
Miglustat Therapy for Niemann-Pick Type C Disease

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- **Drug Regulatory Affairs** **Frances Duffy-Warren, PhD**
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Agenda

- Overview
- NP-C disease and the rationale for miglustat treatment
- Clinical pharmacology, efficacy and safety
- Benefit – Risk assessment
- Clinical perspective

NP-C Disease Overview

- **NP-C is an extremely rare (“ultra-orphan”) genetic disease**
 - **About 500 known cases worldwide; approximately 200 in the US**
- **NP-C is dominated by progressive nervous system involvement leading to premature death**
- **There is no approved therapy in the US**

Miglustat Development Overview

- Miglustat is the first potentially disease-modifying agent studied in NP-C disease
- Large proportion of known NP-C patients participated in the miglustat development program
- Spontaneous improvement of neurological disease is not observed in long term follow up
 - Creates a basis for documenting efficacy outside conventional methodology of RCTs
- Totality of data indicates that miglustat stabilizes the progression of neurological disease in NP-C
- Safety of miglustat is well characterized and manageable

Miglustat (Zavesca®)

- **2003: approved in US for type 1 Gaucher disease (GD-1) in patients for whom enzyme replacement therapy is not a therapeutic option**
 - **Also approved in EU and 10 other countries**
- **2009: approved in the EU for progressive neurological manifestations in adult and pediatric NP-C patients**
 - **Also approved in Brazil, South Korea, Russia (and Australia)**

Niemann-Pick Type C Disease and the Rationale for Miglustat Treatment

Marc C. Patterson, MD

Professor of Neurology, Pediatrics and Medical Genetics
Chair, Division of Child and Adolescent Neurology
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Niemann-Pick Type C Disease

Extremely rare pan-ethnic inherited lysosomal storage disorder (LSD)

Autosomal recessive inheritance

- **90–95% of cases due to mutations in NPC1 gene**
- **4% due to mutations in NPC2 gene**

NPC1 and NPC2 have roles in intracellular lipid trafficking

- **Abnormal intracellular lipid accumulation of mainly unesterified cholesterol and glycosphingolipids (GSL)**
- **Imbalance between normal production (Golgi) and defective trafficking / degradation (late endosomes, lysosomes)**

Niemann-Pick Type C Disease

Calculated birth incidence: approximately 1:150,000

- **Approximately 500 known NP-C patients worldwide**
 - **~200 NP-C patients in the US**

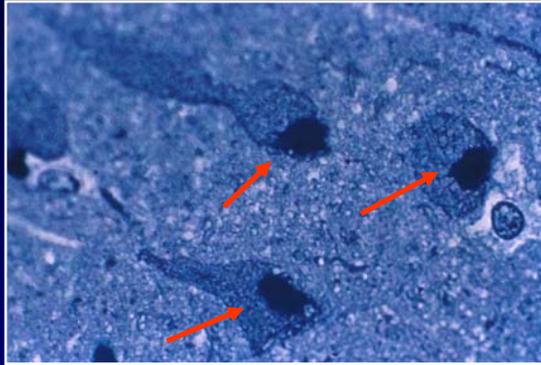
Wide heterogeneity of clinical picture

- **Delayed diagnosis**
- **CNS manifestations**
- **Visceral manifestations (e.g., liver, spleen, lungs)**

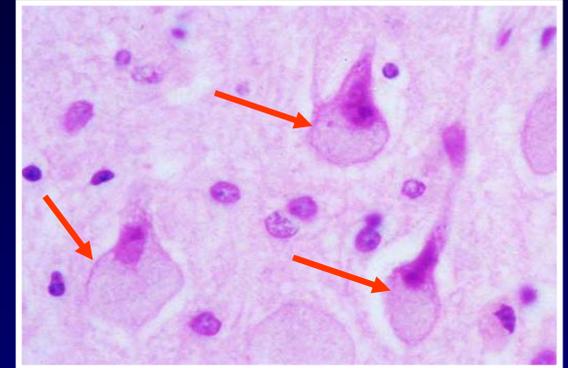
Age at Onset and Disease Manifestation

< 3 months	3 mo to < 2yrs	2 to < 6 yrs	6-15 yrs	>15 yrs
Systemic manifestations	Hypotonia and developmental delay	VSGP, cerebellar and brain stem signs	VSGP, cerebellar, cortical and brain stem signs	Cortical signs

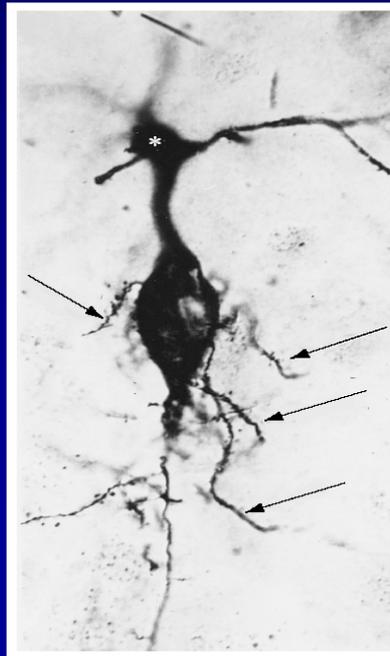
NP-C Disease: Neuropathological Changes



Meganeurites

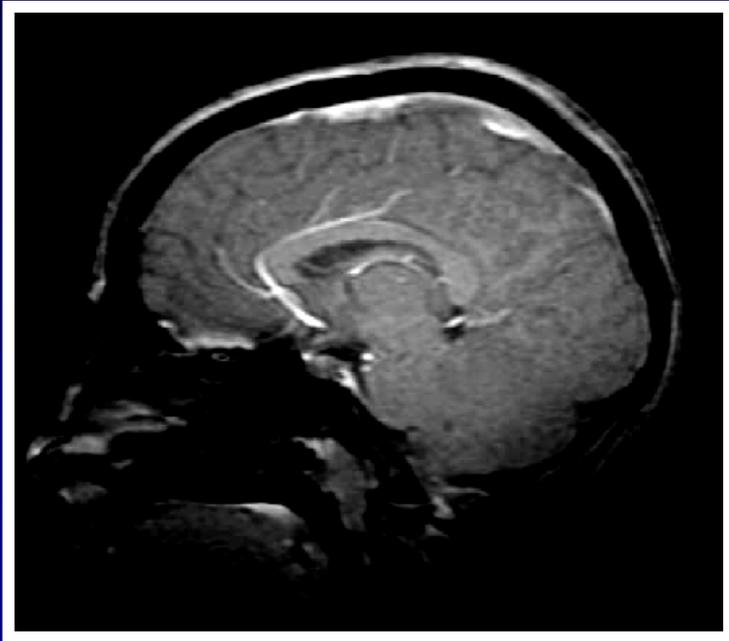


Balloon cells

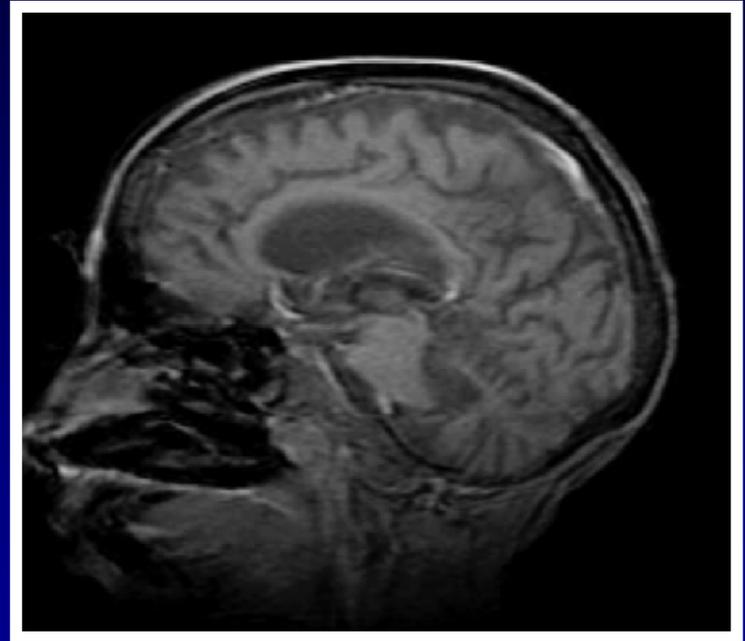


New ectopic dendrites

Brain MRI in NP-C Disease

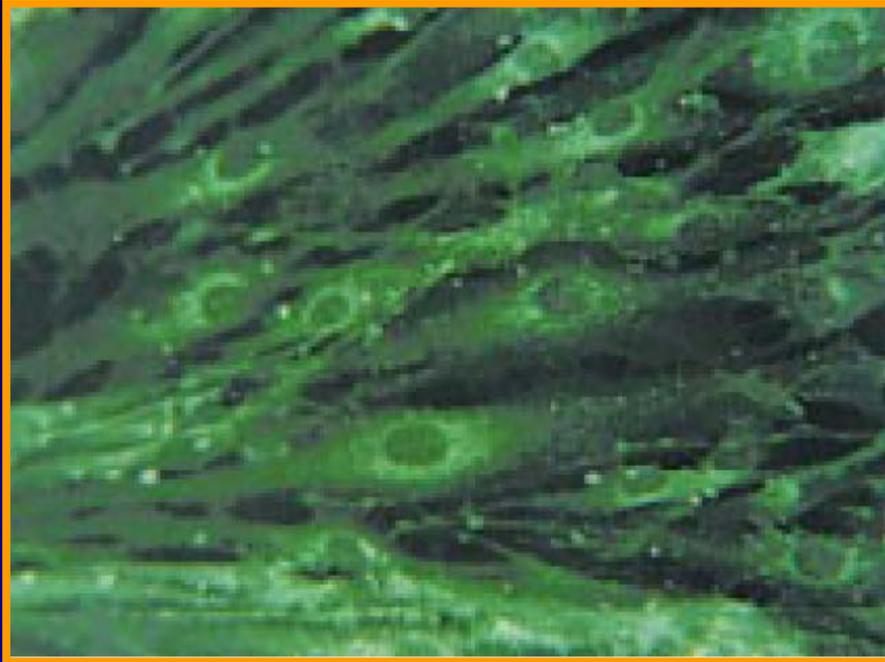


Normal

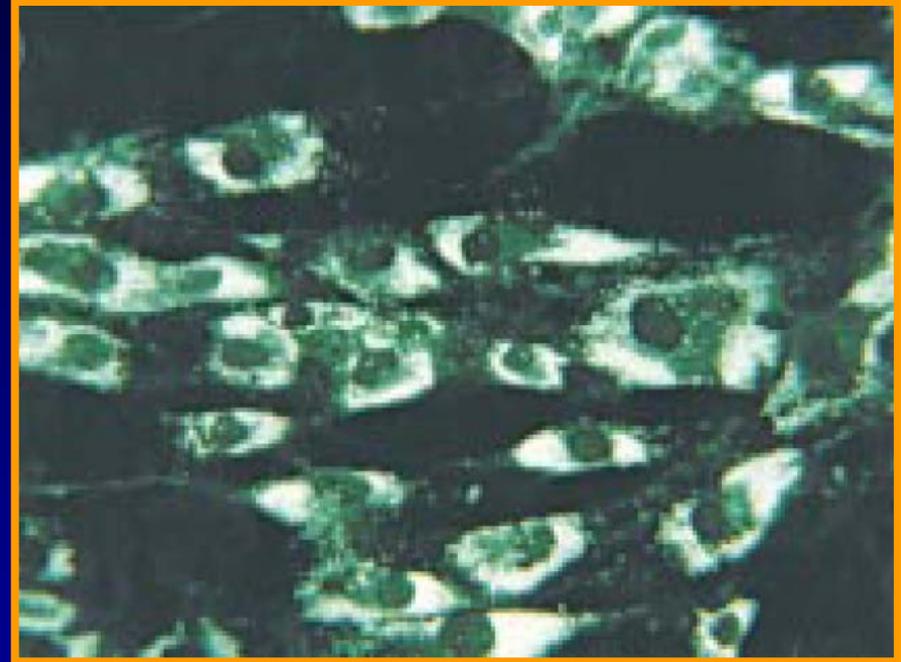


**NP-C
Disease**

Diagnosis of NP-C Filipin Staining



Normal fibroblasts

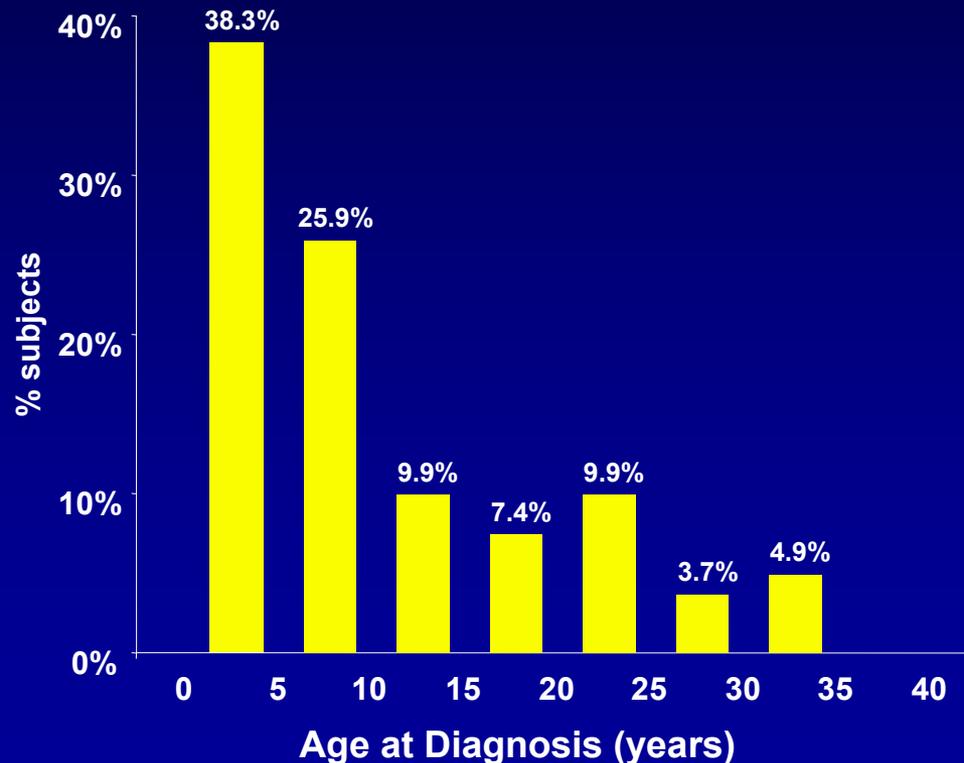


NP-C fibroblasts

Age at Diagnosis and at Death

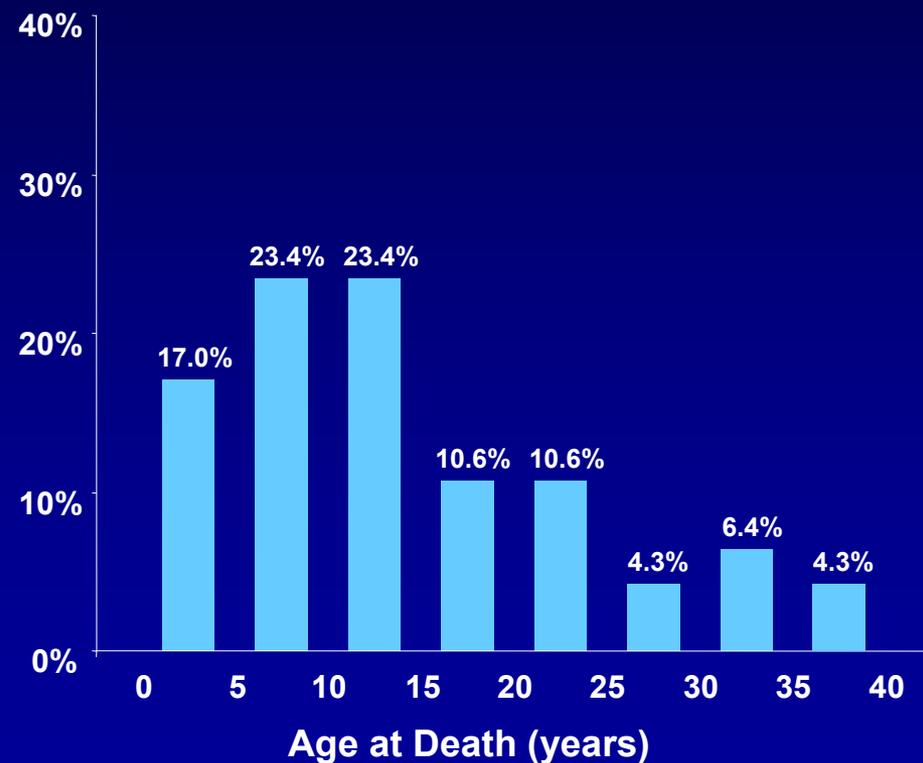
N=82

Mean (SD): 10.4 (9.3) years
Median: 6.9 years



N=50

Mean (SD): 16.2 (11.1) years
Median: 12.5 years

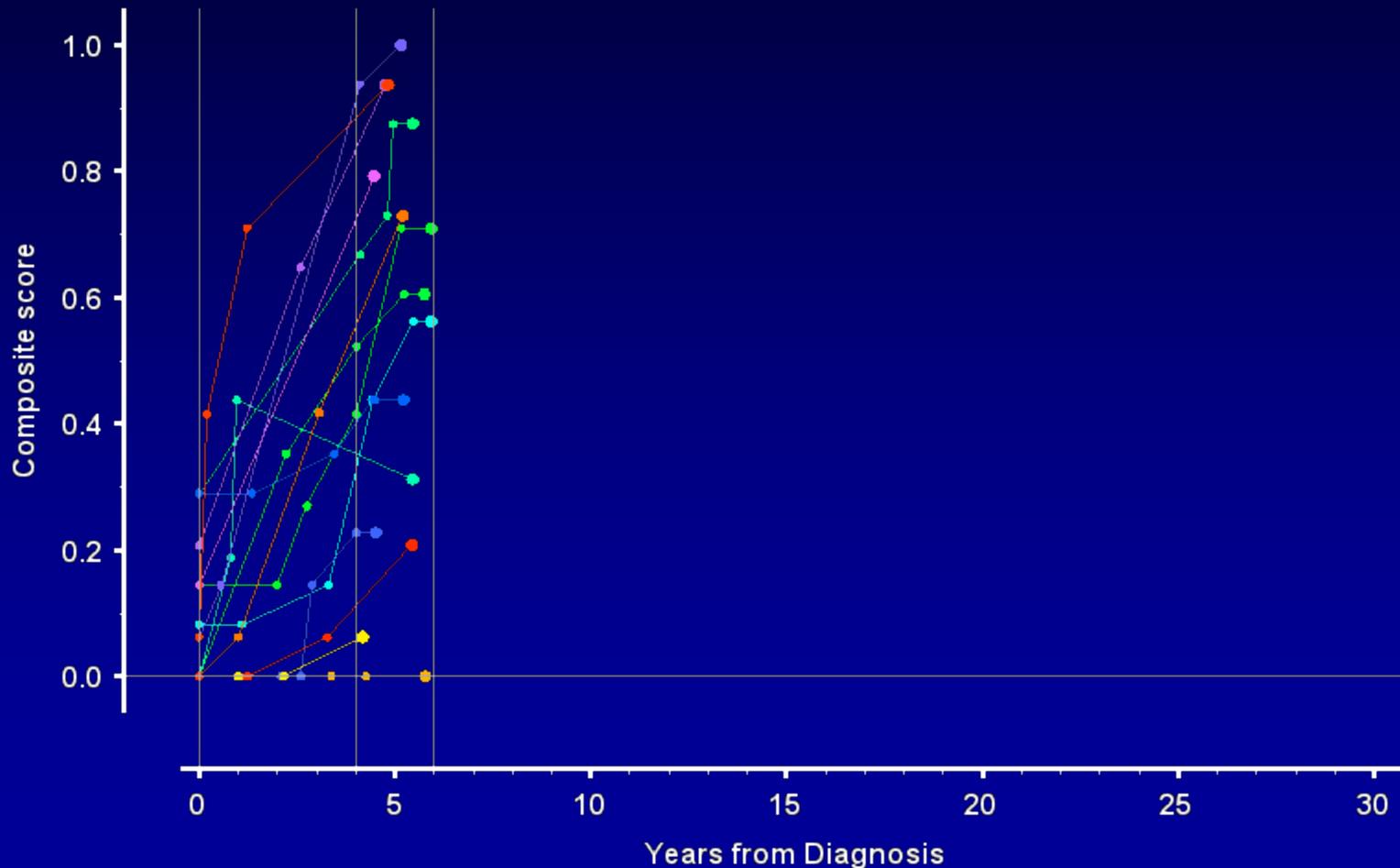


Mail survey conducted among NP-C patients' families and caregivers. Data from 87 questionnaires available

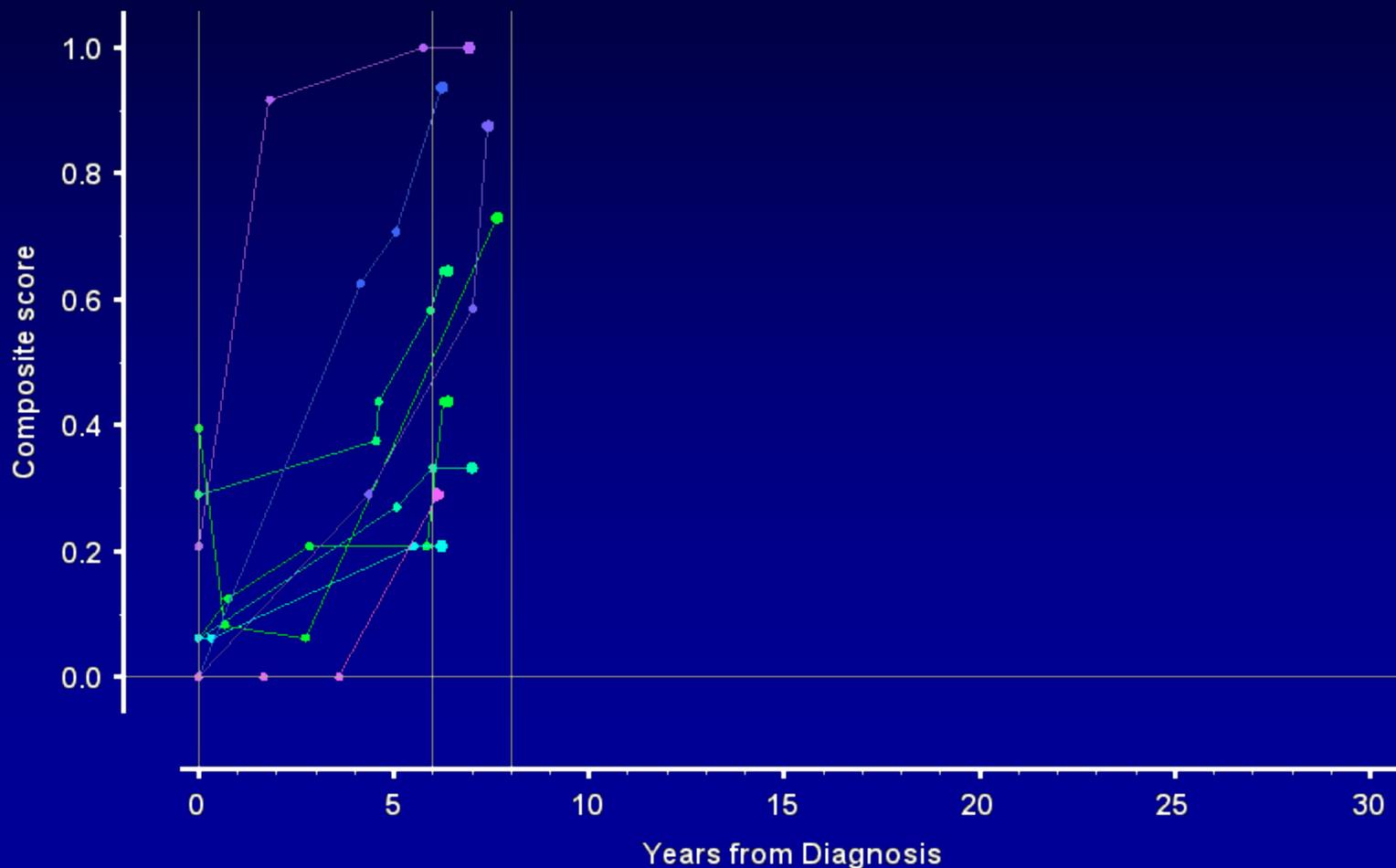
Neurological Manifestations of NP-C Disease Do Not Improve Spontaneously

Natural History Data from Survey II (n=57)

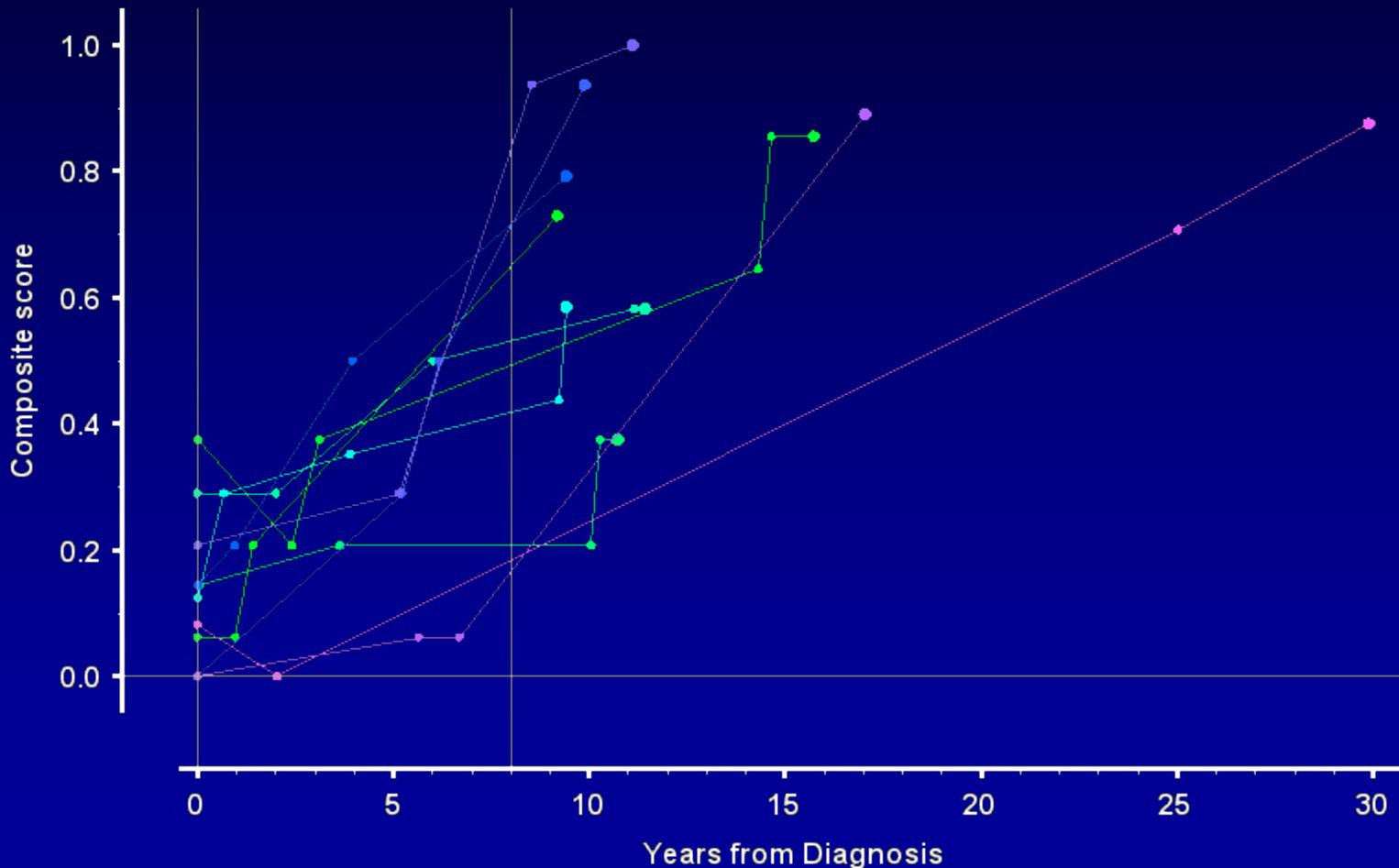
Composite Neurological Disability Score in Patients with 4 - 6 Years of Follow-Up



Composite Neurological Disability Score in Patients with 6 - 8 Years of Follow-Up



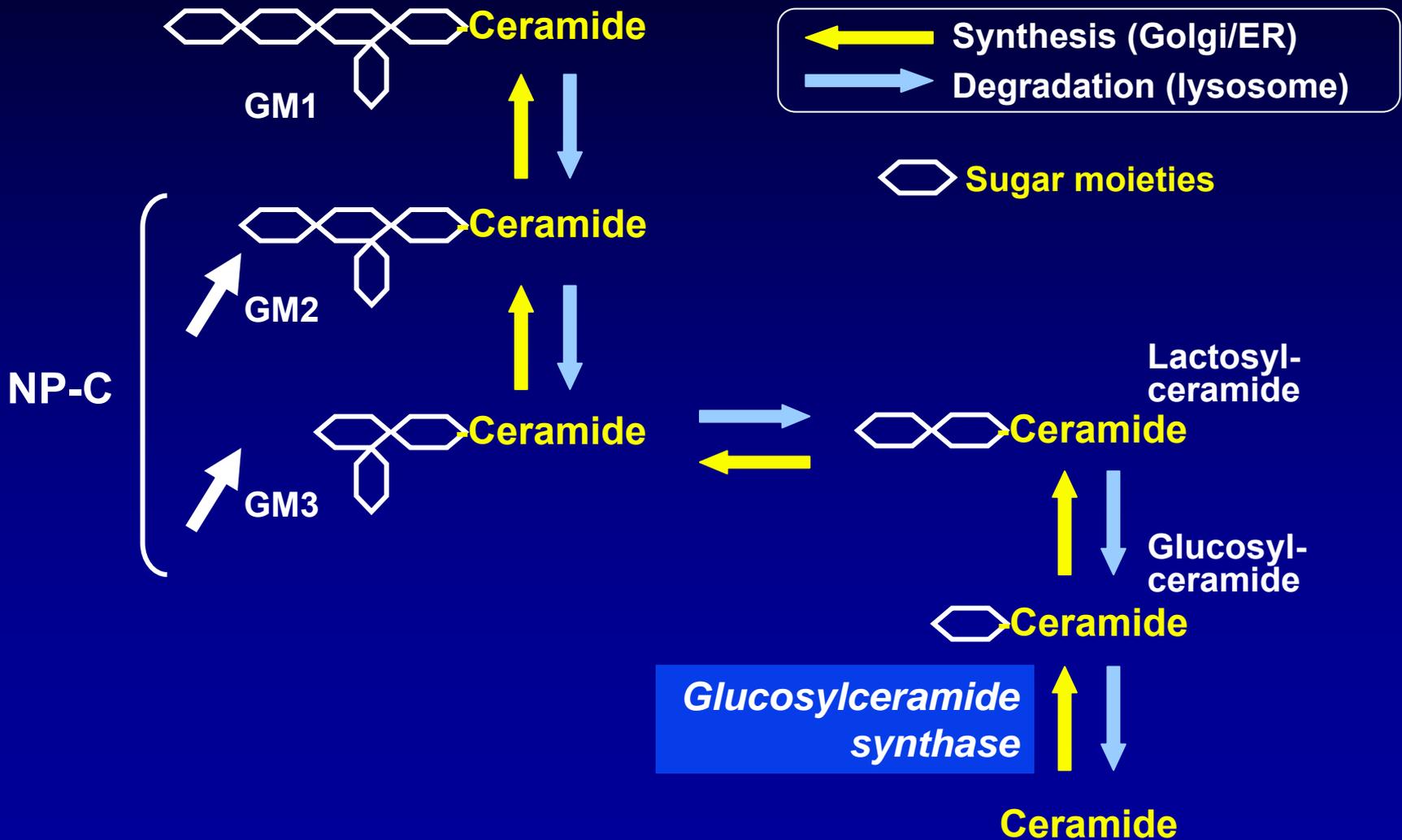
Composite Neurological Disability Score in Patients with >8 Years of Follow-Up



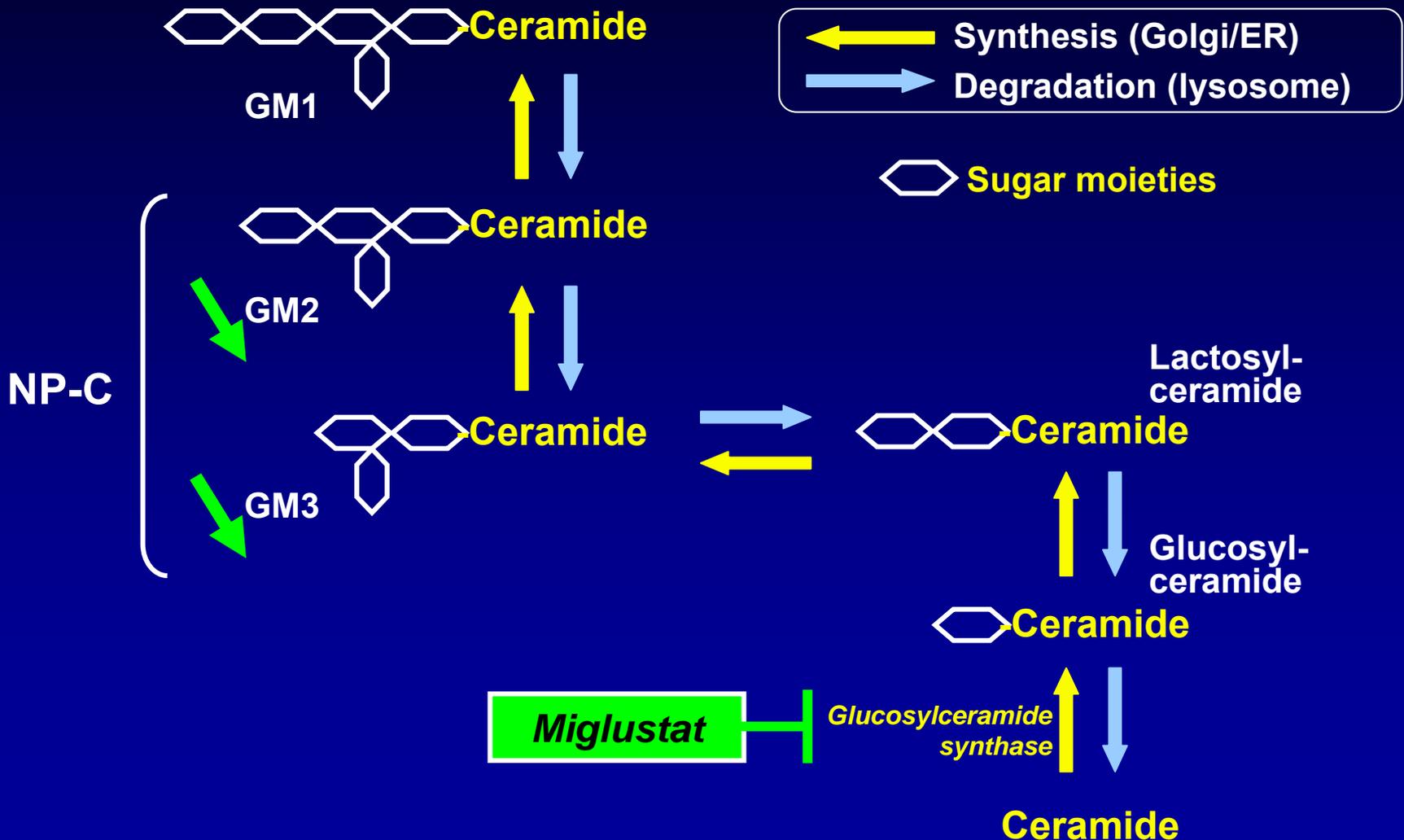
Goal of Therapy in NP-C Disease

- Neurological function is proportional to the sum pool of CNS neurons retaining functional capacity
- This pool forms the primary therapeutic target in NP-C disease
- Slowing or stabilization of neurological disease progression is likely the best attainable goal for long-term therapy

