the use of Myotrophin

Thomas W. Dobbins, Ph.D.

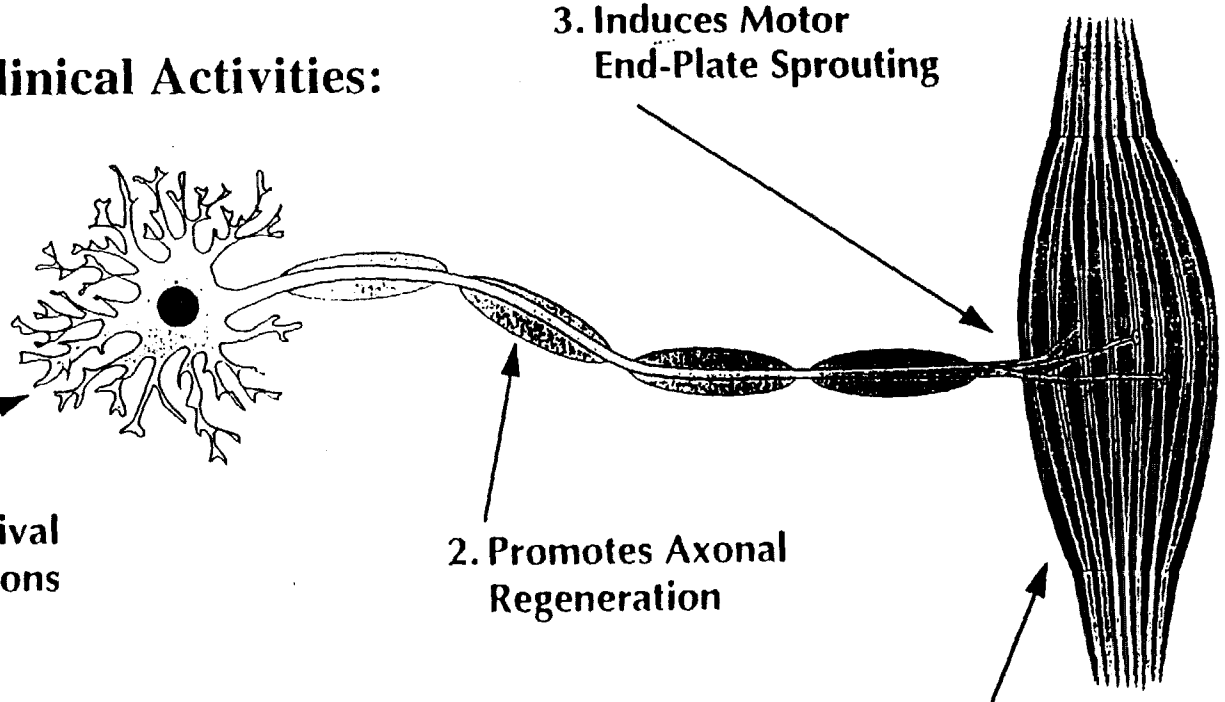
- Patient withdrawal does not influence study conclusions
- Stratification correlates with clinical progression

Robert Miller, M.D.

- Clinical interpretation

Mechanism of Myotrophin-Induced Benefit in Motor Neuron Disease

Primary Preclinical Activities:



Deborah F. Gelinas, M.D.

California Pacific Medical Center

AMYOTROPHIC LATERAL SCLEROSIS

- Progressive degenerative disorder of motor neurons in the spinal cord, brainstem and motor cortex.

- Characterized clinically by muscle wasting, weaknes and corticospinal tract signs.

- Absence of significant sensory, bowel or bladder abnormalities.

DIAGNOSIS OF ALS

- Upper motor neuron (UMN) signs
- Lower motor neuron (LMN) signs
- Progression

ONSET FORMS OF ALS

- Limb or spinal onset
  - ♦ Weakness or difficulty in coordination in one or more limbs
- Bulbar onset
  - ♦ Changes in speech or swallowing
- Most patients eventually develop the full blown syndrome of ALS

NATURAL HISTORY OF ALS

- Steady decline in strength and respiratory muscle function.

- Rate of decline varies from patient to patient.

Study Objective

To demonstrate that Myotrophin slows the progressive deterioration of muscle strength and function in ALS

AALS Scale

- Quantitative assessment of clinical disease severity and muscle strength and function in ALS
- Total AALS Score is an index of disability
- Rate of change of AALS correlates with disease progression

AALS Rating Scale

- **Bulbar**
  - Swallowing
  - Speech
- **Respiratory**
  - Forced vital capacity
- **Muscle Strength**
  - Upper Extremity
  - Grip
  - Lower Extremity
  - Lateral pinch
- **Muscle Function, Lower Extremity**
  - Standing from sitting
  - Assistive devices
  - Standing from supine
  - Climb/descend stairs
  - Walking 20 feet
- **Muscle Function, Upper Extremity**
  - Dress/feed
  - Pegboard
  - Wheelchair
  - Blocks
  - Cutting

Lifestyle Deterioration

AALS Total Score

Appel Score / Function	52	75	99	119	135
Diet	General to Soft	Soft	Pudding	Thick Liquids	Tube Feeding
Speech	Normal to Slurred	Slurred	Slurred	Not Understandable	None
Respiratory FVC	Within 500 cc of Predicted	> 500 cc Change	> 1,000 cc Change	Considering Tracheostomy	Tracheostomy
Mobility	Possible Cane	Walker/Occasional Wheelchair	Wheelchair Most of the Time	Wheelchair Bound	Bedridden
Independence	Independent	Needs Caretaker Assistance	Caretaker Provides Most of Care	Dependent	Total Care

[Appel V. et al. Ann Neurol 22:328-333, 1987]

SLIDE PLACEHOLDER

ALS Patient Case Study
(Moderate Progressor)

SLIDE PLACEHOLDER

ALS Patient Case Study
(Rapid Progressor)

The Baylor Natural History Database
Strata Differences

Disease-Related Characteristics Which Reflect Current Disease Severity or Progression (means ± sem)

	Moderate Progressors	Rapid Progressors
N (%)	60 (33%)	121 (67%)
Age (years)	52.3 ± 1.5	54.1 ± 1.2
Gender (M:F)	5:1	1.7:1
Bulbar onset (yes)	17%	23%
Time/Symptom (mo)	13.5 ± 0.8	15.6 ± 0.6
FVC Baseline (%)	89.3 ± 1.9	76.5 ± 1.5
Preslope (pts/mo)	3.84 ± 0.3	6.35 ± 0.3

Patients matched for inclusion/exclusion criteria in the North American and European ALS investigations

Strata

	AALS Total Score	Slope (Points/Mo) mean ± sem
• Moderate progressors	≤ 60	3.54 ± 0.15 (N=136)
• Rapid progressors	> 60	5.41 ± 0.17 (N=313)

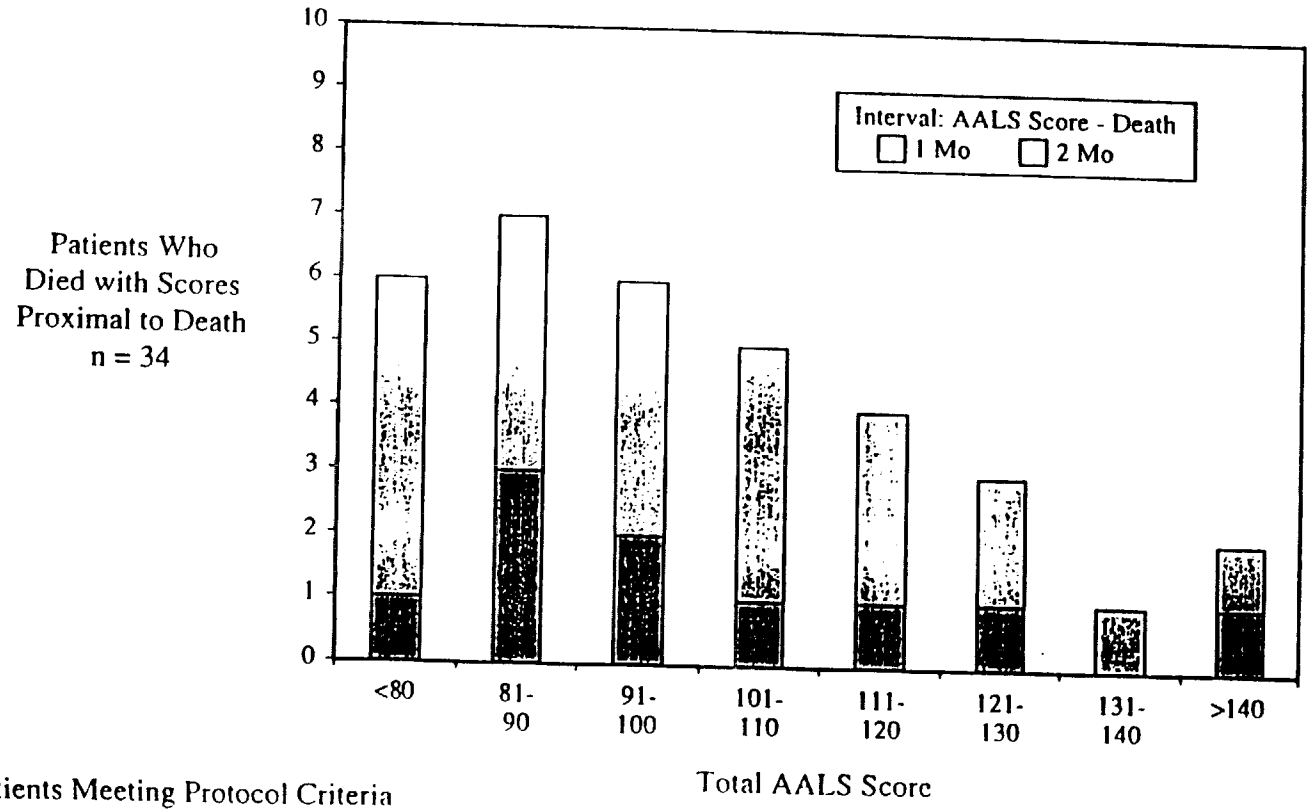
- Based on observations in North American and European studies

