

A Retrospective Natural History Study in Fabry Disease: Challenges and Uses

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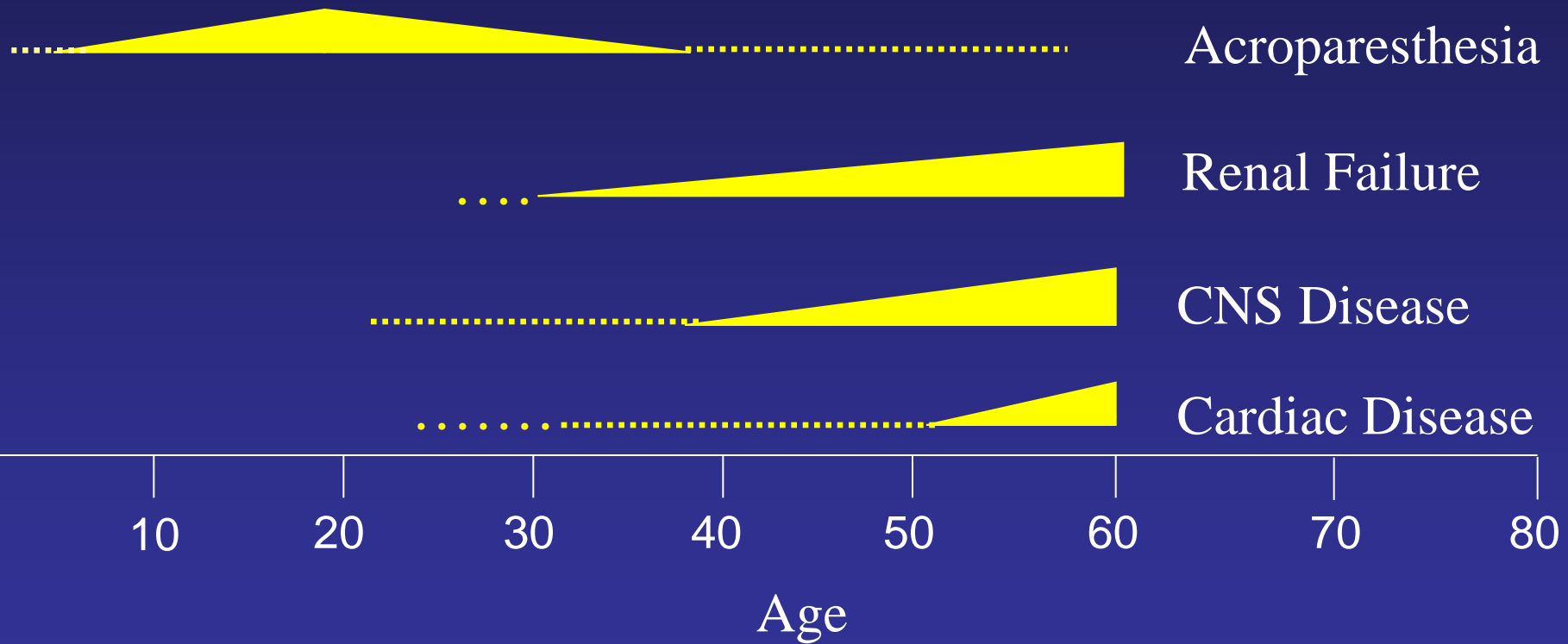
Fabry Disease

- Rare, lethal, X-linked inborn error of metabolism
- U.S. prevalence estimated at 3500 classic Fabry patients
- Deficient α -Galactosidase A (α -GAL A) activity
- Deficient α -GAL A activity leads to progressive globotriaosylceramide (GL-3) accumulation in multiple cell types and tissues culminating in end organ impairment
- **Key pathology: vascular endothelial deposition**

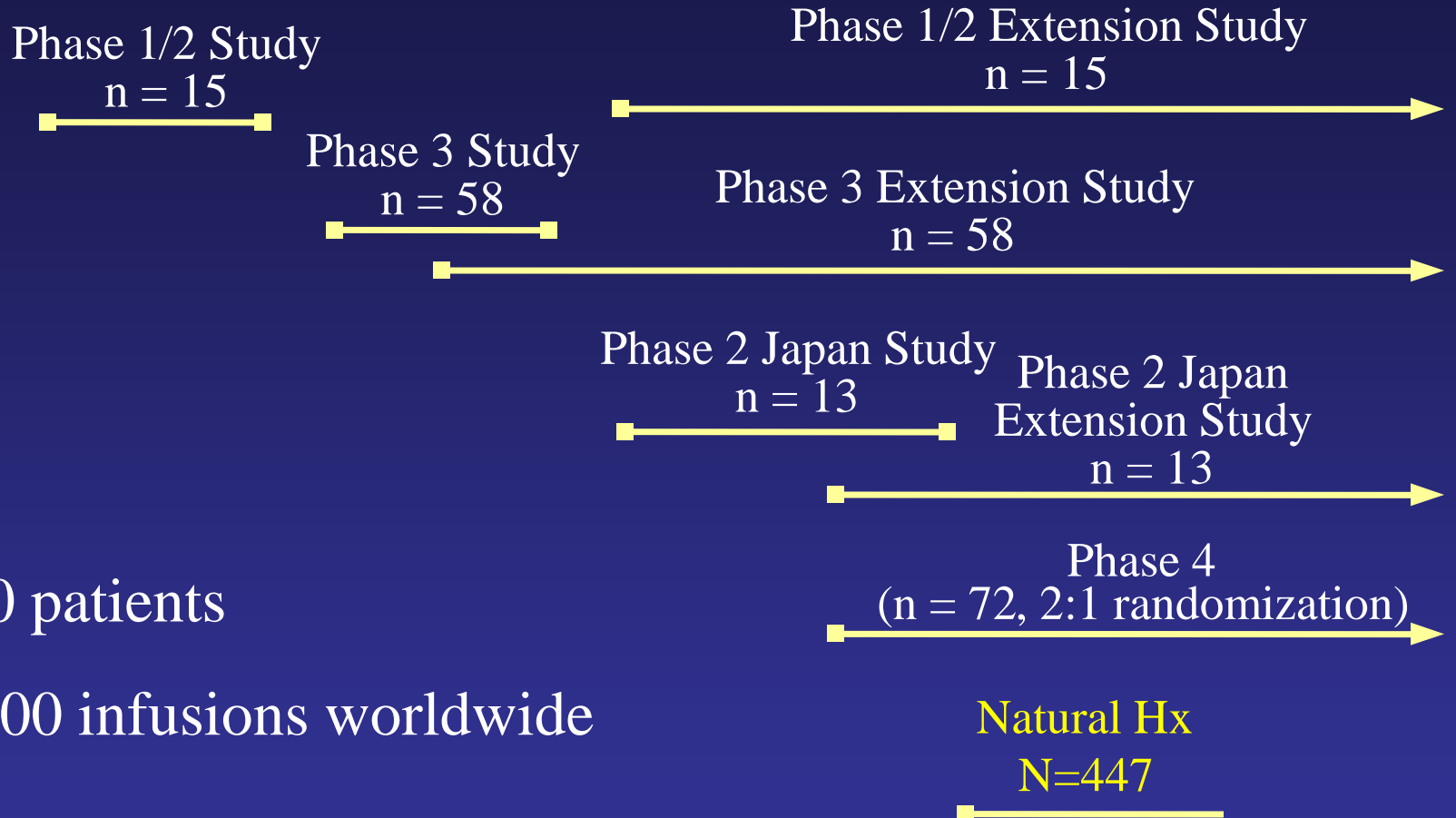
Fabry Disease: Clinical Manifestations

Classical Phenotype (< 1% activity)

+++ endothelial accumulation



Clinical Studies



> 300 patients

> 4,000 infusions worldwide



Natural History Fabry Disease Study

(AGAL-014-01)

Objectives

- To estimate the event rates of renal, cardiac, cerebral vascular diseases, and/or death.
- To characterize the natural history of Fabry Disease.
- To provide a historical control group for comparison to data from the Phase 3 and its extension and for the Phase 4 study.