GSL Metabolism in NP-C

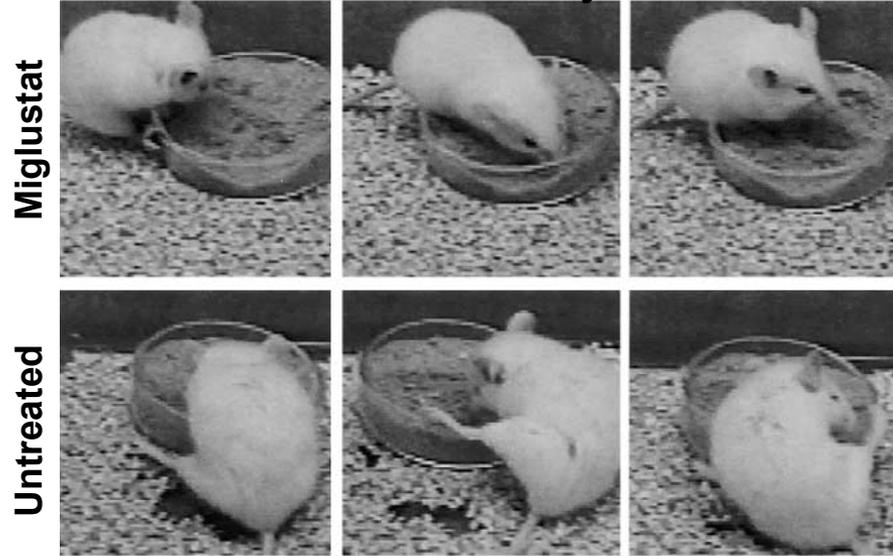


GSL Metabolism in NP-C

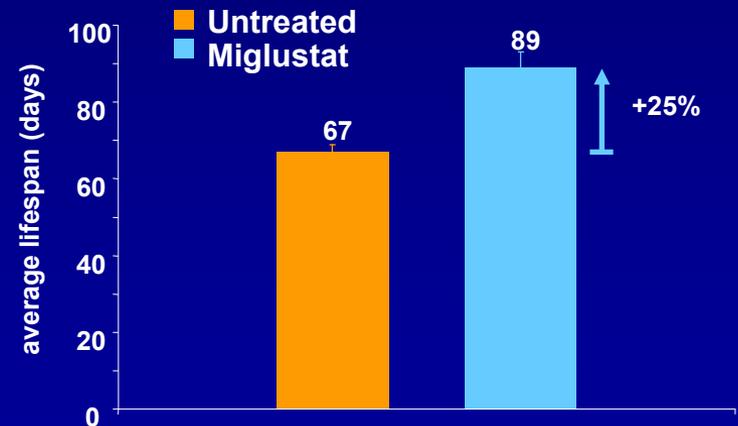
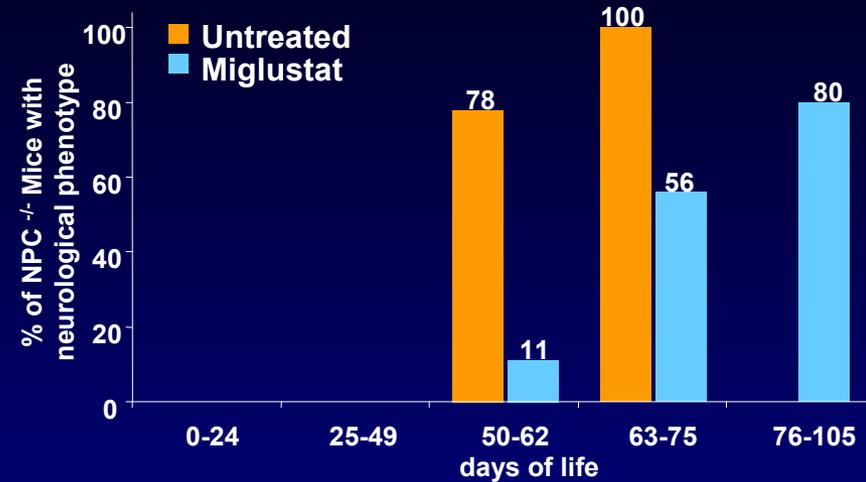
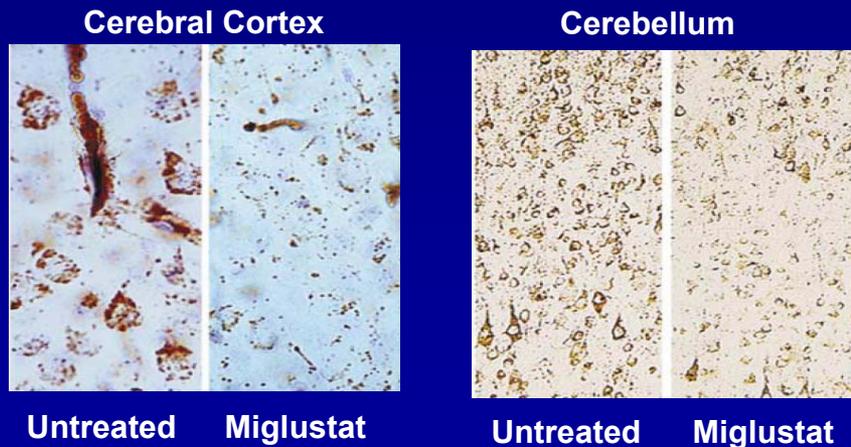


Miglustat in the NPC^{NIH} Mouse Model

11-week and 5-day-old



9-week and 5-day-old



Conclusions

- **NP-C is a predictably and invariably progressive neurodegenerative disease**
- **Therapeutic goal is to slow down or stabilize disease progression by salvaging dysfunctional or normal neurons**
- **Based on mode of action and preclinical observations, miglustat could slow disease progression in NP-C patients**

Clinical Program

Isaac Kobrin, MD

Clinical Pharmacology

Miglustat Pharmacokinetic (PK) Characteristics (Current USPI)

- Rapid absorption
- No clinically relevant food effect
- Low inter-subject variability
- Elimination half-life: 6 - 7 hours
- Dose proportional
- Independent of treatment duration
- Independent of age, gender, body weight or disease

Metabolism and Excretion (Current USPI)

- Eliminated unchanged mainly by the kidneys
- Exposure not affected by liver impairment
- Low potential for drug-drug interactions
 - No inhibition of cytochrome P450 isoenzymes
 - Not metabolized by cytochrome P450 isoenzymes

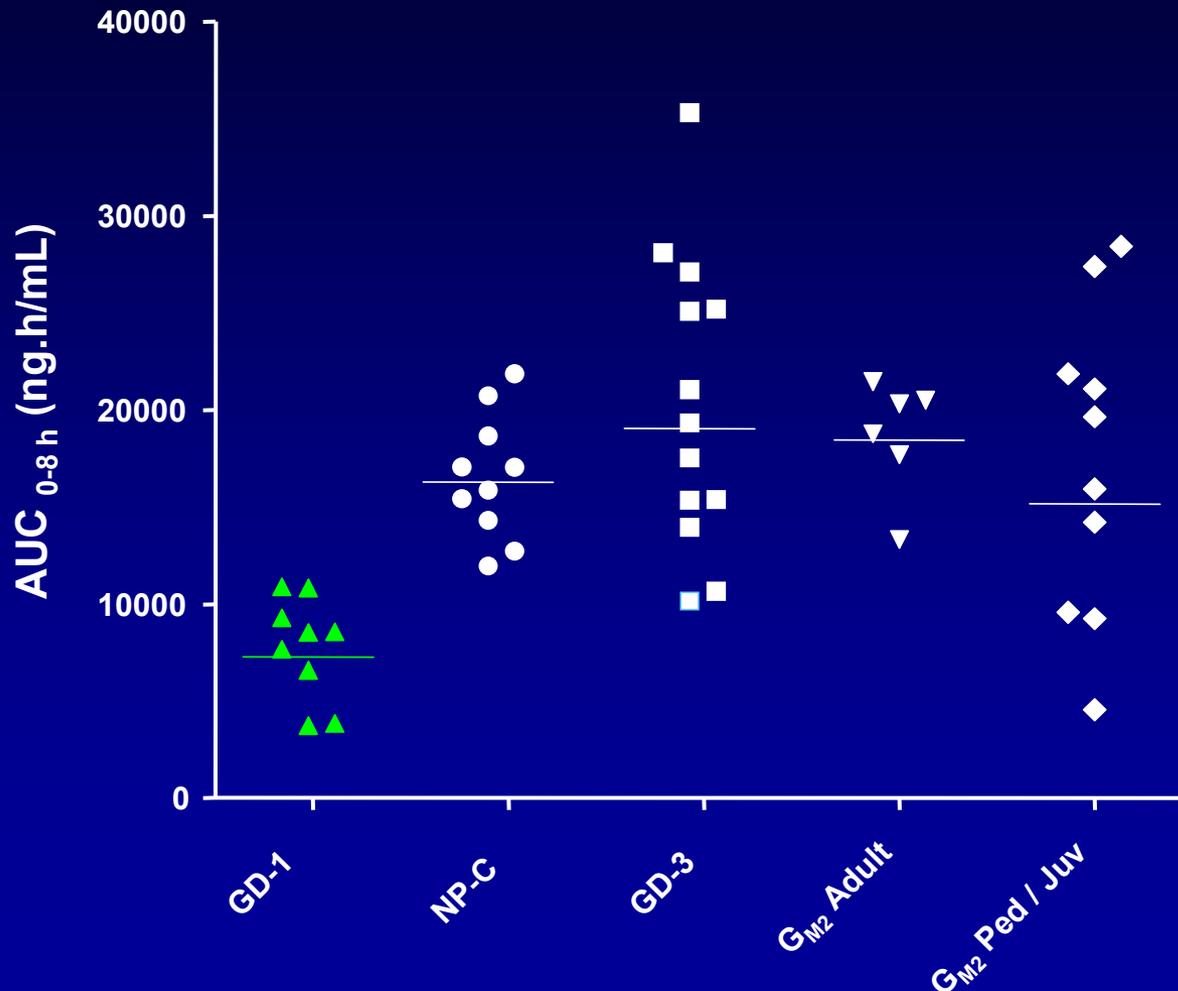
Miglustat New PK Data

40 patients; 18 patients < 12 years

- **NP-C (n = 10)**
 - 4 patients < 12 years
- **GD-3 (n = 13)**
 - 6 patients < 12 years
- **Adult G_{M2} gangliosidosis (n = 6)**
- **Pediatric and Adolescent G_{M2} gangliosidosis (n = 11)¹**
 - 8 patients < 12 years

¹ Maegawa GHB et al Mol. Gen. Metab. 2009; 97:284-291

Miglustat Exposure Across Indications



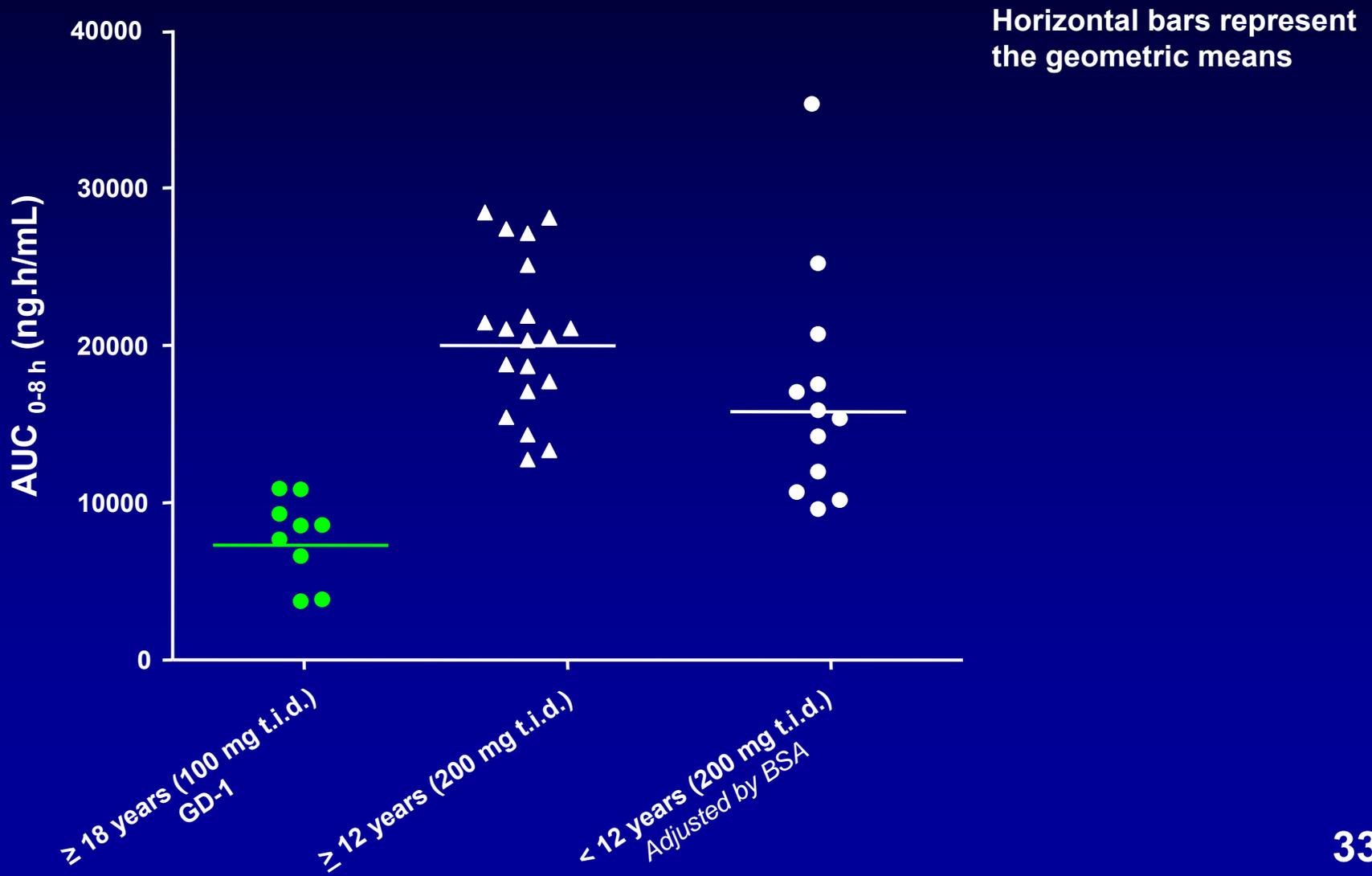
Horizontal bars represent the geometric means

GD-1: 100 mg t.i.d.

NLSD: 200 mg t.i.d.

< 12 y adjusted to BSA

Miglustat Exposure Across Age Groups



Miglustat Dose Rationale in NP-C Patients

- Inhibition of systemic glucosylceramide synthase is the goal of treatment in GD-1
- Effective dosing regimen in GD-1 is 100 mg t.i.d.
- Inhibition of CNS glucosylceramide synthase is the goal of treatment in NP-C disease
- CSF concentration of miglustat is approximately 40% of plasma levels (200 mg t.i.d.)
 - Evaluated in 8 patients (4 pts < 12 years)
- Regimen of 200 mg t.i.d. is required to achieve effective concentration in CNS
 - Adjusted to BSA in patients < 12 years of age

Clinical Program Efficacy Evaluation

Program Objectives

- **To evaluate the effects of miglustat on clinically relevant neurological manifestations in adult / adolescent and pediatric NP-C patients**
 - **Reduction in the rate of neurological progression or disease stabilization are considered appropriate treatment goals**

Development Considerations

- **Randomized controlled trials are a recognized method for assessing efficacy in diseases whose clinical course in individual patients is unpredictable**
- **Cohort studies can provide essential data for assessing efficacy in diseases whose clinical course in individual patients is highly predictable**
 - **Have formed the basis of regulatory approval of some drugs for rare disorders**

Randomized Controlled Trials in NP-C Disease

- **Challenging because rarity of disease makes patient recruitment difficult**
- **Clinical or surrogate endpoints have not been established**
- **Availability of miglustat for GD-1 led to off-label use in a large proportion of NP-C patients**
- **Required sample size based on traditional clinical outcome measures is likely to exceed the total number of available patients**

Cohort Studies in NP-C Disease

- Natural history is characterized by inexorable progression of neurological disease over time
- Off-label utilization in NP-C patients created a miglustat-treated cohort representing a large proportion of patients with the disease
- Cohort studies were feasible because most patients with NP-C disease are seen in a few specialized centers and undergo standardized assessments

Development of Miglustat in NP-C Disease

- **Retrospective cohort studies**
 - Survey II (Natural History)
 - Survey I
- **Prospective randomized trial**
 - OGT 918-007 (Study 007)

Cohort Studies

- Survey II: retrospective study of the natural history of neurological disease progression
 - 57 patients
- Survey I: retrospective study of neurological disease progression prior to and during treatment with miglustat
 - 66 patients not enrolled in clinical trials
- Neurologic disease progression assessed by NP-C disability scale based on rating of:
 - Swallowing, ambulation, manipulation (dysmetria / dystonia) and language abilities

Cohort Studies

Organization and Data Collection

Survey II (Natural History)

- **7 sites from 6 countries identified by the coordinating PI**
- **Data collected for each NP-C patient at multiple time points (at least 3) during the natural course of the disease**

Survey I (prior to and during miglustat)

- **25 sites from 12 countries identified by the coordinating PI**
- **Data collected for each NP-C patient treated with commercially available miglustat**
 - **At diagnosis, treatment start and last visit during miglustat treatment**

Cohort Studies Demographics

	Survey II N=57	Survey I N=66
M:F (%)	44:56	47:53
Age at diagnosis (yrs)	10.7 ± 9.6	9.7 ± 7.6
Age groups (<12, ≥ 12) (%)	61, 39	67, 33
Time between diagnosis and treatment (yrs)	-	3.1 ± 3.4
Treatment duration	-	1.5 ± 1.1
Time from diagnosis to last visit (yrs)	5.5 ± 4.8	4.6 ± 3.5
Mean dose (mg) (min., max.)	-	361 (18, 600)

Numbers are % or mean ± SD

NP-C Functional Disability Scale

Original Iturriaga Score

Swallowing	Score	Manipulation	Score
Normal	1	Normal	1
Occasional dysphagia	2	Slight dysmetria/dystonia	2
Daily dysphagia	3	Mild dysmetria/dystonia	3
NG tube or gastric button feeding	4	Severe dysmetria/dystonia	4
Ambulation	Score	Language	Score
Normal	1	Normal	1
Autonomous ataxic gait	2	Mild dysarthria	2
Outdoor-assisted ambulation	3	Severe dysarthria	3
Indoor-assisted ambulation	4	Non-verbal communication	4
Wheelchair bound	5	Absence of communication	5

NP-C Functional Disability Scale Modified Score

Swallowing	Score	Manipulation	Score
Normal	0	Normal	0
Occasional dysphagia	.33	Slight dysmetria/dystonia	.33
Daily dysphagia	.67	Mild dysmetria/dystonia	.67
NG tube or gastric button feeding	1	Severe dysmetria/dystonia	1
Ambulation	Score	Language	Score
Normal	0	Normal	0
Autonomous ataxic gait	.25	Mild dysarthria	.25
Outdoor-assisted ambulation	.50	Severe dysarthria	.50
Indoor-assisted ambulation	.75	Non-verbal communication	.75
Wheelchair bound	1	Absence of communication	1

Cohort Studies

NP-C Characteristics at Diagnosis

Variable / Domain	Survey II N=57	Survey I N=66
Swallowing	n=56	n=62
abnormal	11 (20%)	20 (32%)
Ambulation	n=57	n=64
abnormal	35 (61%)	42 (66%)
Manipulation	n=57	n=64
abnormal	29 (51%)	40 (62%)
Language	n=57	n=64
abnormal	24 (42%)	40 (62%)

Statistical Analysis Cohort Studies

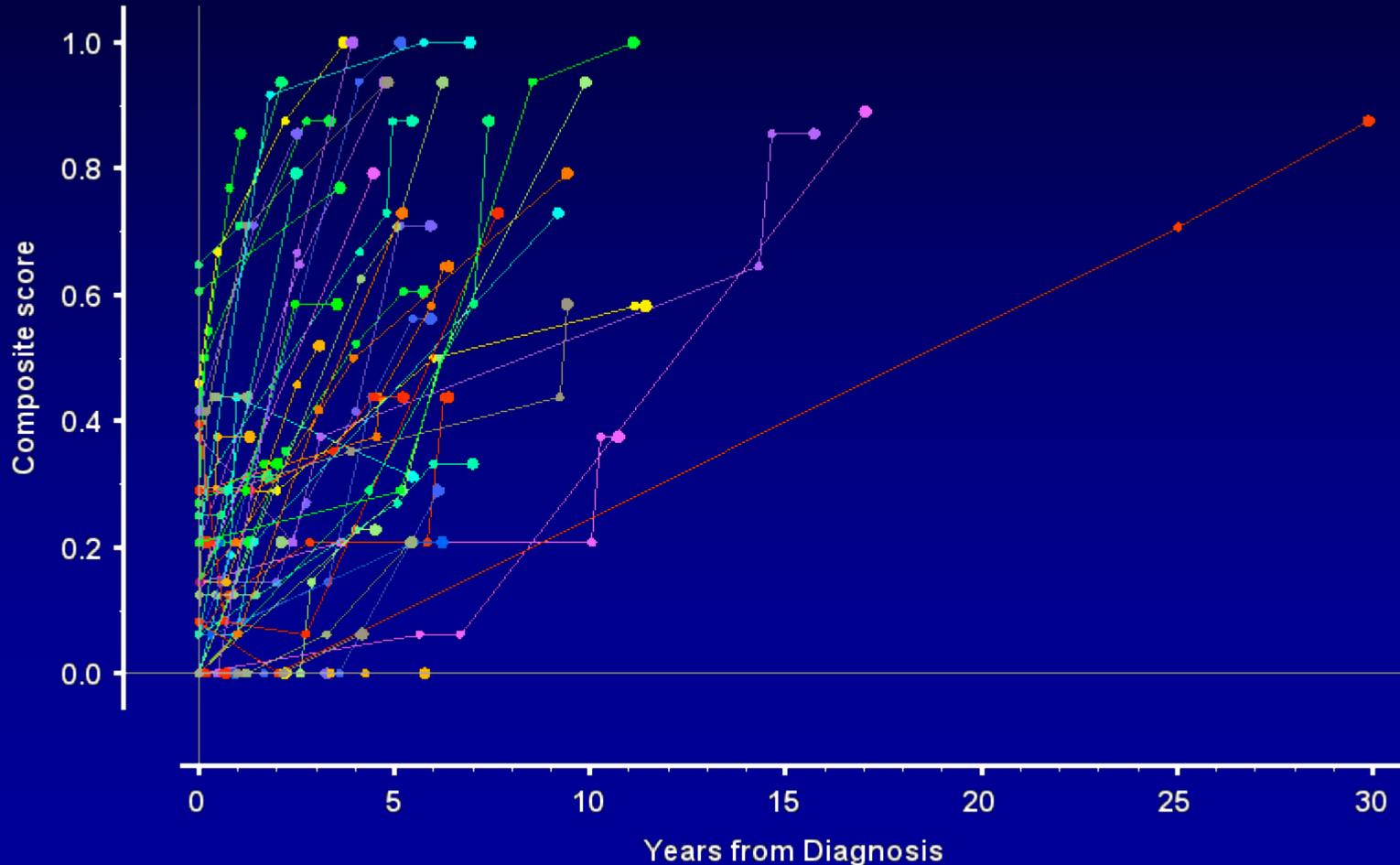
Survey II

- Annualized progression rate in each domain and composite score
 - Between diagnosis and last visit
 - Across multiple time points

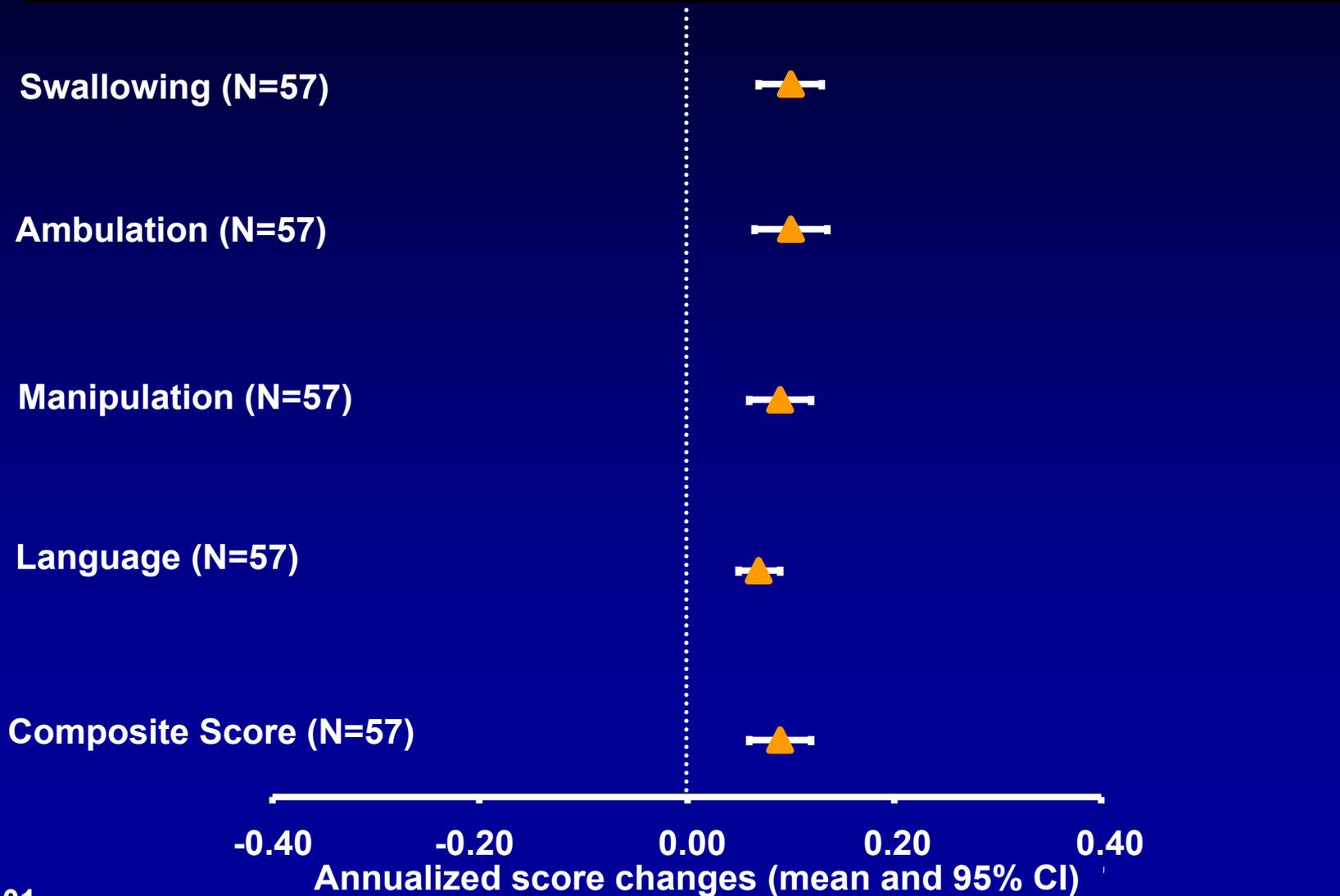
Survey I

- Similar to Survey II
 - Between diagnosis and treatment start
 - Between treatment start and last visit on treatment

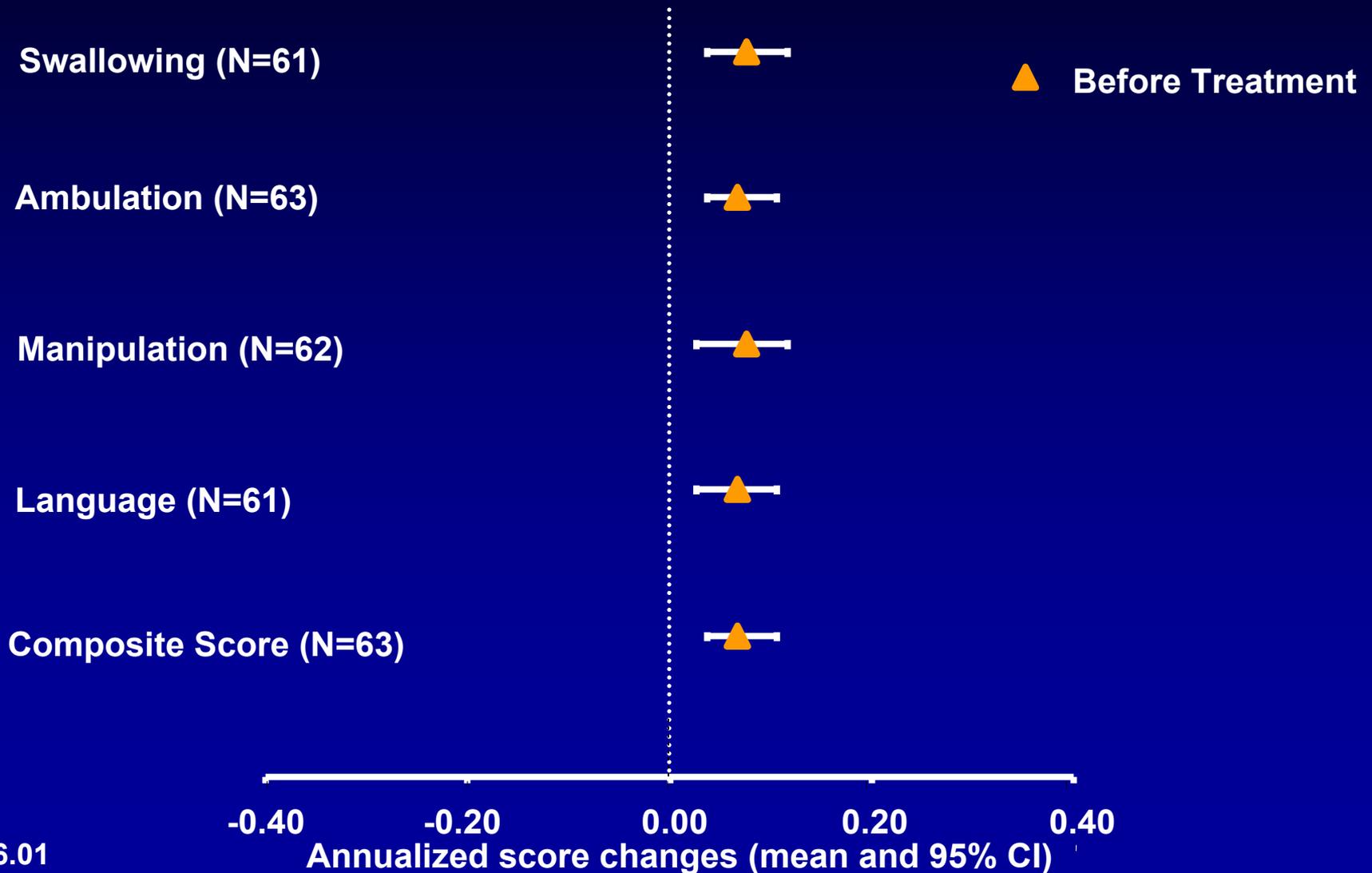
Composite Disability Score During Natural History (Survey II, n=57)



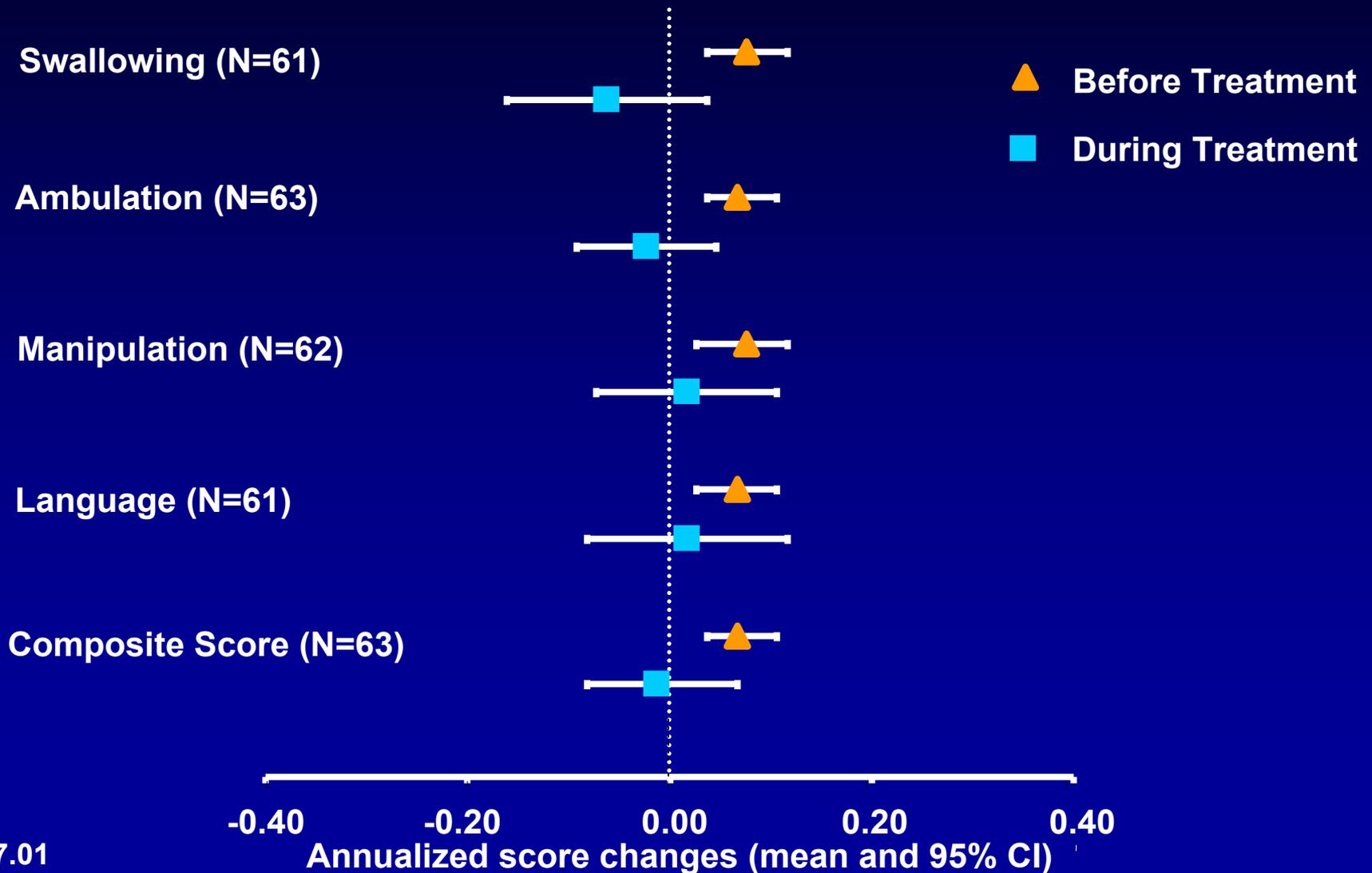
Survey II (Natural History): Annualized Progression Rate Across Neurological Domains



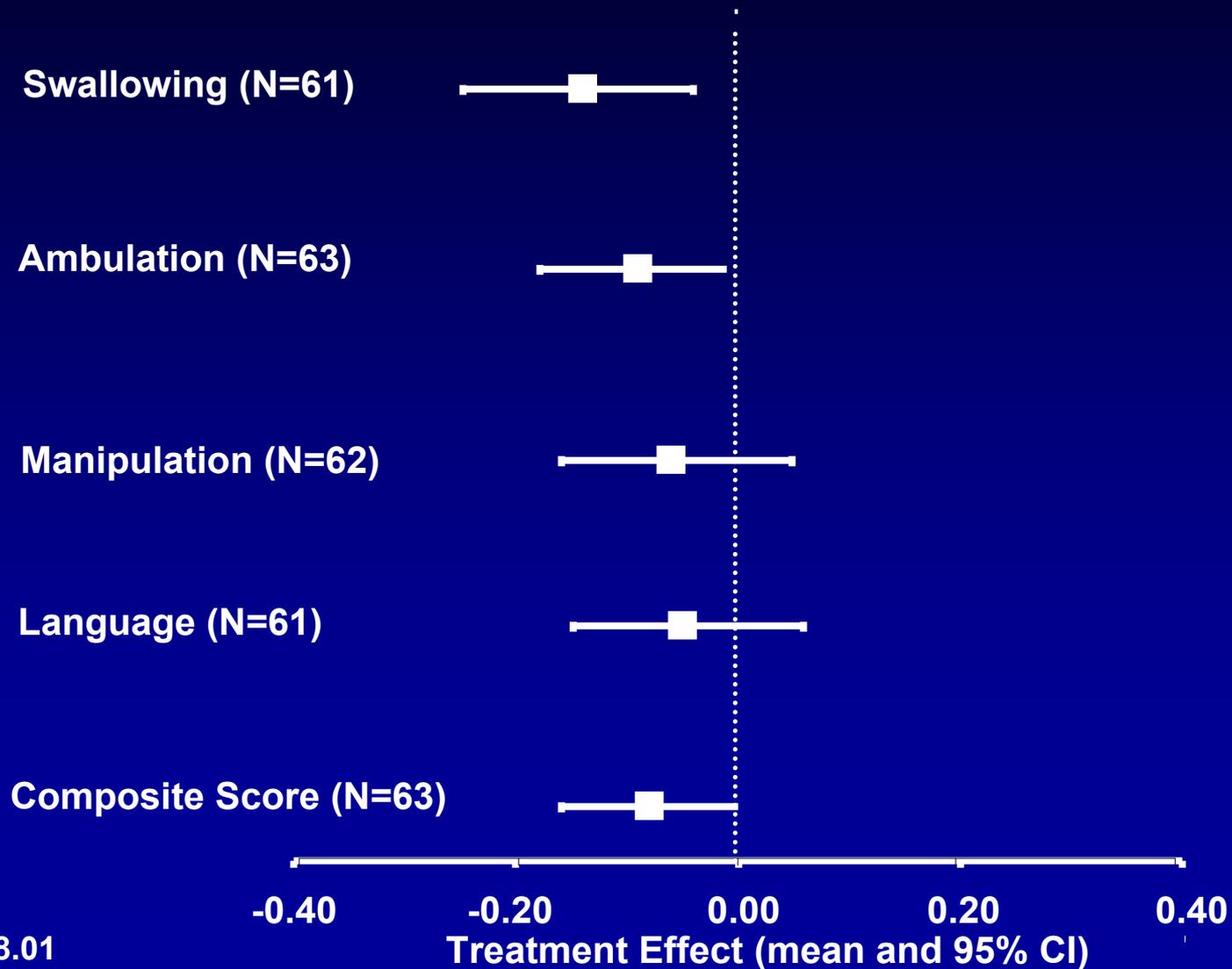
Survey I: Annualized Progression Across Neurological Domains