Protocol-Specified Termination

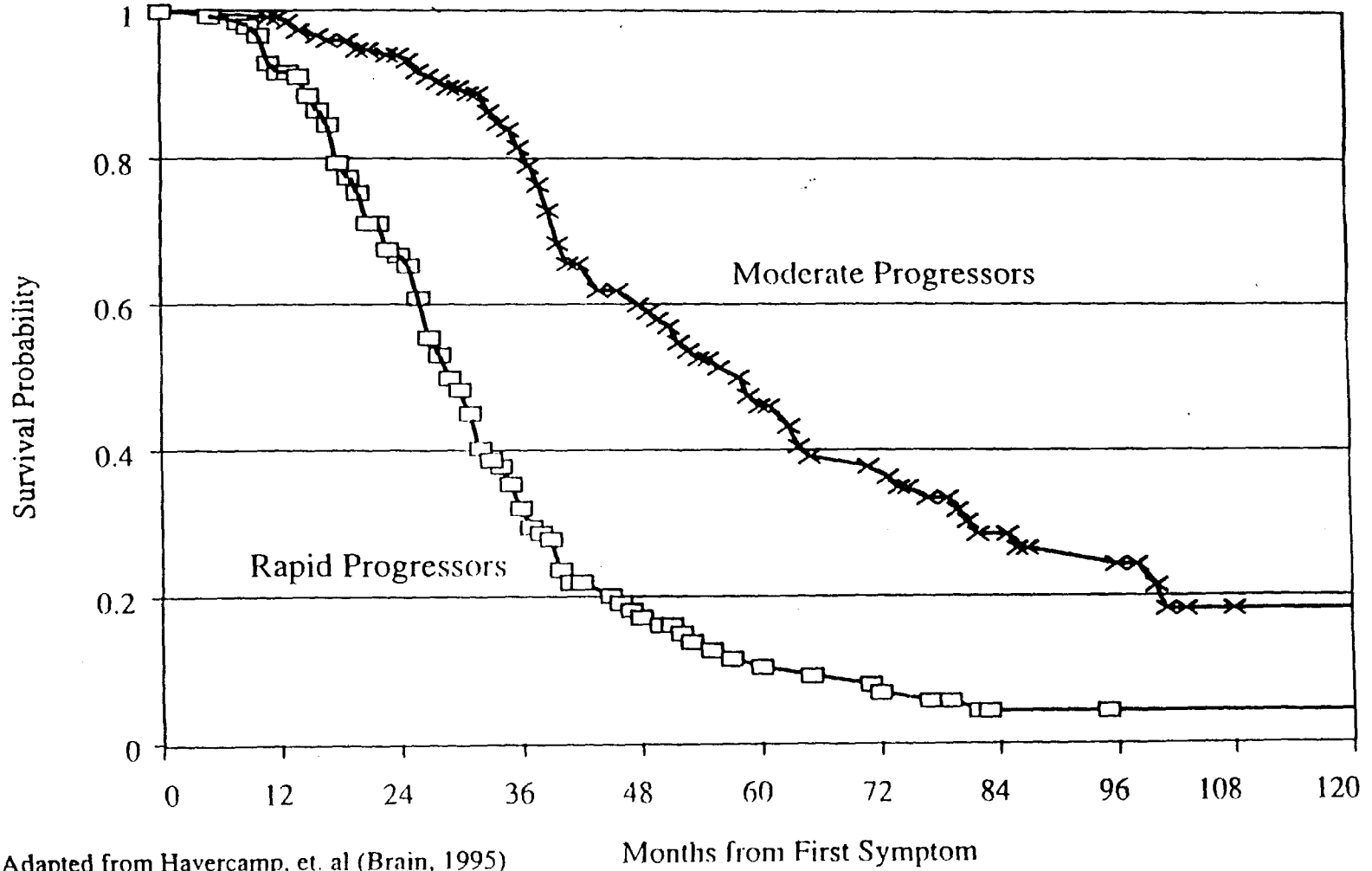
- Criteria:
  - AALS Total Score ≥ 115
  - FVC $< 39\%$

- Beyond these limits, patients are too disabled to participate in the study

The Baylor Natural History Database
Disassociation of Total AALS Score and Death



Rate Change in AALS Score Correlates with Survival



Adapted from Havercamp, et. al (Brain, 1995)

Outcome Measures

- AALS analyses to assess disease progression
  - Slope
  - Change score
  - Time to event
    - AALS $\geq$ 115 points or FVC <39%
- Sickness Impact Profile (SIP)

Sickness Impact Profile
Dimensions and Categories

Dimension	Category
Physical	Ambulation
	Mobility
	Body Care and Movement
Psychosocial	Communication
	Alertness Behavior
	Emotional Behavior
	Social Interaction
Independent Categories	Sleep and Rest
	Eating
	Work
	Home Management
	Recreation and Pastimes

Conclusions

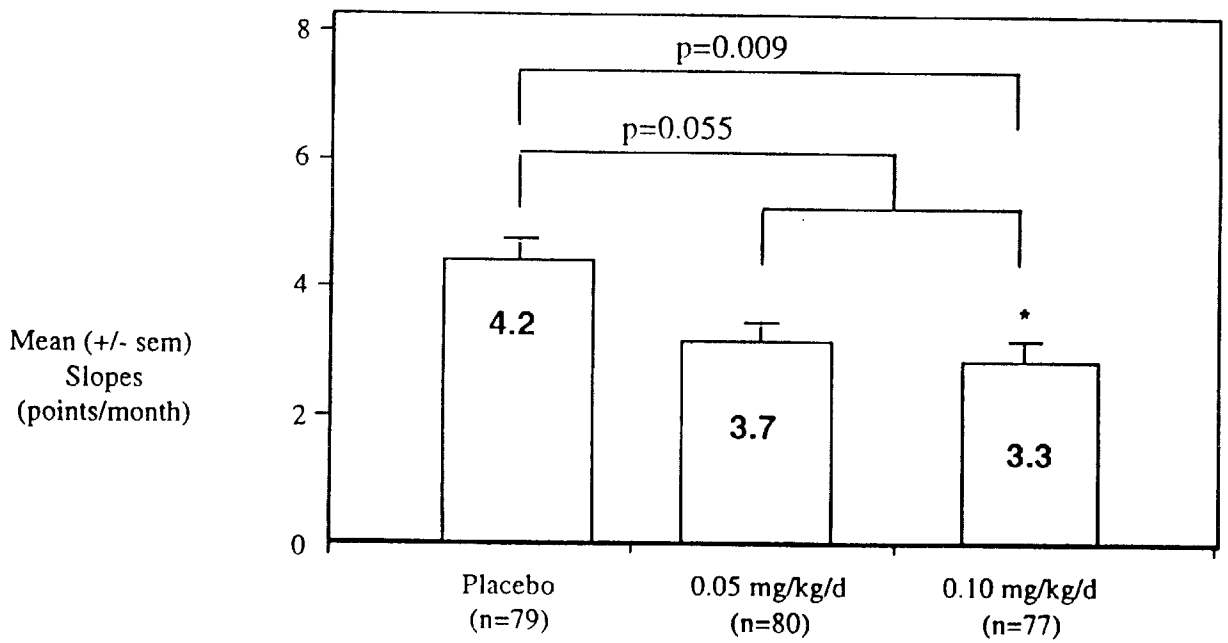
- ALS is a relentlessly progressing and uniformly fatal disease
- AALS scale is a clinically relevant, valid and reliable measure of disease progression
- Partitioning patients based upon disease progression is clinically meaningful and prognostically important
- No therapy is currently available to reduce the relentless progression of disability in ALS

William F. Graney, M.D.

Efficacy

- Effects on AALS related endpoints are directionally consistent in both studies
- Effects on time to protocol specified termination criteria were also directionally consistent
- The therapeutic effect was most evident in rapidly progressing patients in both studies

North American Study
Rate of Disease Progression



Patients with at least 3 post baseline assessments

Note: p-values from protocol-specified covariate model.

North American Study

AALS Slope Change (Points/Month)