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Minimization of Bias

- The data is being collected by an independent CRO (Abt. Associates) – expert in epidemiology and survey data collection methodology.
- All possible investigator sites, both international and domestic, were given an opportunity to participate in the trial.
- All clinically relevant information on Fabry patients is being collected i.e., no pre-selection of data points.
- Prospectively designed case record forms were used

Natural History Fabry Disease Study

Data Collection

- Demographics
- Fabry Disease History
- Cerebral Vascular Disease
 - TIA
 - Stroke
- Renal Disease
 - Acute Dialysis
 - Chronic Dialysis
 - Change in Status
 - Transplantation
- Cardiac Disease
 - MI
 - Arrhythmia
 - Angina
 - Cardiac Failure
 - NYHA Classification
- Death

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Data Collection

- Chemistry
 - Serum Creatinine
 - BUN
 - Glucose
 - Uric Acid
 - Total Protein
 - Albumin
- Hematology
 - Hemoglobin
 - Hematocrit
 - RBC
 - WBC
 - Platelets
- Urinalysis
- Hospitalization - All Causes

Collection of Data

- Study Conducted July 2001 - July 2002
- Total # of Unique Patients: 447
- 27 sites enrolled patients
 - 19 US, 5 Canada, 1 Czech Republic, 1 Denmark,
1 The Netherlands
- The data from the Historical Study Qualified Patients is recent, with 75% of the serum creatinine measurements occurring after February 1996

Natural History Fabry Disease Study

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Number of Serum Creatinine Records:

	Number of Patients (%)	
	<u>All Patients</u>	<u>Phase 4 Study Qualifiers</u>
	(n = 447)	(n = 103)
No Records	54 (12.1%)	0
1 record	105 (23.5%)	18 (17.5%)
2 records	84 (18.8%)	22 (21.4%)
3-5 records	96 (21.5%)	27 (26.2%)
> 5 records	108 (24.2%)	36 (35.0%)

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Populations Being Analyzed

	n
1. All Patients	447
2. Patients with initial value of Serum Creatinine 1.2 to 3.0 mg/dL	128 (29%)
3. Qualified Patients – who met Ph4 Trial Criteria	103 (23%)
• Patients with ≥ 2 obs./patient for SeCr	85 (19%)
• Patients with ≥ 3 obs./patient for SeCr	63 (14%)

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Number of Events (%) - Phase 4 Study Qualified Patients (n=103)

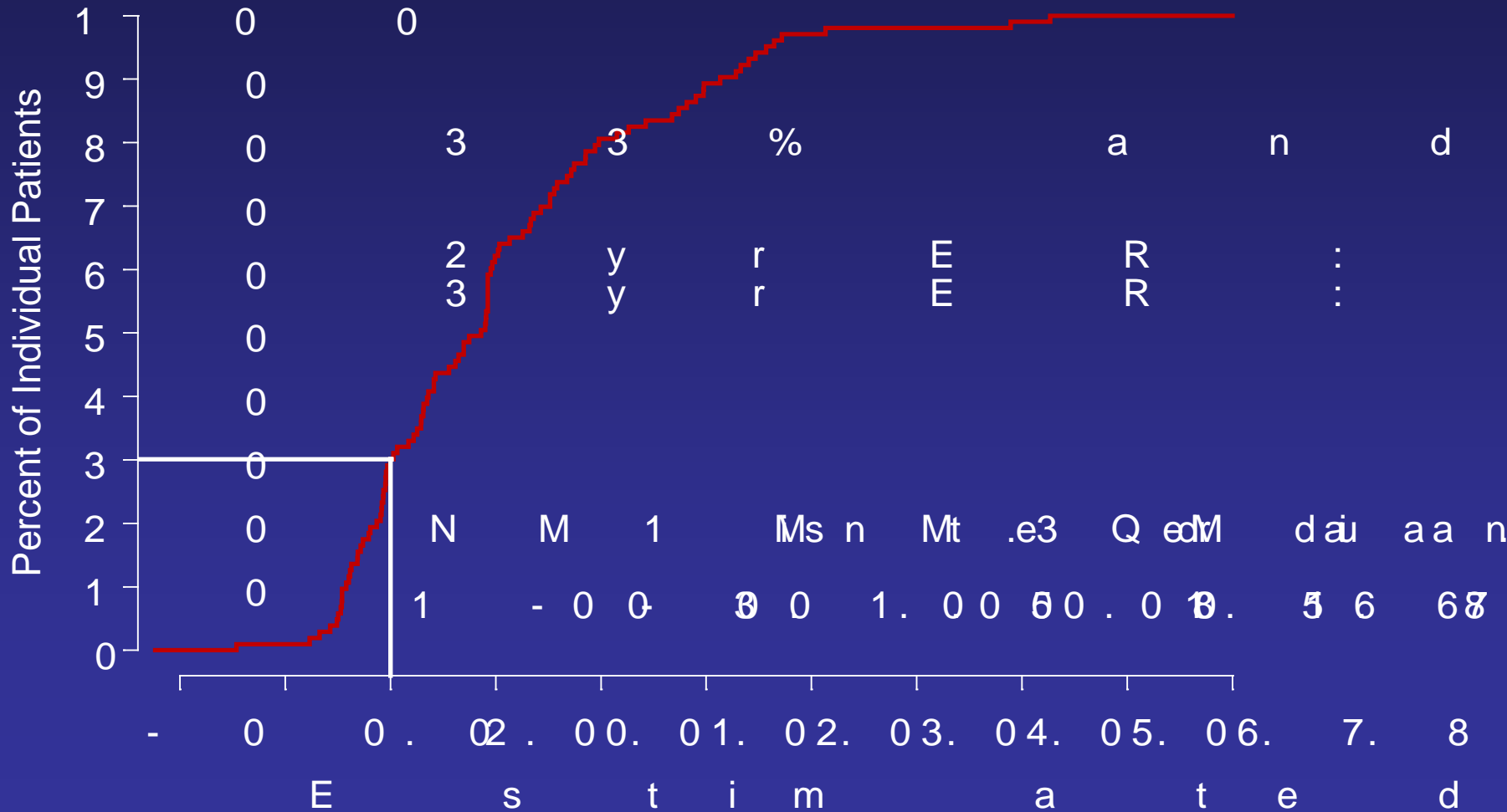
	2 years	3 years	4 years	5 years
Renal	13 (13%)	16 (16%)	18 (17%)	20 (19%)
Cardiac	28 (27%)	35 (34%)	38 (37%)	42 (41%)
CVD	4 (4%)	6 (6%)	7 (7%)	7 (7%)
Death	0 (0%)	0 (0%)	2 (2%)	2 (2%)
Any Event	41 (40%)	48 (47%)	52 (50%)	55 (53%)