Survey I: Annualized Progression Across Neurological Domains

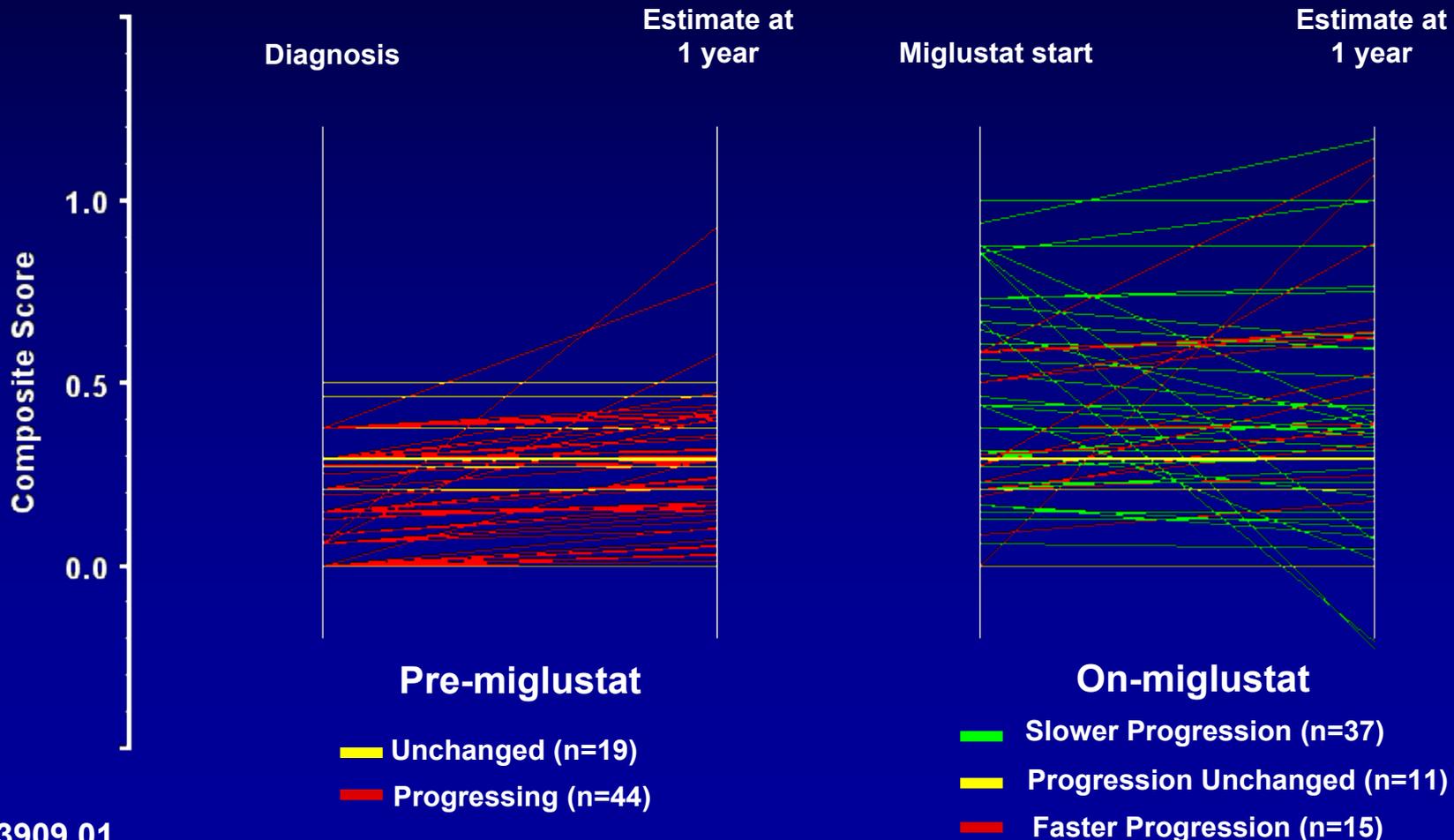


Survey I (Treatment Effect): Annualized Progression Across Neurological Domains

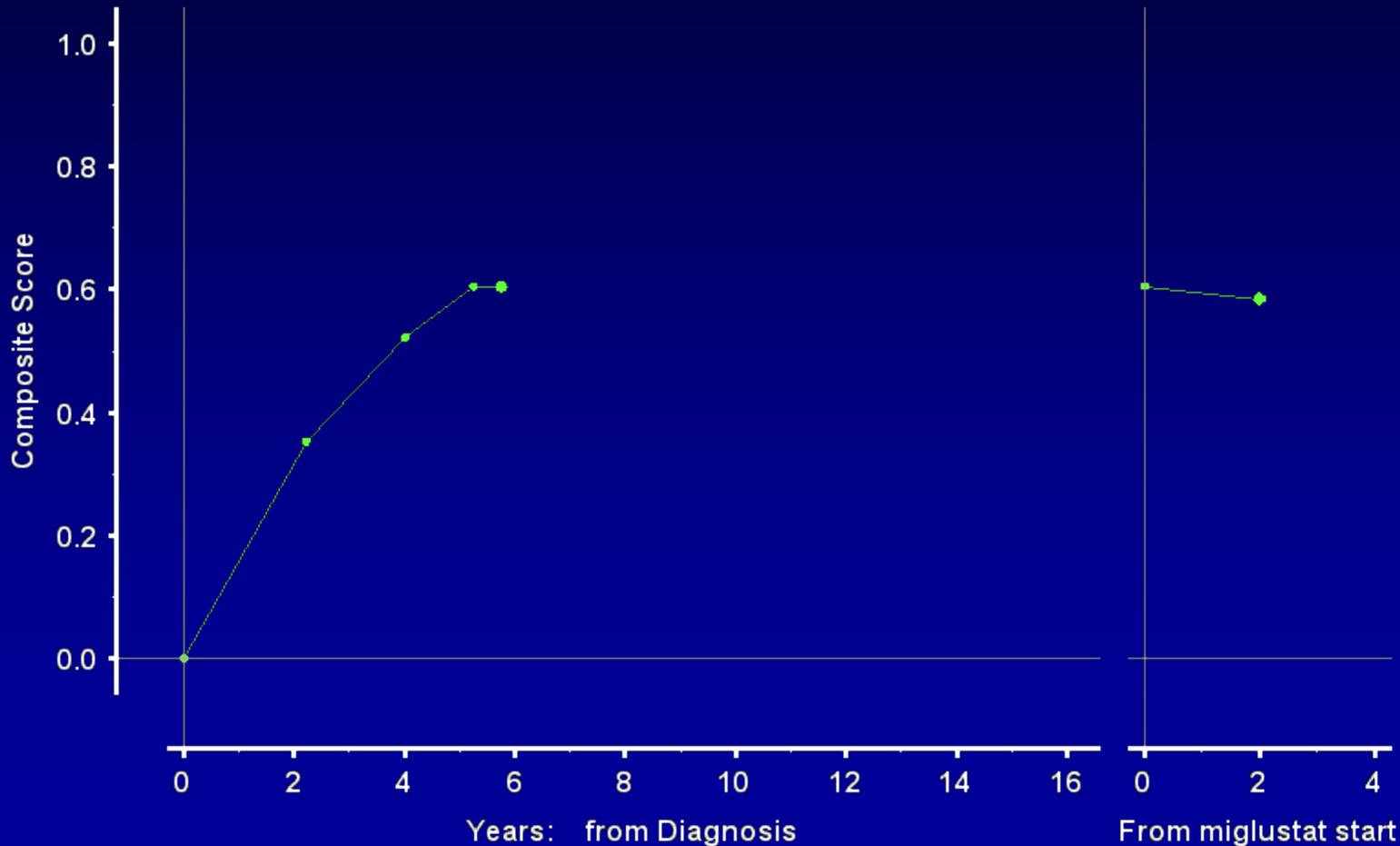


Composite Score Pre- and During Treatment with Miglustat in Survey I

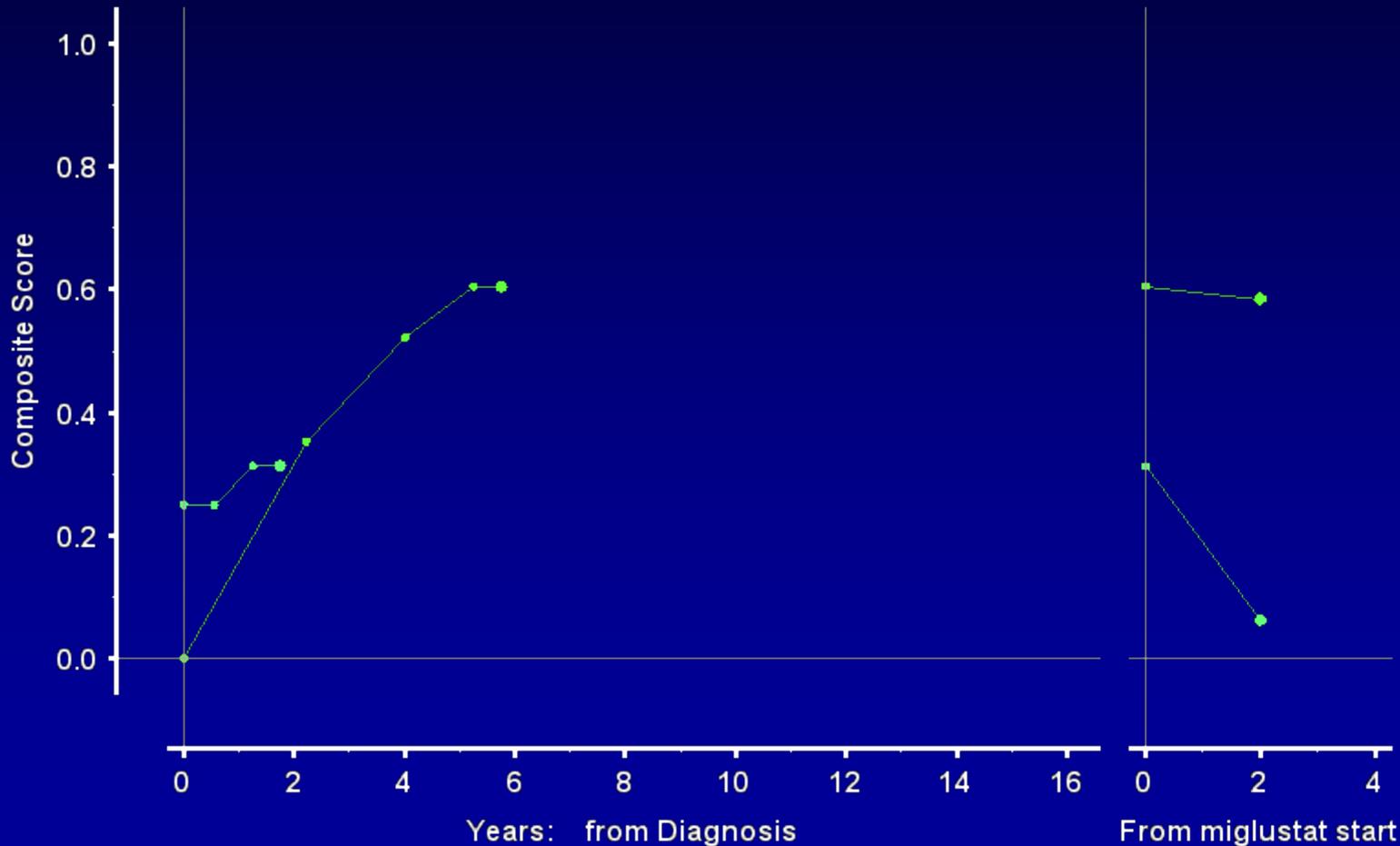
Individual Annualized Progression Rate (N=63)



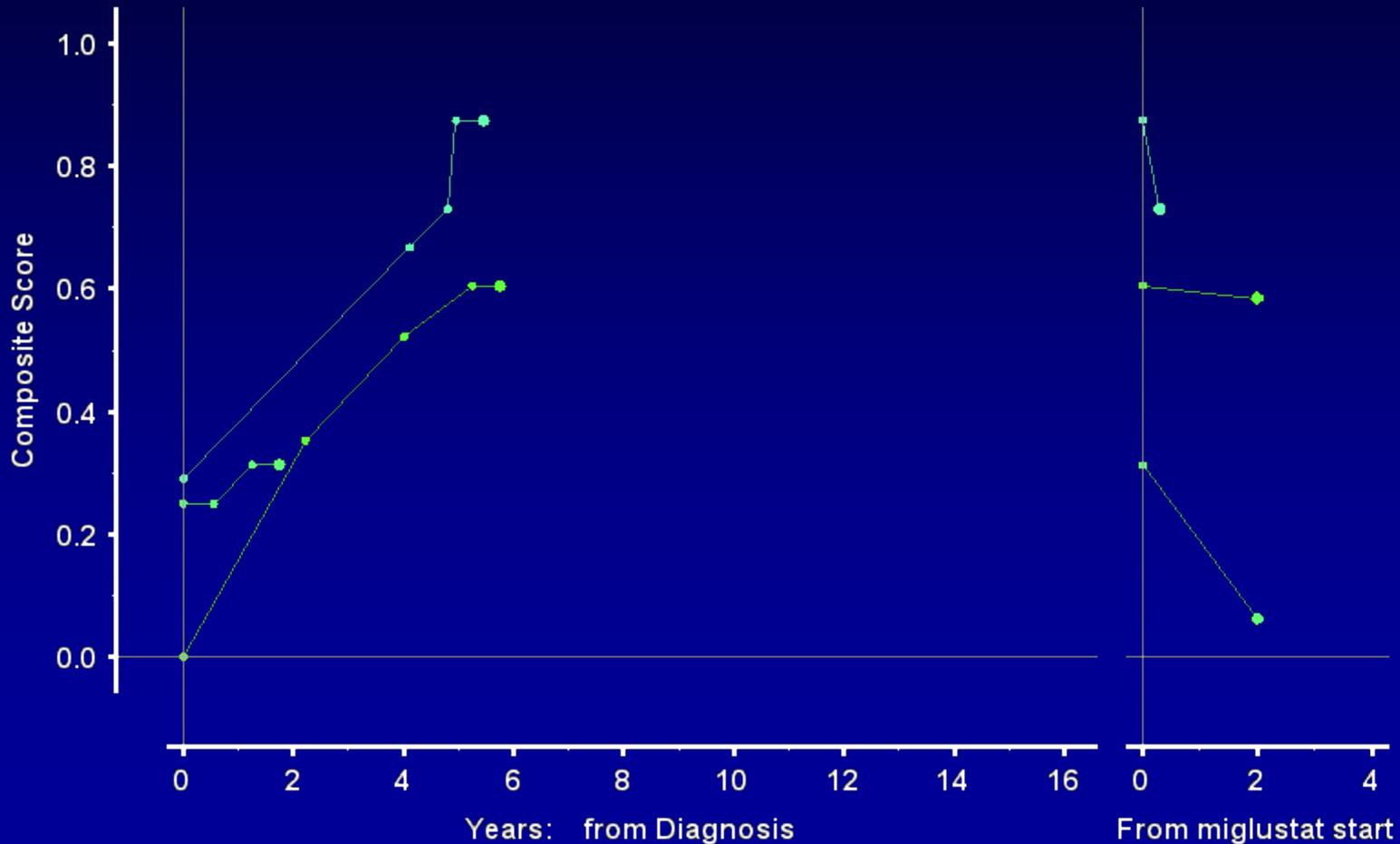
Clinical Course Before and During Miglustat in 19 Patients Represented in Both Surveys