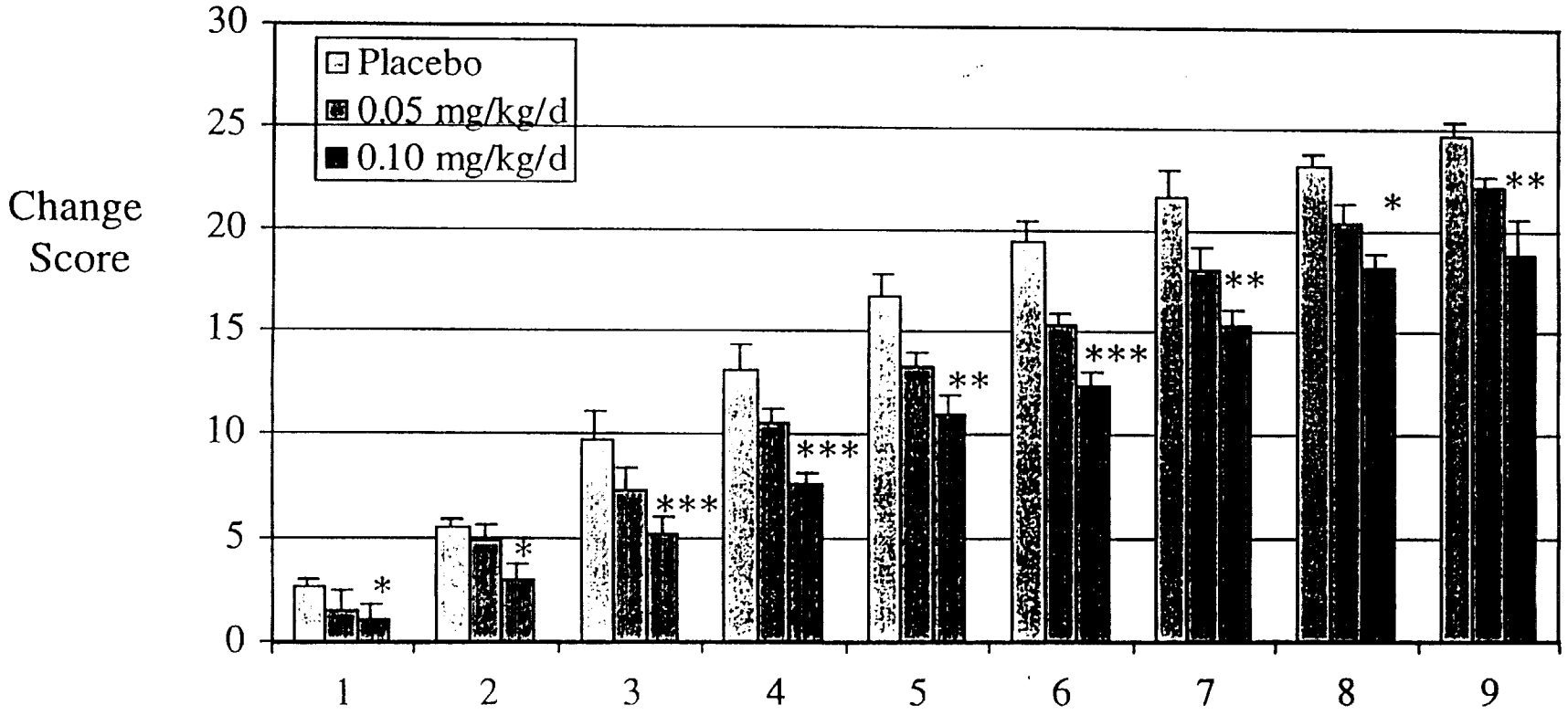
Post-Treatment Versus Pre-Treatment

Patient Group	N	Post- Minus Pre-Treatment Slope[a]	Difference From Placebo
Evaluable Patients	236		
0.10 mg/kg/d	77	-0.64	-0.80
0.05 mg/kg/d	80	-0.51	-0.67
Placebo	79	0.16	

a: Least Squares means; ANOVA model with treatment and investigator effects

North American Study

Change in AALS Total Score From Baseline - LOCF

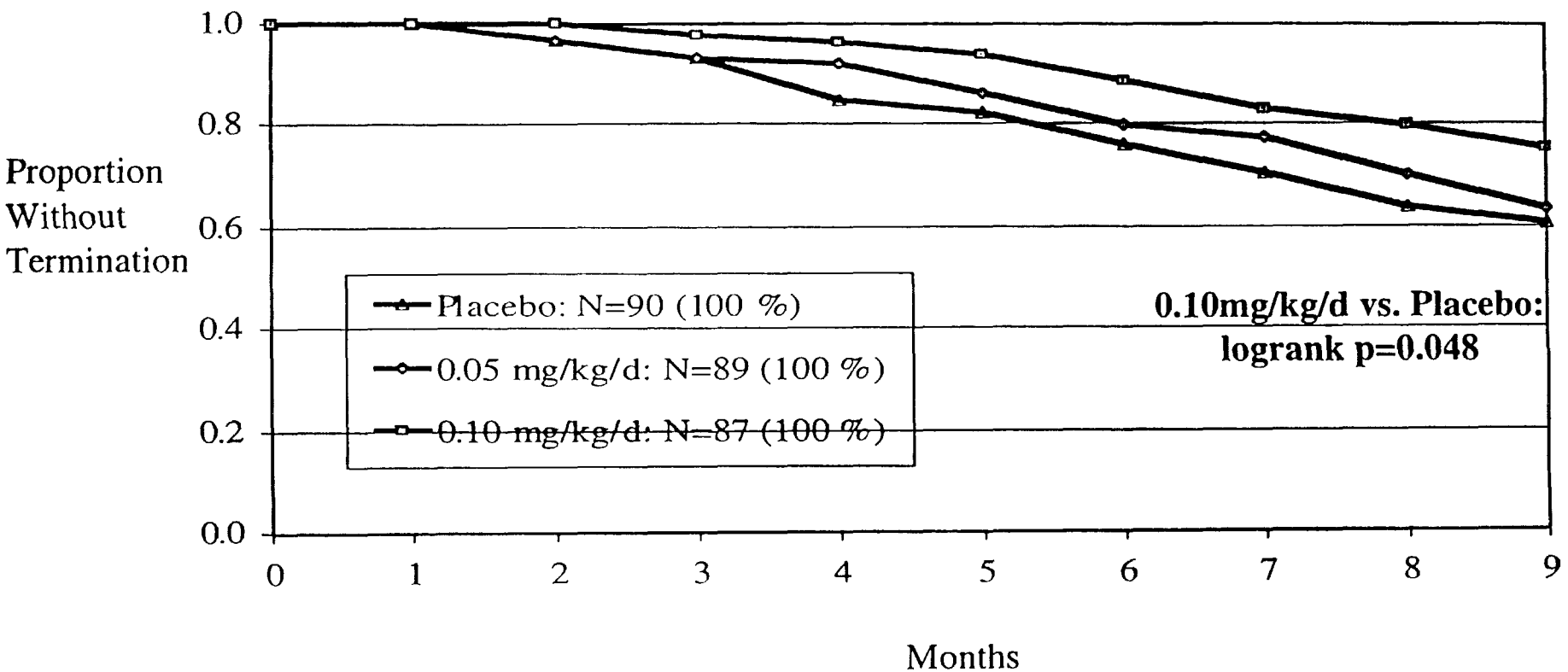


***p≤0.0001, **p≤0.01, *p≤0.05

Placebo N=88 (98%)
0.05 mg/kg/d: N=88 (99%)
0.10 mg/kg/d: N=86 (99%)

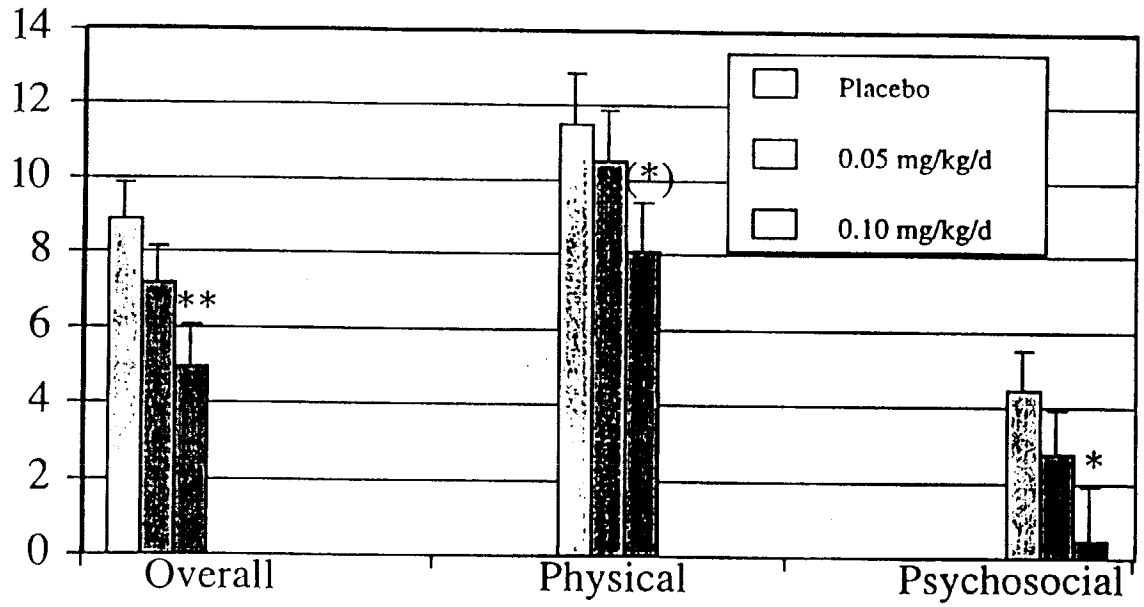
North American Study

AALS Total Score ≥ 115 or FVC < 39%



North American Study
Sickness Impact Profile
Endpoint Analysis (mean ± sem)

Change Score from Baseline



** p≤ 0.01, * p≤0.05, (*) p≤ 0.10

cephalon 58196 Graney

Placebo: N = 74 (83%)
0.05 mg/kg/d: N = 68 (78 %)
0.10 mg/kg/d: N = 72 (83 %)

Summary of North American Study

- Myotrophin produced dose-related slowing of disease progression compared to placebo:
  - Rate of change in AALS total score (slope)
  - Change in AALS total score from baseline
  - Time to AALS total score $\geq$ 115 or FVC < 39%