Statistical Methodology

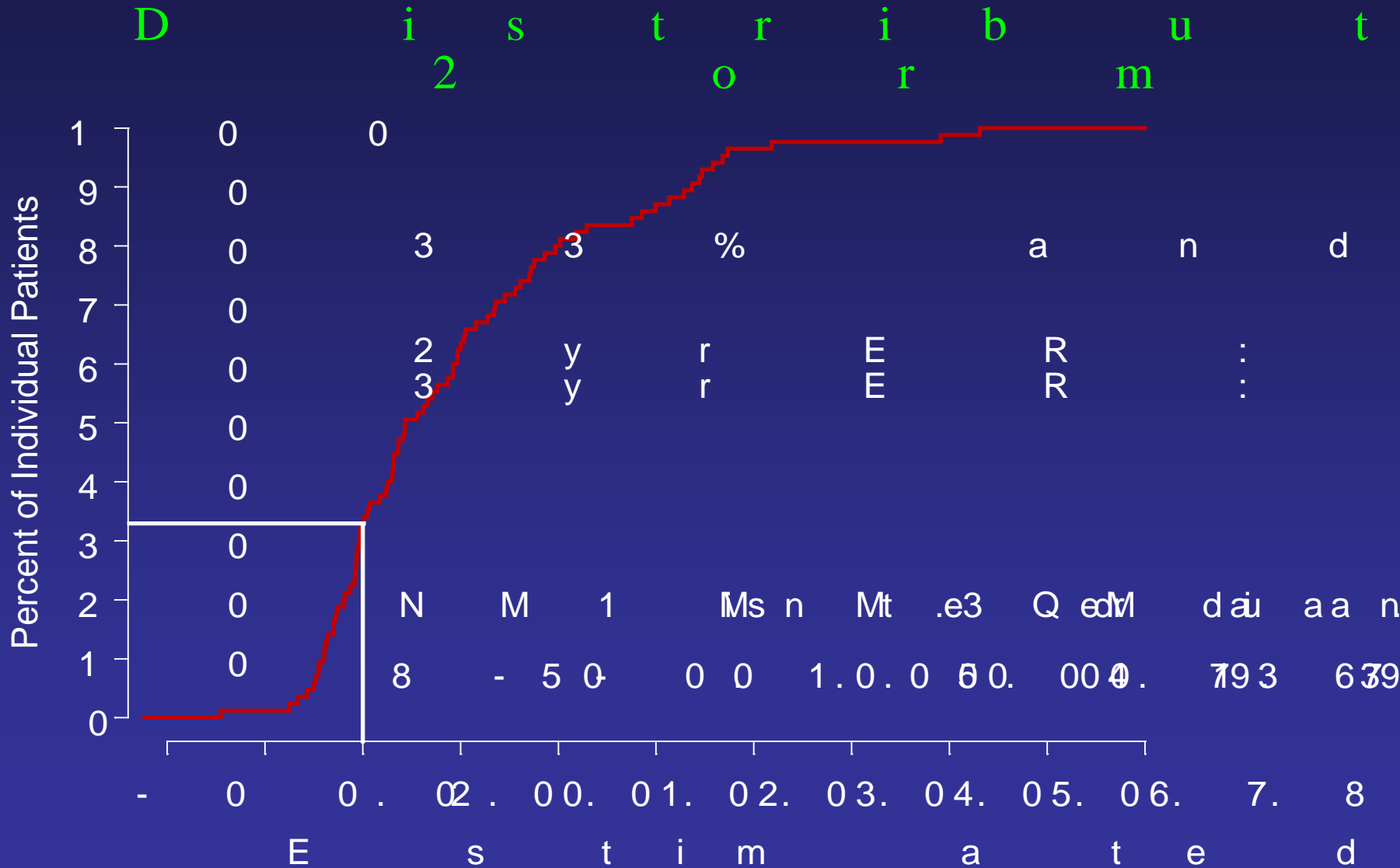
- Log serum creatinine analyzed
- Random effects model used (Laird and Ware, 1982)
- The random effects model incorporates all of the available data (avoids selection bias)
- Based on the model, a random regression line is estimated for each patient

Natural History Fabry Disease Study (AGAL-014-01)

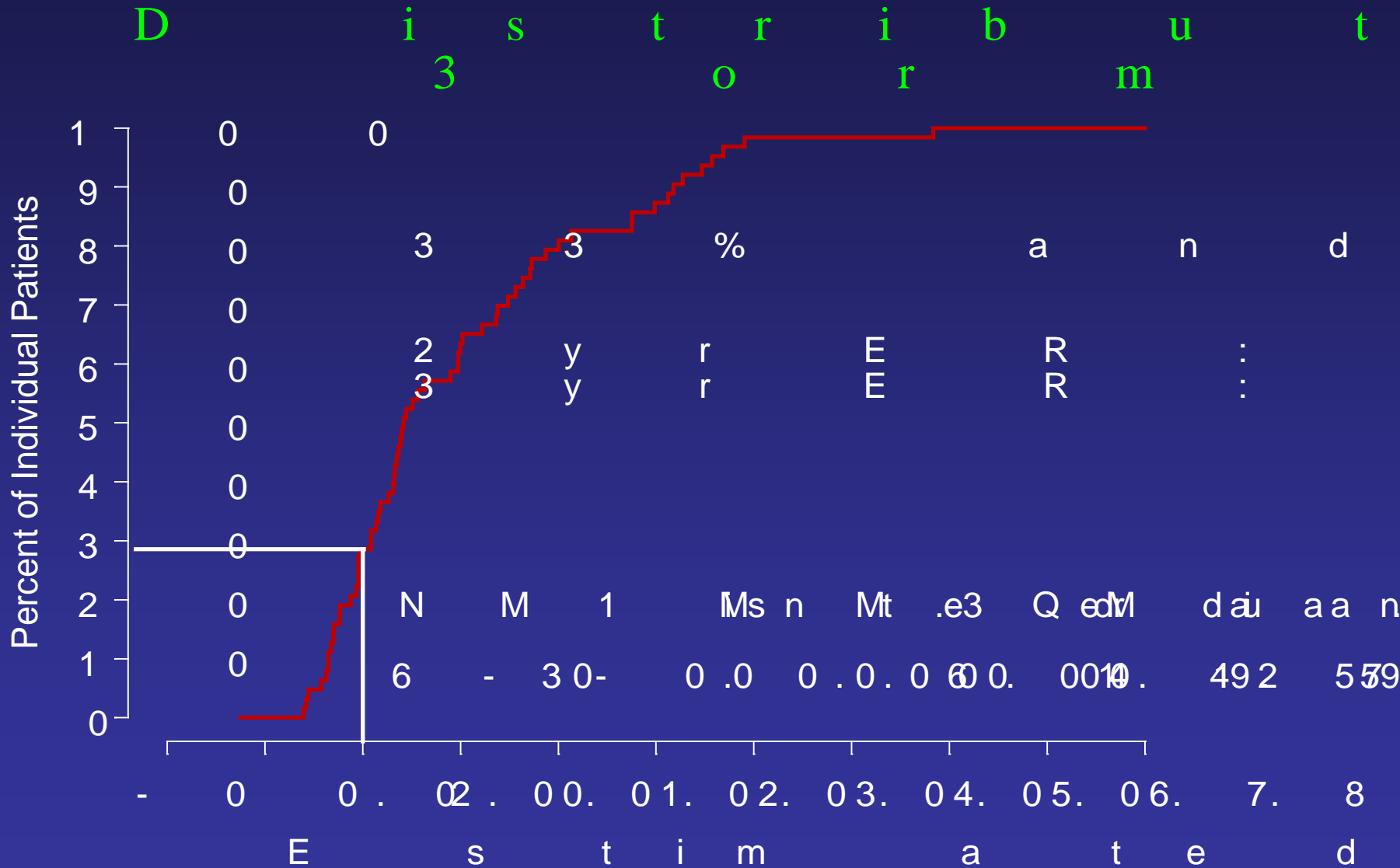
D i s t r i b u t i o n



Natural History Fabry Disease Study (AGAL-014-01)



Natural History Fabry Disease Study (AGAL-014-01)