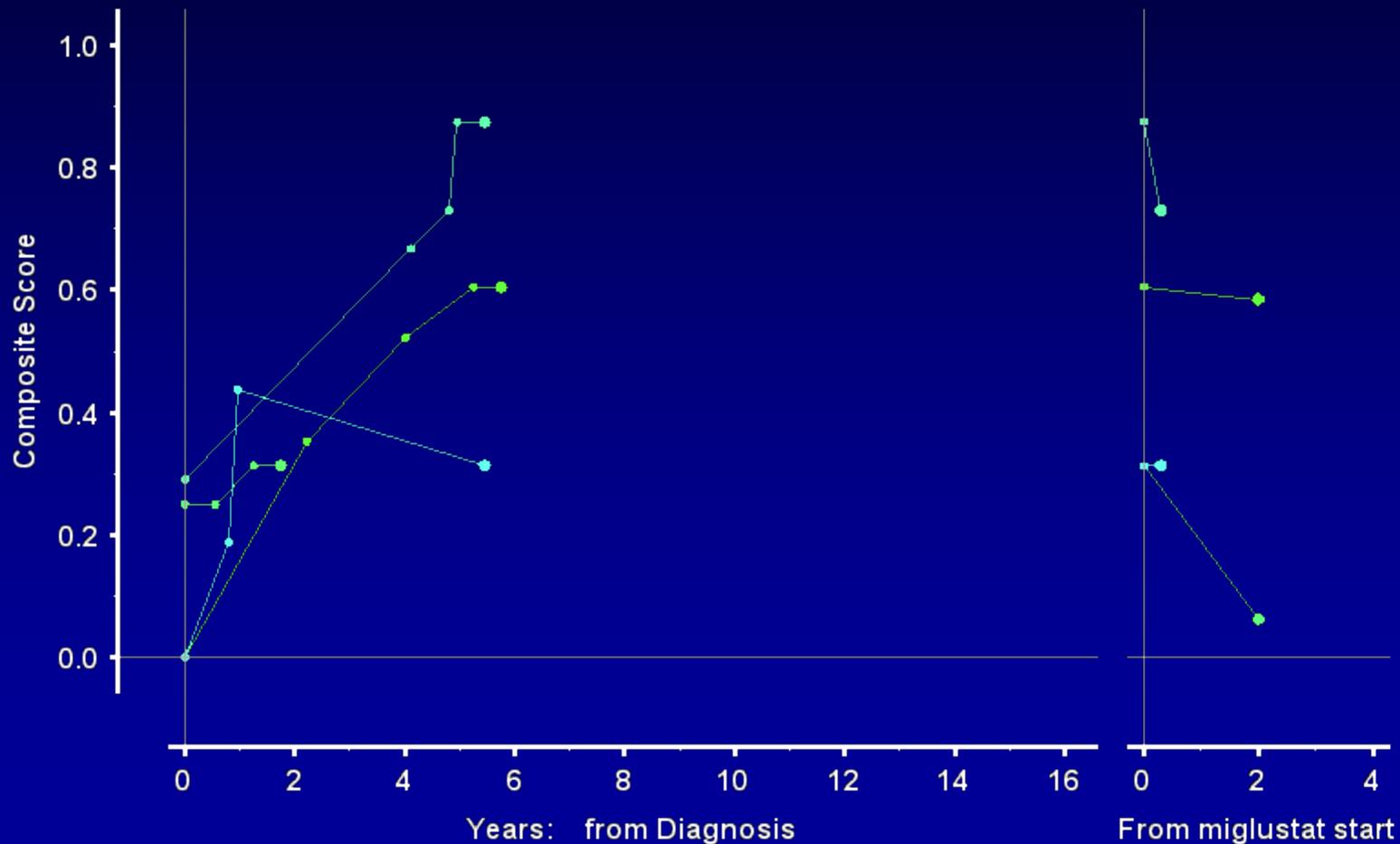
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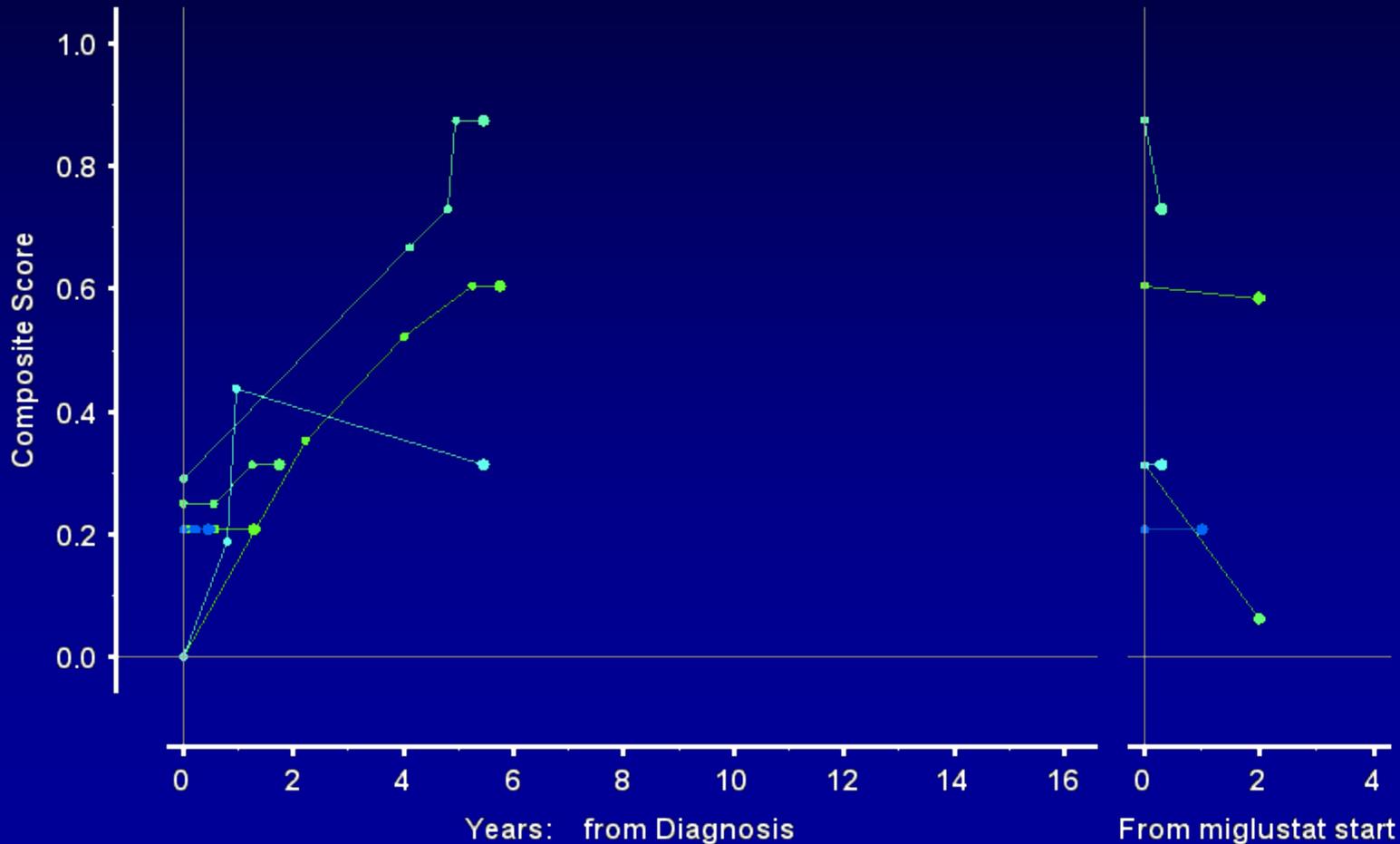
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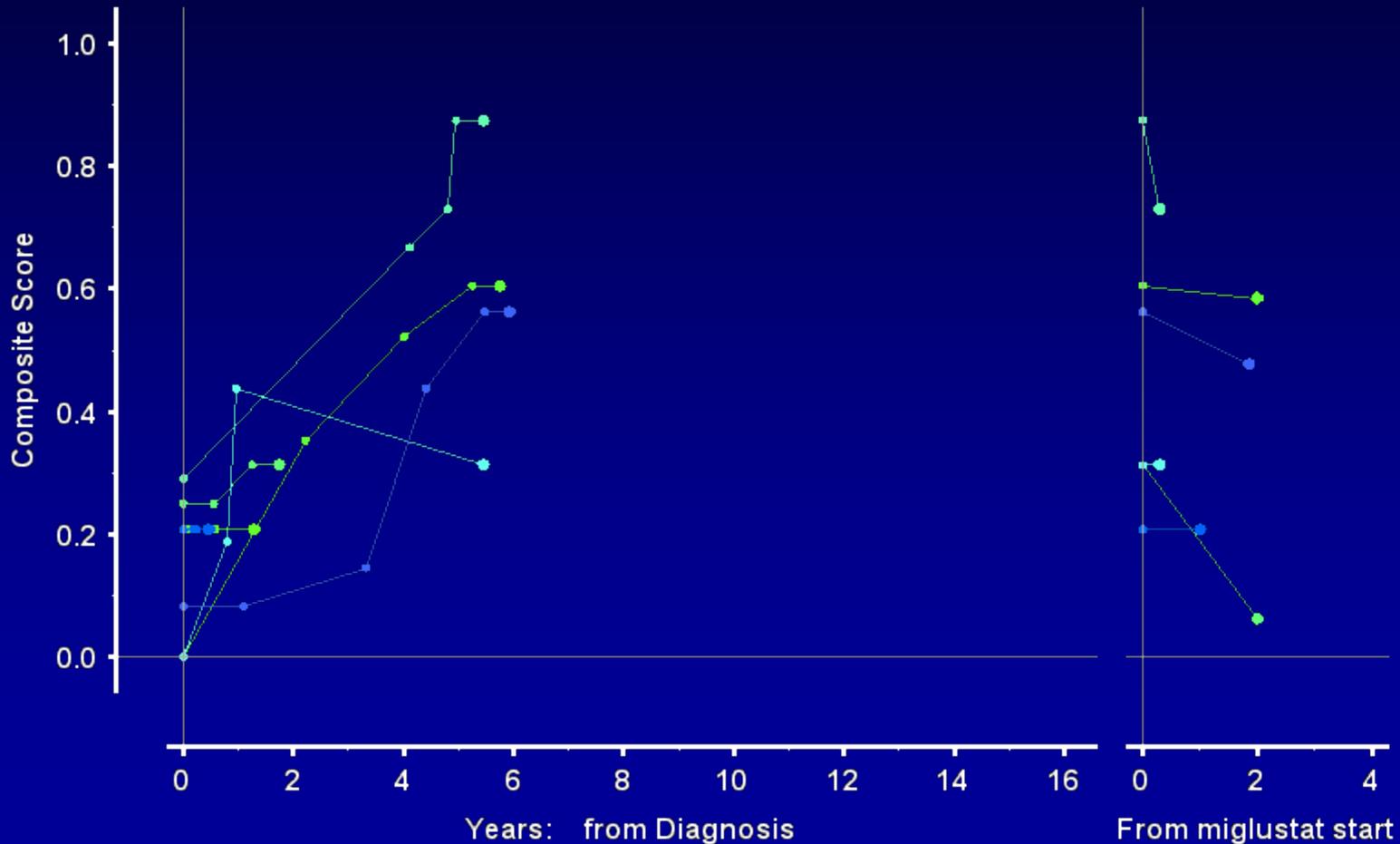
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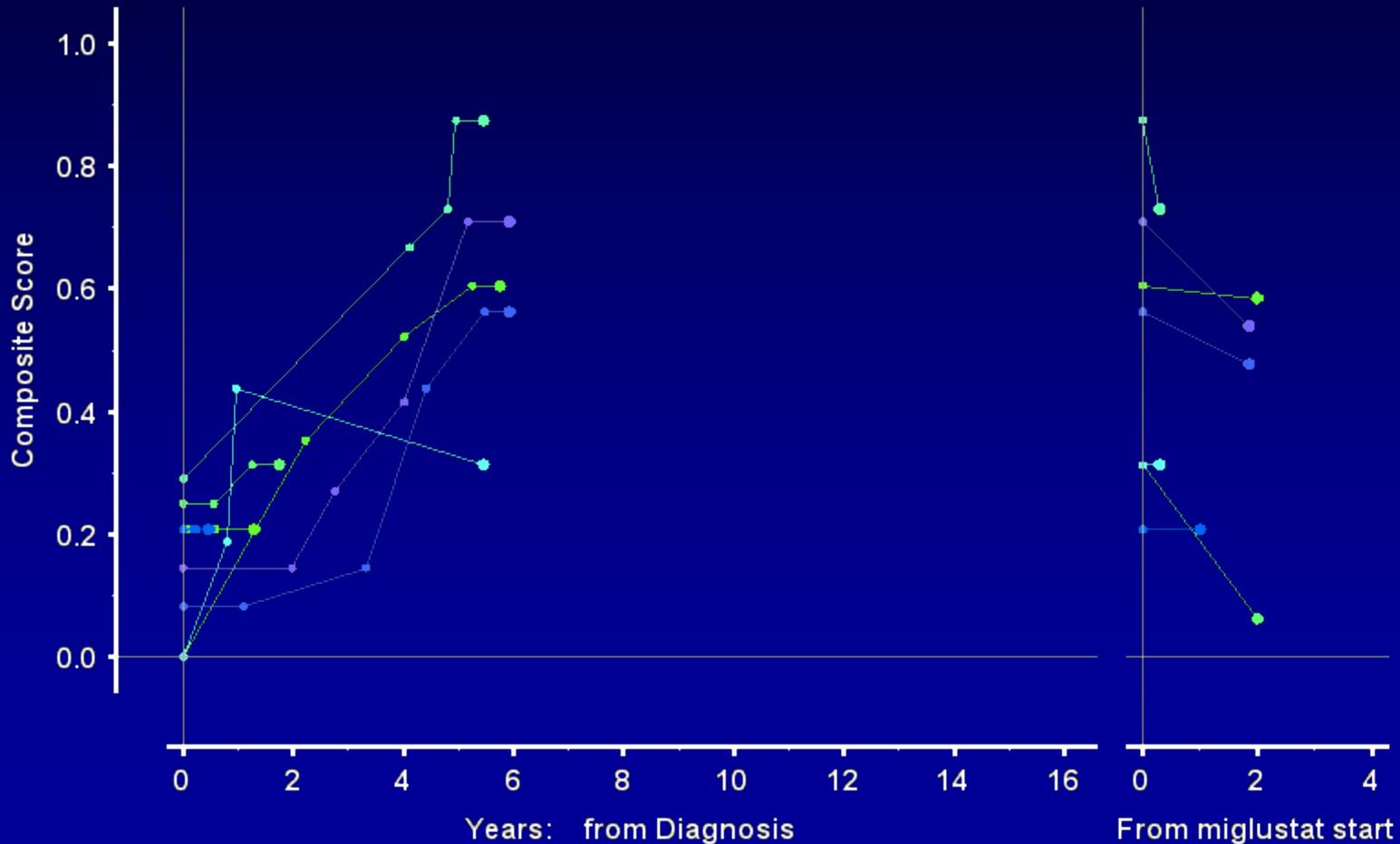
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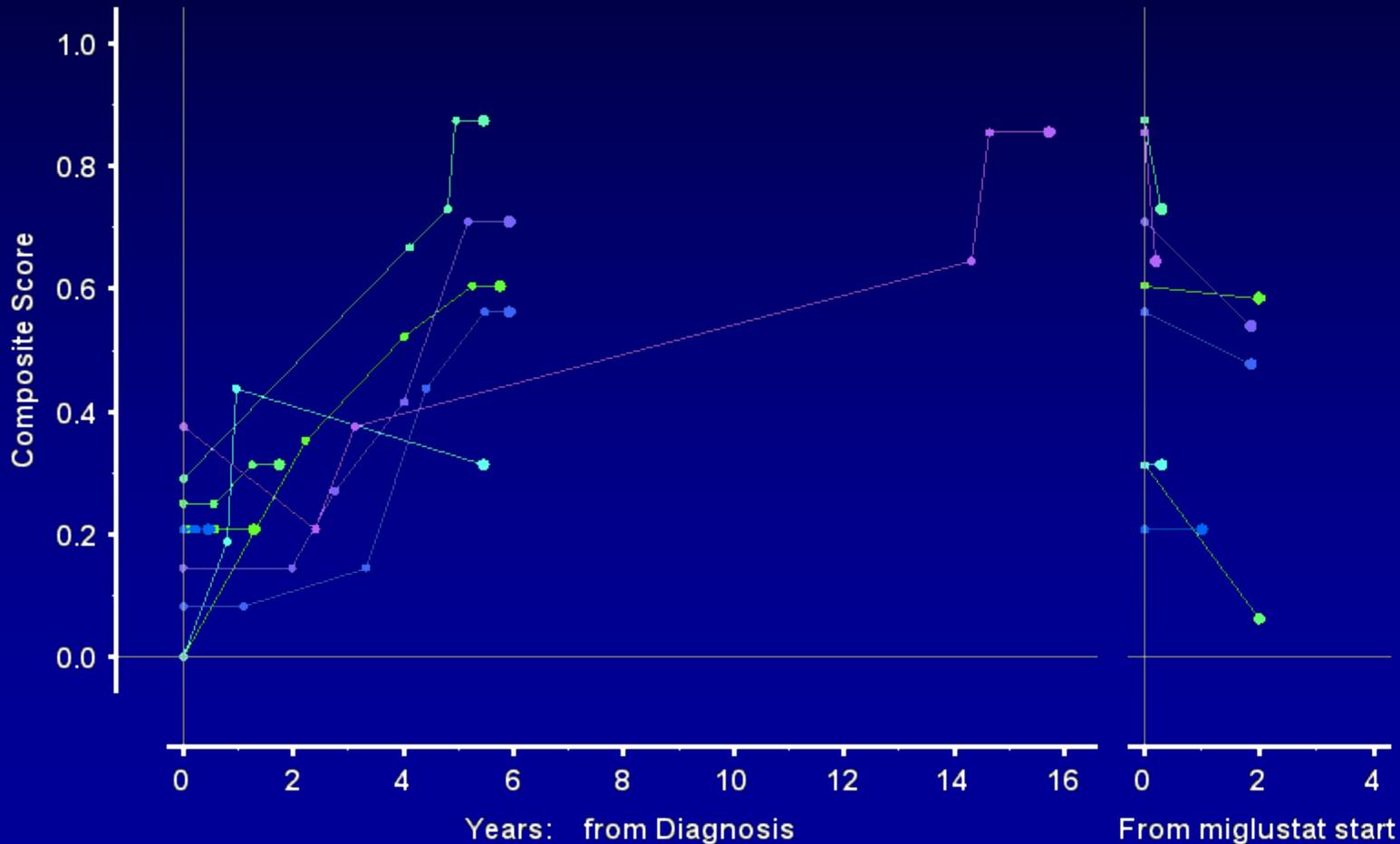
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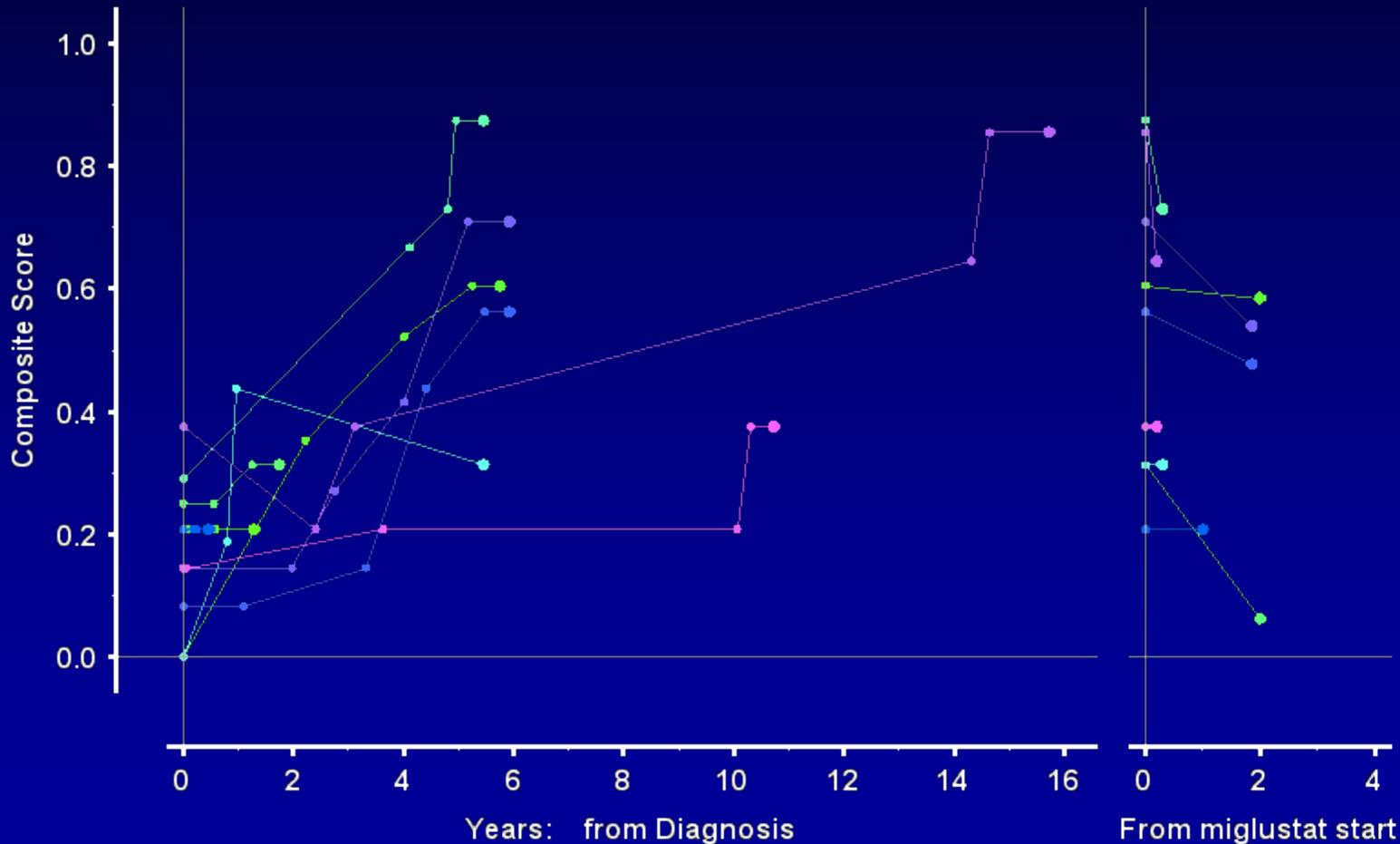
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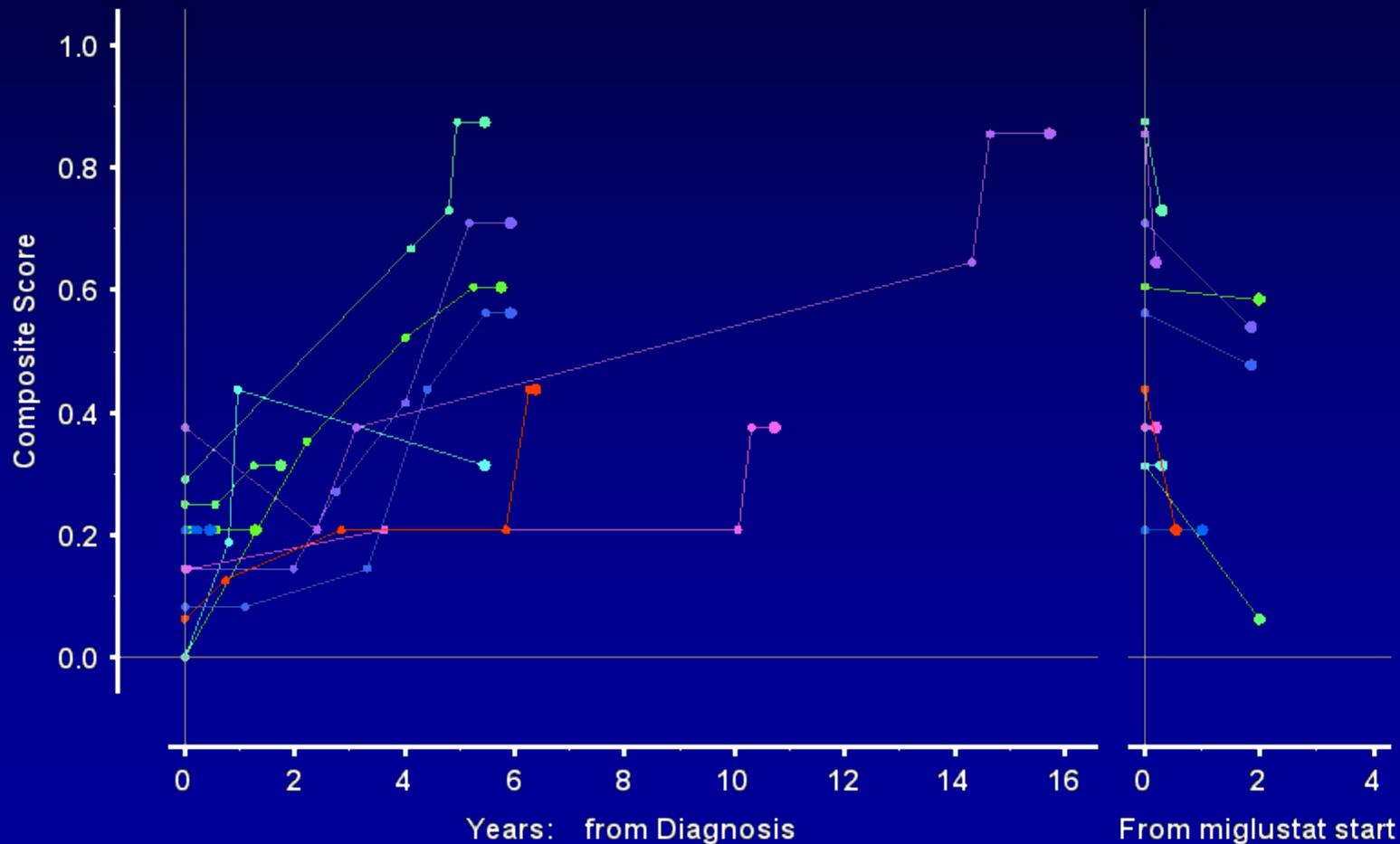
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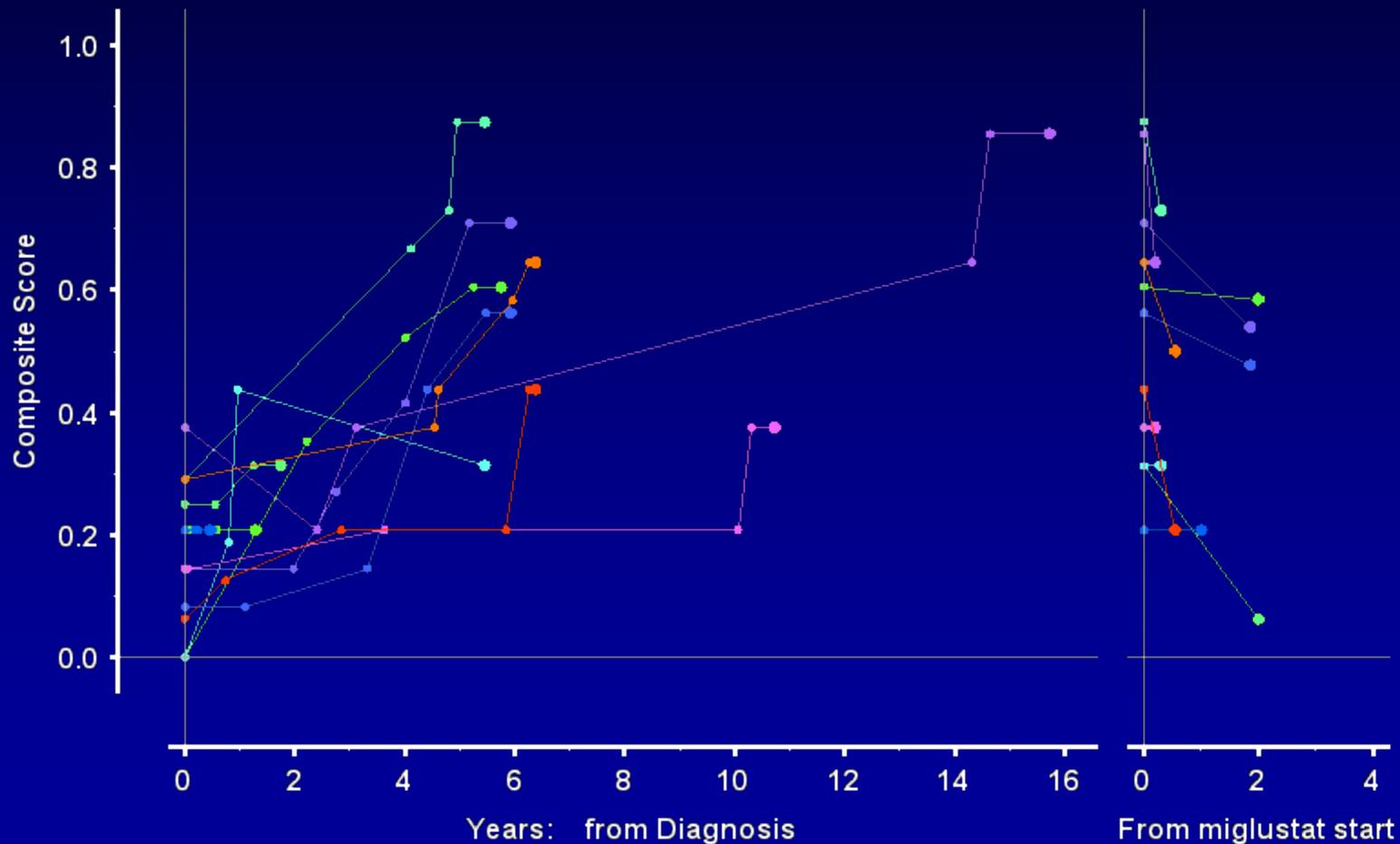
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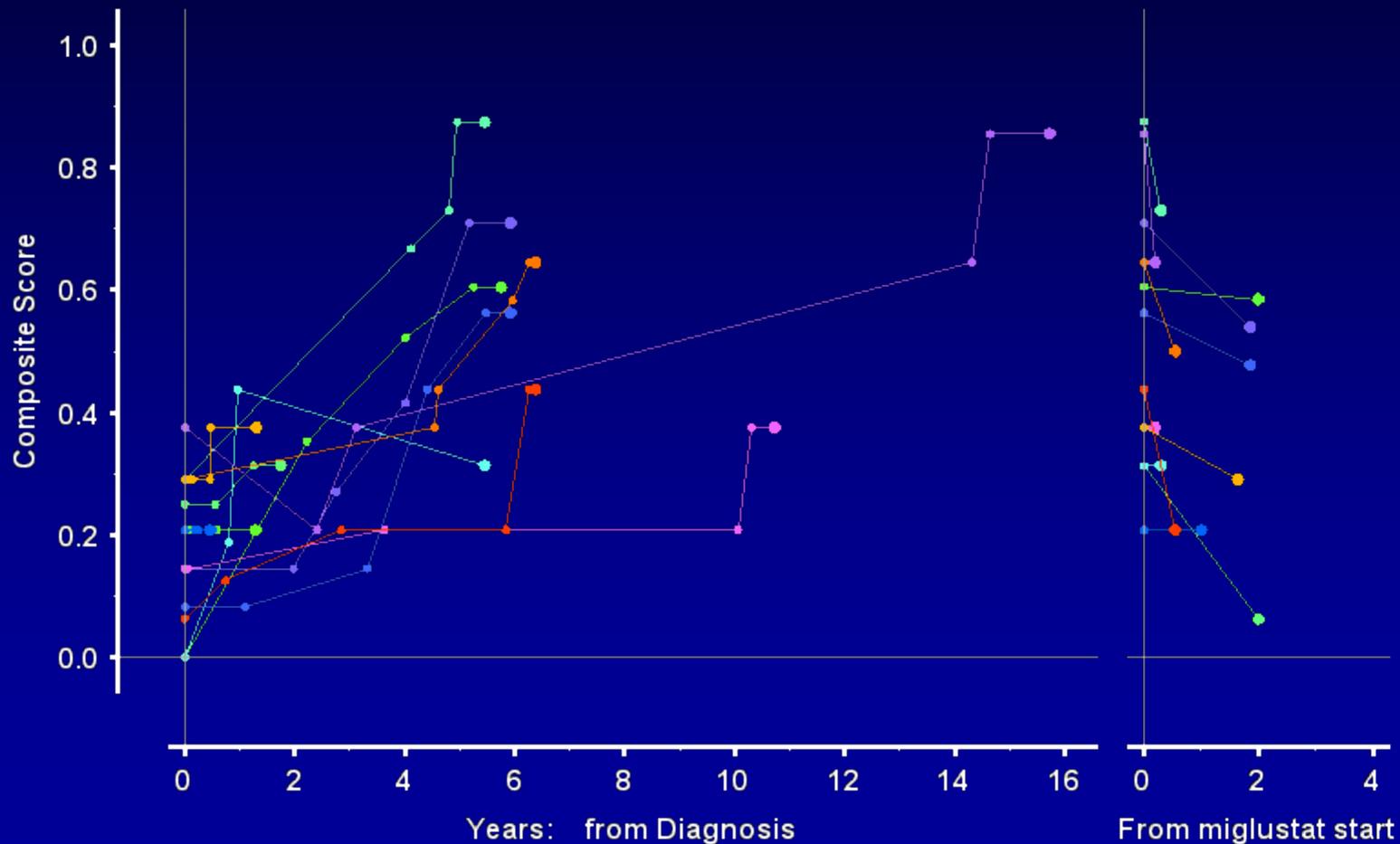
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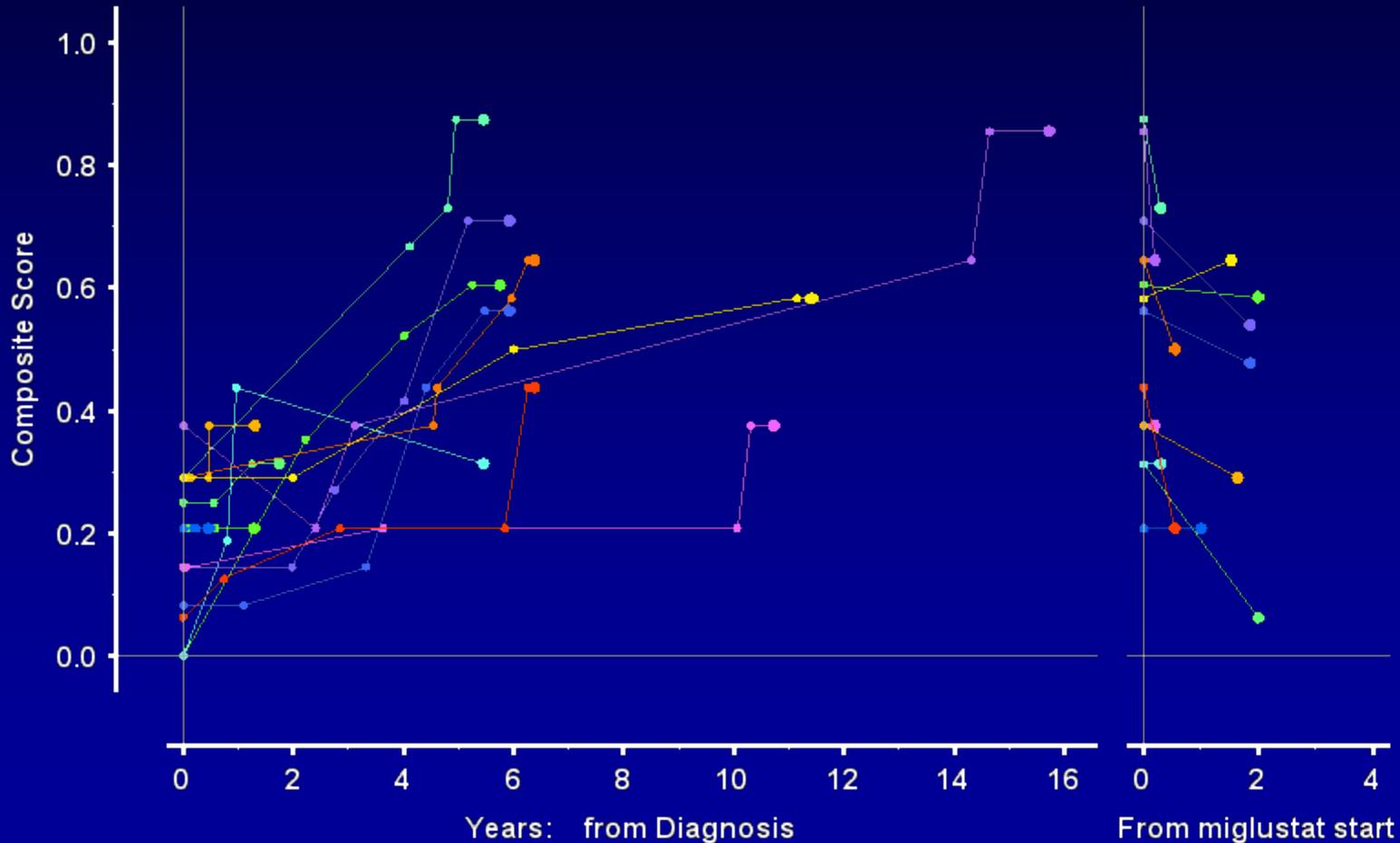
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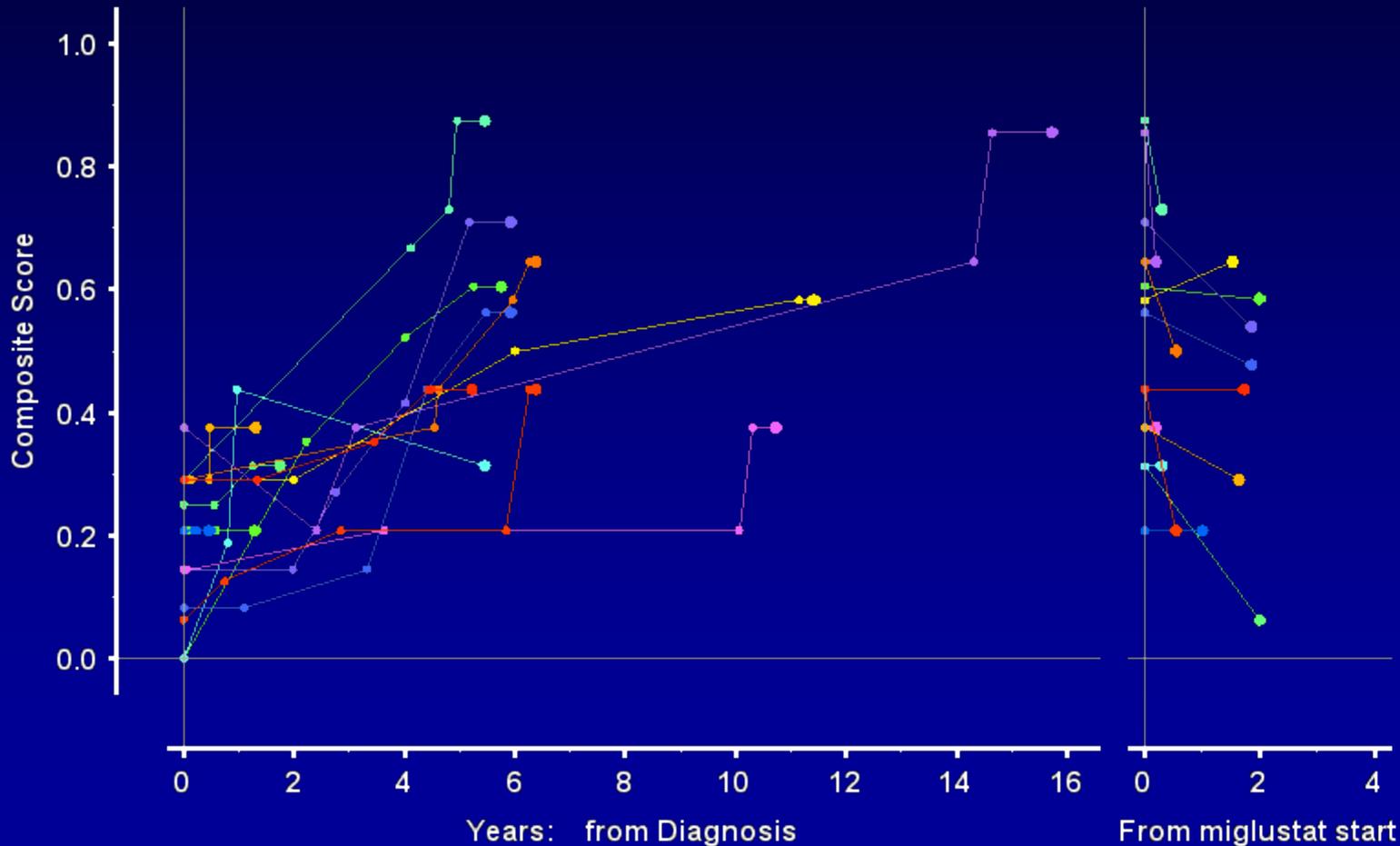
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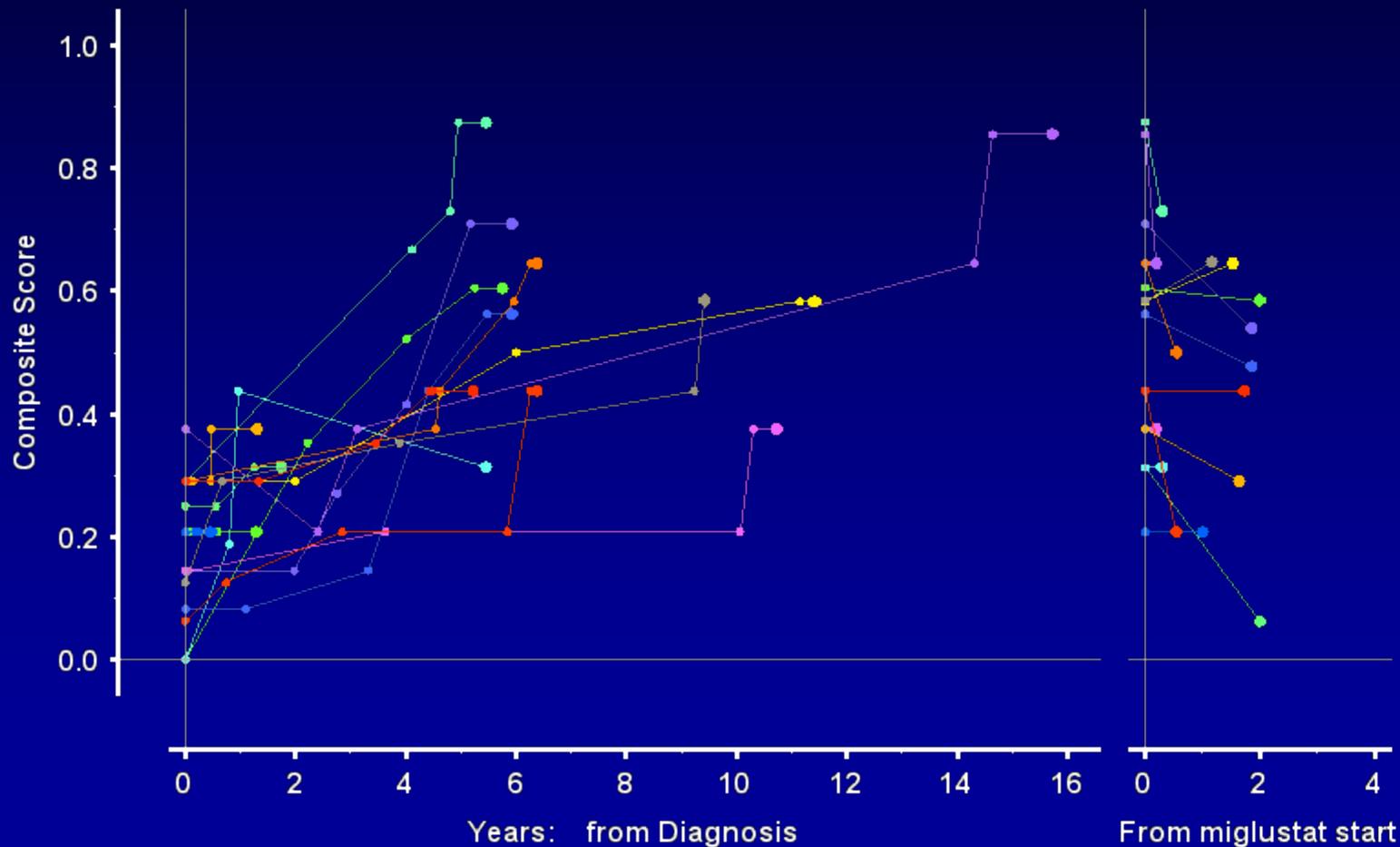
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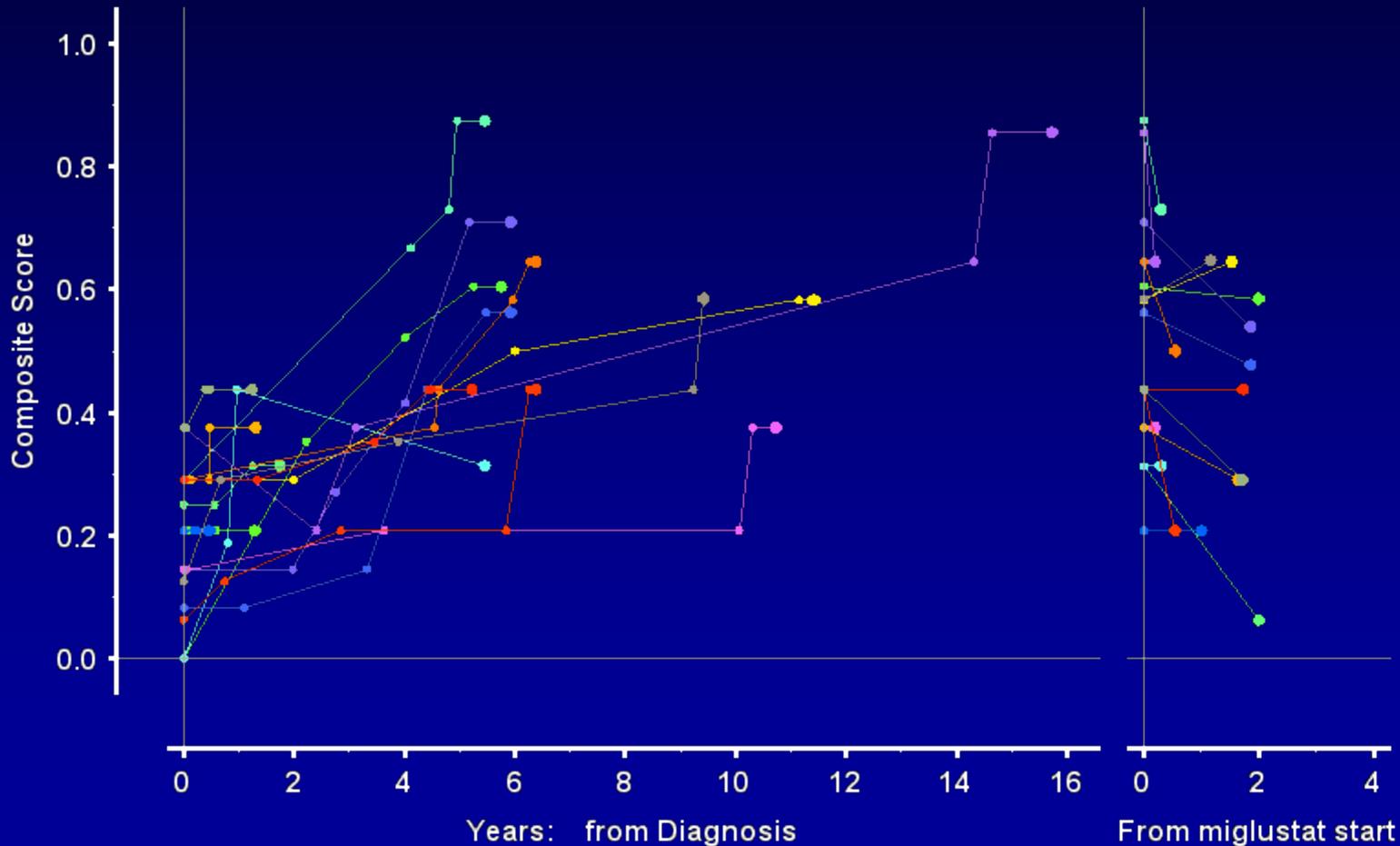
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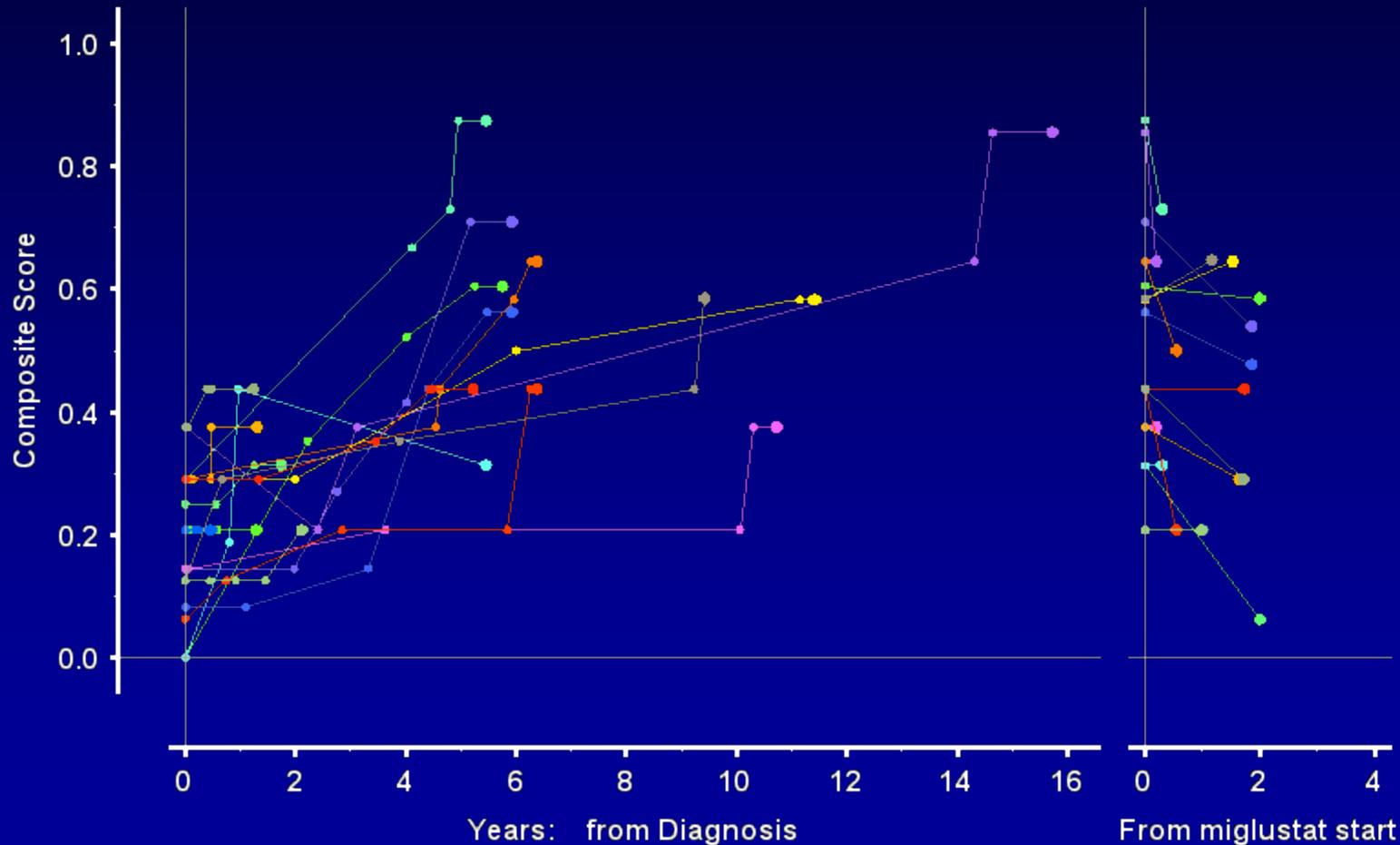
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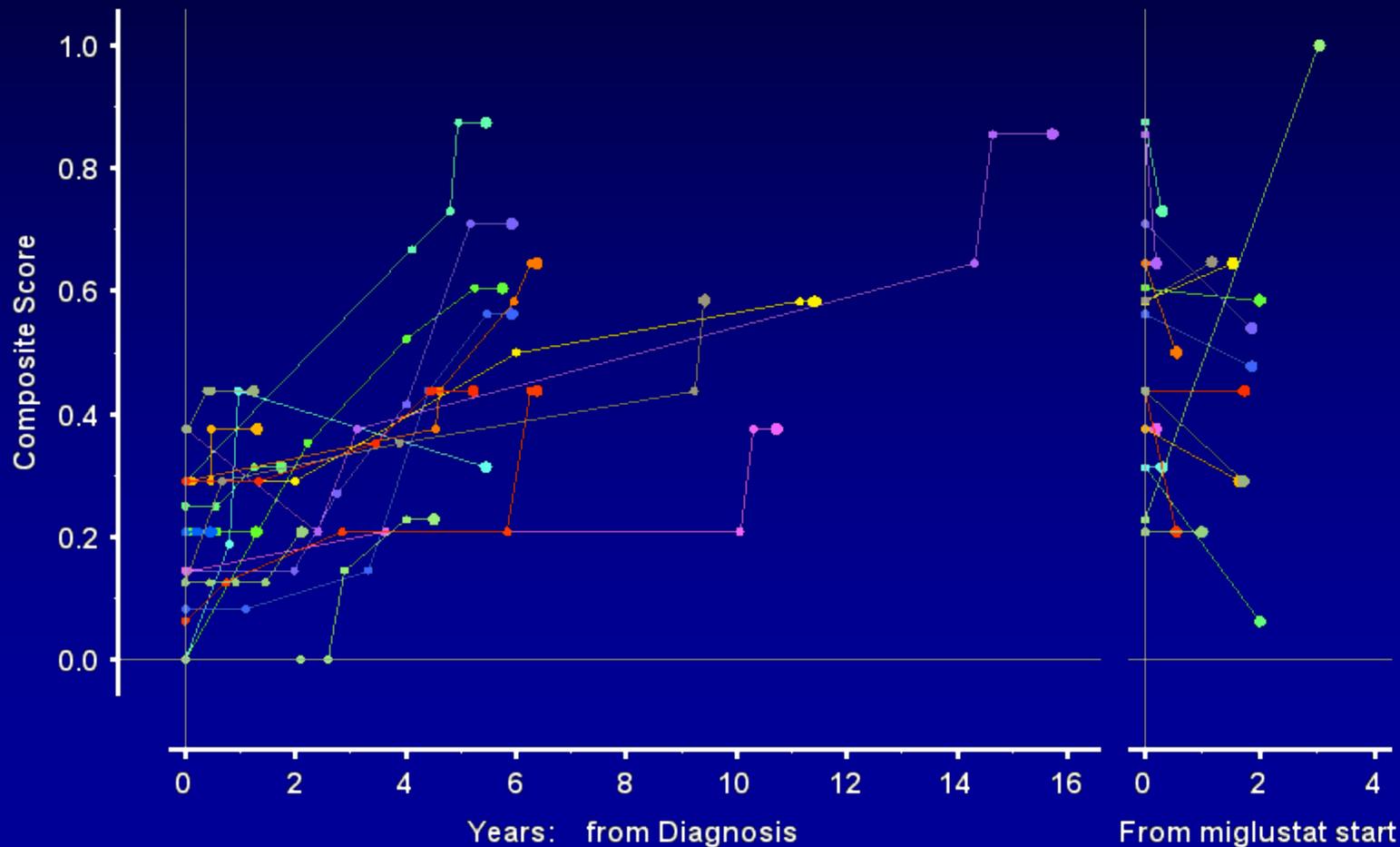
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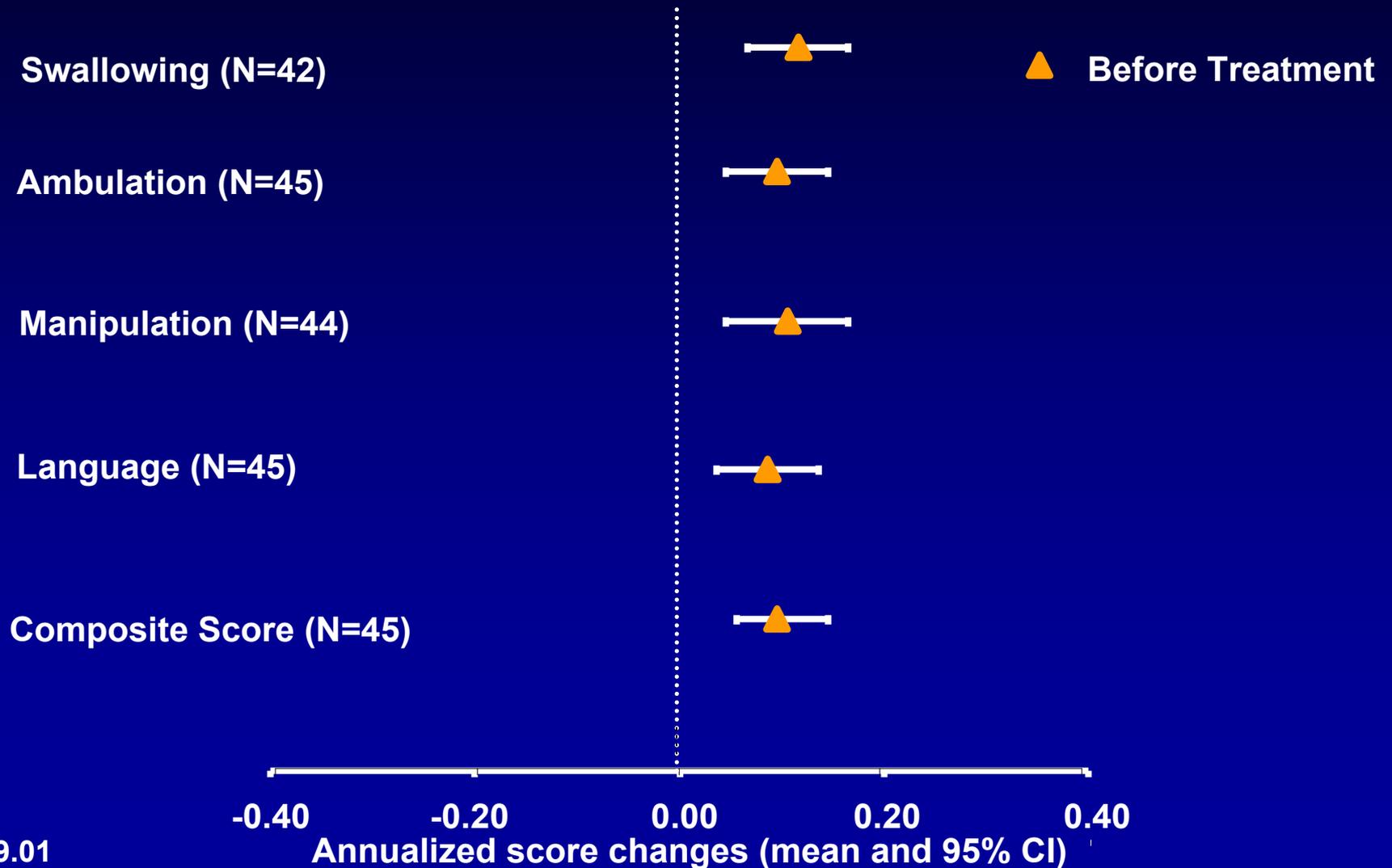
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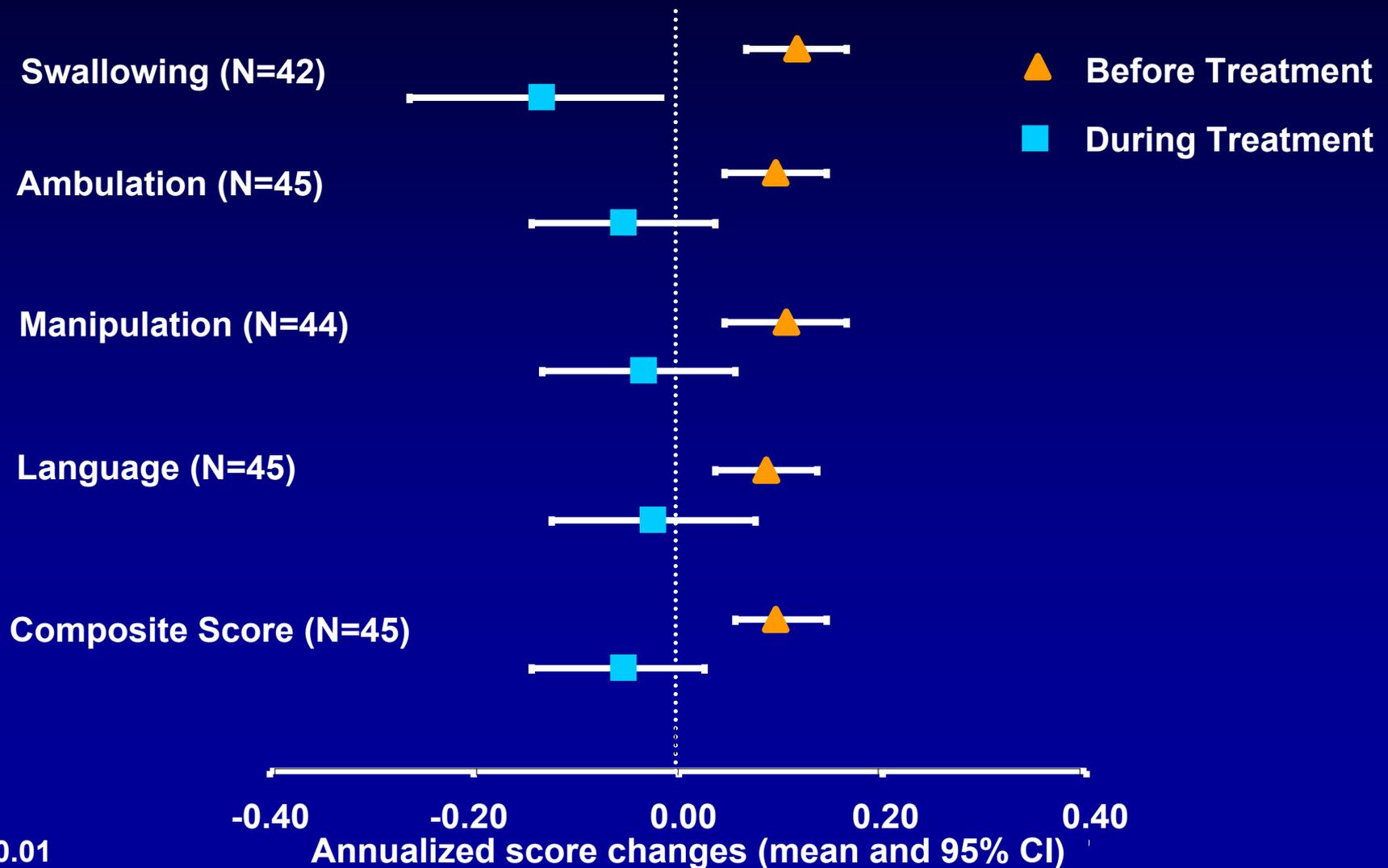
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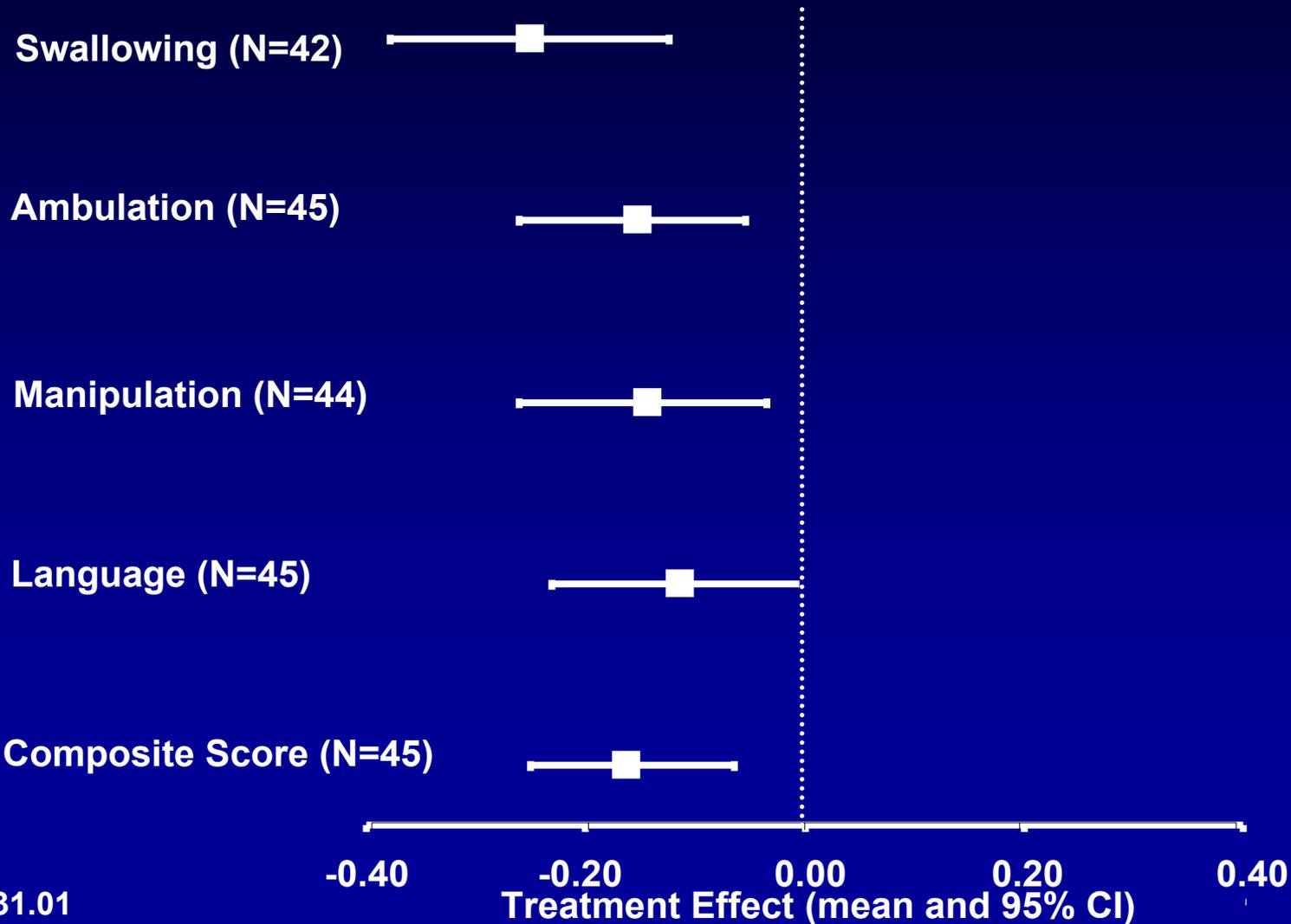
Survey I: Annualized Progression in Patients with Progressive Neurological Disease