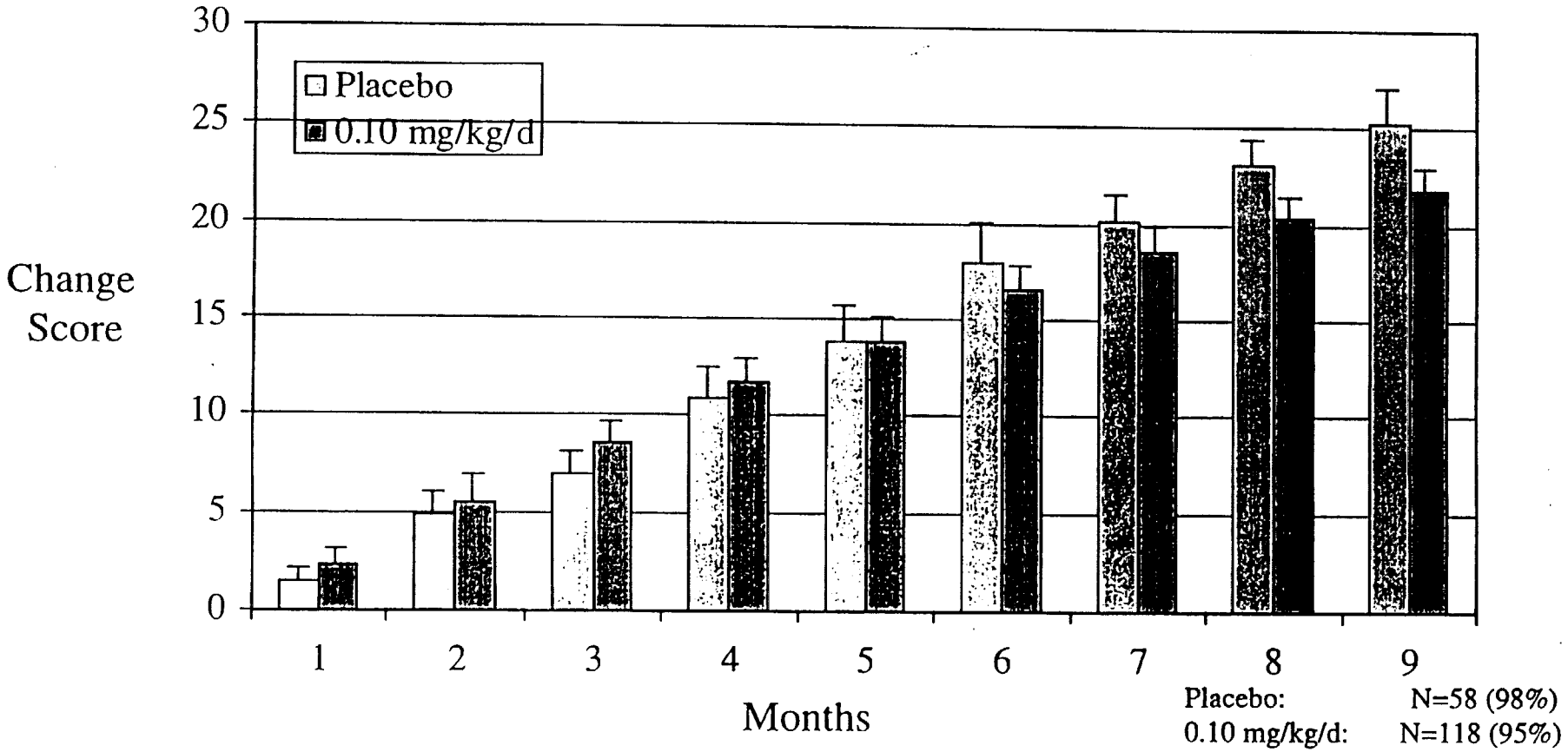
- Myotrophin produced beneficial, dose-related effects in the Sickness Impact Profile compared to placebo

Design Differences Between Studies

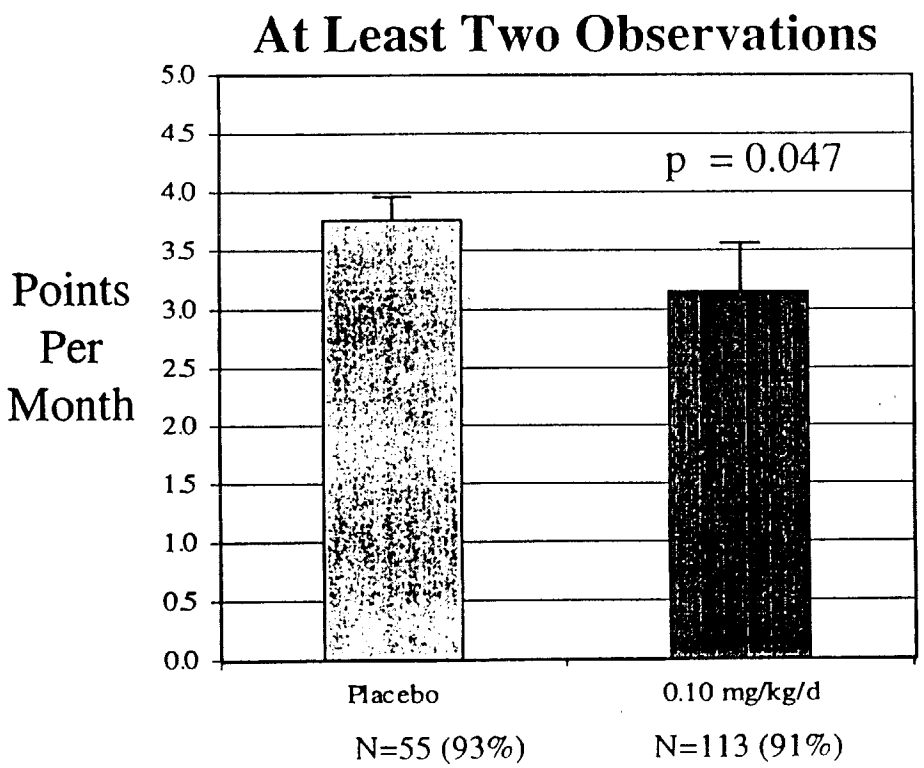
	North America	Europe
Treatment Arms	3	2
Regimen	0.05 mg/kg/d 0.10 mg/kg/d Placebo	--- 0.10 mg/kg/d Placebo
Randomization	1:1:1	2:1
Number of Patients	266	183
Primary Endpoints	AALS slopes	AALS change score

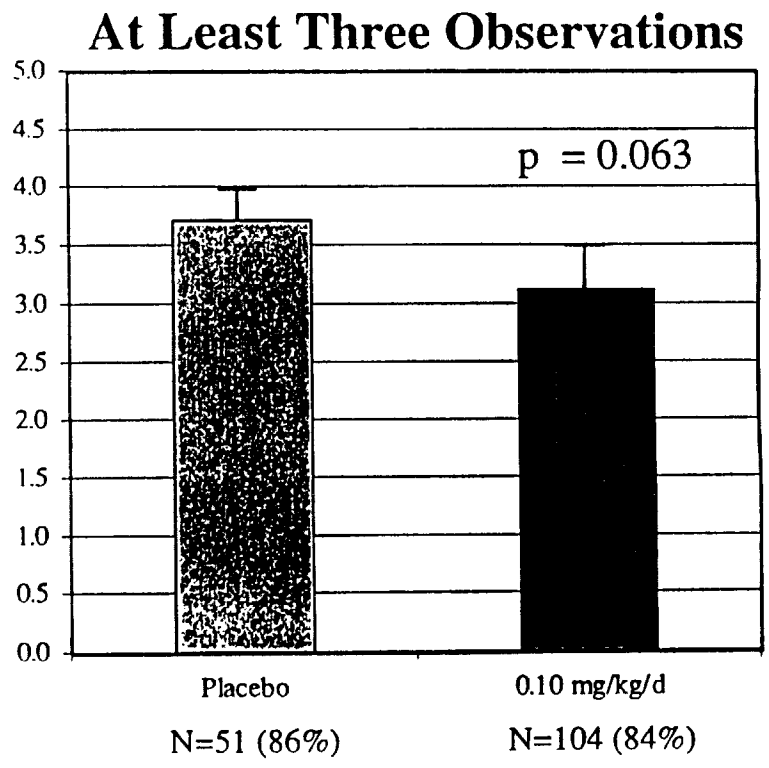
European Study

Change in AALS Total Score From Baseline - LOCF



European Study
Rate of Disease Progression
Repeated Measures
AALS Total Slope (mean ± sem)





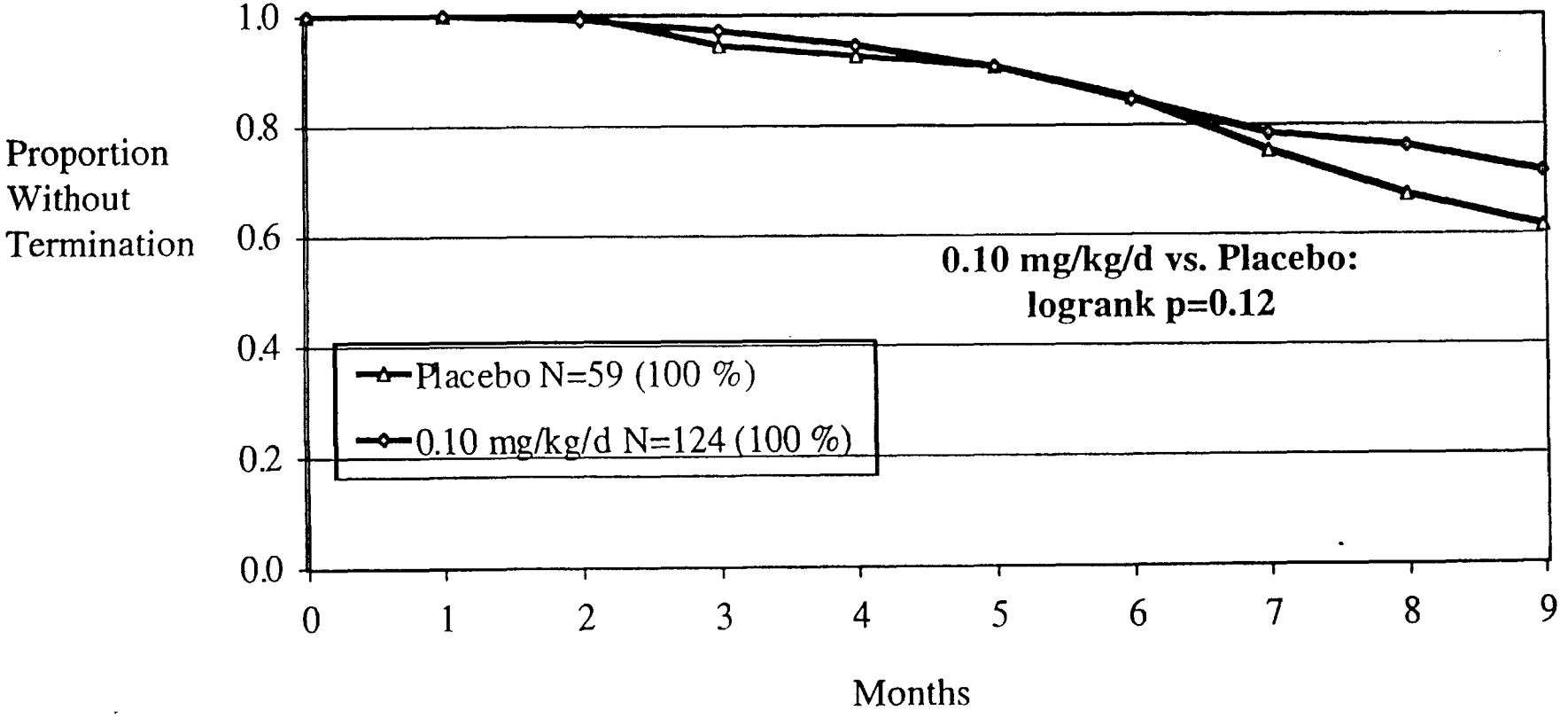
European Study
AALS Slope Change (Points/Month)
Post-Treatment Versus Pre-Treatment