Natural History Fabry Disease Study

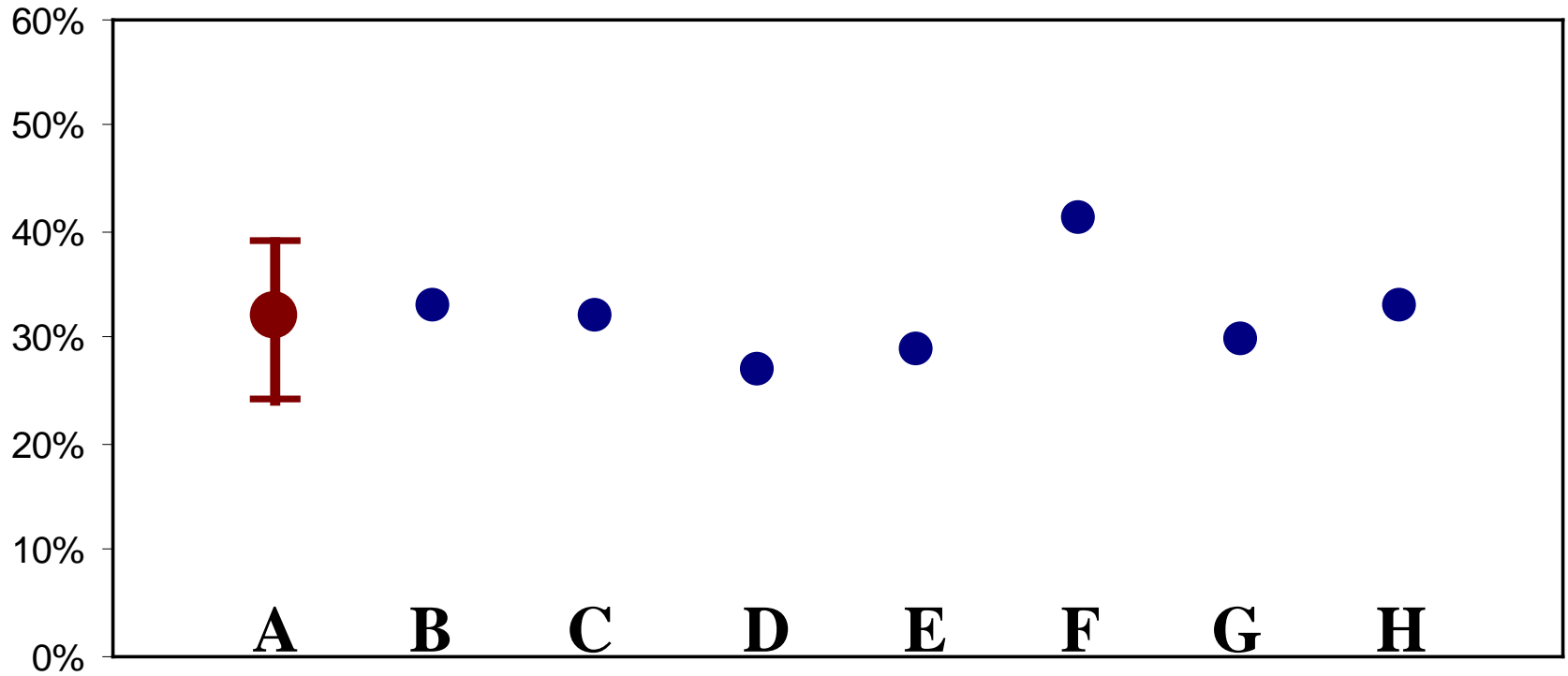
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Type of Analyses

- Reciprocal of Serum Creatinine Data (1/serum creatinine)
- Distribution for Slope of Log Serum Creatinine (Cumulative Distribution Function)
- Estimated Renal Event Rates
 - 33% and 50% Increase in Serum Creatinine
 - Estimated Event Rates Subset by Duration for Follow-up
 - Confidence Interval for Estimated 3-Year Event Rate
 - A Comparison of the Estimated 3-Year Event Rates from Historical Control Population versus the Projected 3-Year Event Rates from r-hαGAL (AGAL-008-00) Patients
- Justification of 84% Confidence Interval
- Distribution of the Estimated Slopes and Intercepts
- Empirical Estimation of Renal Event Rates
- Covariate Analyses
- Linear Regression Analysis by-Patient
- Subset Analyses
- A Comparison of Estimated Renal Event Rates Between Phase 3 Fabrazyme Treated Patients and a Corresponding Cohort of Untreated Historical Control Patients

Robustness of Renal Event Estimate

Estimated Renal Event Rate



Supplementary Analysis Groups

A: Primary

B: Time ≤ 5 yrs.

C: Quad. Term (≤ 5 yrs)

D: 1/Serum Creat. (≤ 5 yrs)

E: ≥ 2 Obs.

F: Empirical

G: Cov: Blood Grp.

H: Regression

Natural History Fabry Disease Study

(AGAL-014-01)

Two-Year Event Rate Estimates (33% Increase) Phase 3 Extension compared to Historical Control

	Estimated Event Rate		P-Value	Age-Adjusted Odds Ratio and CI	Risk Reduction
	Phase 3 Extension (Fabrazyme)	Historical Control			
All Observations	3.4% (2/58)	8.4% (16/190)	0.24	0.40 (0.09, 1.85)	60%
≥ 2 Observations	3.5% (2/57)	9.8% (15/153)	0.15	0.32 (0.07, 1.52)	68%
≥ 3 Observations	3.6% (2/56)	13.0% (14/108)	0.10	0.26 (0.05, 1.29)	74%

CI = 95% Confidence Interval

Risk Reduction = (1-Odds Ratio)×100

Phase 4 Study Investigational Plan

- Study Design
 - Multi-national, multi-center, randomized, double-blind, placebo-controlled trial
 - Target sample size of approximately 70 patients with mild to moderate renal disease
 - 2:1 randomization
 - Minimum ~35 months study duration
- Must have one or more of the following:
 - Serum creatinine measurement of 1.2 to 3.0 mg/dL OR
 - Estimated GFR < 80 mL/min