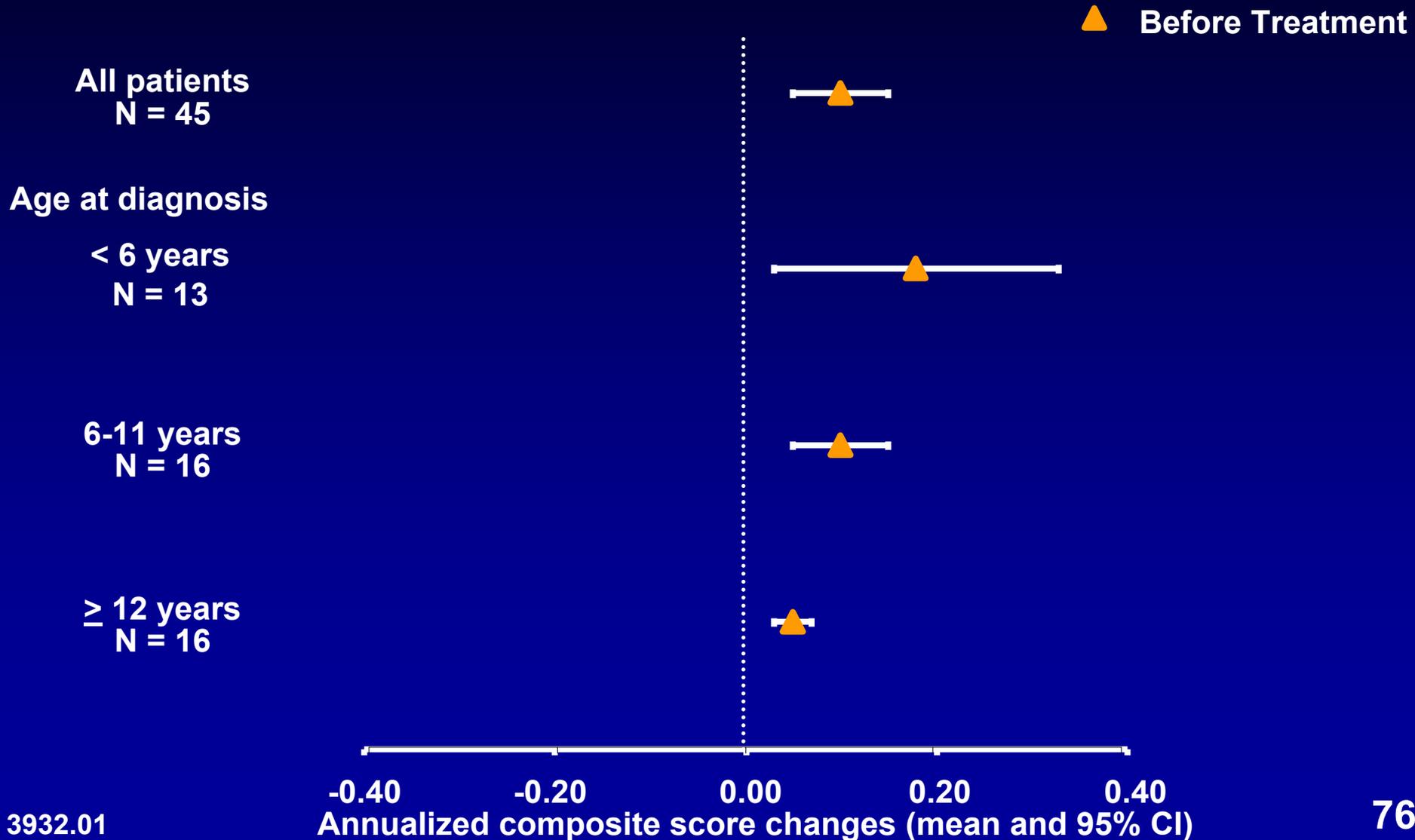
Survey I: Annualized Progression in Patients with Progressive Neurological Disease



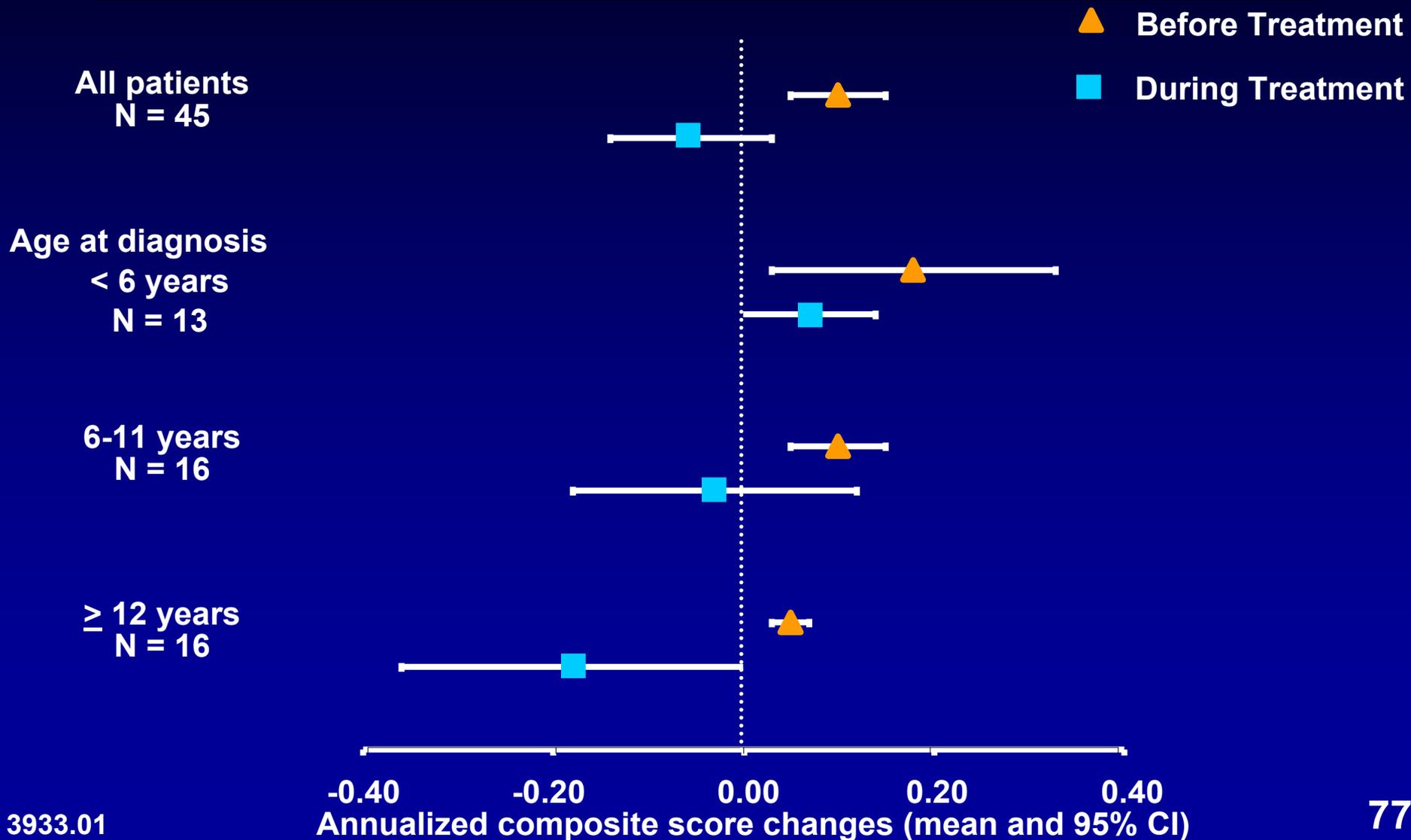
Survey I (Treatment Effect): Annualized Progression in Patients with Progressive Neurological Disease



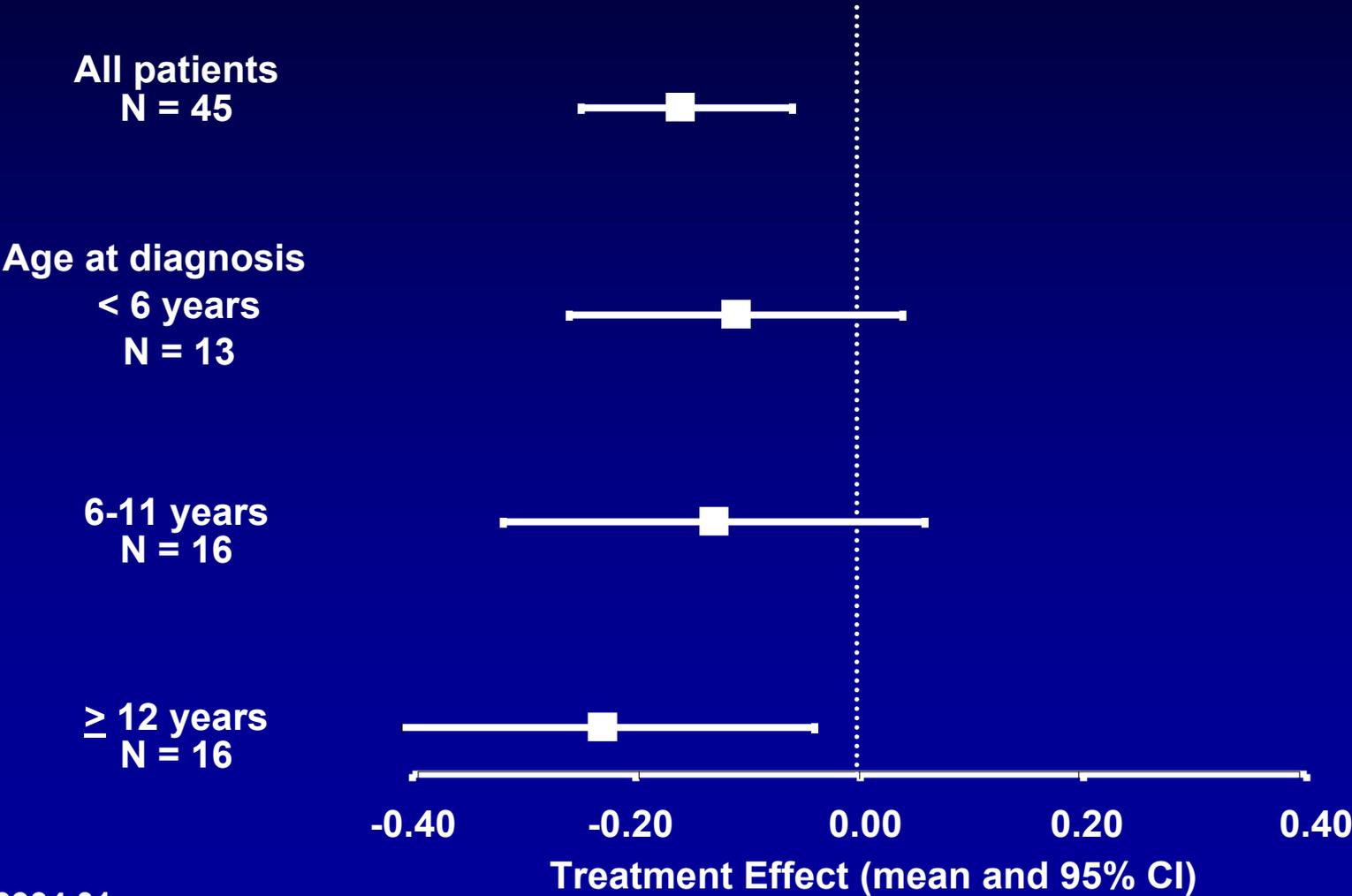
Survey I: Patients with Progressive Neurologic Disease – Composite Score



Survey I: Patients with Progressive Neurologic Disease – Composite Score



Survey I (Treatment Effect): Patients with Progressive Neurologic Disease – Composite Score



Summary of Cohort Studies

- **The cohort studies demonstrate the relentless progression of neurological disease in untreated patients**
- **Treatment with miglustat was characterized by slowing down or stabilization of neurologic disease progression over clinically meaningful durations of follow-up**
- **Effect was most pronounced in patients with progressive neurologic disease in the pre-treatment phase**

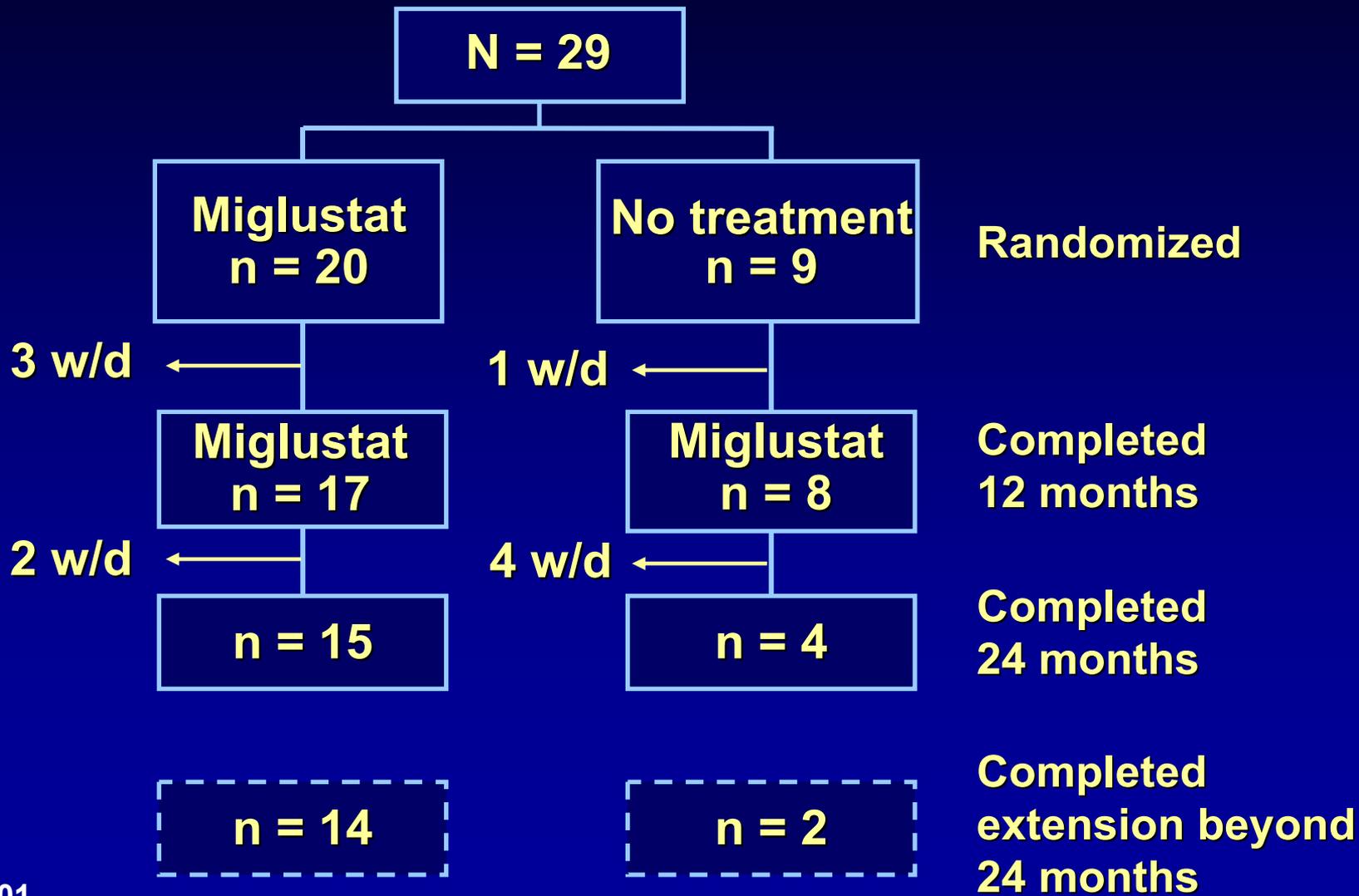
Randomized Controlled Trials in NP-C Disease

- Recruitment difficult in such rare disease
- No established endpoints
- Unrealistic sample size requirement
- Miglustat already available on the market

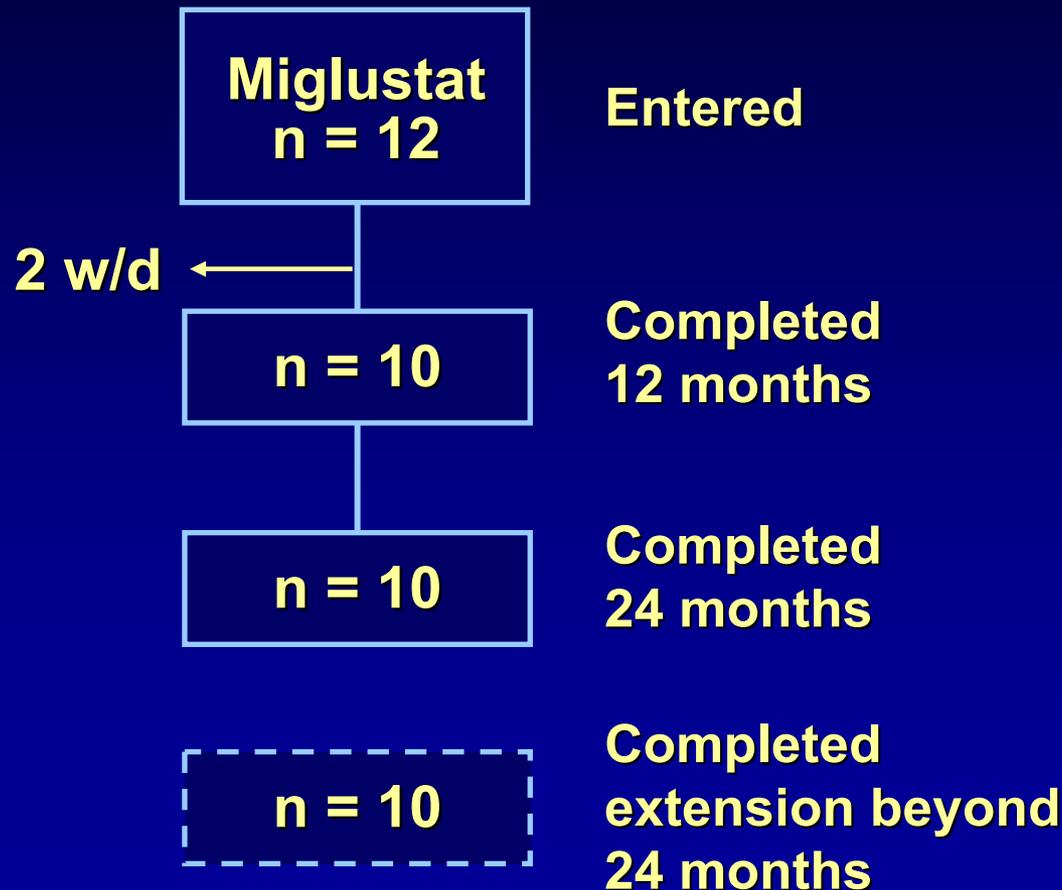
Development of Miglustat in NP-C Disease

- **Retrospective cohort studies**
 - Survey II (Natural History)
 - Survey I
- **Prospective randomized trial**
 - OGT 918-007 (Study 007)

Main Study (Adults / Adolescents) Patient Disposition



Pediatric Sub-study Patient Disposition



Study 007

Baseline NP-C Manifestations

NP-C disease manifestations (%)	Adult/Adolescent		Pediatrics
	No Treatment (n = 9)	Miglustat (n = 20)	Miglustat (n = 12)
At least 1	100	100	100
Vertical gaze palsy	78	100	100
Ataxia	56	100	83
Impaired cognition	78	90	67
Dysarthria	44	90	58
Dystonia	44	70	42
Dysphagia	67	60	33
Pyramidal tract dysf.	33	50	42
Splenomegaly	56	35	83
Hepatomegaly	44	30	58

Choice of Horizontal SEM- α Primary Endpoint

- Quantitative measure expected to be evaluable in a small study
- Horizontal saccadic eye movements (HSEM) are affected later than Vertical SEM
- HSEM- α reflects SEM velocity for large saccades
 - Expressed as ms/deg
 - Decrease in α = improvement of SEM
- Assessed by blinded central assessor

Limitations of HSEM- α Endpoint

- **HSEM- α is not a validated surrogate for clinical manifestations in NP-C**
 - Not used in clinical practice
- **HSEM- α not previously used as a primary endpoint in a clinical study**
- **HSEM- α assessments carried out using two different methods**
 - One method was associated with higher degree of scatter, causing uncertainty in the evaluation

HSEM- α Over 12 Months Adult / Adolescent Patients

	No Treatment	Miglustat
N	8	18
Baseline (mean \pm SD)	2.48 \pm 1.43	3.02 \pm 2.17
Main analysis (baseline values, age)		
Δ from baseline (mean) (95% CI)	-0.05 (-0.61, 0.51)	-0.37 (-0.75, -0.01)
Treatment effect (mean, 95% CI)	-0.33 (-1.00, 0.35) P-value = 0.327	
Supplemental analysis (baseline values, center)		
Δ from baseline (mean) (95% CI)	0.06 (-0.44, 0.55)	-0.46 (-0.80, -0.13)
Treatment effect (mean, 95% CI)	-0.52 (-1.12, 0.09) Nominal P-value = 0.091	

Key Efficacy Variables

Study 007 and Cohort Studies

Variable	Study 007	Cohort Studies
Horizontal saccadic eye movement α	√ (primary EP)	
Swallowing	√	√
Ambulation	√	√
Manipulation (dysmetria / dystonia)		√
Cognitive function	√	
Language function		√

Swallowing Assessment Study 007

Four substances

- 5 mL water
- 1 teaspoon puree
- 1 teaspoon soft lumps
- One-third cookie

Investigator evaluation of patient's ease of swallowing of each substance

- Easy swallowing
- Mild, moderate or severe problems
- Could not swallow the substance at all

Deterioration defined as worsening of swallowing of at least 1 food substance

Hauser Standard Ambulation Index (SAI)

Mobility assessed by time and degree of assistance required to walk 25 feet

0	Asymptomatic; fully active.
1	Walks normally but reports fatigue which interferes with athletic or other demanding activities.
2	Abnormal gait or episodic imbalance; gait disorder is noticeable to family and friends. Able to walk 25 feet in 10 seconds or less.
3	Walks independently; able to walk 25 feet in 20 seconds or less.
4	Requires unilateral support to walk; uses support more than 80% of the time. Walks 25 feet in 20 seconds or less.
5	Requires bilateral support and walks 25 feet in greater than 20 seconds.
6	Requires bilateral support and walks 25 feet in greater than 20 seconds. May use wheelchair on occasion.
7	Walking limited to several steps with bilateral support; unable to walk 25 feet. May use wheelchair for most activities.
8	Restricted to wheelchair; able to transfer independently.
9	Restricted to wheelchair; unable to transfer independently.

Cognitive Function – MMSE

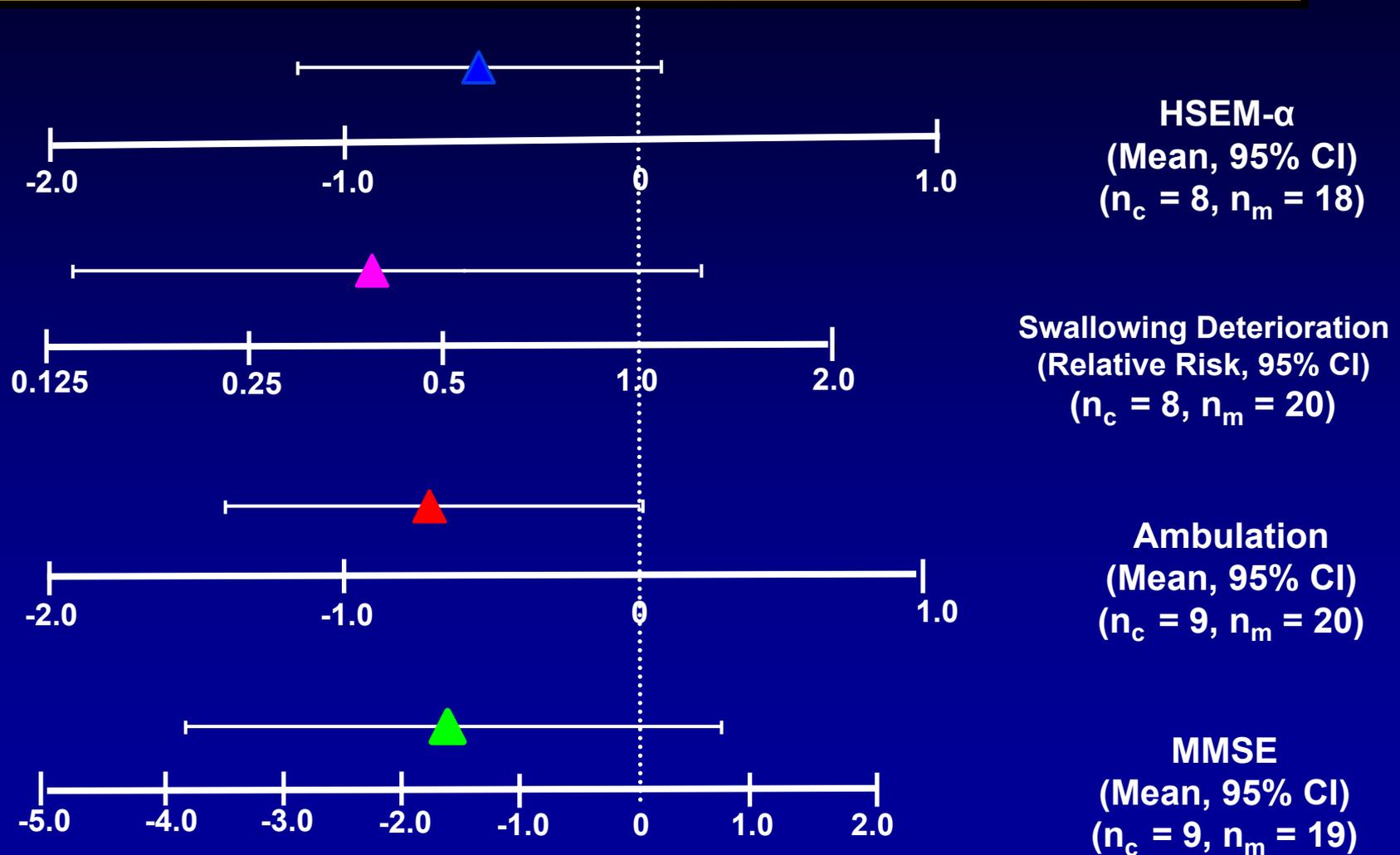
<u>Item</u>	<u>Max. score</u>
Date orientation	5
Place orientation	5
Register 3 objects	3
Serial sevens	5
Recall 3 objects	3
Naming	2
Repeating a phrase	1
Verbal commands	3
Written commands	1
Writing	1
Drawing	1

Max. score = 30

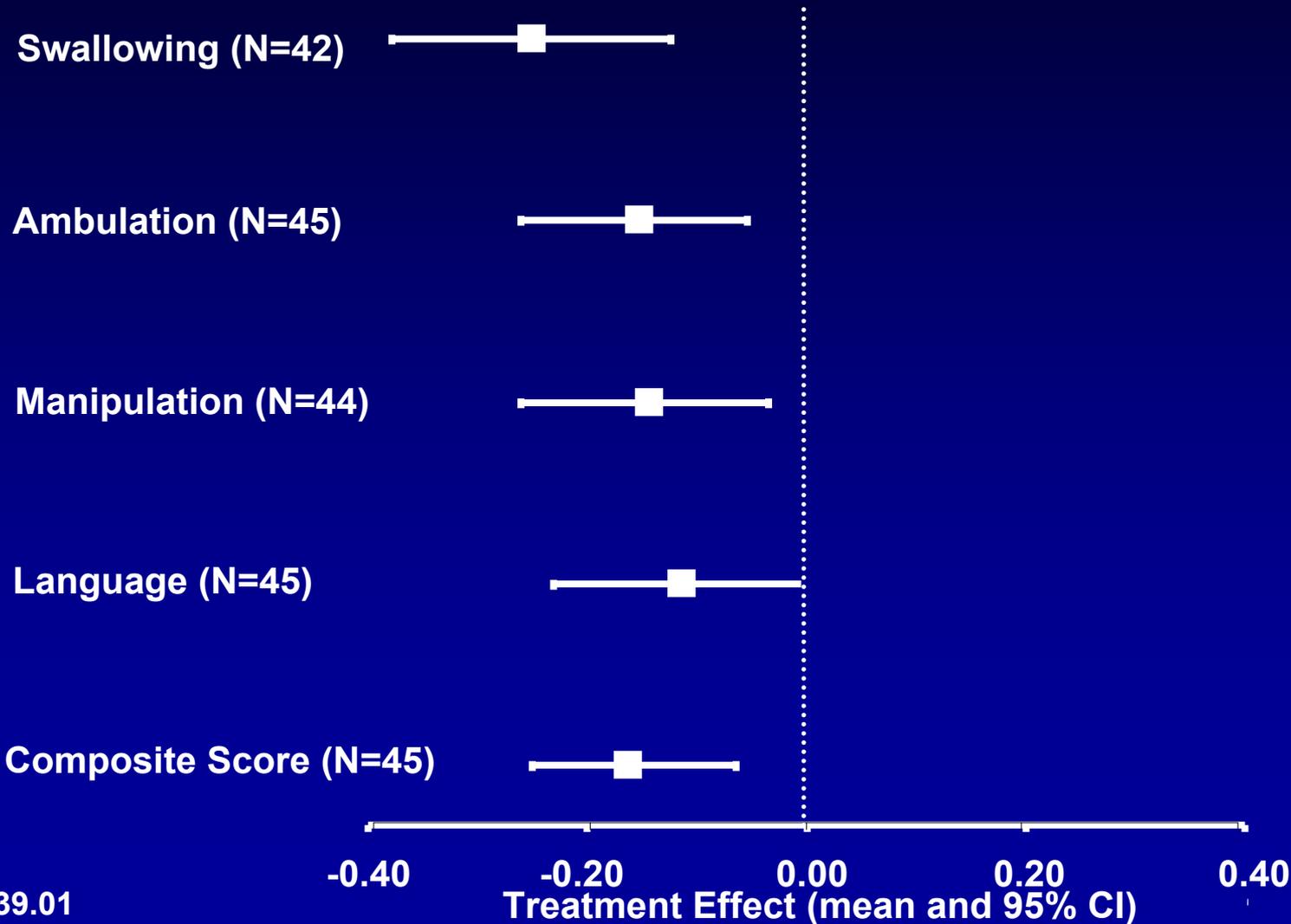
Score \leq 24 indicates
cognitive disorders

Treatment Effect Across Variables

Study 007 – Initial 12 Months



Survey I (Treatment Effect): Annualized Progression in Patients with Progressive Neurologic Disease