Patient Group	N	Post- Minus Pre-Treatment Slope[a]	Difference From Placebo
Evaluable Patients	155		
0.10 mg/kg/d	104	-0.65	-0.34
Placebo	51	-0.31	

a: Least Squares means; ANOVA model with treatment and investigator effects

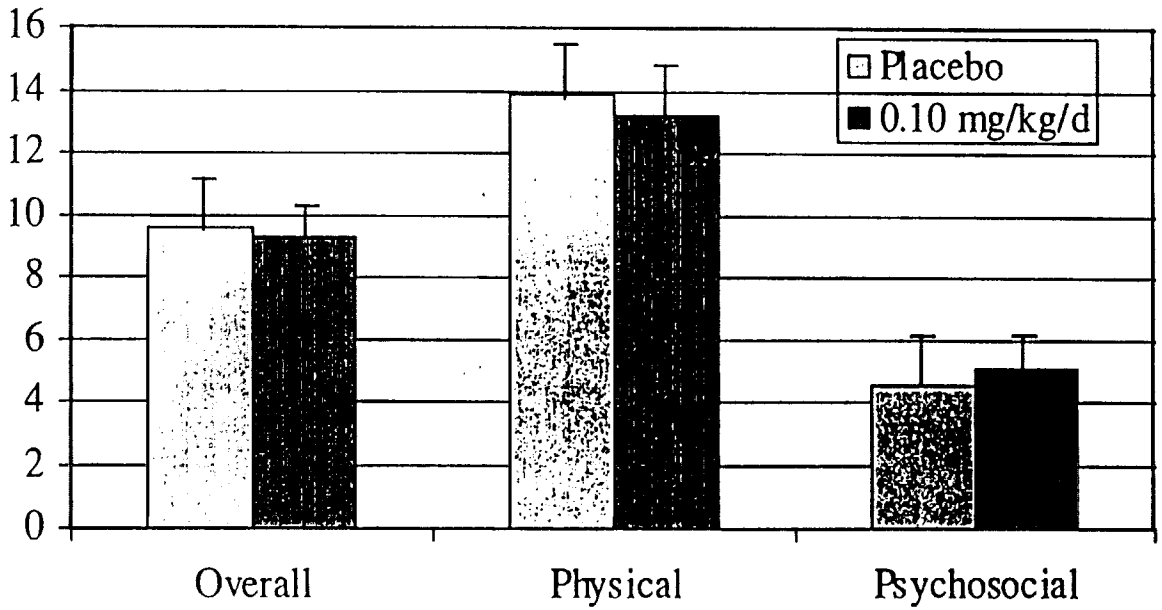
European Study

AALS Total Score ≥ 115 or FVC < 39%



European Study
Sickness Impact Profile
Endpoint Analysis

Change Score from Baseline



Placebo: N=48 (81%)
0.10 mg/kg/d: N=99 (80%)

Strata

	AALS Total Score	Slope (Points/Mo) mean ± sem
• Moderate progressors	≤ 60	3.54 ± 0.15 (N=136)
• Rapid progressors	> 60	5.41 ± 0.17 (N=313)

- Based on observations in North American and European studies

Treatment Difference Myotrophin vs. Placebo
Analyses by Baseline AALS Stratum (post-hoc)
Rapid Progressors

	Slopes	Change Score
North American Study	-1.2 (p = 0.009)	-7.8 (p = 0.005)
European Study	-1.3 (p = 0.10)	-7.8 (p = 0.02)

North American Slopes	N = 109
North American Change Score	N = 126
European Slopes	N = 100
European Change Score	N = 117

Treatment Difference Myotrophin vs. Placebo
Analyses by Baseline AALS Stratum (post-hoc)
Moderate Progressors

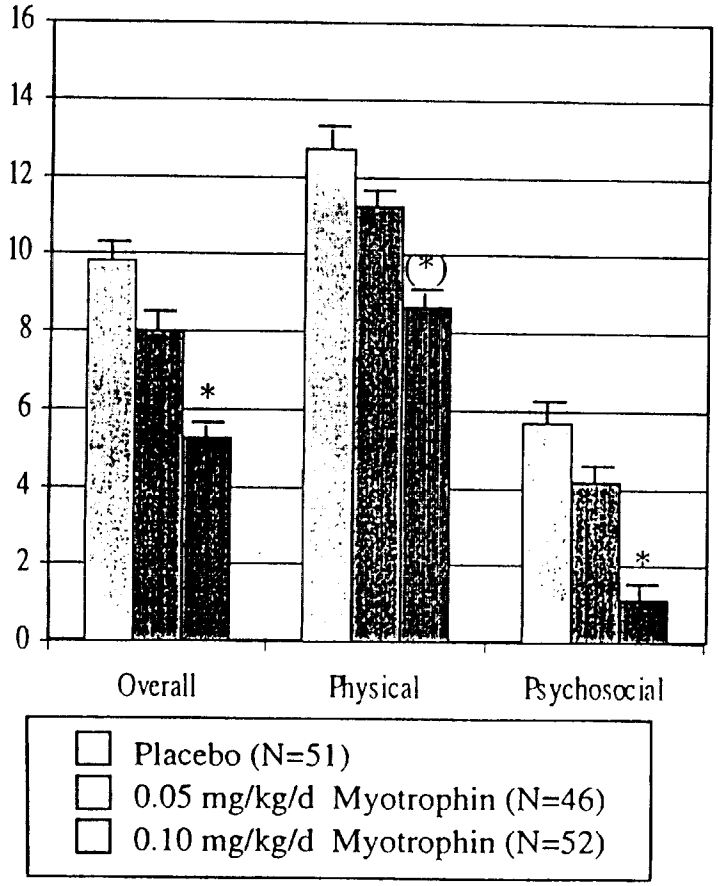
	Slopes	Change Score
North American Study	-0.1 (p = 0.75)	-1.0 (p = 0.76)
European Study	0.8 (p = 0.42)	5.2 (p = 0.31)

North American Slopes	N = 47
North American Change Score	N = 48
European Slopes	N = 56
European Change Score	N = 59

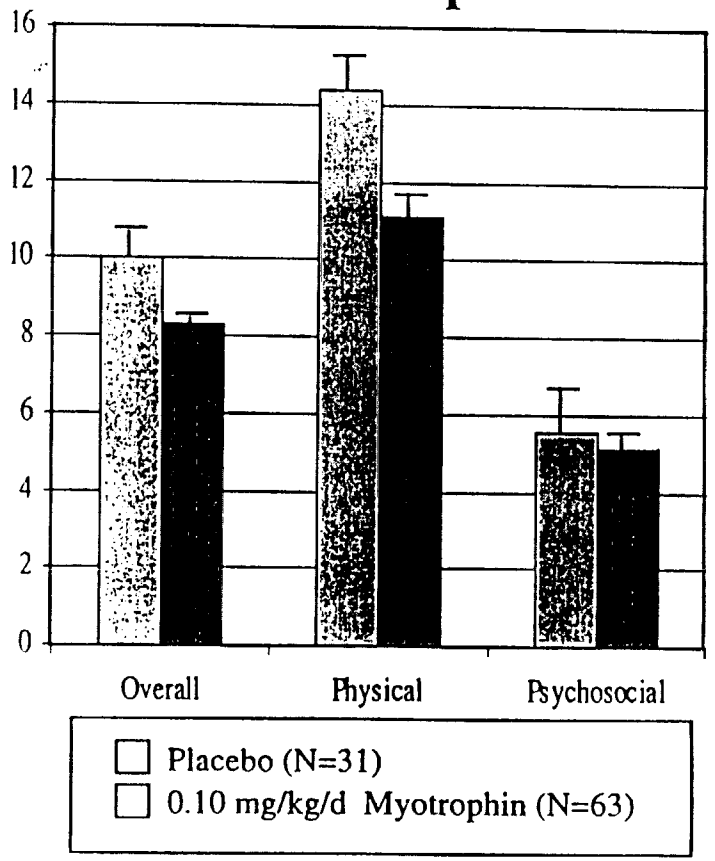
Sickness Impact Profile

Endpoint Analysis - Rapid Progressors

North America



Europe



* p <0.05, (*) p<0.10

Efficacy Summary

- North American study demonstrates Myotrophin's effectiveness in ALS
- European study is supportive of Myotrophin's effectiveness
- Therapeutic effect most evident in rapidly progressing patients as measured by both AALS and SIP
- North American and European studies provide sufficient evidence of efficacy to support treatment use of Myotrophin in patients with ALS

Thomas W. Dobbins, Ph.D.