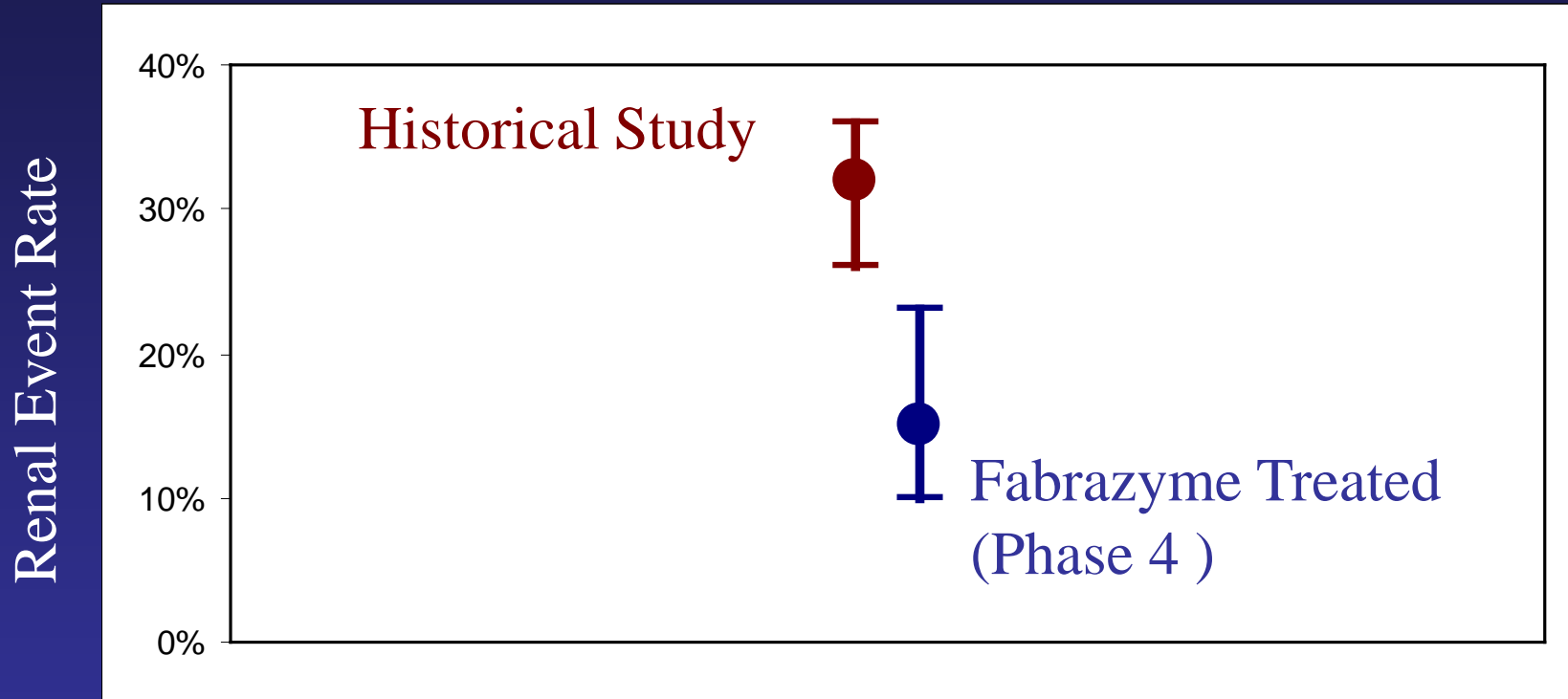
Phase 4 Study: Objective/Endpoints

To assess the effectiveness of Fabrazyme vs. placebo in prolonging the time to clinically significant deterioration in:

- Renal function
 - 33% increase in serum creatinine
 - Progression to dialysis
 - Renal transplant
- Cardiac function
 - Myocardial infarction
 - Unstable angina
 - Requirement of surgical intervention
 - Progression of congestive heart failure
 - Clinically significant arrhythmia
- CNS disease
 - Stroke
 - Transient ischemic attack
- Death

How to Compare to Phase IV

- Non-overlapping CIs (84%)

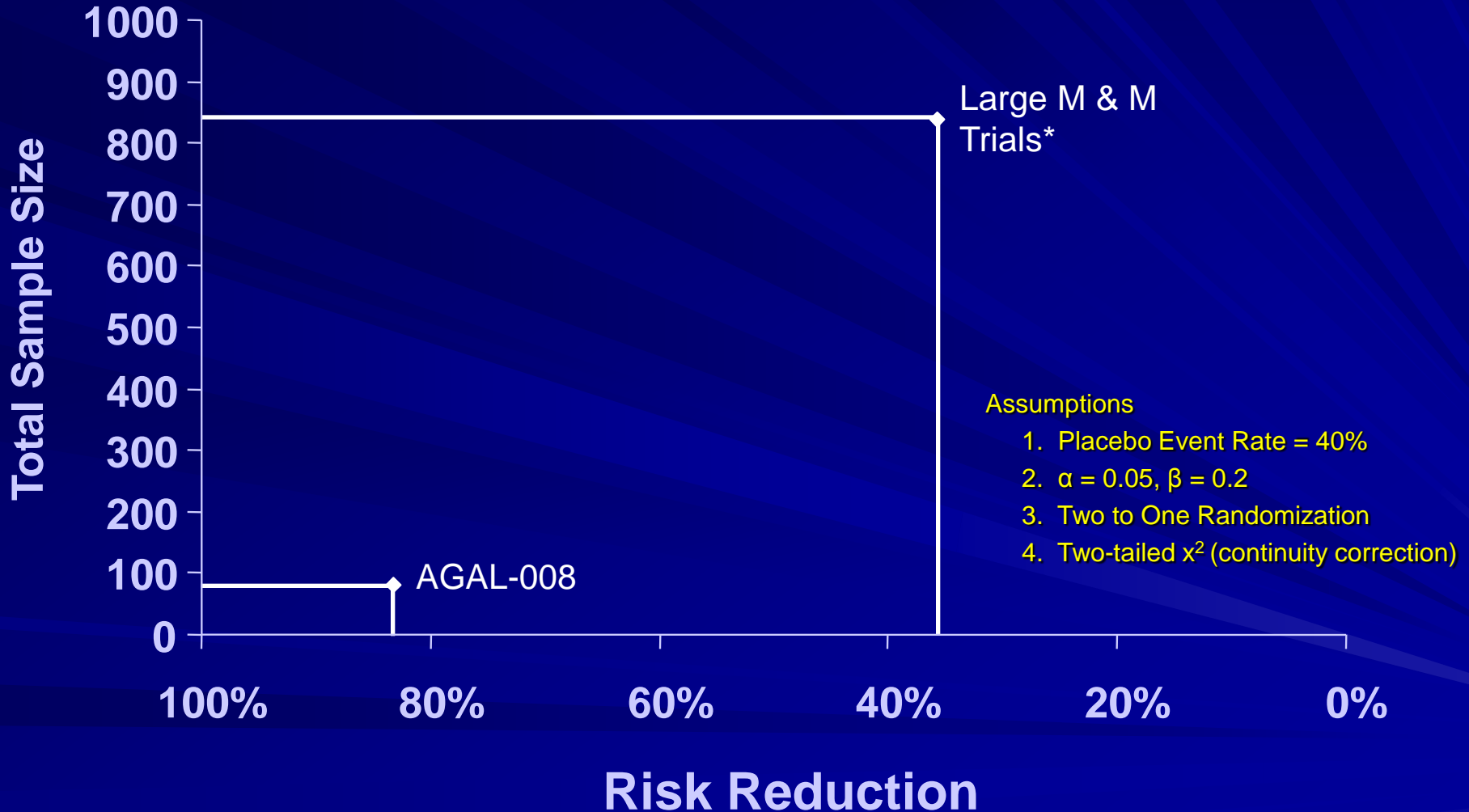


- Logistic regression adjusting for covariates

Deficiencies with Genzyme's proposal to use Natural History study (AGAL-014) as comparator to Phase 4 study

- Non-robust nature of the dataset for proposed use
 - The set of qualified patients is derived from a small minority of all fabry patients identified, Most patients have few data points
 - Very few patients have a duration of valid data long enough to permit determination of renal progression estimation
 - Removal of a minority of data values markedly altered the projected progression rate (i.e, extreme values of Cr that could be observed in proposed clinical trial or gaps of data collection times when marked increases in Cr occur)
- Inability to adequately determine and adjust for important baseline characteristics
- Absence of an understanding of the range of uncertainty in the estimated progression rate
- No way to assure historical database patients are comparable to patients enrolled in prospective study
- Influence of selection bias and blood group of patients cannot be determined.
- Dataset does not permit a precise estimate of the expected progression rate
 - Assumption of linearity challenged
 - Modeling method that ignores baseline Cr levels to calculate estimates of predicted group rates of progression will not be well suited for comparison to another group that has a different distribution of BL Cr levels