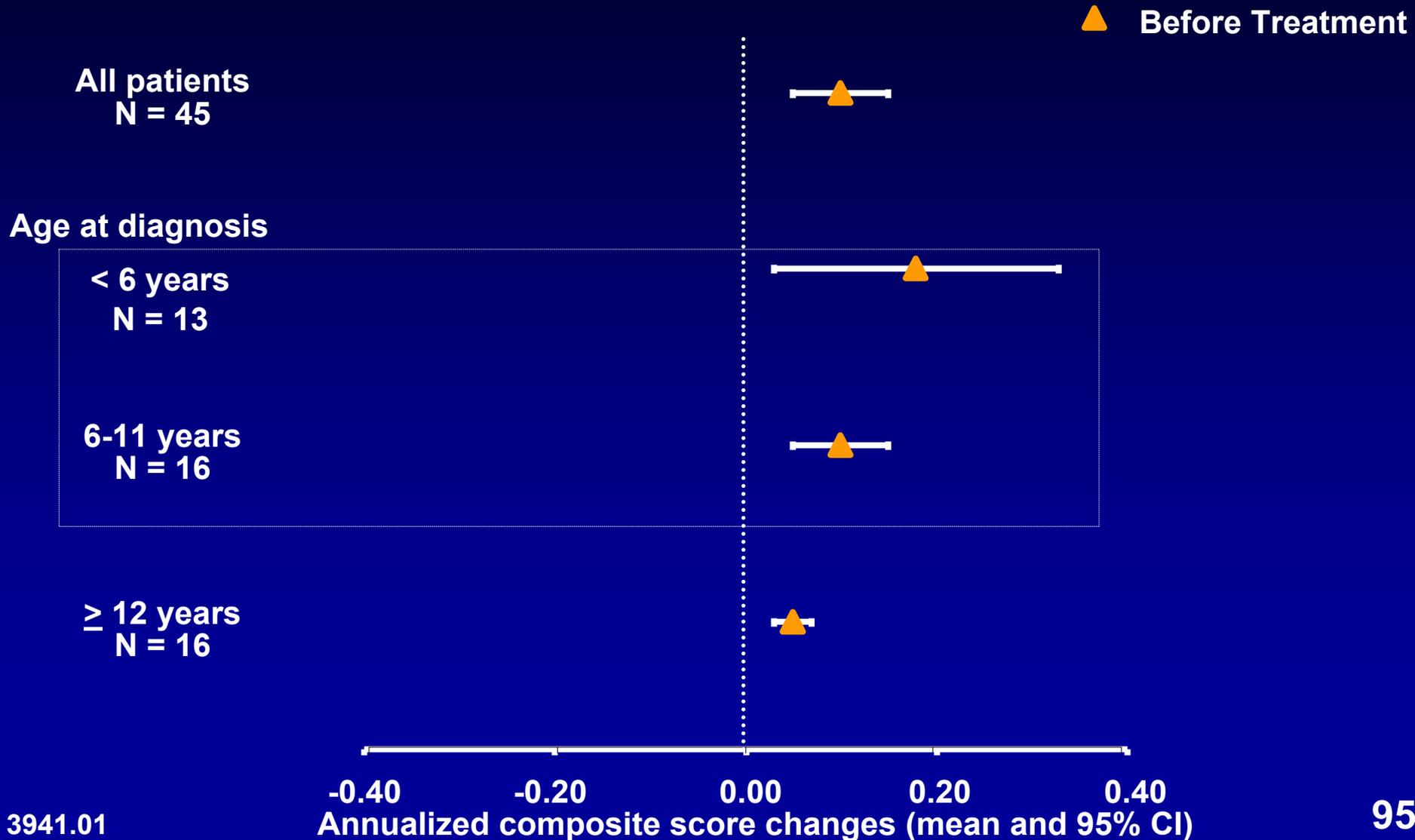


Pediatric Sub-Study

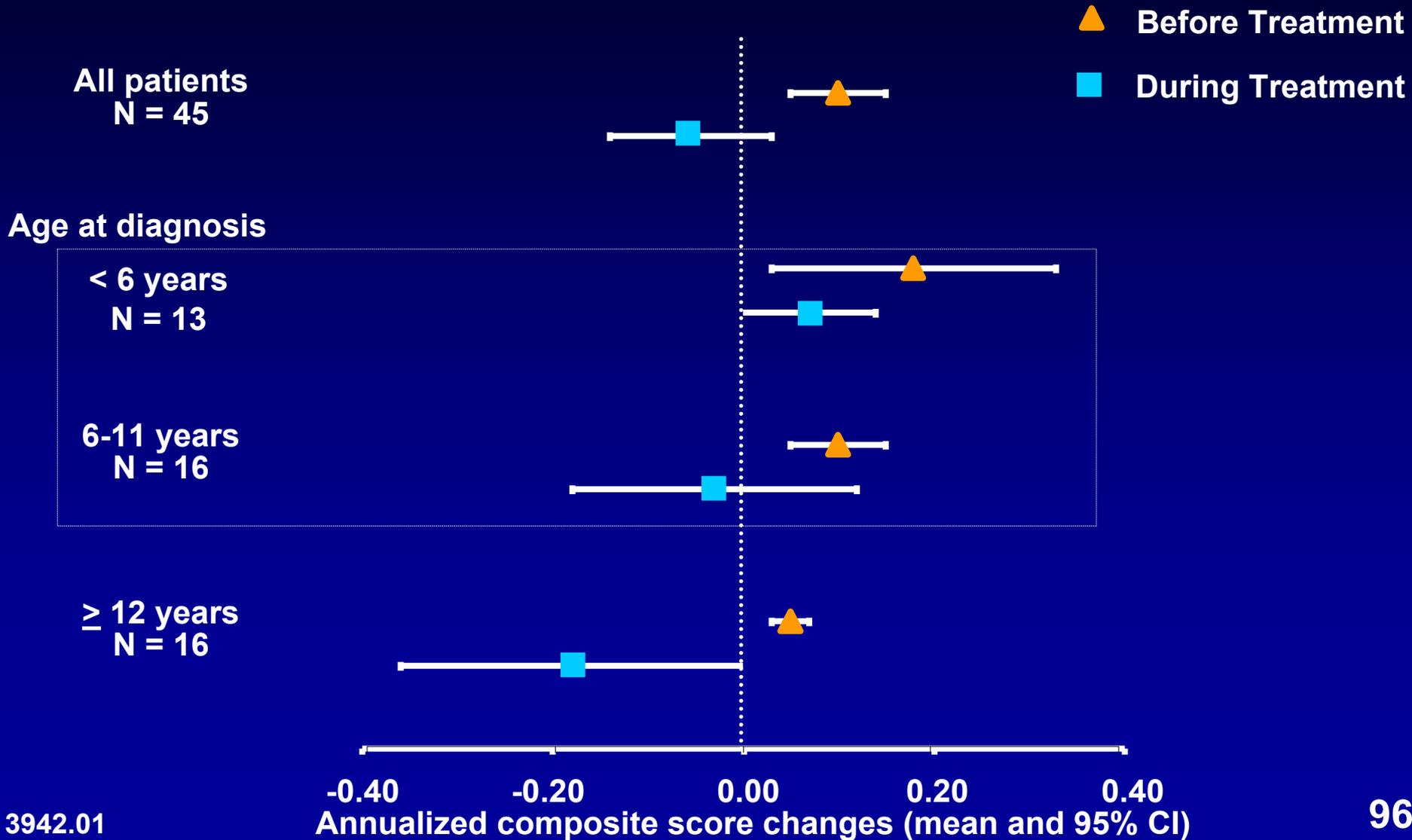
Change from Baseline

Variable	At Month 12	At Month 24
HSEM-α mean change (95% CI)	n = 10 -0.47 (-0.75, -0.18)	n = 9 -0.08 (-1.02, 0.87)
Swallowing Deterioration % patients (95% CI)	n = 11 27 (6, 61)	n = 10 10 (2, 41)
Ambulation mean change (95% CI)	n = 11 0.4 (-0.1, 0.8)	n = 10 0.6 (-0.4, 1.6)

Survey I: Patients with Progressive Neurological Disease – Composite Score

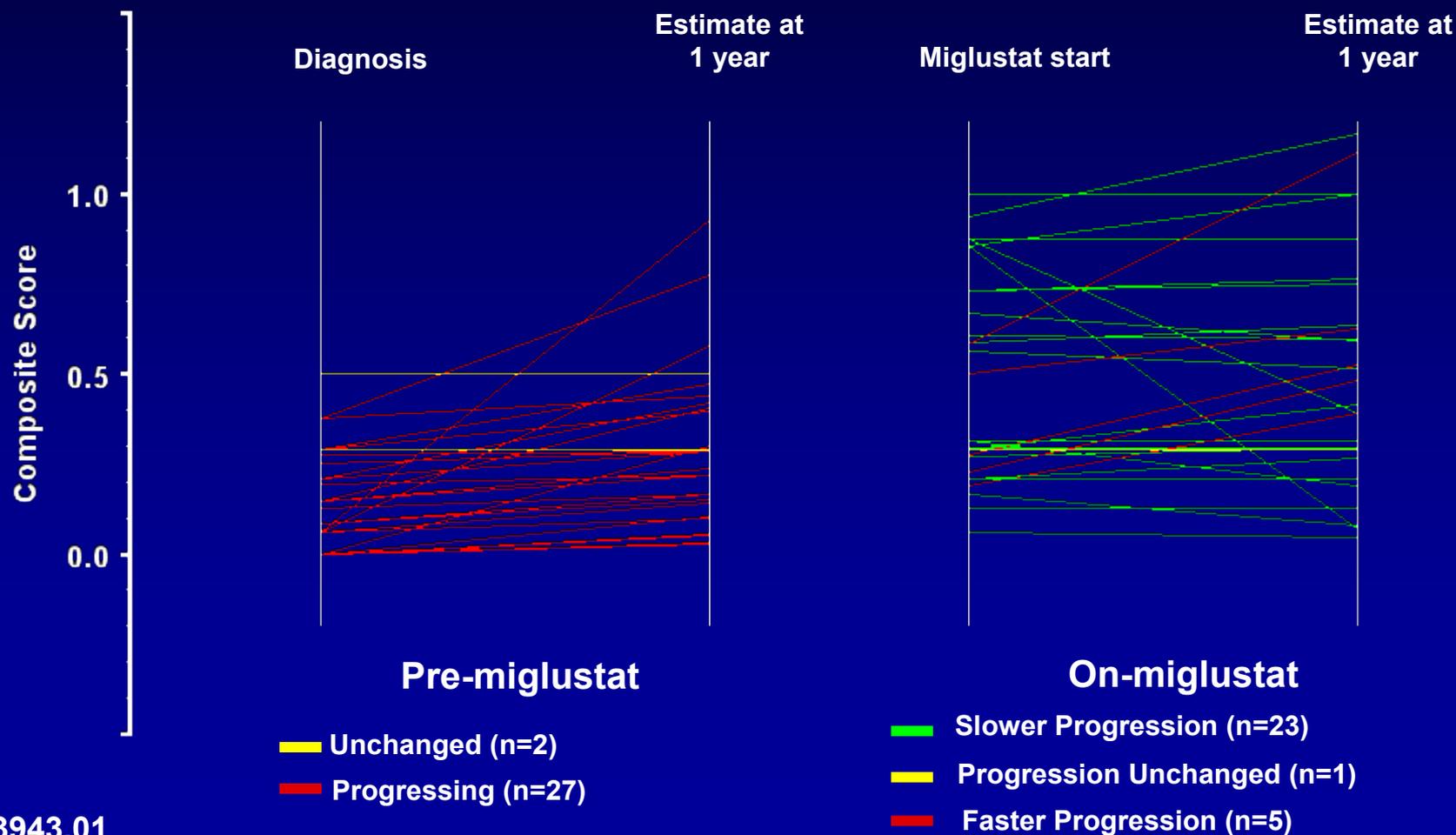


Survey I: Patients with Progressive Neurological Disease – Composite Score



Composite Score Pre- and During Treatment with Miglustat in Survey I – Pediatric Patients

Individual Annualized Progression Rate (N=29)



Efficacy Conclusions

Treatment with miglustat in NP-C patients is associated with stabilization of clinically important neurologic manifestations

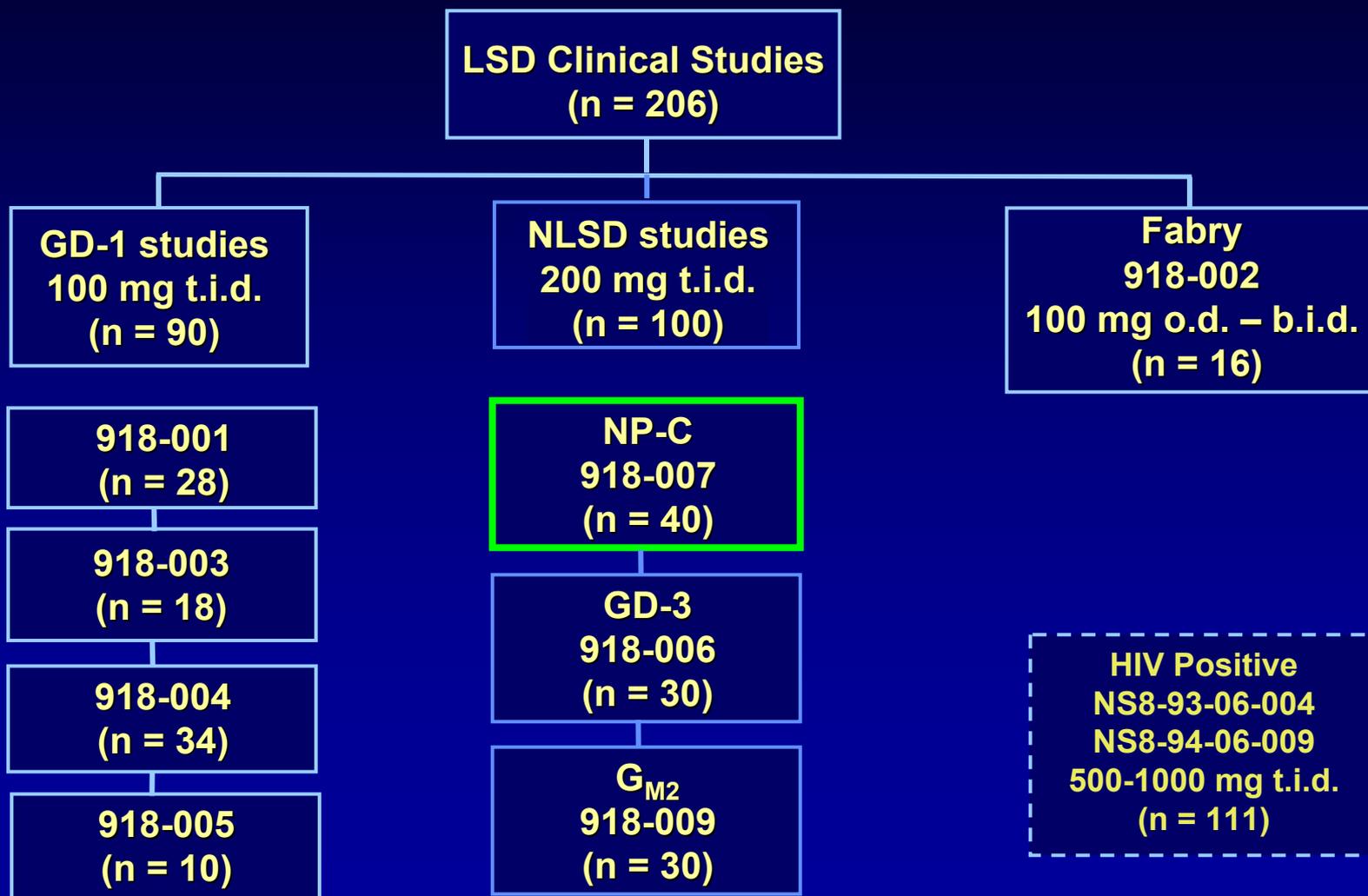
- **Swallowing**
- **Ambulation**
- **Manipulation (dysmetria / dystonia)**
- **Cognition**
- **Language**
- **Composite disability score**

Treatment effect of miglustat is more pronounced in NP-C patients with progressive neurologic disease and is independent of age at diagnosis in these patients

Clinical Program

Safety and Tolerability

Miglustat Safety Database in LSD



Patient Demographics

	Overall (N=206)	NP-C (N=40)
Gender (% M:F)	53:47	48:52
Age (years)	33 ± 17	20 ± 11
Weight (kg)	62 ± 21	59 ± 27
Race (% W:B:O)	84:4:9	78:5:15
US : Non-US (%)	41:59	55:45

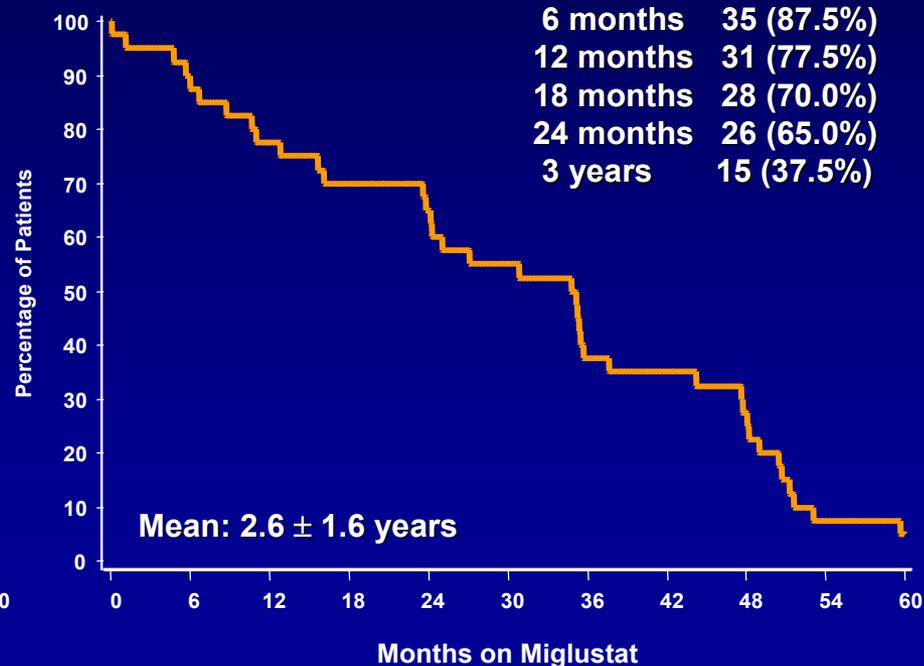
Percent or mean ± SD

Exposure to Miglustat

Overall (N = 206)



NP-C (N = 40)



Patient Demographics By Age Group

	Adults (N=161)	Adolescents (N=16)	Pediatrics (N=29)
Gender (% M:F)	56:44	50:50	38:62
Age (years)	39 ± 13	14 ± 2	7 ± 2
Weight (kg)	69 ± 16	53 ± 18	26 ± 8
Race (% W:B:O)	96:1:3	50:19:31	59:10:31
US : Non-US (%)	37:63	63:37	52:48

Numbers are % or mean ± SD

Patient Disposition by Indication

	Adults (N=161) n (%)	Adolescents (N=16) n (%)	Pediatrics (N=29) n (%)
NP-C	21 (13.0)	7 (43.8)	12 (41.4)
GD-1	90 (55.9)	-	-
GD-3	4 (2.5)	9 (56.3)	17 (58.6)
G_{M2}	30 (18.6)	-	-
Fabry	16 (9.9)	-	-
Exposure (years)	2.1 ± 1.5	2.3 ± 1.5	2.4 ± 1.1

Frequent AEs

Overall and by Indication

	Overall (N=206) %	NP-C (N=40) %	NLSD (N=100) %	GD-1 (N=90) %
Diarrhea	85	83	77	91
Weight Decrease	63	60	55	70
Tremor	46	58	48	38
Flatulence	44	55	34	53
Abdominal Pain	43	35	40	51
Fatigue	30	45	32	28
Headache	29	43	30	32
Nasopharyngitis	27	40	31	24
Vomiting	22	35	30	12
Nausea	21	25	22	19
Fall	20	25	37	6

Frequent AEs in NLSD Studies (Initial 12 months)

	Miglustat (N = 72) %	No Treatment (N = 29) %
Diarrhea	82	31
Weight Decrease	54	7
Tremor	46	7
Flatulence	39	0
Abdominal Pain	32	0
Vomiting	26	3
Headache	26	14
Fatigue	23	10
Pyrexia	19	7
Nausea	18	10
Cough	17	7
Paresthesia	14	3

Frequent AEs

NP-C Patients (Initial 12 months)

	Miglustat (N = 20) %	No Treatment (N = 9) %
Diarrhea	85	44
Flatulence	70	0
Weight Decrease	65	0
Abdominal Pain	50	0
Headache	45	33
Tremor	45	22
Nausea	35	11
Fatigue	35	11
Insomnia	30	0
Vomiting	30	0
Gait Spastic	25	11
Appetite Decrease	25	0

Frequent AEs Overall and by Age Group

	Overall (N=206) %	Adults (N=161) %	Adolescents (N=16) %	Pediatrics (N=29) %
Diarrhea	85	88	81	66
Weight Decrease	63	71	56	21
Tremor	46	46	44	48
Flatulence	44	50	44	14
Abdominal Pain	43	43	63	35
Fatigue	30	32	25	21
Headache	29	26	56	31
Vomiting	22	21	25	31
Nausea	21	22	38	7
Cough	19	13	44	38
Paresthesia	16	17	13	7
Pyrexia	15	11	25	28

Based on the frequent AEs observed during the first 12 months in NLSD patients

Dosing Regimen and AEs

First 6 Months of Treatment

	GD-1 N=18 50mg t.i.d. %	GD-1 N=72 100mg t.i.d. %	NLSD N=100 200mg t.i.d. %
Diarrhea	94	88	76
Weight Decreased	67	51	42
Flatulence	50	49	32
Tremor	44	25	41
Headache	44	25	21
Abdominal Pain	28	25	16
Vomiting	17	7	22
Fatigue	11	15	19

Frequent AEs (1000 mg t.i.d. for 12 - 24 Weeks) HIV-Positive Patients

	Miglustat (N = 87) %	Placebo (N = 74) %
Diarrhea	89	34
Flatulence	59	22
Nausea	46	28
Fatigue	45	28
Headache	44	30
Abdominal Pain	31	20

AEs incidence with miglustat > 5% difference from Placebo

Deaths Among NP-C Patients

- **22 year old female**
 - Died of respiratory distress
 - 2 weeks after stopping treatment due to disease progression
 - Treatment duration 13 months
- **20 year old male**
 - Died of traffic accident
 - 6 months after stopping treatment at his own request
 - Treatment duration > 3 years
- **11 year old female**
 - Died of pneumonia
 - 8 months after stopping treatment because of painful defecation / Crohn's disease
 - Treatment duration 4 years

Serious AEs

41 of 206 (19.9%) patients experienced an SAE

- **Viral infection in 3 patients (1.5%)**
- **Other SAEs were reported in 1-2 patients each**

11 of 40 (27.5%) NP-C patients experienced an SAE

- **Viral infection in 2 patients (5%)**

Initial 12-month period in NLSD studies

- **8 of 72 (11.1%) of miglustat patients and 4 of 29 (13.8 %) of No-Treatment patients had at least 1 SAE**

AEs Leading to Discontinuation (D/C)

37 of 206 (18.0%) patients experienced an AE leading to D/C

- **Diarrhea (8 patients – 3.9%)**
- **Tremor (5 patients – 2.4%)**
- **Flatulence and weight loss (4 patients each – 1.9%)**

9 of 40 (22.5%) NP-C patients

- **Depression (2 patients – 5%)**

Initial 12-month period in NLSD studies

- **6 of 72 (8.3%) patients D/C miglustat treatment**
- **Depression and weight loss (2 patients each – 2.8%)**

Other Safety Observations

Laboratory tests

- Small reduction in platelets during the first year of treatment
- No clinically relevant changes in any other laboratory tests

Vital signs

- No evidence for any effect on heart rate or blood pressure

ECGs

- No clinically relevant changes in ECG variables

AEs of Interest

GI disorders

- Diarrhea, flatulence, nausea, vomiting and abdominal pain

Nervous system disorders

- Tremor, headache and paresthesia

Other AEs

- Weight loss

Laboratory abnormalities

- Decreased platelets

Gastrointestinal AEs

Diarrhea, flatulence, nausea, vomiting and abdominal pain

- Most AEs mild or moderate, not dose related
- Inhibition of intestinal sucrase and isomaltase
- 4 (1.9%) patients experienced GI SAEs
 - Diarrhea / Crohn's disease and vomiting / viral infection (NP-C)
 - Constipation 2 patients (GD-3)
- 8 (3.9%) patients D/C due to diarrhea
 - 1 NP-C patient
- Manageable in clinical practice, decrease over time, most patients tolerate long term treatment, reversible upon D/C

Neurological AEs

- Tremor, headache and paresthesia
 - Most AEs were mild to moderate
 - No cases reported as SAEs
 - Relatedness difficult to assess in patients with neurological disease
- New-onset tremor led to D/C of 5 pts (2.4%), none in NP-C
- Paresthesia led to D/C in 2 GD-1 patients
- 3 NP-C patients (7.5%) D/C due to neurological AEs
- Most patients tolerate long-term treatment
- Reversible upon D/C

Weight Loss

The second most frequently reported AE

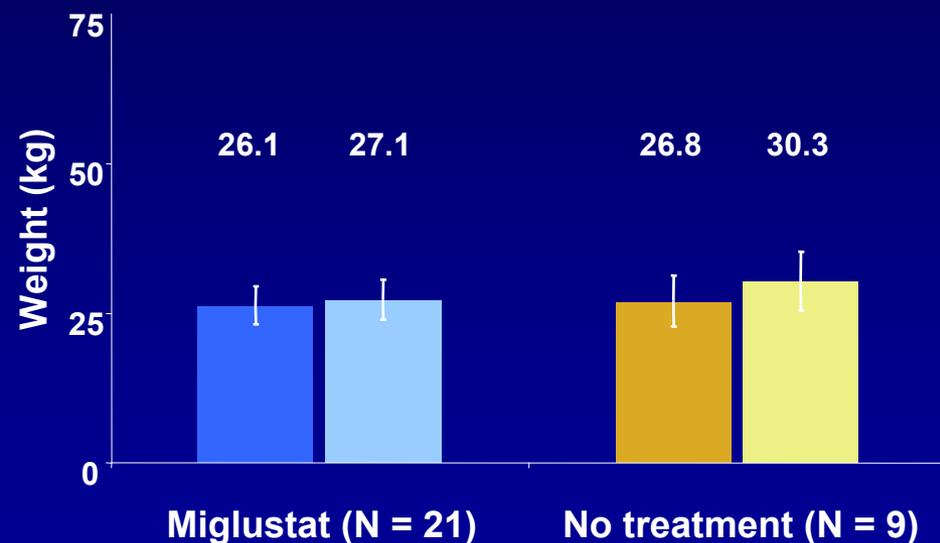
- **129 (63%) patients of the overall population**
- **Mild or moderate in 95% of the cases**
- **Observed mainly during the first year of treatment**
- **No SAE**
- **Led to D/C in 4 cases (< 2%)**
 - **No D/C among children**
 - **No D/C in NP-C patients**

Weight and Height Changes Pediatric NLSD Patients

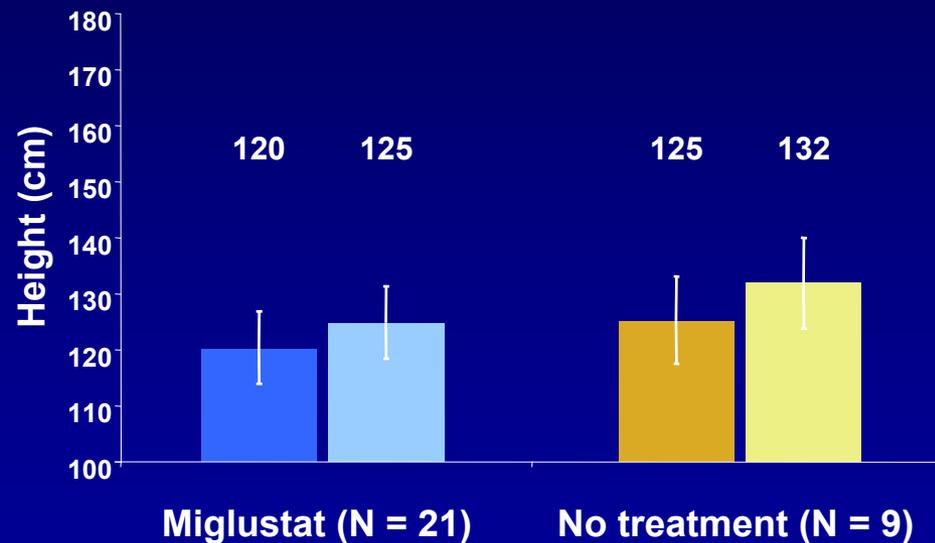
Initial 12 Months

- Baseline
- Month 12/LV
- Baseline
- Month 12/LV

Weight



Height



Data displayed as mean and 95% CI

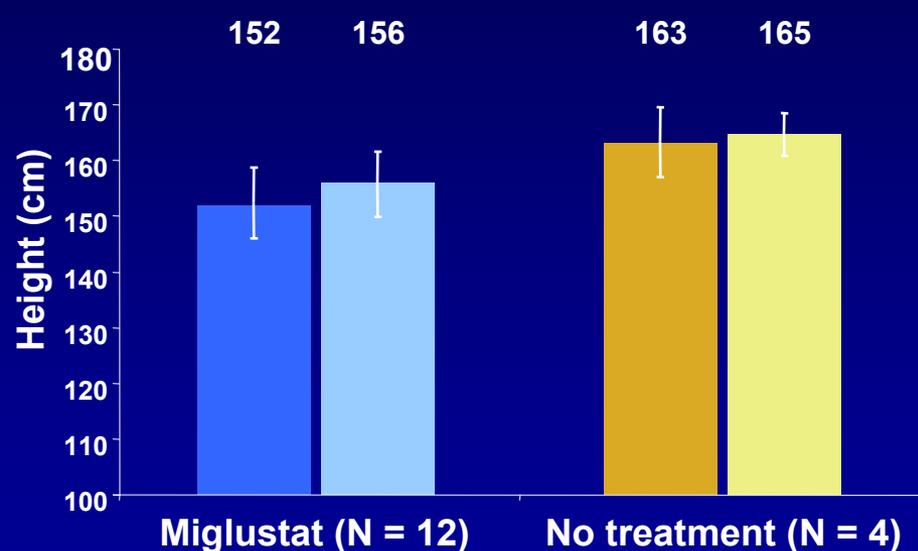
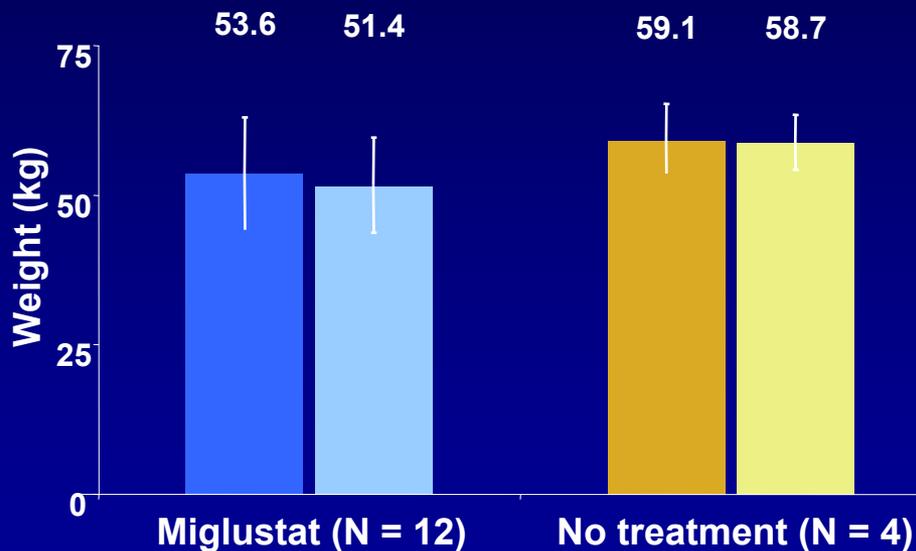
Weight and Height Changes Adolescent NLSD Patients

Initial 12 Months

- Baseline
- Month 12/LV
- Baseline
- Month 12/LV

Weight

Height



Data displayed as mean and 95% CI

Platelet Count in NP-C

- No progressive reduction over time
- 6 patients with platelet count $< 100 \times 10^9/L$
- No patient with platelet count $< 50 \times 10^9/L$
- No D/C due to thrombocytopenia and no bleeding episodes
- Reduced platelet count is known to be associated with NP-C (residual splenomegaly)
- Platelet monitoring recommended

Safety Conclusions

- **Safety profile of miglustat in neuronopathic LSD (including NP-C) is comparable with GD-1**
- **AE profile of miglustat treatment is well characterized and consistent across doses, diseases and age groups**
- **With the proposed recommendations for monitoring (platelets and growth) the USPI provides adequate information to physicians and patients**

Benefit – Risk Assessment

Benefit – Risk Background

- NP-C disease is a very rare, genetic disorder dominated by central nervous system involvement
- NP-C neurologic disease is progressively disabling and leads to early death
- There is no approved therapy for NP-C disease in the US
- Availability of treatment that can stabilize or reduce the rate of neurologic deterioration would represent an important advancement in the clinical management of NP-C disease

Benefits of Miglustat Treatment

Treatment with miglustat in patients suffering from NP-C disease is associated with stabilization of clinically important neurologic manifestations

- Swallowing
- Ambulation
- Manipulation (dysmetria / dystonia)
- Cognition
- Language
- Composite disability score

Risks of Miglustat Treatment

- **GI intolerance**
 - Diarrhea, flatulence, abdominal pain, nausea and vomiting
- **Nervous system side effects**
 - Tremor, headache and paresthesia
- **Weight loss**
- **Growth in children**
- **Platelet reduction**

NP-C Disease Registry

Ongoing registry collecting prospective data in NP-C patients (treated or not treated with miglustat)

- Natural history of the disease
- Treatment outcomes / effectiveness
 - NP-C disability scale
- Monitoring of safety
 - Gastrointestinal, neurological and other AEs
 - Platelet counts
 - Growth in children

Benefit – Risk Conclusions

- **Treatment with miglustat has clinically meaningful benefits that outweigh its well characterized and manageable risks**
- **Miglustat addresses an unmet medical need in the treatment of patients with progressive neurologic manifestations of NP-C disease**

Proposed Indication

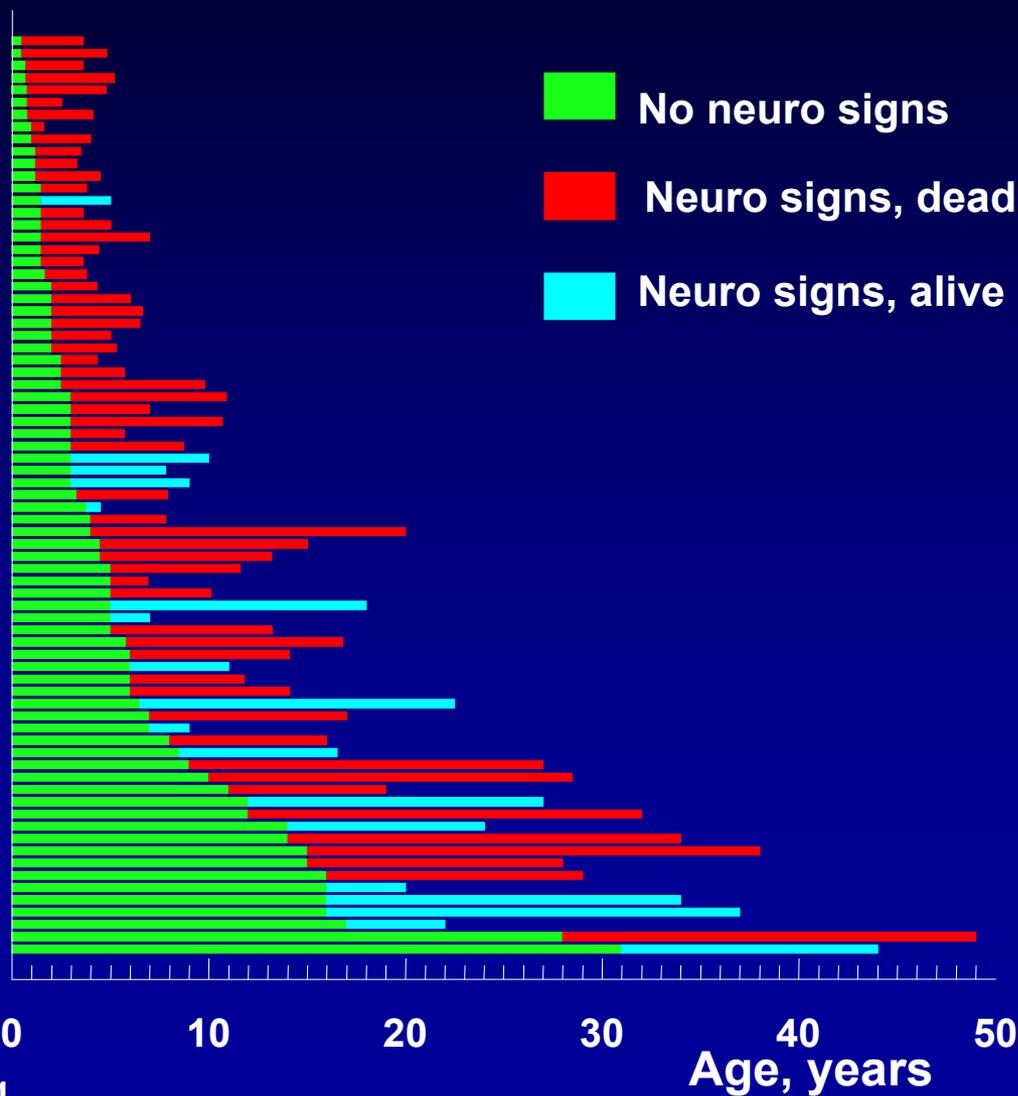
Miglustat is indicated for the treatment of progressive neurological manifestations in adult and pediatric patients with Niemann-Pick type C disease

Clinical Perspective

Marc C. Patterson, MD

Professor of Neurology, Pediatrics and Medical Genetics
Chair, Division of Child and Adolescent Neurology
Mayo Clinic, Rochester, MN

Clinical Experience Before Miglustat Availability



N=78

[unpublished data of
the CETNP]