Key Point

- Patient withdrawal does not influence conclusions from either study

Patient Disposition
North American Study

	Myotrophin 0.10 mg/kg (N = 87)	Myotrophin 0.05 mg/kg (N = 89)	Placebo (N = 90)
• Protocol-specified termination			
AALS total score ≥115	7%	10%	14%
FVC < 39% predicted value	10%	16%	18%
Either AALS ≥ 115 or FVC < 39%	*17%*	*26%*	*33%*
• Patient withdrawal			
Death	9%	12%	8%
Adverse experience	3%	2%	0%
All other	14%	3%	13%
Withdrawal	*26%*	*17%*	*21%*
• Total discontinued	44%	44%	53%

Patient Disposition
European Study

	Myotrophin 0.10 mg/kg (N = 124)	Placebo (N = 59)
• Protocol-specified termination		
AALS total score ≥115	12%	19%
FVC < 39% predicted value	8%	15%
Either AALS ≥ 115 or FVC < 39%	*20%*	*34%*
• Patient withdrawal		
Death	15%	8%
Adverse experience	4%	0%
All other	9%	5%
Withdrawal	*28%*	*13%*
• Total discontinued	48%	47%

AALS Total Score Change from Baseline

LOCF Analysis - Rapid Progressors
European Study

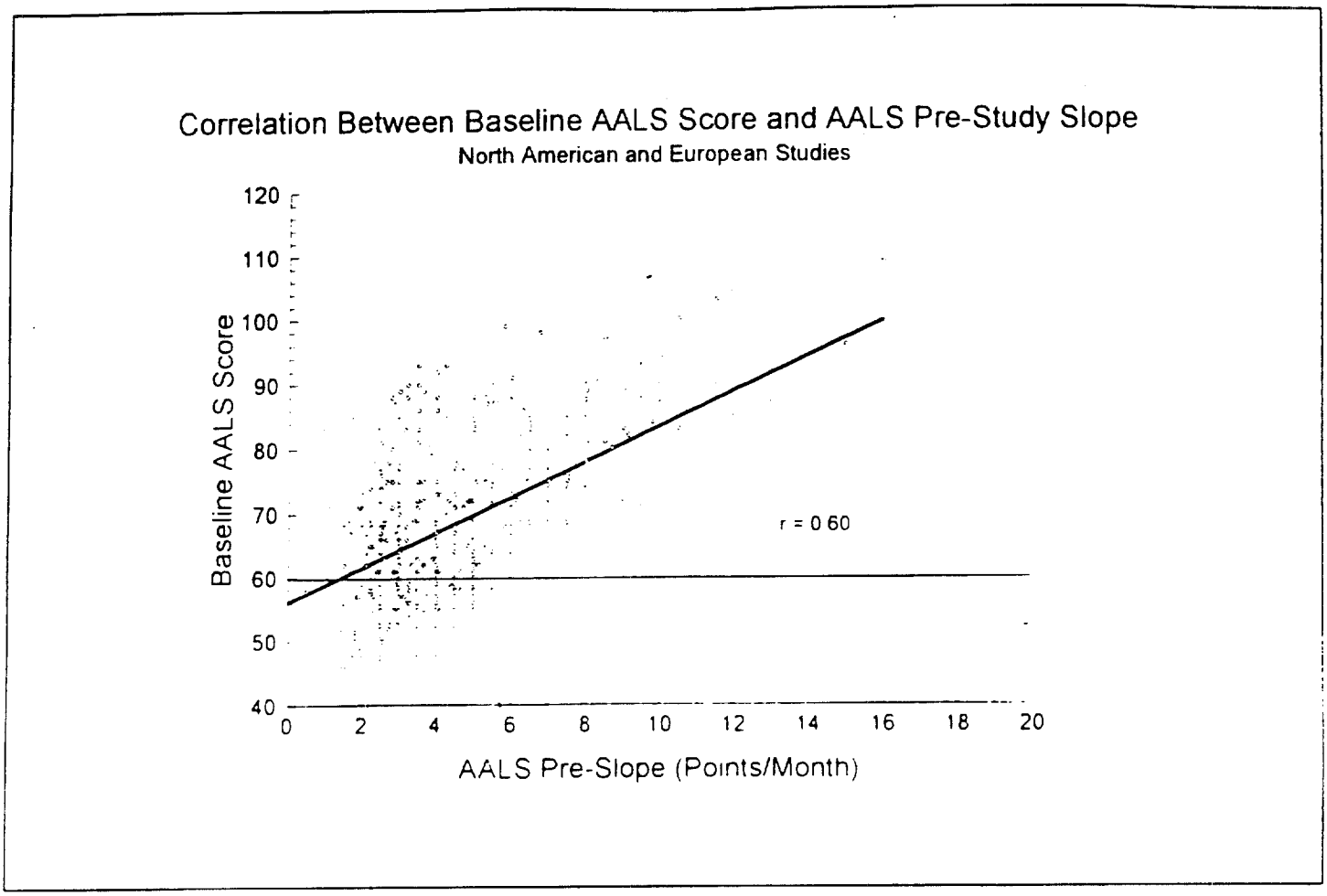
Treatment	N	Mean	Difference
ALL PATIENTS			
Myotrophin 0.10 mg/kg/d	79	21.3	- 7.8
Placebo	38	29.1	
REMOVING DEATHS			
Myotrophin 0.10 mg/kg/d	66	21.2	- 8.6
Placebo	36	29.8	
REMOVING ALL WITHDRAWALS			
Myotrophin 0.10 mg kg d	54	23.1	- 7.9
Placebo	34	31.0	

Conclusion

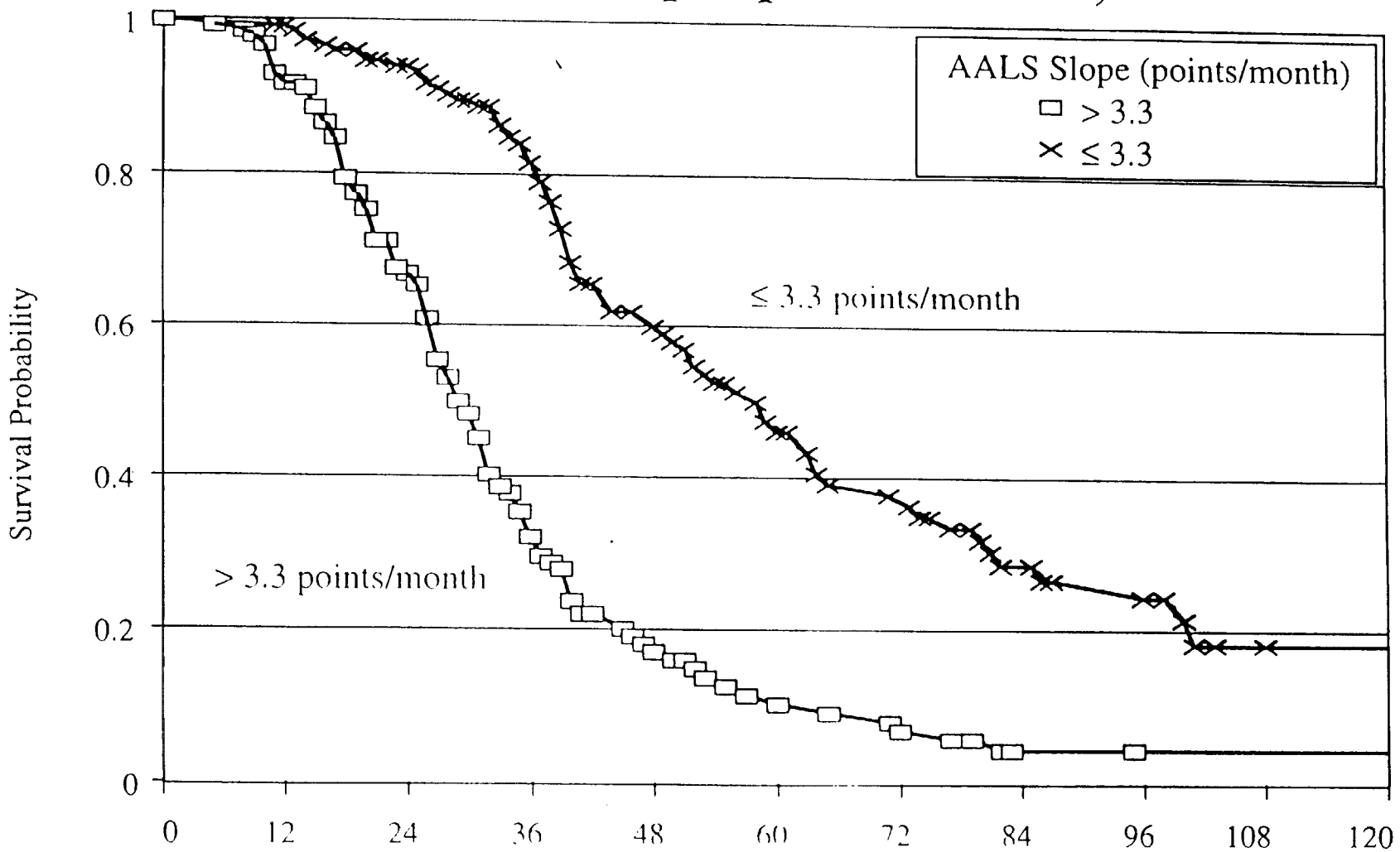
- Patient withdrawal does not influence conclusions from either study

Key Point

- Stratification based upon AALS score at baseline delineates rapid progressors



AALS Slope (points/month)



Adapted from Havercamp, et. al (Brain, 1995)

Stratification: Moderate Progression
North American Study

	AALS PRE-SLOPE ≤ 3.3			AALS SCORE ≤ 60		
TREATMENT	N	MEAN	DIFF	N	MEAN	DIFF
0 10 mg/kg/d	38	3.3	-0.1	23	3.2	-0 1
0 05 mg/kg/d	28	2.8	-0 6	27	2 2	-1 1
Placebo	33	3 4		24	3 3	

- Results consistent whether patients stratified by pre-slope or baseline AALS score

Stratification: Moderate Progression
European Study

	AALS PRE-SLOPE ≤ 3.3			AALS SCORE ≤ 60		
TREATMENT	N	MEAN	DIFF	N	MEAN	DIFF
0.10 mg/kg/d	41	2.6	-0.2	38	3.3	0.8
Placebo	20	2.8		18	2.5	

- Non-significant positive difference resolved when patients are stratified directly by disease progression

Stratification: Rapid Progression
North American Study

	AALS PRE-SLOPE >3.3			AALS SCORE >60		
TREATMENT	N	MEAN	DIFF	N	MEAN	DIFF
0.10 mg/kg/d	39	3.3	-1.6	54	3.4	-1.2
0.05 mg/kg/d	52	4.2	-0.7	53	4.4	-0.2
Placebo	46	4.9		55	4.6	

- Therapeutic effect evident whether patients stratified by pre-slope or baseline AALS score

Stratification: Rapid Progression
European Study

	AALS PRE-SLOPE > 3.3			AALS SCORE > 60		
TREATMENT	N	MEAN	DIFF	N	MEAN	DIFF
0.10 mg/kg/d	63	4.8	-0.7	66	4.3	-1.3
Placebo	31	5.5		34	5.6	

- Therapeutic effect evident whether patients stratified by pre-slope or baseline AALS score

Key Point

- Stratification based upon AALS score at baseline delineates rapid progressors

Safety of Myotrophin

North American and European Studies
Ten Most Frequently Reported Clinical Adverse Experiences