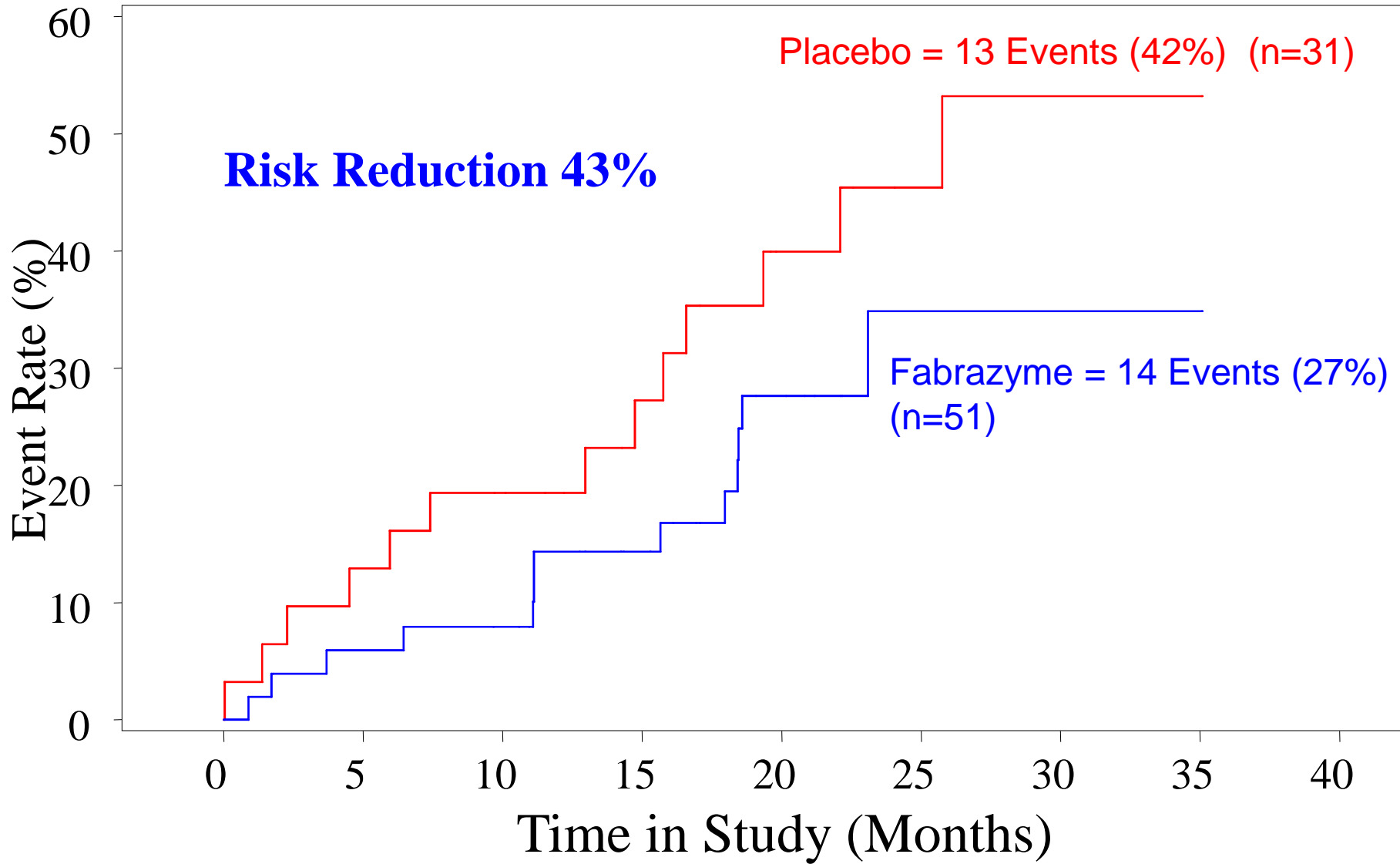
Fabrazyme - Sample Size Implications



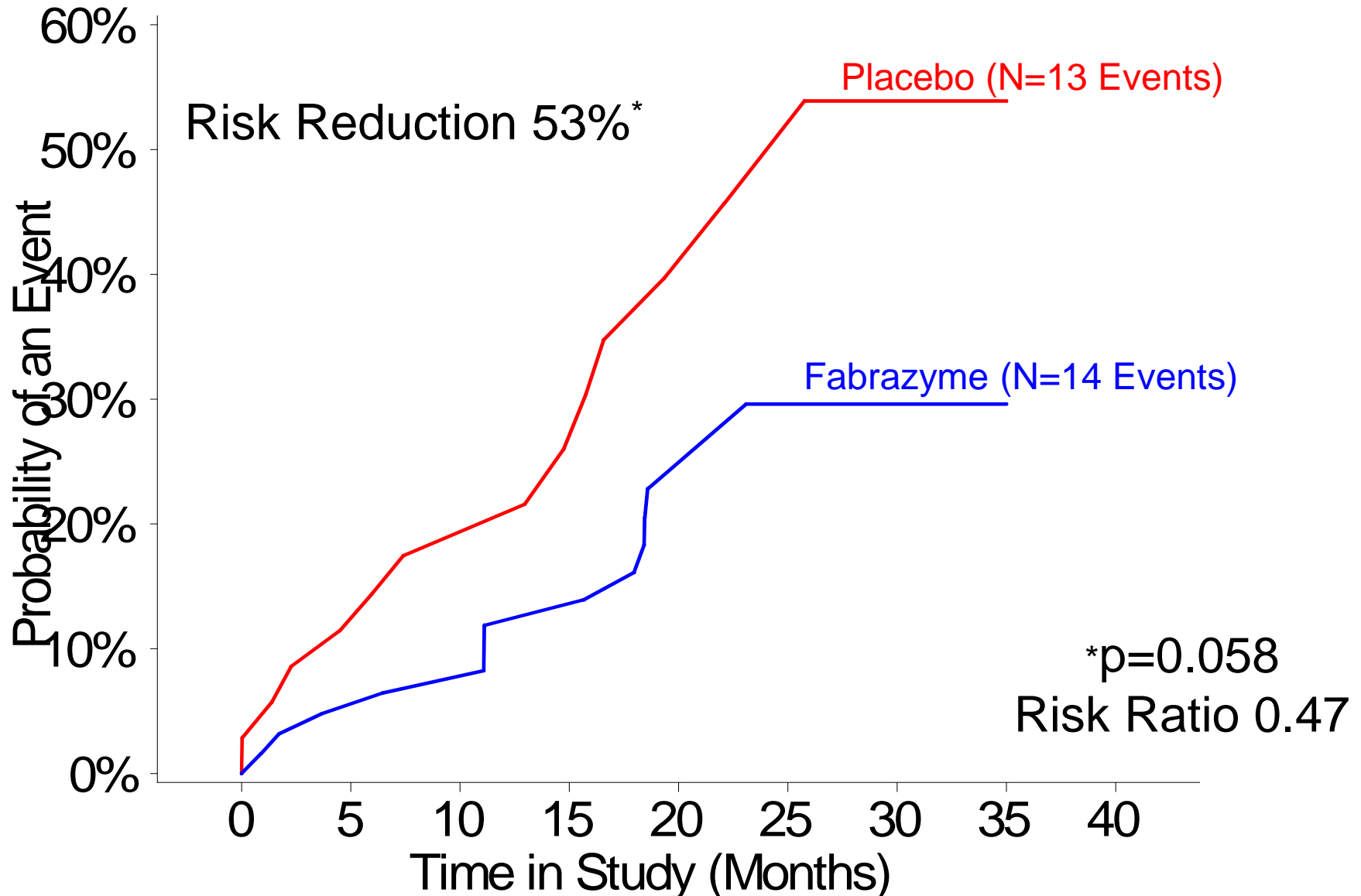
*Diabetic nephropathy trials: RENAAL (N=1513), IDNT (N=1715), IRMA (N=590)