Case History 1 – Early Development and Presentation

- Normal gestation, delivery and infancy
- Speech therapy (articulation) for one year pre-kindergarten
- 3 years – impaired attention, impulsivity, impaired language
 - **composite score 0.15**
- 6 years – absence seizures
- 7 years – complex partial seizures
- 10 years – increasing hypersomnolence, dysarthria, dysphagia, dystonia, vertical gaze palsy, intractable seizures
- 10 years, 7 months
 - **composite score 0.28**

Case History 1 – Current (13 years old)

- **Cerebellum**
 - severely ataxic, walking only with assistance
 - severe dysarthria, drooling, coughing
 - gastrostomy tube feeding
- **Brainstem**
 - sleep inversion, cataplexy
 - complete VSGP, early HSGP
- **Basal ganglia**
 - dystonia
- **Cortex**
 - pseudobulbar affect, depression
 - uncontrolled seizures
 - school failure
- **No organomegaly, systemic findings**
 - **composite score – 0.73**

Case History 2

- Normal gestation, delivery and infancy
- 3.5 years – splenomegaly
- 5 years – NP-C diagnosed
- 9 years – early VSGP
 - **Composite score 0**
- 19.25 years – mild ataxia, dystonia, dysarthria
 - **Composite score 0.21**
 - Miglustat introduced
- 24.75 years – last follow-up
 - Ataxia, dystonia, dysarthria stable
 - **Composite score 0.21**

Conclusions

- **Relentlessly progressive, lethal neurologic disease**
- **Until miglustat, no disease-modifying therapy available**
- **Treatment with miglustat in NP-C patients is associated with stabilization of neurologic disease**

Miglustat Therapy for Niemann-Pick Type C Disease

Actelion Pharmaceuticals Ltd

Physician's assessment of the change in patient's general health since treatment start - Survey I

	N	%
Much better	6	10.0
Somewhat better	16	26.7
About the same	24	40.0
Somewhat worse	12	20.0
Much worse	2	3.3

Missing value N=6

Physician's assessment of patient's benefit Survey I

	N	%
Excellent	2	3.4
Good	22	37.9
Fair	19	32.8
Poor	10	17.2
None	5	8.6

Missing value N=8

Withdrawals up to Month 24 in Study 007 Adult/ Adolescent Patient

Study phase/treatment	Patient No	Reason for withdrawal	Time in study / time on miglustat (mo)	
12-month comparative Miglustat	007-102	NP-C disease progression	5.9	
	007-103	NP-C disease progression	11.0	
	007-109	Diarrhea, Crohn's disease	6.6	
	No-Treatment	007-213	Family request (return to alternative therapy)	3.1
12-month extended therapy Continued miglustat	007-104	Axonal neuropathy	12.7	
	007-212	Patient request (travel difficulties)	23.5	
	No-Treatment switched to miglustat after Month 12	007-101	Hemorrhagic diarrhea	22.1 / 10.6
		007-108	Patient request (based on impression of risk and GI adverse events [abdominal pain, diarrhea, flatulence])	13.5 / 1.1
		007-113	Patient request (concern about side effects [adverse events]; abdominal pain, diarrhea, nausea, flatulence and aggravated tremor)	16.4 / 4.7
		007-208	Worsening of Tremor	20.3 / 8.7

Withdrawals beyond Month 24 in Study 007 Adult/ Adolescent Patient

Study phase/treatment	Patient No	Reason for withdrawal	Time in study / time on miglustat (months)
Continued extension therapy			
Miglustat	007-210	Non-compliance (refusal to take drug)	30.7 / 18.7
	007-105	Lost to follow up	59.2 / 47.5
No-Treatment switched to miglustat after Month 12	007-112	Patient request	38.7 / 27.0

HSEM- α by Center

12 Months Adult/Adolescent Patients

	No Treatment	Miglustat
Center 1		
N	5	7
BL (mean \pm SD)	1.77 \pm 1.16	2.94 \pm 2.09
Δ from BL (mean) (95% CI)	-0.12 (-0.36, 0.12)	-0.76 (-1.47, -0.05)
Center 2		
N	3	11
BL (mean \pm SD)	3.68 \pm 1.01	3.07 \pm 2.31
Δ from BL (mean) (95% CI)	+0.49 (-1.19, 1.98)	-0.22 (-0.76, 0.32)

Responder Analysis

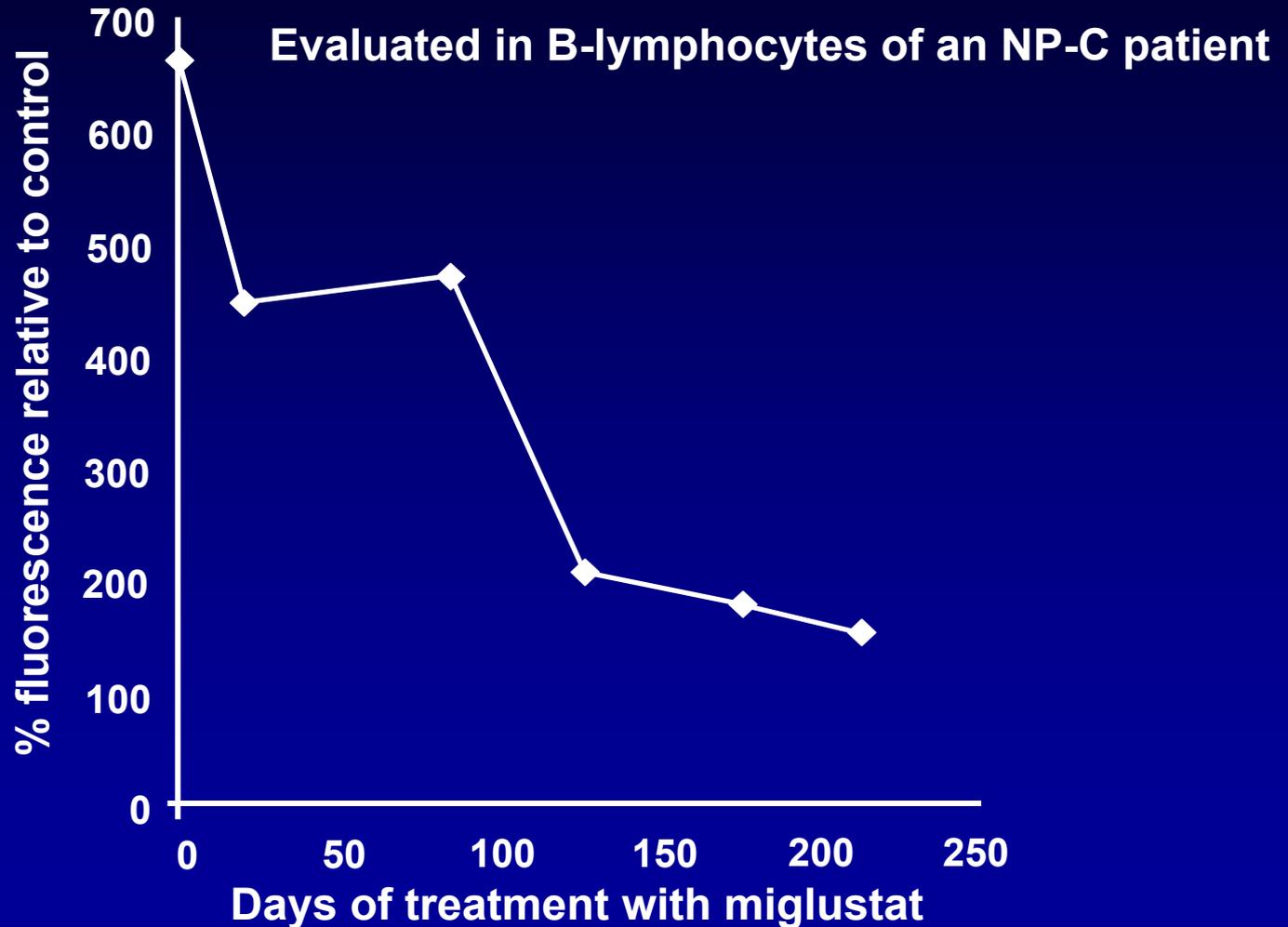
	Swallowing	Ambulation	Cognitive function	Overall disease stability [†]
Adults/ Adolescents with available data*	19	19	18	19
Improved / stable, n (%)	15 (79)	17 (90)	14 (78)	13 (68)
Children with available data*	9	10	–	10
Improved / stable, n (%)	9 (100)	8 (80)	–	8 (80)

[†] Patients were classified as having stable disease if there was no deterioration in swallowing, ambulation (SAI) and cognitive function (MMSE; in adolescents and adults only)

SF-36[®] Over 12 Months Adult / Adolescent Patients

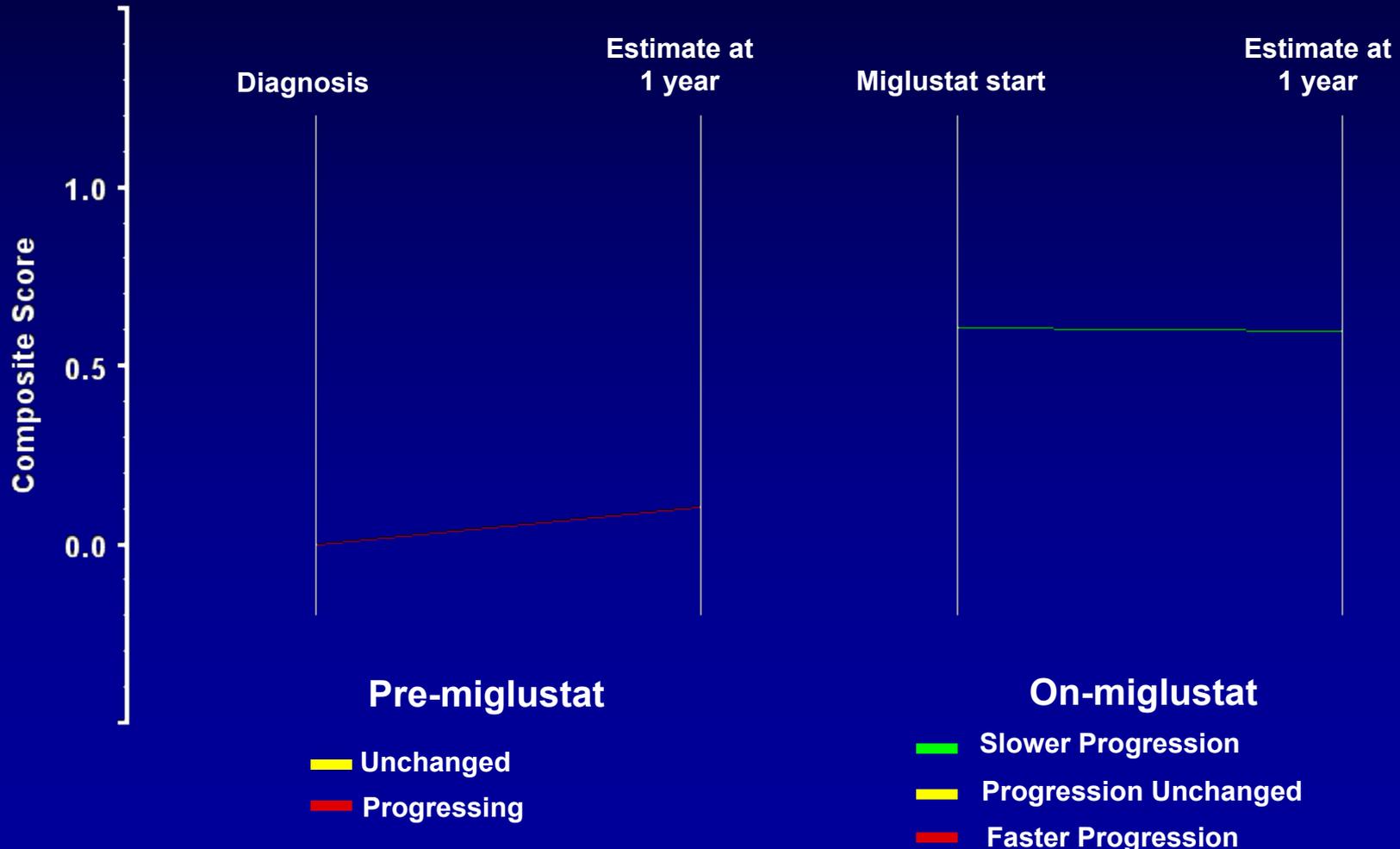
	No Treatment			Miglustat		
	N	Baseline value (Mean ± SD)	Mean change from baseline (95% CI)	N	Baseline value (Mean ± SD)	Mean change from baseline (95% CI)
Physical functioning	8	81.3 ± 24.6	2.5 (-11.4, 16.4)	17	60.3 ± 34.5	-2.9 (-17.7, 11.9)
Role-physical	8	87.5 ± 26.7	-12.5 (-37.0, 12.0)	17	75.0 ± 35.4	-7.8 (-28.6, 13.0)
Bodily pain	8	90.0 ± 17.0	-6.6 (-21.8, 8.6)	17	77.7 ± 23.1	6.7 (-0.6, 14.0)
General health	7	71.7 ± 19.5	-2.6 (-13.8, 8.6)	17	53.7 ± 26.4	9.4 (0.8, 18.0)
Vitality	8	62.5 ± 16.5	-1.5 (-11.6, 8.6)	17	54.4 ± 25.7	-0.9 (-11.1, 9.3)
Social functioning	8	89.1 ± 14.1	-6.3 (-22.4, 9.8)	17	76.5 ± 27.9	1.5 (-11.1, 14.1)
Role-emotional	8	75.0 ± 38.8	20.8 (-6.6, 48.2)	17	74.5 ± 36.4	-7.8 (-37.2, 21.6)
Mental health	8	80.5 ± 12.6	-3.0 (-13.5, 7.5)	17	66.4 ± 22.8	4.4 (-5.6, 14.4)
Physical component	7	51.2 ± 6.5	-3.6 (-8.3, 1.1)	17	44.0 ± 11.2	0.6 (-2.3, 3.5)
Mental component	7	49.9 ± 7.2	2.5 (-3.9, 8.9)	17	48.1 ± 12.7	0.5 (-5.4, 6.4)

Normalization in Lysosomal Volume with Miglustat Treatment

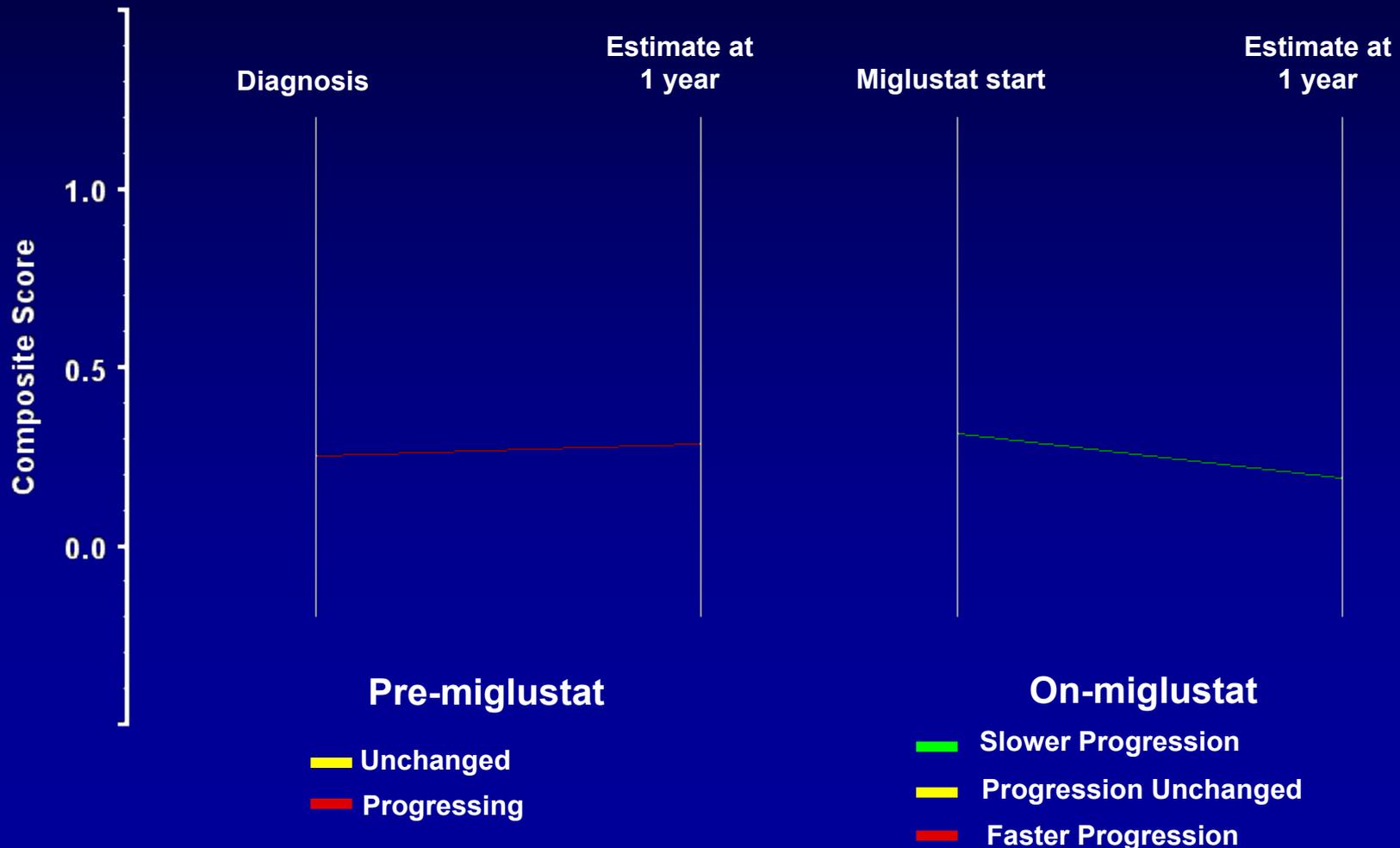


Composite Score Pre- and During Treatment with Miglustat

Individual Annualized Progression Rate

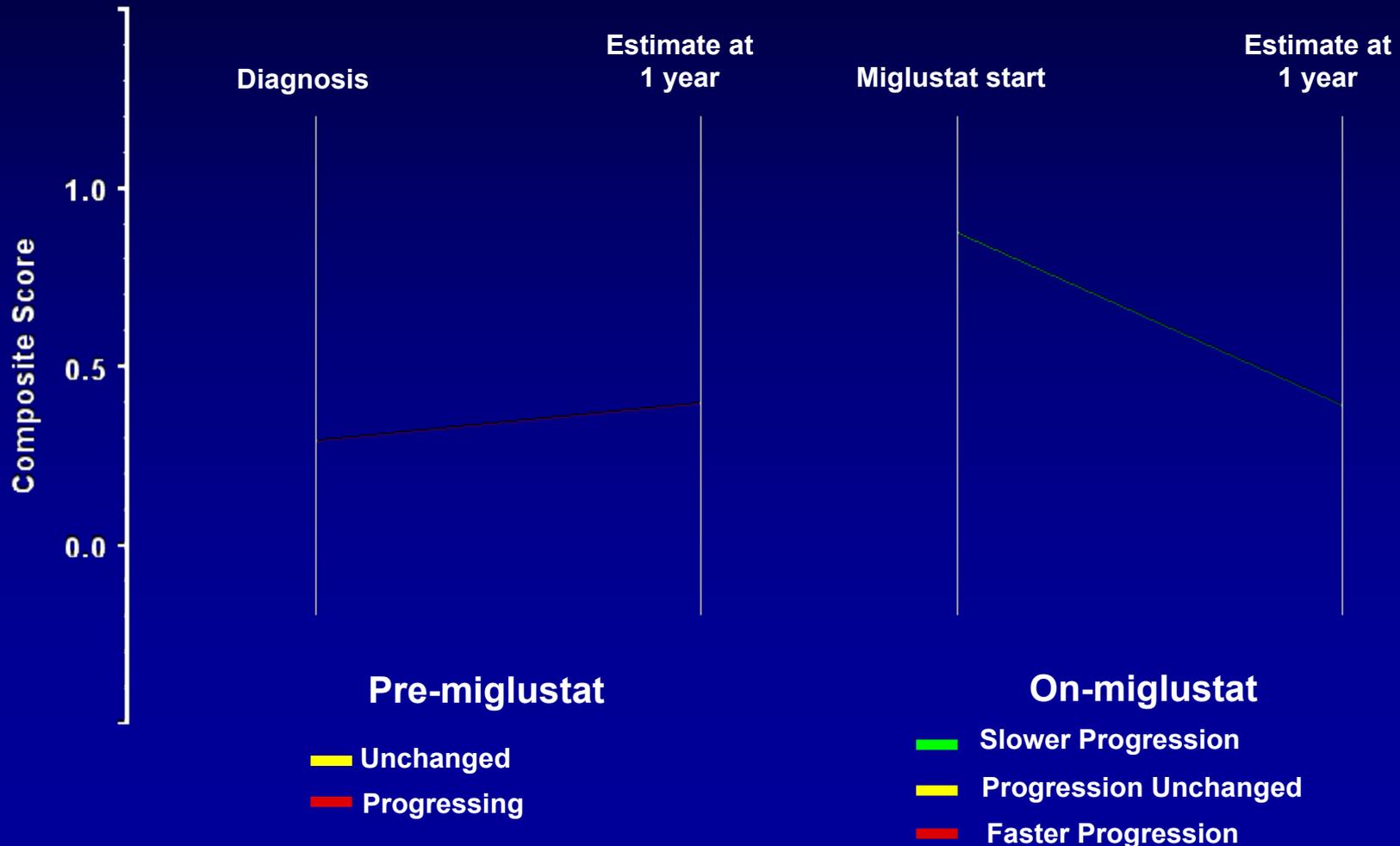


Composite Score Pre- and During Treatment with Miglustat



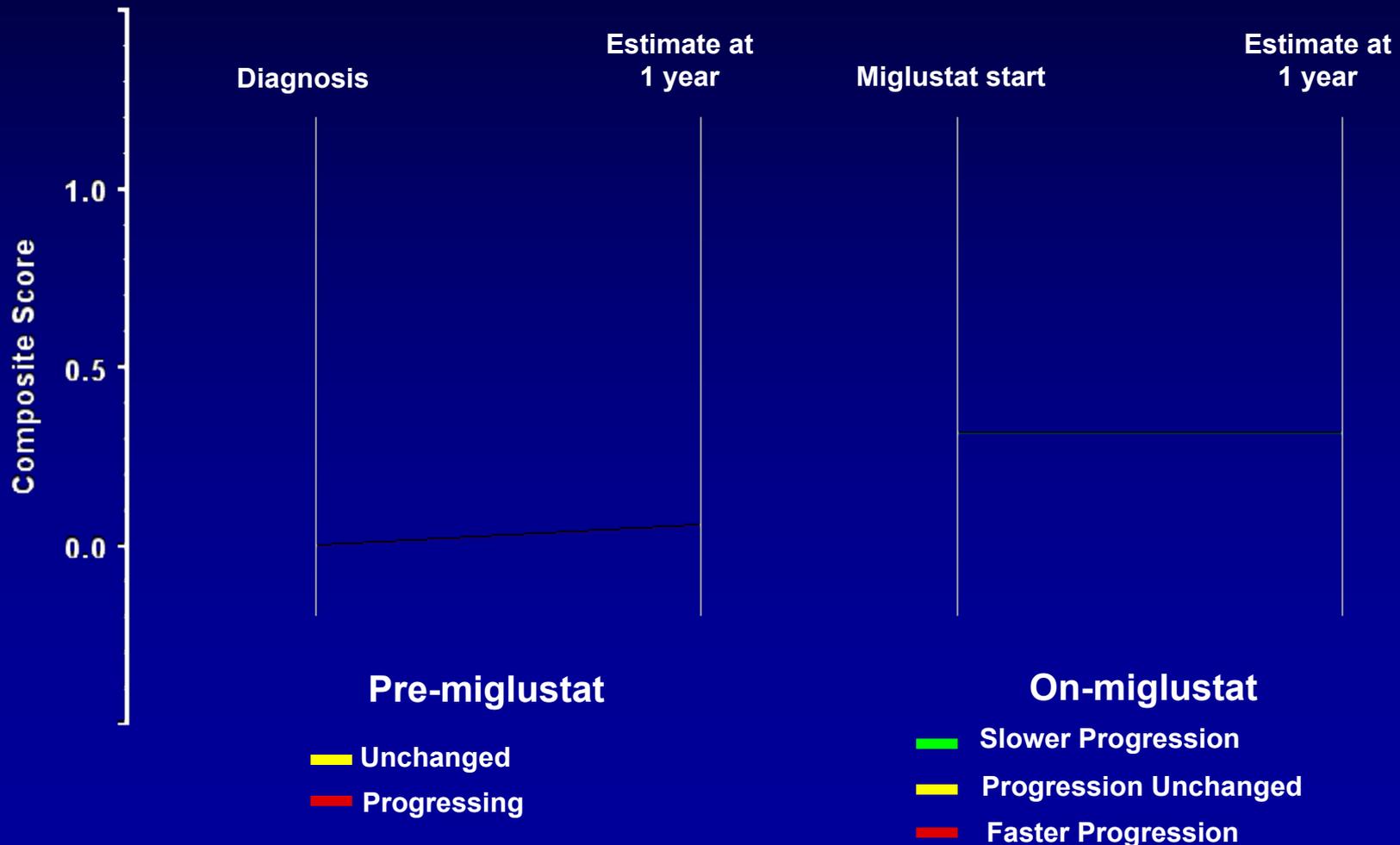
Composite Score Pre- and During Treatment with Miglustat

Individual Annualized Progression Rate



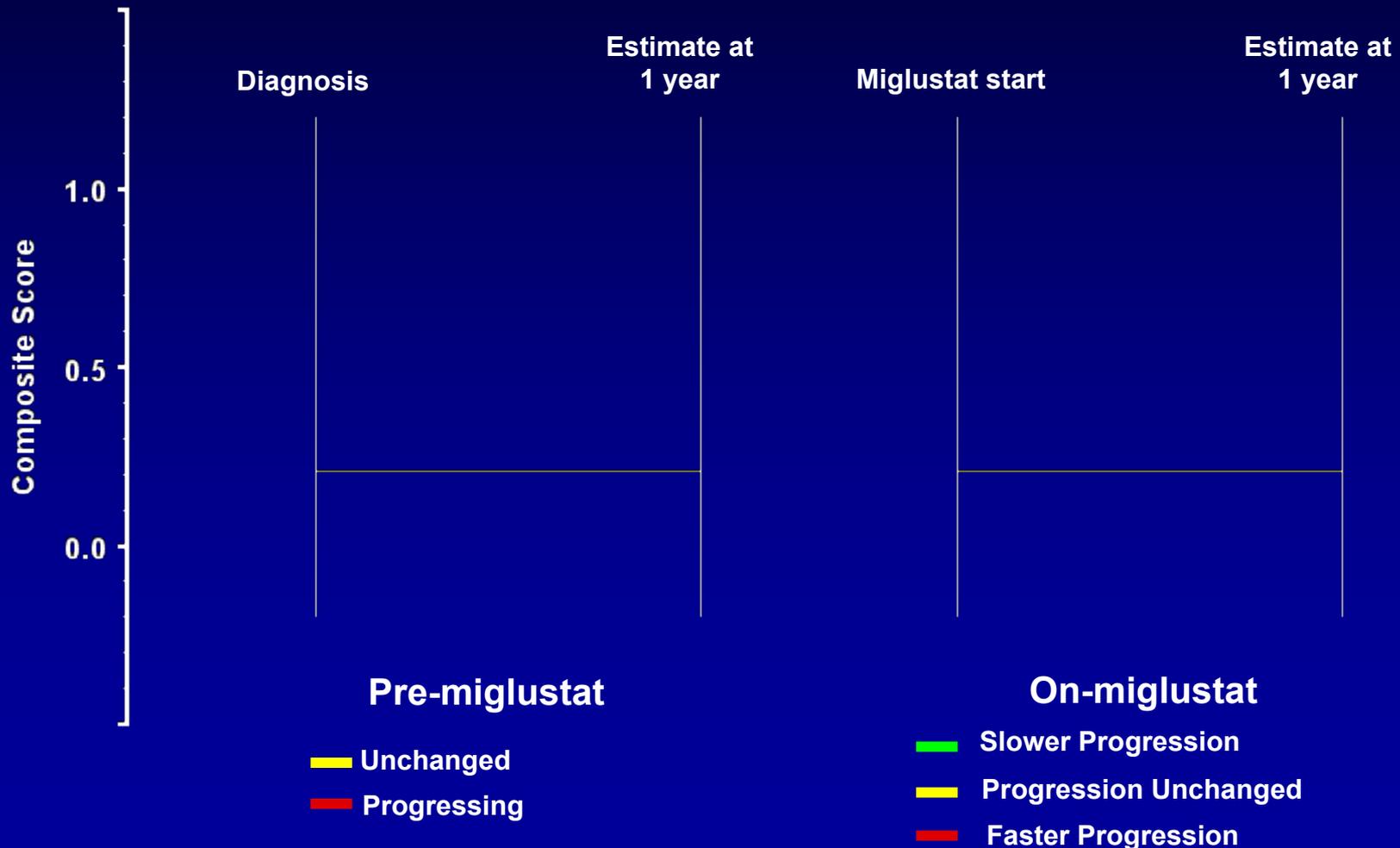
Composite Score Pre- and During Treatment with Miglustat

Individual Annualized Progression Rate



Composite Score Pre- and During Treatment with Miglustat

Individual Annualized Progression Rate



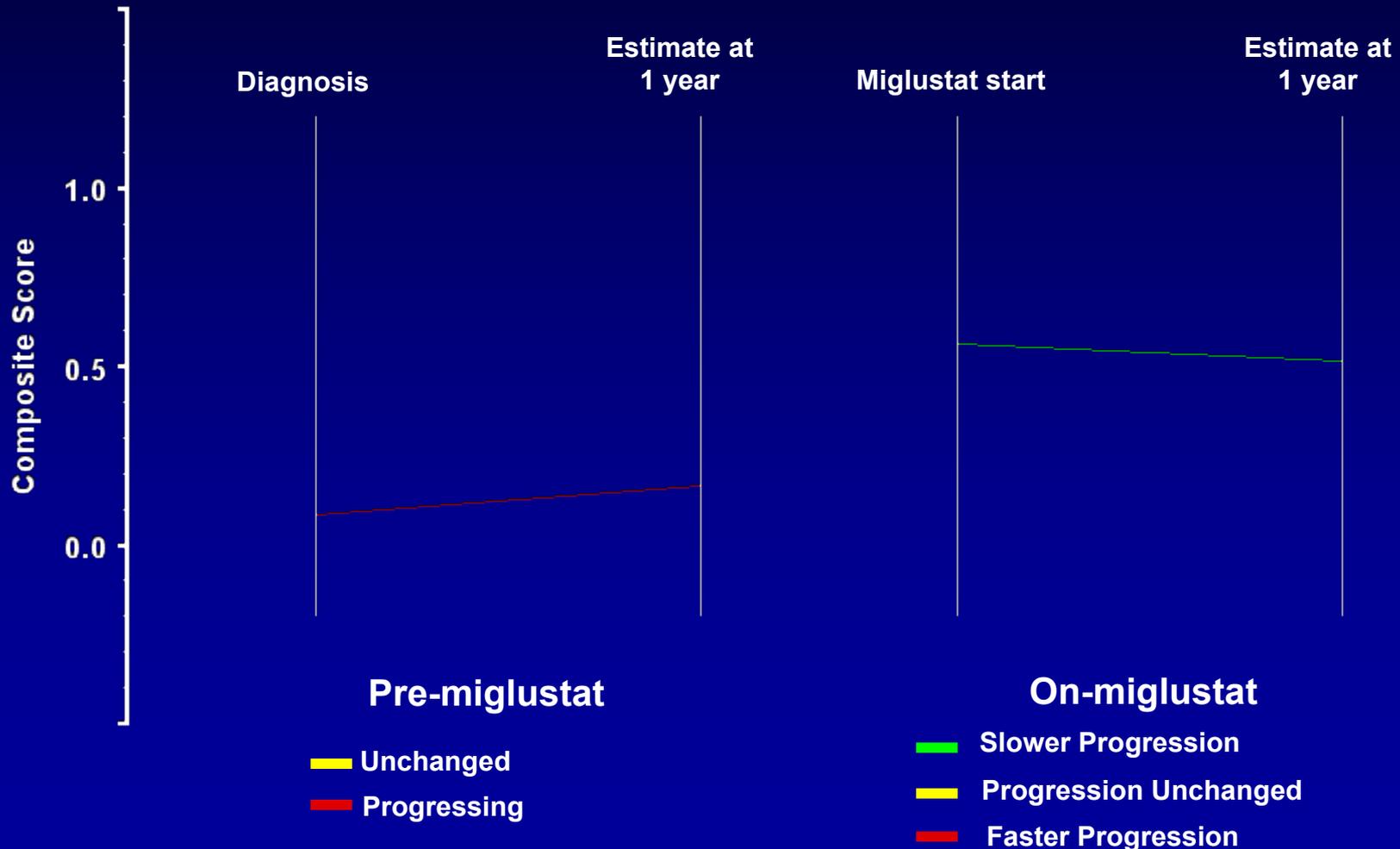
Composite Score Pre- and During Treatment with Miglustat

Individual Annualized Progression Rate



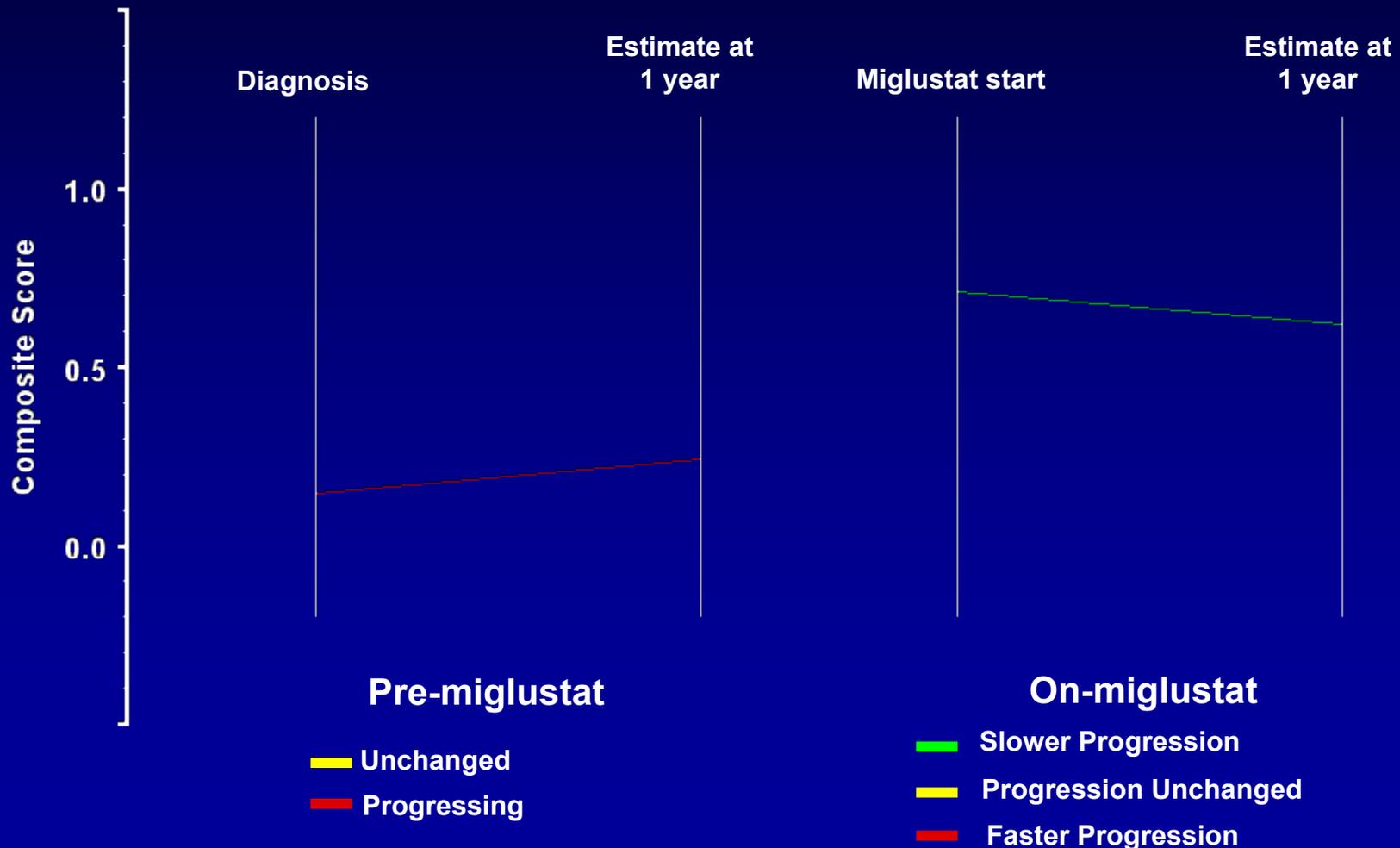
Composite Score Pre- and During Treatment with Miglustat