	0.05 mg/kg/d N = 89 n (%)	0.10 mg/kg/d N = 211 n (%)	Placebo N = 149 n (%)
Weakness **	65 (73)	132 (62)	94 (63)
Injection Site Pain	60 (67)	121 (57)*	106 (71)
Dyspnea	33 (37)	78 (37)	45 (30)
Headache	29 (32)	76 (36)	55 (36)
Coordination Abnormality	34 (38)	66 (31)	46 (30)
Constipation	28 (31)	58 (27)	34 (22)
Sweating	18 (20)	58 (27)*	23 (15)
Dysphagia	31 (34)	56 (26)	47 (31)
Dysarthria	15 (16)	51 (24)	30 (20)
Dizziness	30 (33)	50 (23)	36 (24)

* $p <= 0.05$ versus placebo

** Includes weakness reported under body as a whole and under nervous system

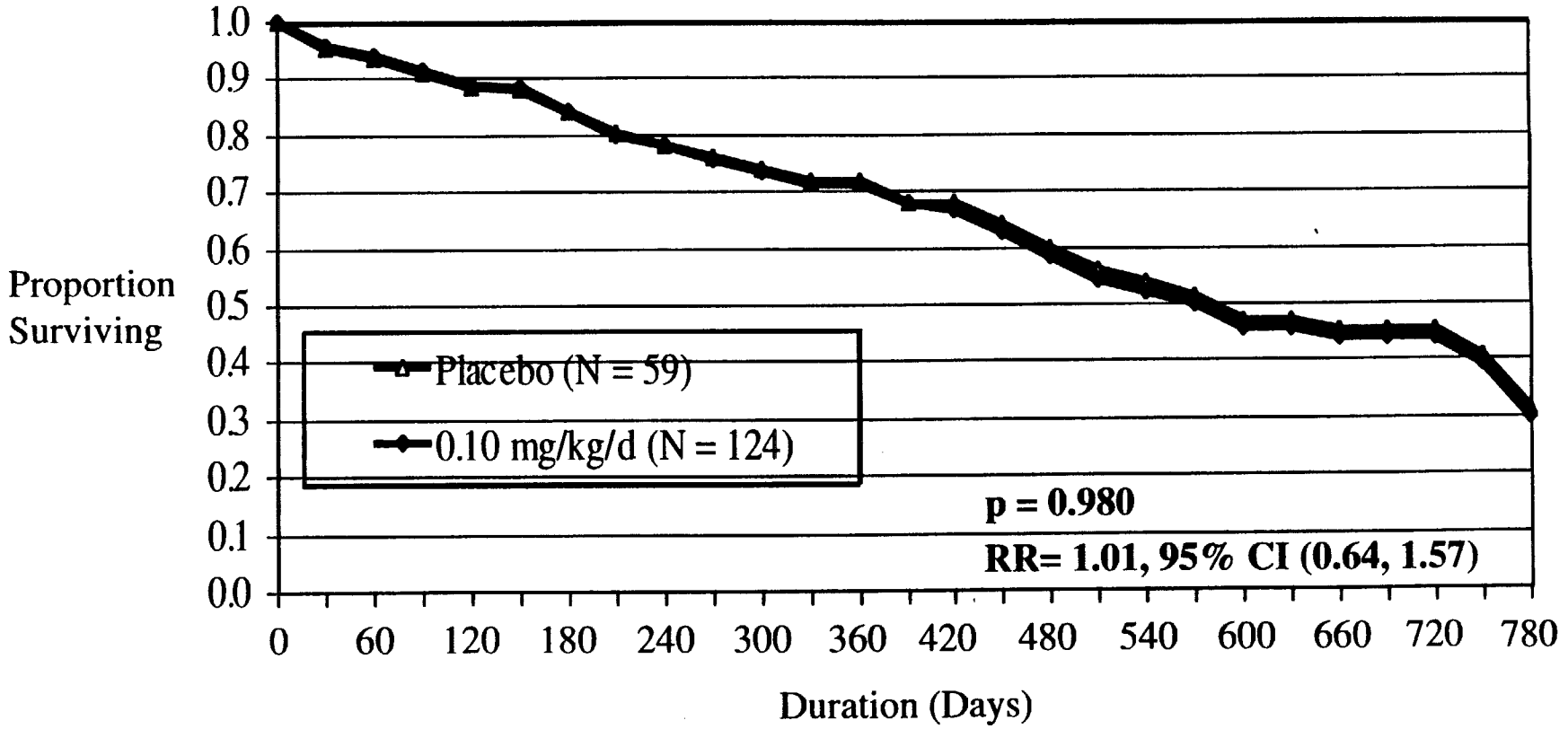
North American and European Studies
Mortality

	North America			Europe	
	Placebo N = 90	**0.05 mg/kg/d N = 89**	**0.10 mg/kg/d N = 87**	**Placebo N = 59**	**0.10 mg/kg/d N = 124**
Double-Blind Treatment	7 (7.8%)	11 (12.4%)	8 (9.2%)	5 (8.5%)	18 (14.5%)
Up to Day 300	22 (24.4%)	20 (22.5%)	17 (19.5%)	13 (22.0%)	36 (29.0%)

Risk Factors for Death

- Greater age
- Lower vital capacity
- Greater rate of change of AALS total score during screening

Extended Survival Analysis
European Study
Cox Proportional Hazards Regression Model



Safety Summary

Myotrophin is well tolerated and has an acceptable safety profile in ALS

Body of Evidence

- The North American study demonstrates Myotrophin's effectiveness as measured by the AALS total score and the Sickness Impact Profile
- The European study also demonstrates Myotrophin's effectivness and is supportive of the North American study
- Therapeutic effect most evident in rapidly progressing patients as measured by both AALS and SIP
- Myotrophin is well tolerated and reduces disease progression in ALS

Robert G. Miller, M.D.

California Pacific Medical Center

Slide Placeholder

Patient Profile With Dr. Miller

Current Treatments in ALS

1) *Control of spasticity, cramps, saliva, sleep*
2) *Mobility assistance*
3) *Percutaneous gastrostomy*
4) *Nasal mechanical ventilation*

Negative Clinical Trials

TRH	Dextrometorphan	Plasma Exchange
Threonine	Lamotrigine	TLI
BCAA	N-acetyl cysteine	CsA/AZA/CTX
rhGH	Gangliosides	IT Steriods
rhCNTF(2)	Verapamil	Nimodipine

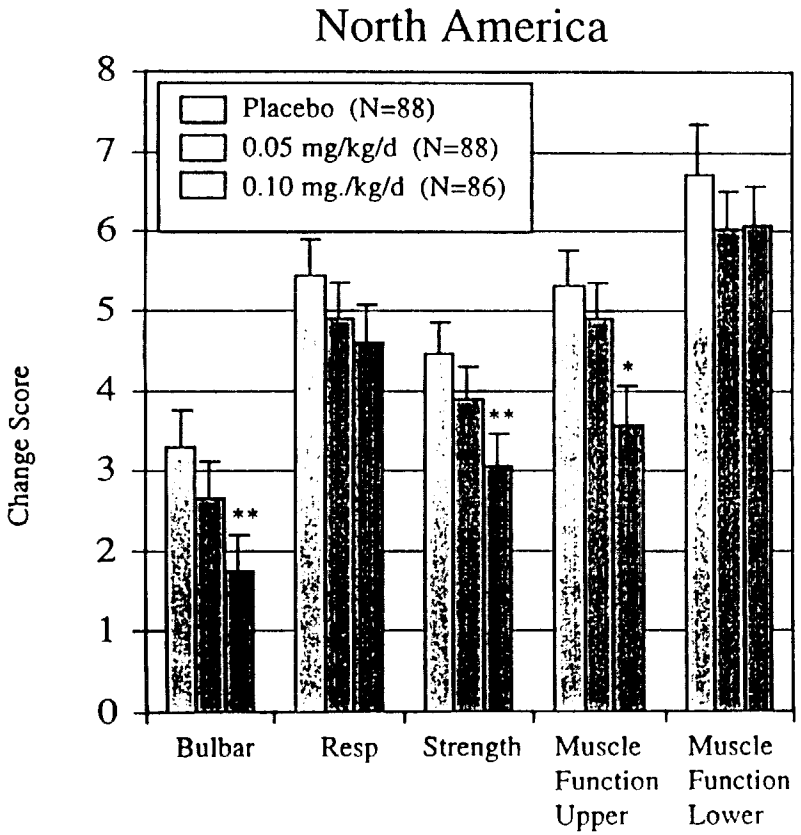
Myotrophin
Clinical Interpretation

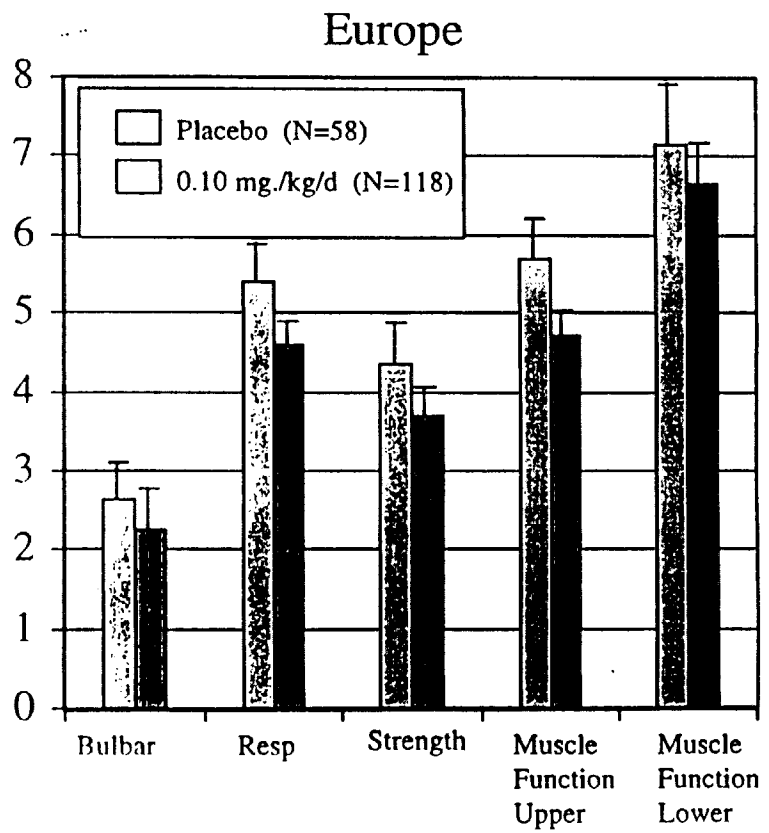
- Results from both studies demonstrate
  - Disease progression slowed
  - Effects most evident in rapidly progressing patients
  - No safety issues