Fabrazyme AGAL-008-00: PRIMARY ENDPOINT

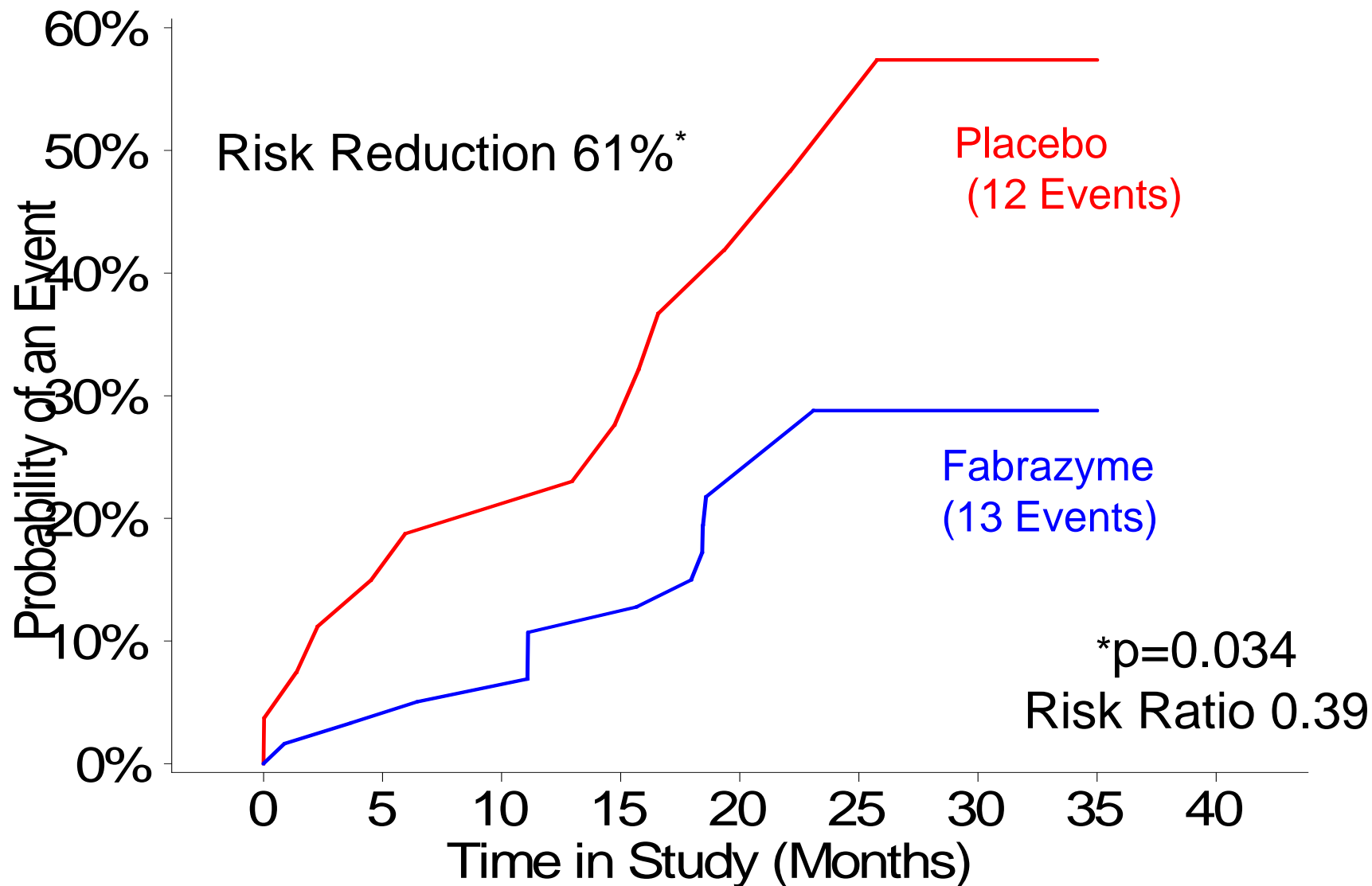
Kaplan-Meier Estimates of Time to the First Occurrence of a Composite Event
(Intent-to-Treat Population)



Proteinuria Ratio Adjusted Predicted Probability of an Event ITT Population (N=82)



Proteinuria Ratio Adjusted Predicted Probability of an Event PP Population (N=74)



Summary

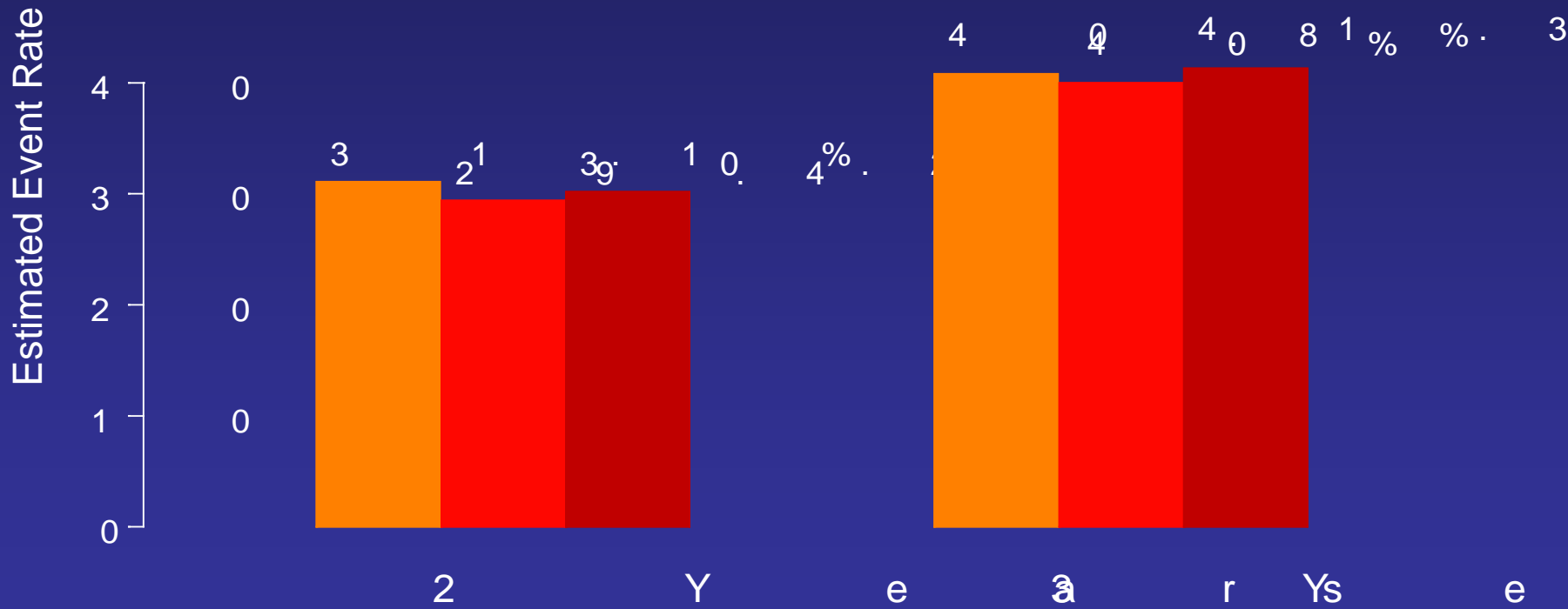
- Even though a chart review, the data were helpful in Fabry disease, though not as a formal comparator group
 - For Fabry disease, the natural hx data suggested a difference in outcomes for patients treated in phase 3 and its extension
 - The natural hx also predicted placebo effects and estimate of the treatment effect
- Even though plausible that serum creatinines and evidence of other major events would be found in a chart review of Fabry patients, they were not extensively present for most patients
- However, statistical modeling can still allow important use of all the data
 - Estimate placebo effect, treatment effect, sample size

Back up slides

Natural History Fabry Disease Study (AGAL-014-01)