Individual Annualized Progression Rate



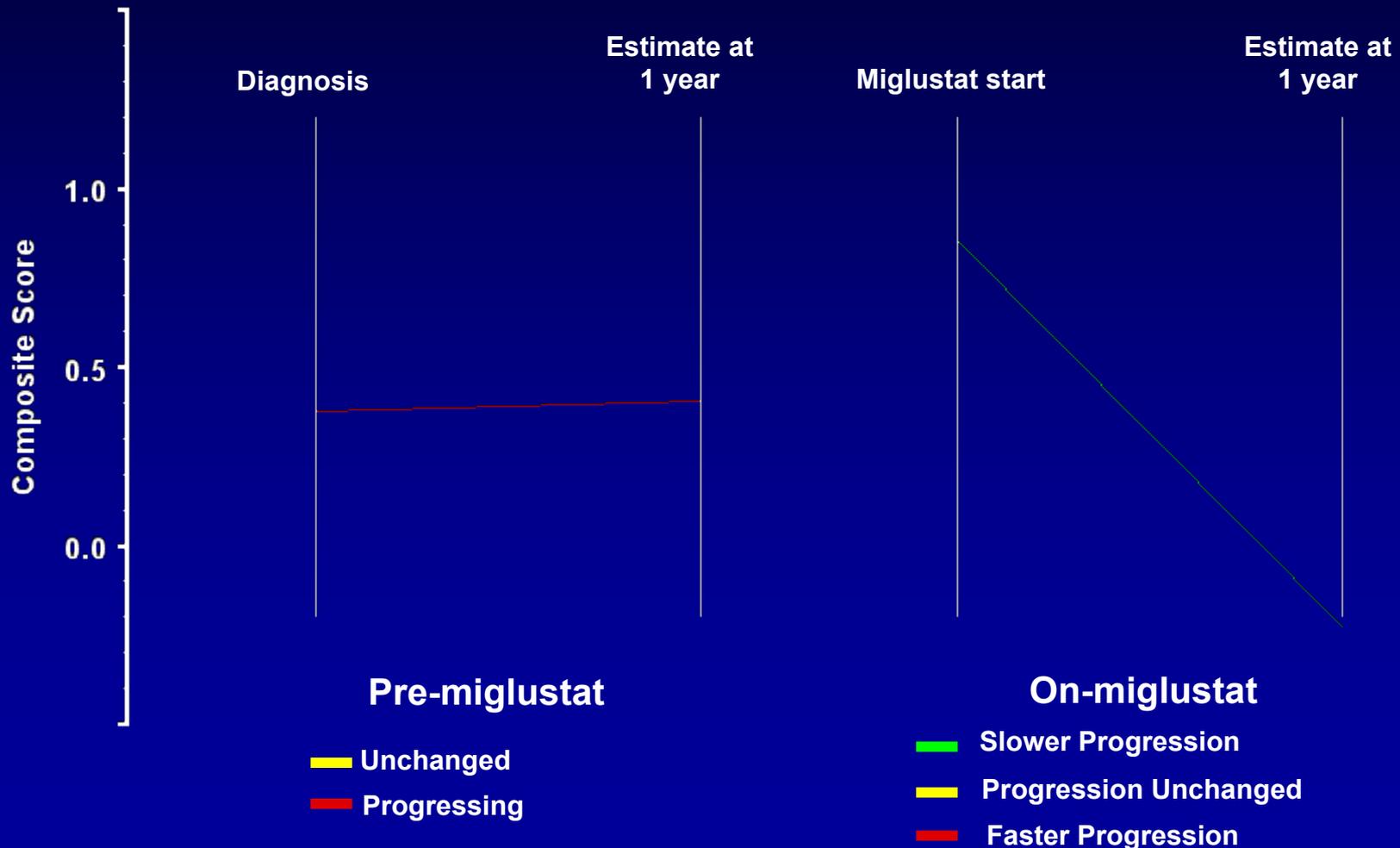
Composite Score Pre- and During Treatment with Miglustat

Individual Annualized Progression Rate



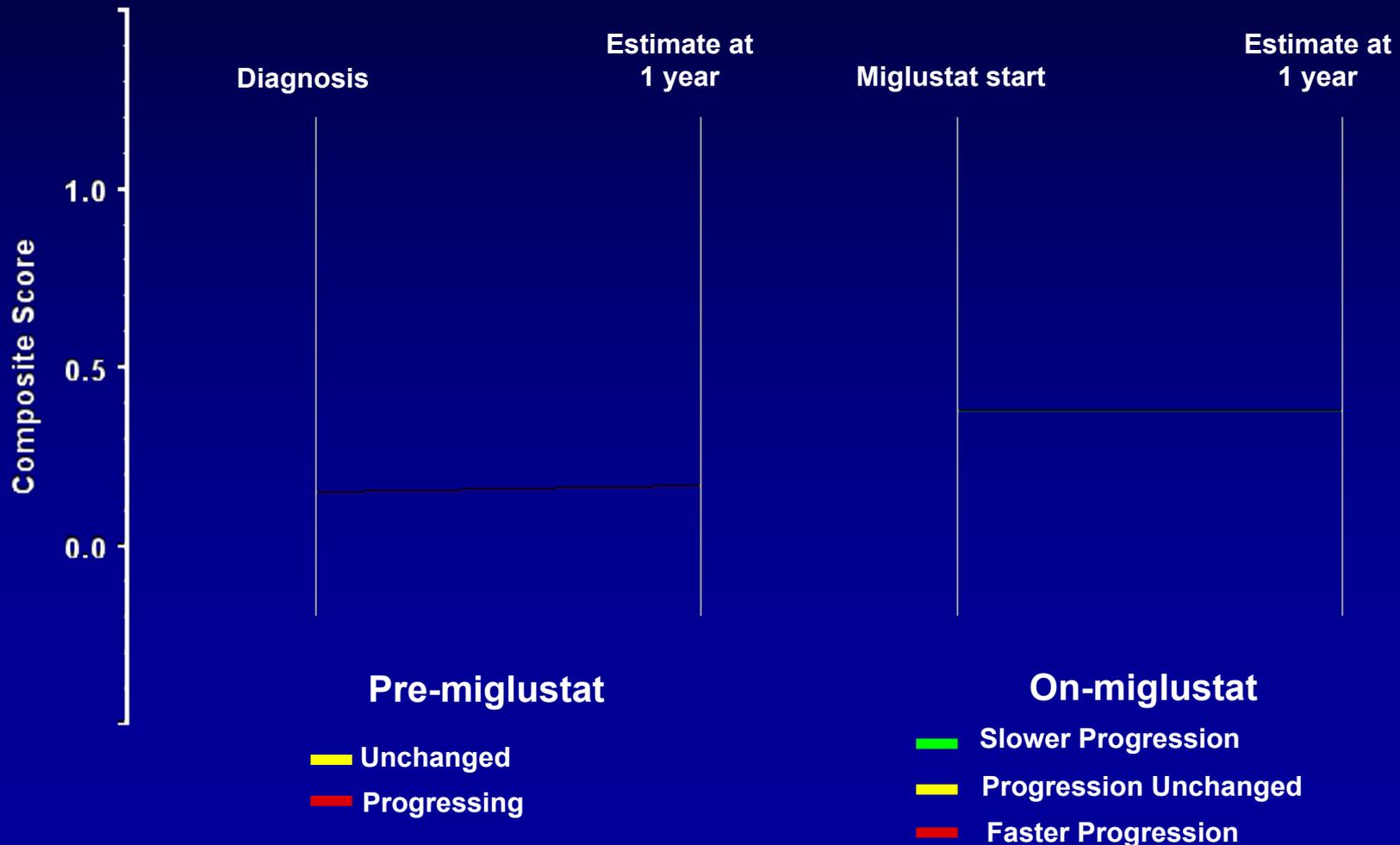
Composite Score Pre- and During Treatment with Miglustat

Individual Annualized Progression Rate



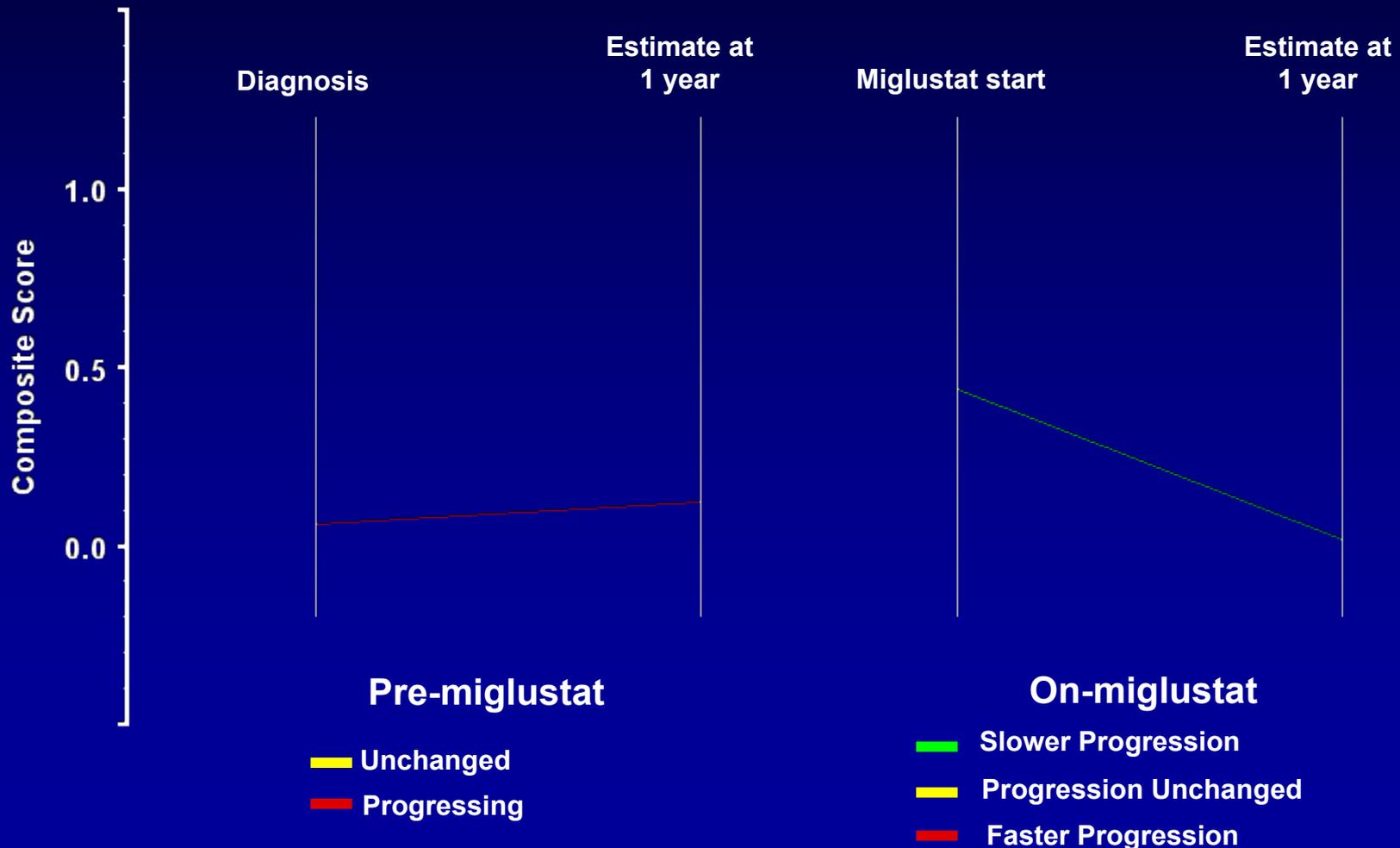
Composite Score Pre- and During Treatment with Miglustat

Individual Annualized Progression Rate



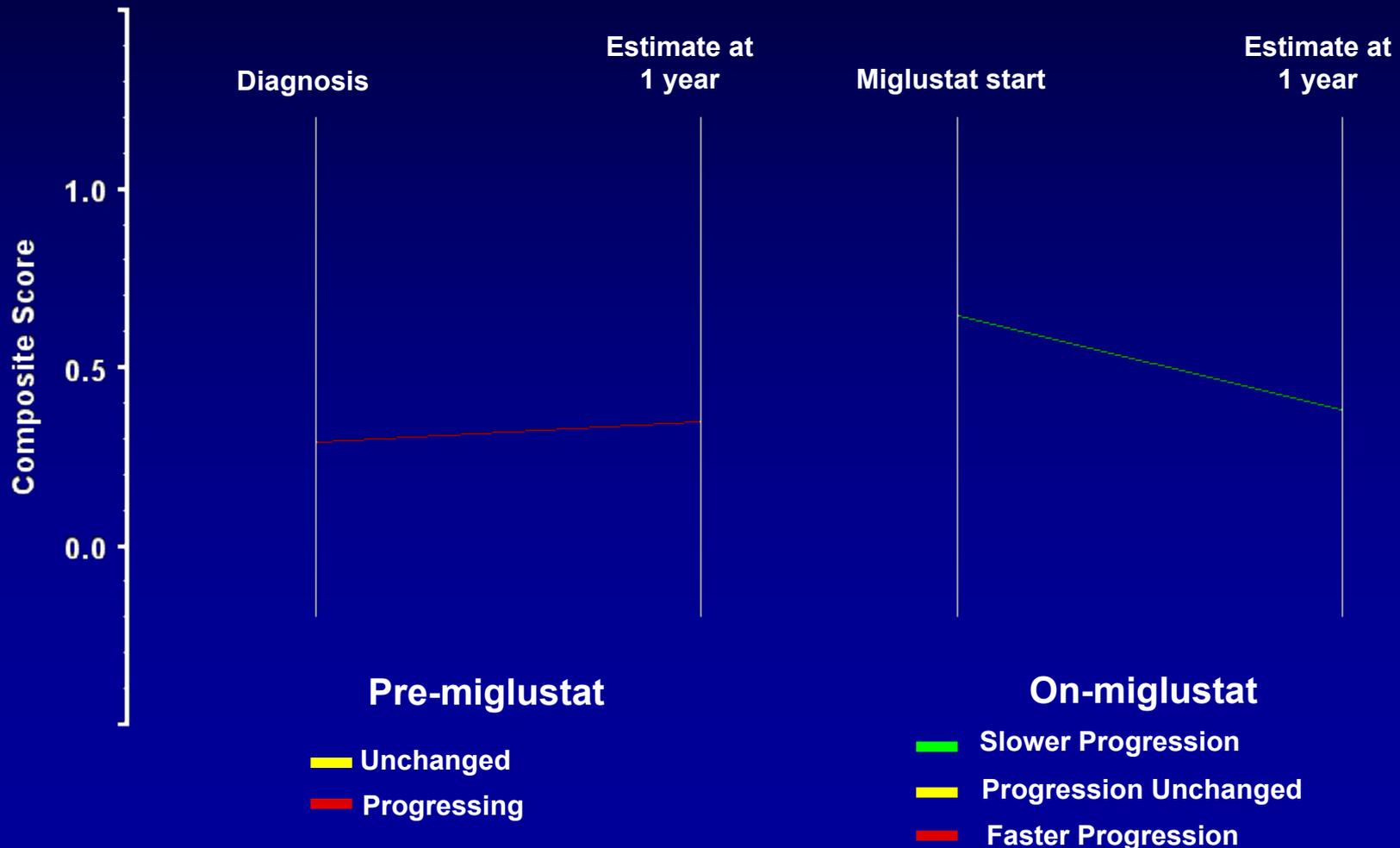
Composite Score Pre- and During Treatment with Miglustat

Individual Annualized Progression Rate



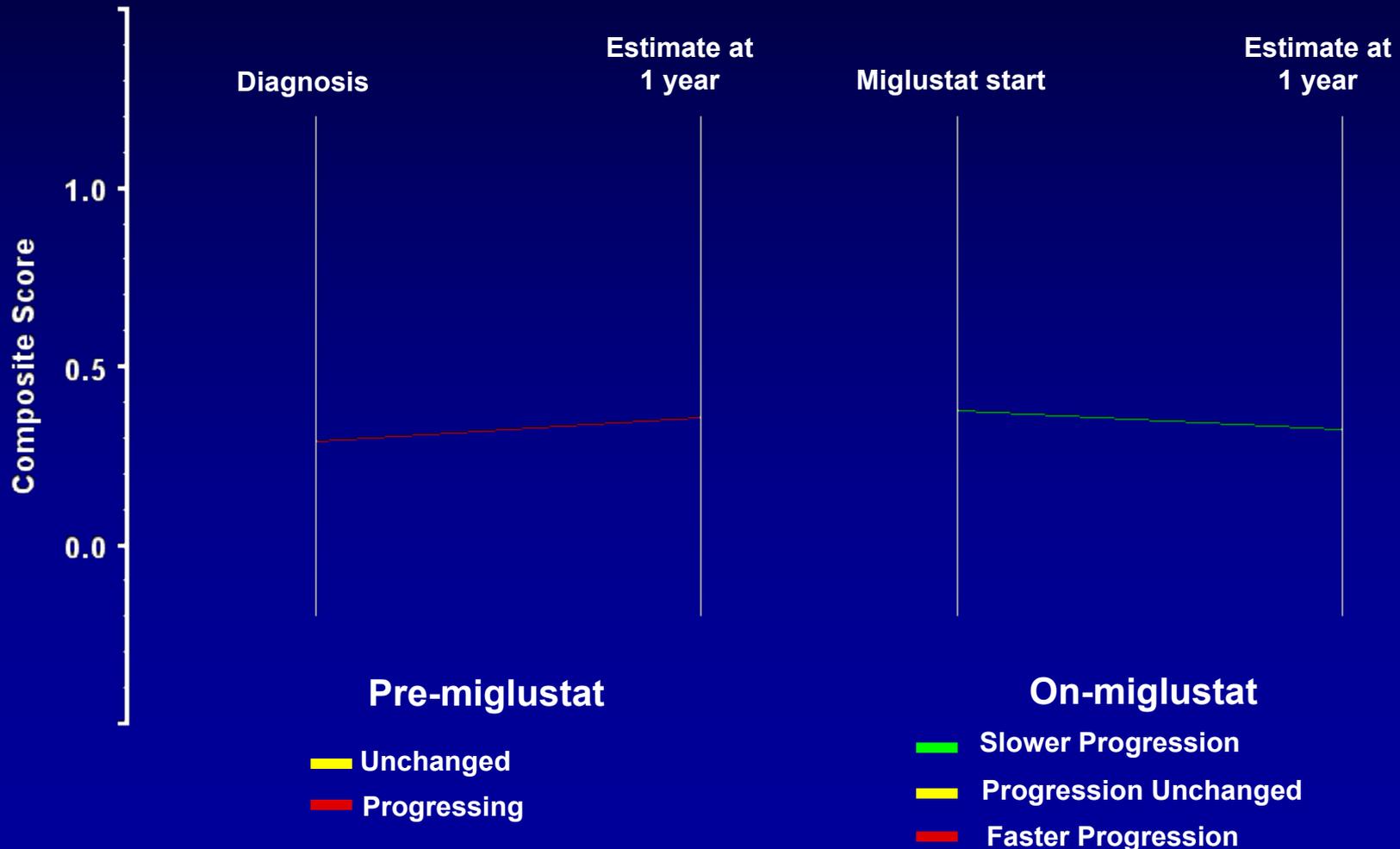
Composite Score Pre- and During Treatment with Miglustat

Individual Annualized Progression Rate



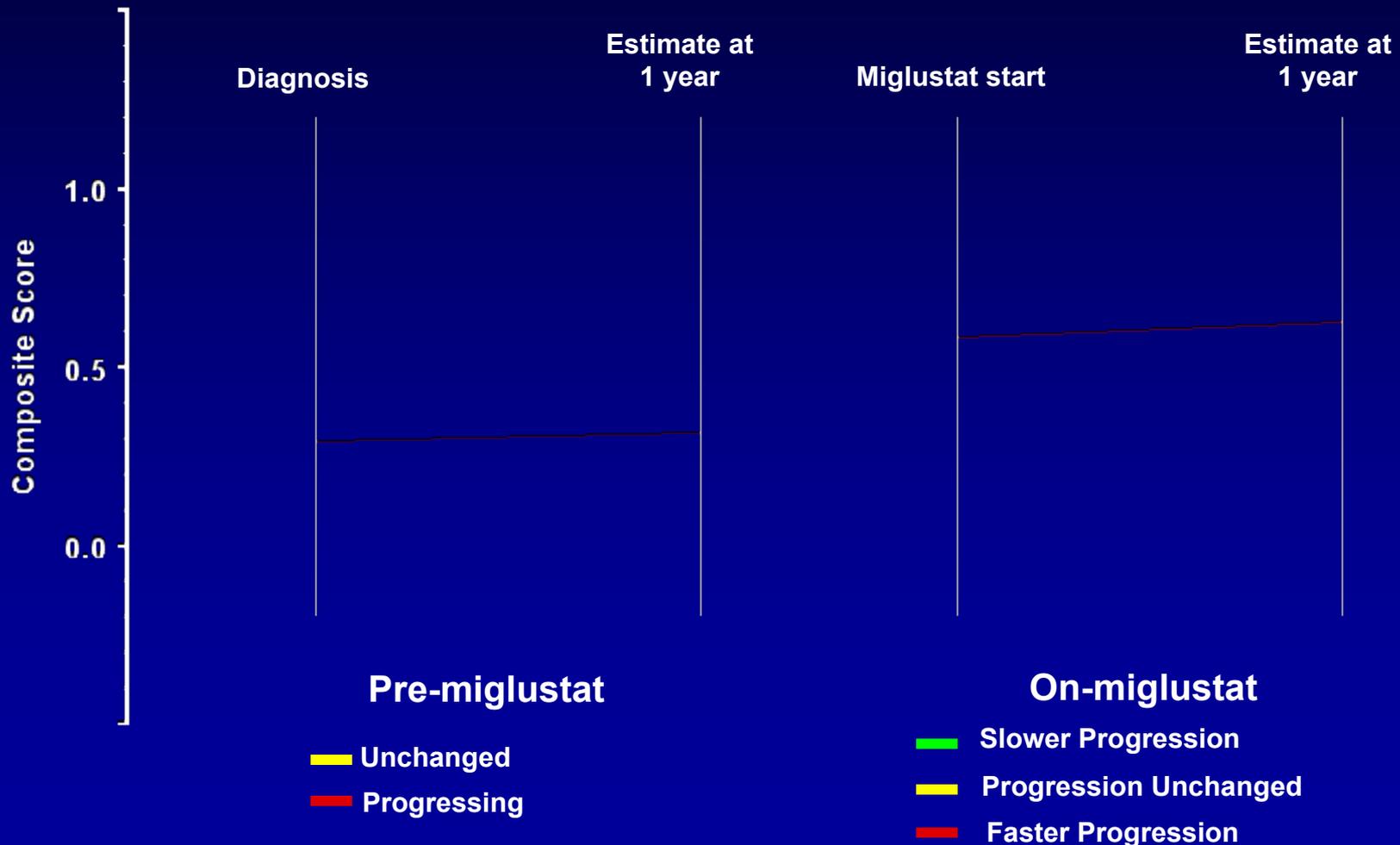
Composite Score Pre- and During Treatment with Miglustat

Individual Annualized Progression Rate



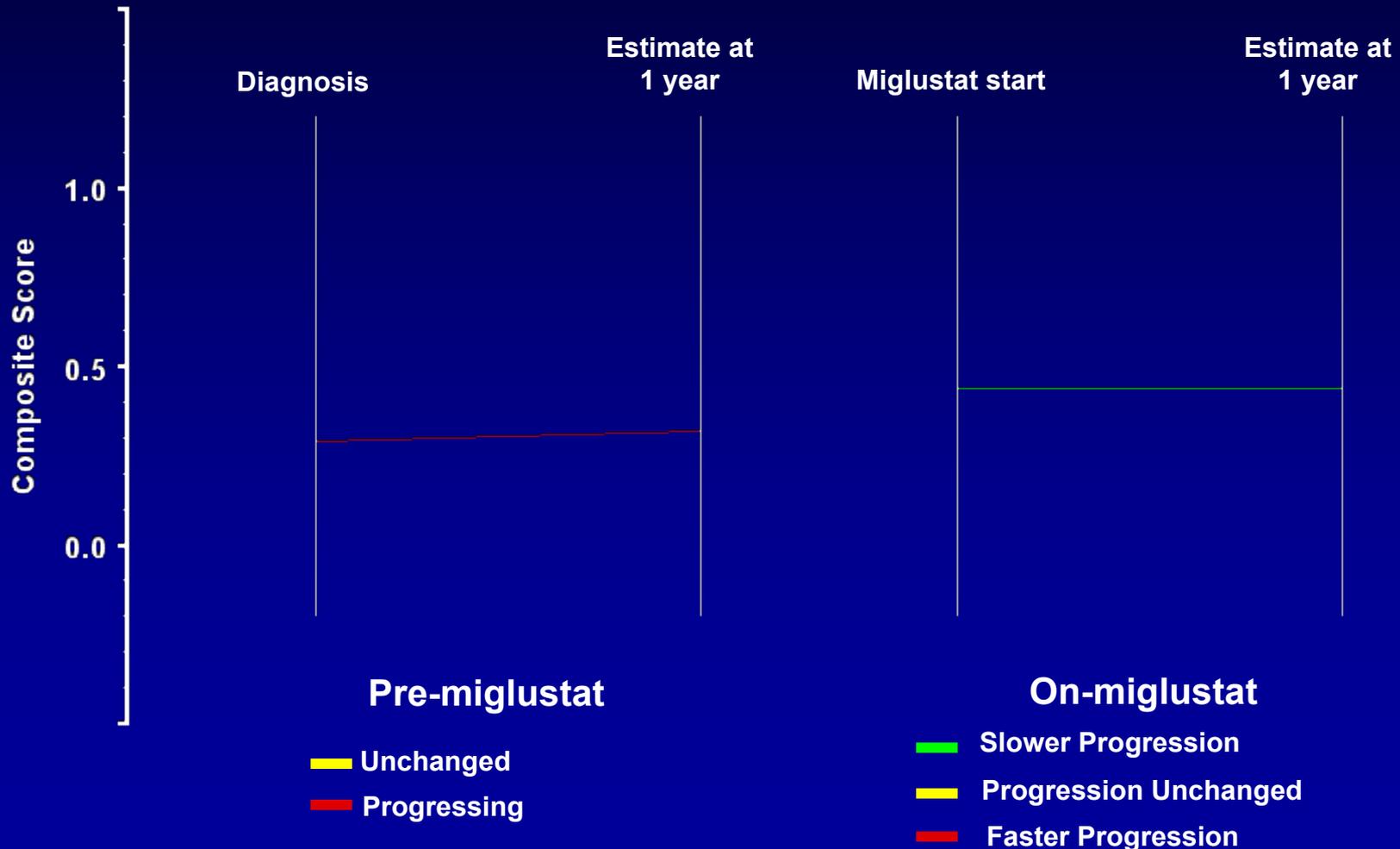
Composite Score Pre- and During Treatment with Miglustat

Individual Annualized Progression Rate



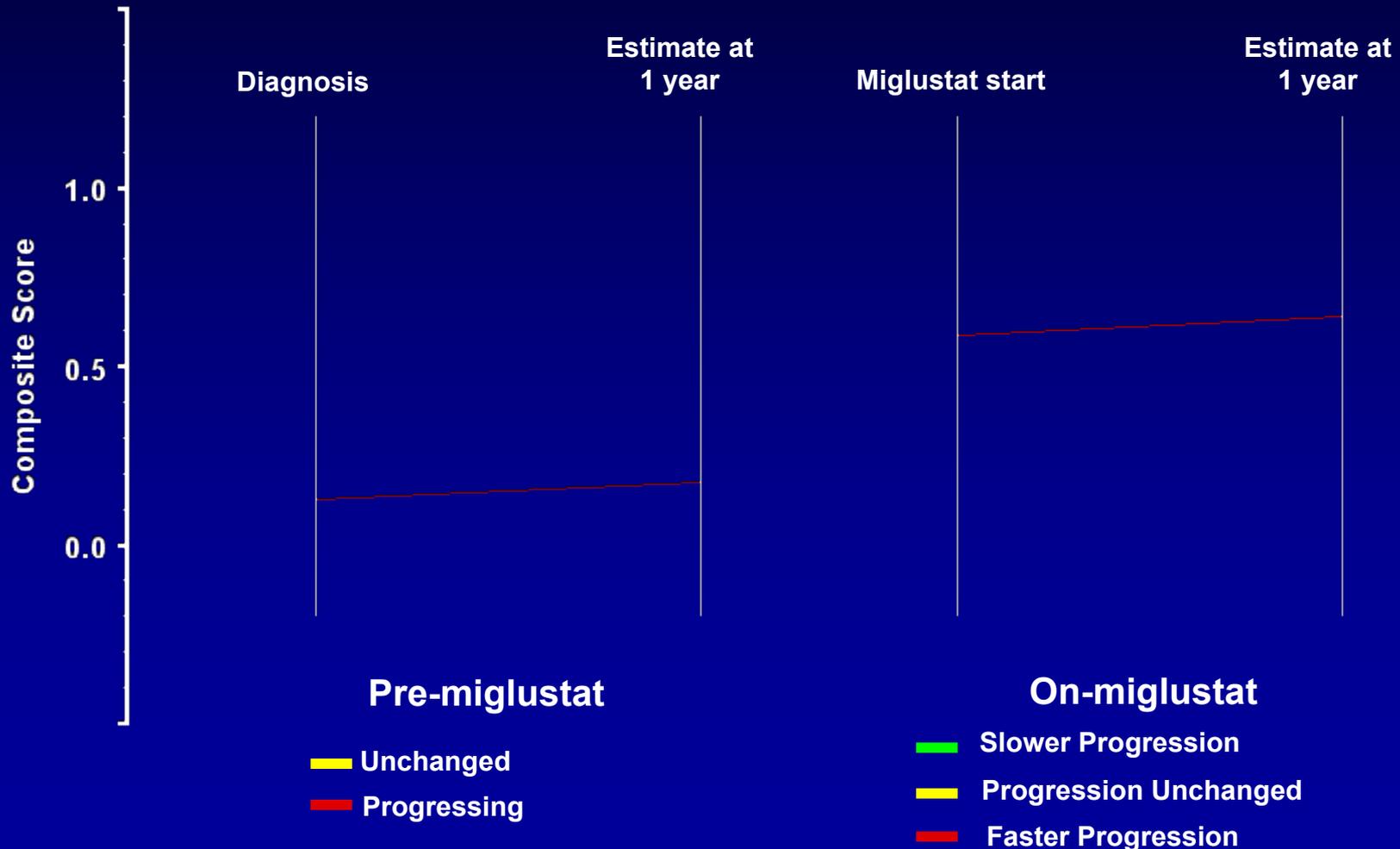
Composite Score Pre- and During Treatment with Miglustat in Survey I

Individual Annualized Progression Rate



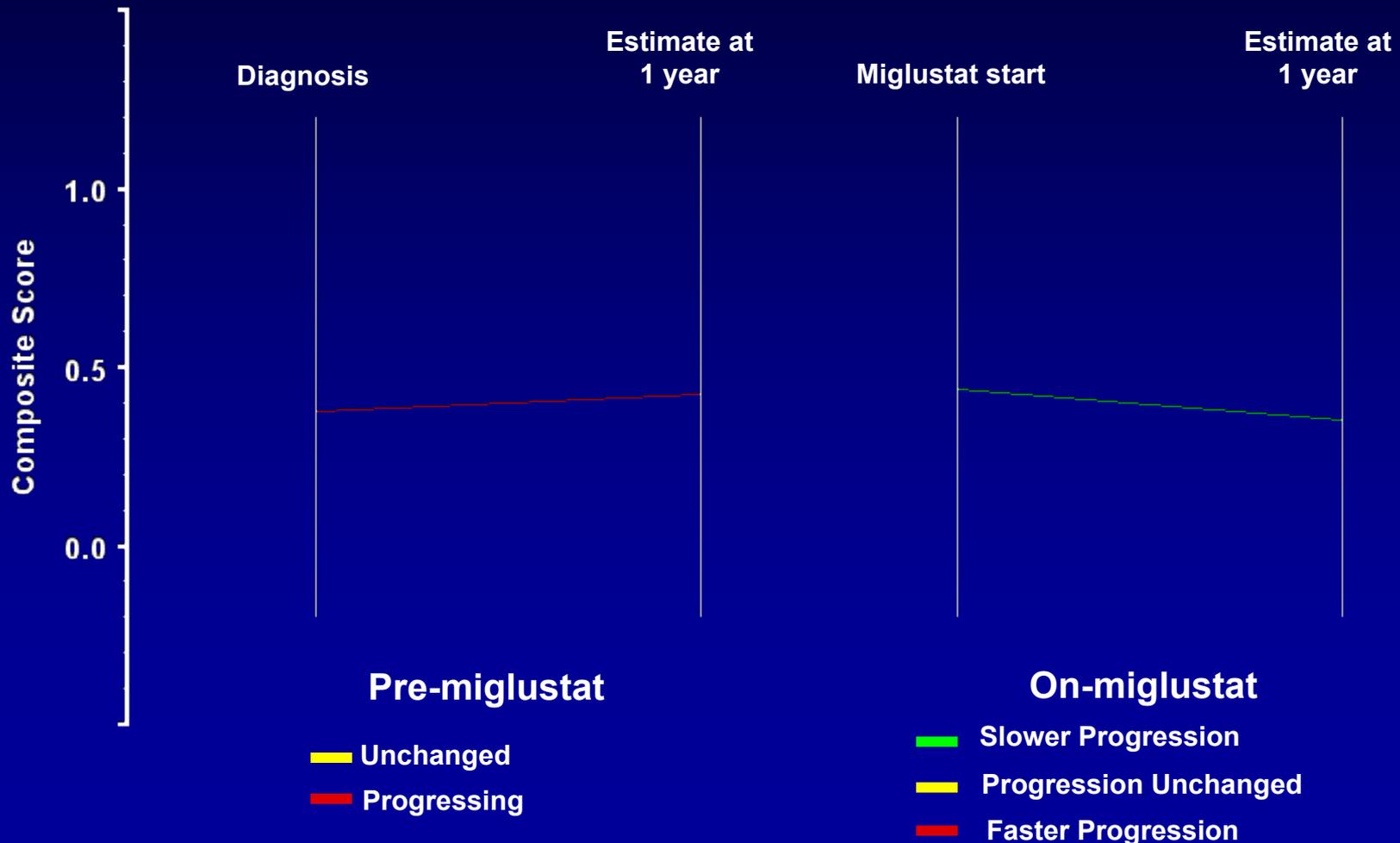
Composite Score Pre- and During Treatment with Miglustat

Individual Annualized Progression Rate



Composite Score Pre- and During Treatment with Miglustat in Survey I

Individual Annualized Progression Rate



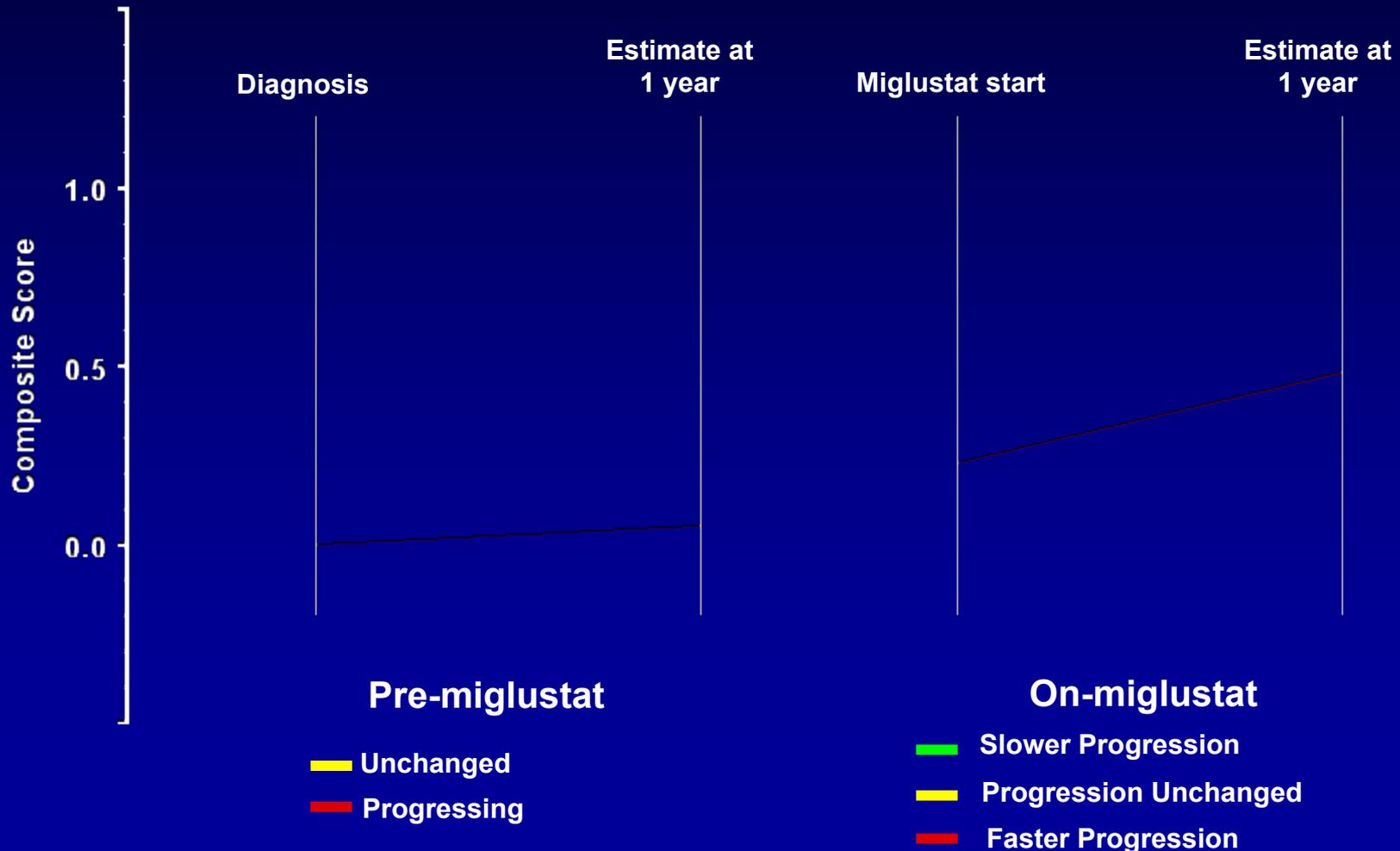
Composite Score Pre- and During Treatment with Miglustat

Individual Annualized Progression Rate



Composite Score Pre- and During Treatment with Miglustat

Individual Annualized Progression Rate



Composite Score Pre- and During Treatment with Miglustat

Individual Annualized Progression Rate (N=19)