Myotrophin
Clinical Interpretation

- Benefits demonstrated in
  - Physician assessment of illness (AALS)
  - Patient perceived illness (SIP)
- Assessments by physician and patient complementary

AALS Components
Change from Baseline --Endpoint

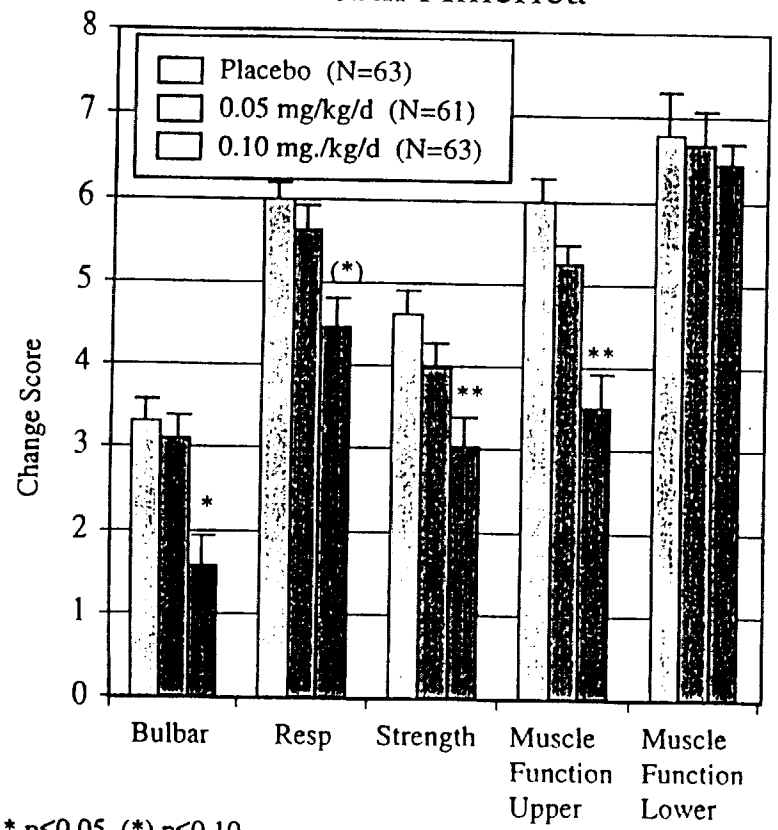




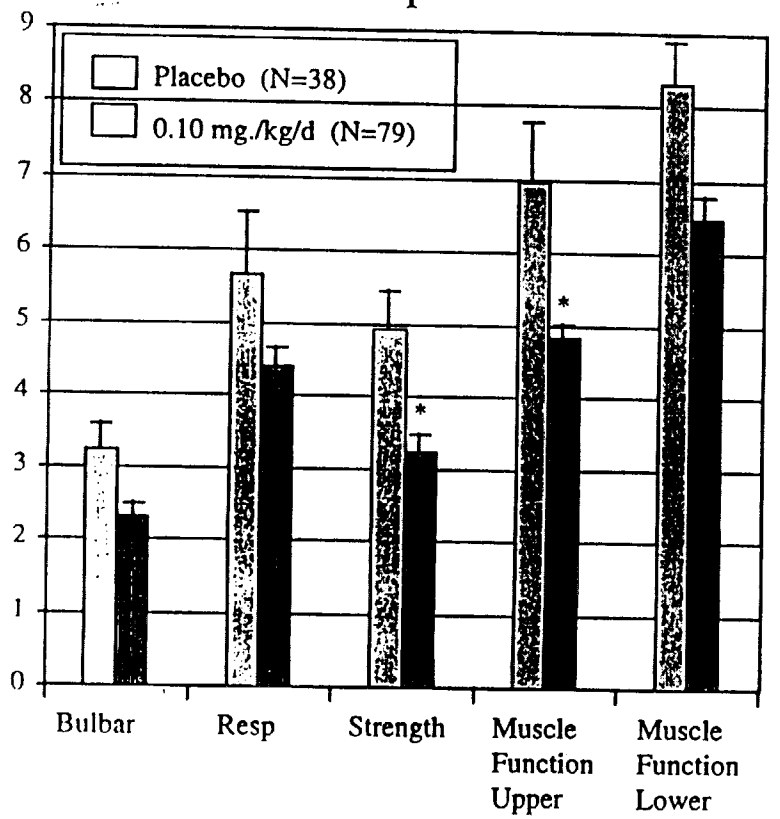
** p≤0.01, * p≤0.05, (*) p≤0.10

AALS Components
Change from Baseline -- Endpoint
Rapid Progressors

North America



Europe

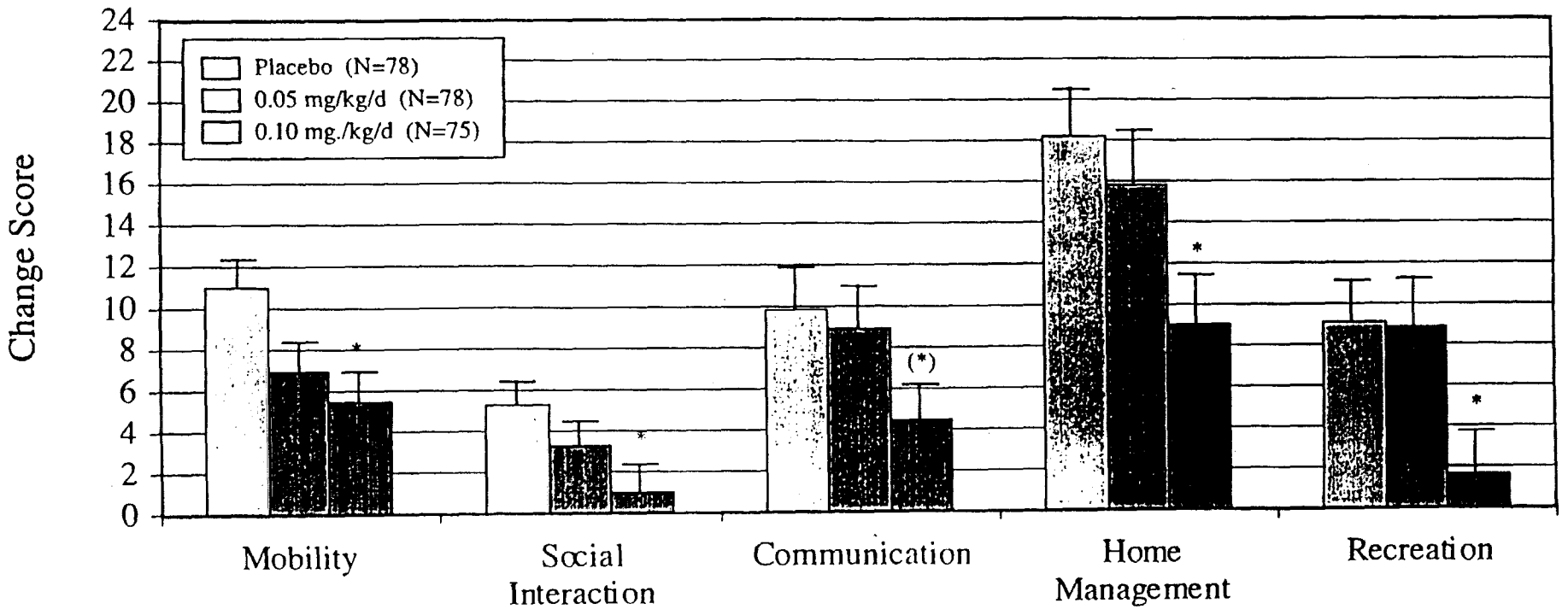


** p≤0.01, * p≤0.05, (*) p≤0.10

European Trial - Design Issues

- Investigator priorities:
  - 2:1, drug:placebo
- Effect size smaller than expected
- Underpowered for observed effect
- Especially for slow progressors

North American Study
Sickness Impact Profile
Change from Baseline - Endpoint



* p≤0.05, (*) p≤0.10

Relationship of the Tufts Quantitative Neuromuscular Exam (TQNE) and the Sickness Impact Profile (SIP) in measuring progression of ALS

Article Abstract - The Tufts Quantitative Neuromuscular Exam (TQNE) is a standardized tool for measuring strength and pulmonary function in patients with amyotrophic lateral sclerosis (ALS). We describe the relationship of TQNE scores to functional disability and health-related quality of life as measured by the Sickness Impact Profile (SIP) in 524 ALS patients. There was a significant relationship ($p < 0.0001$) between TQNE and SIP scores, both in cross section and over time. TQNE scores strongly relate to ALS patients' quality of life and ability to perform activities of daily living.

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Myotrophin
Clinical Interpretation

- Efficacy consistent with known biology
- Efficacy established using a valid, reliable, disease specific measure (AALS)
- Efficacy most evident in patients with rapid disease progression
- First clinical trial in ALS demonstrating slower decline of quality of life rated by patients themselves
- Context of minimal risk

Therapeutic Effect Size

TREATMENT	CLINICALLY APPARENT	IMPACT	SIZE
GBS-Pheresis	0	Slope Recovery	25%
DMD-Prednisone	+	Strength	8%
Riluzole	0	Mortality	4-18%
IGF-1	0	Slope Function	25%

Conclusions

- Currently one approved treatment - survival
- Myotrophin
  - Slows disease progression
  - Delays loss of quality of life
- Analogous to the second drug for cancer, HIV
- Wanted by patients and clinicians

Slide Placeholder

Patient Profile with Family