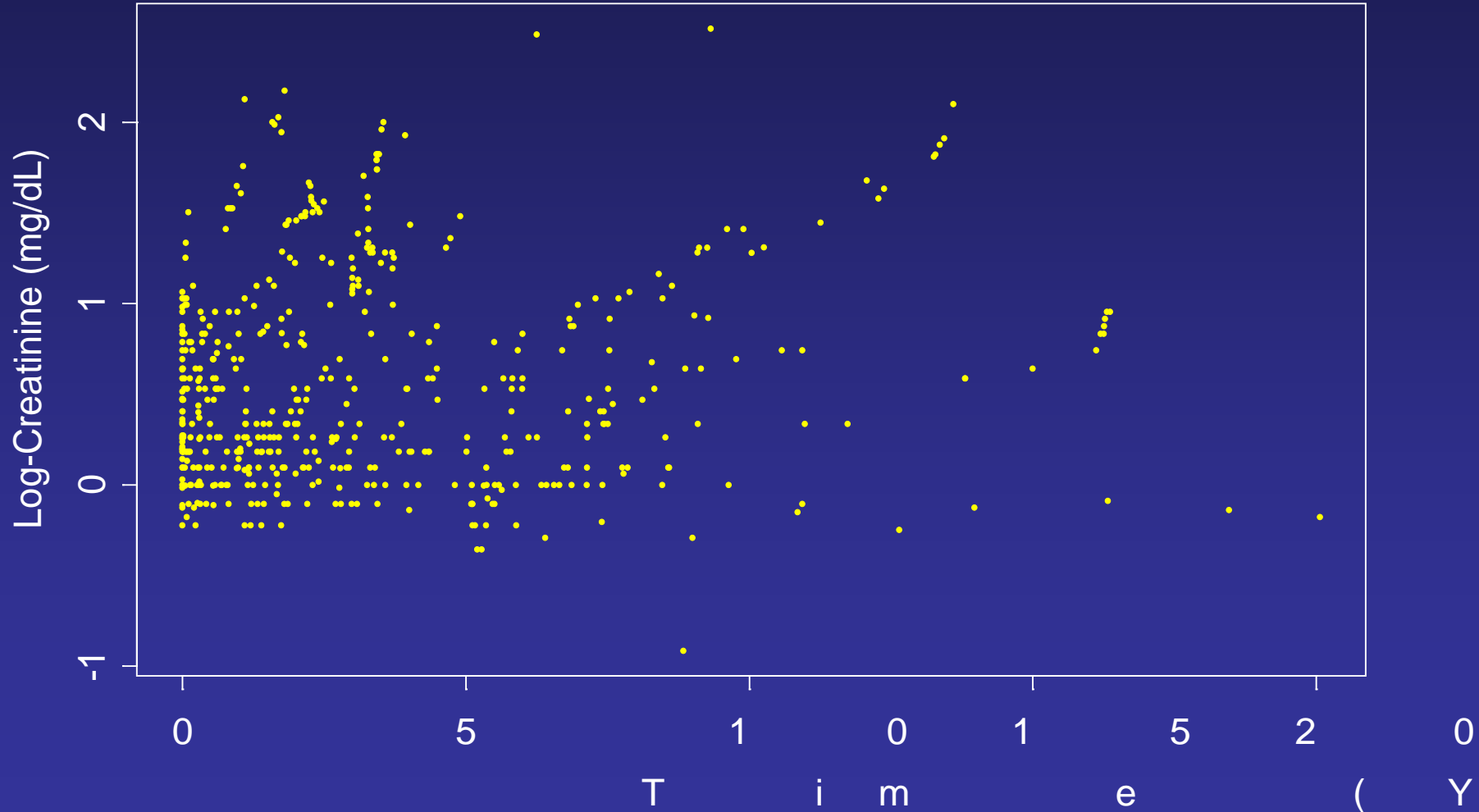
E s t i m a t e

Q u a l i f i e d P h a s e 3 P a t i e n t s



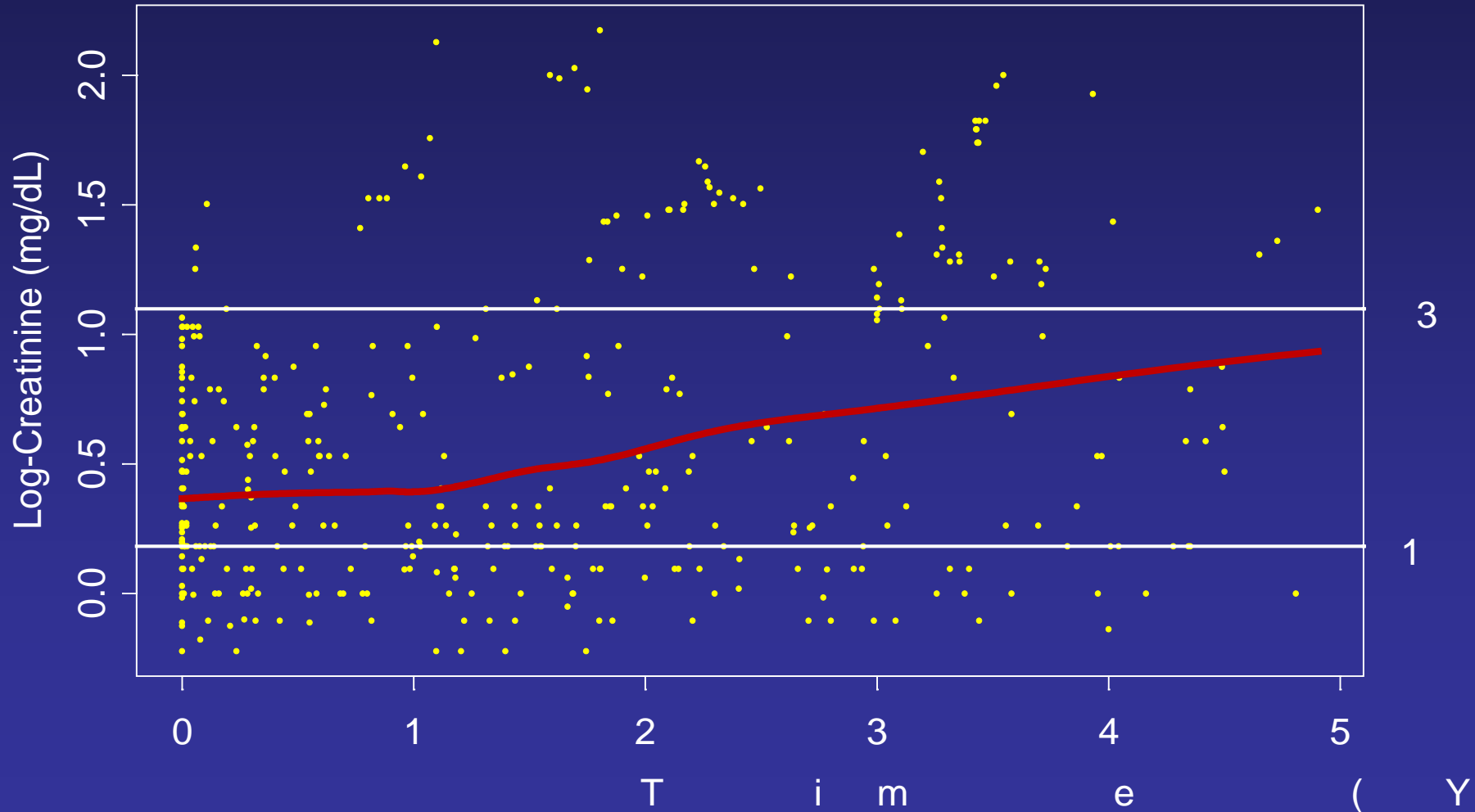
Natural History Fabry Disease Study (AGAL-014-01)

Q u a l i f i e



Natural History Fabry Disease Study (AGAL-014-01)

Q u a l i f i e



Natural History Fabry Disease Study

(AGAL-014-01)

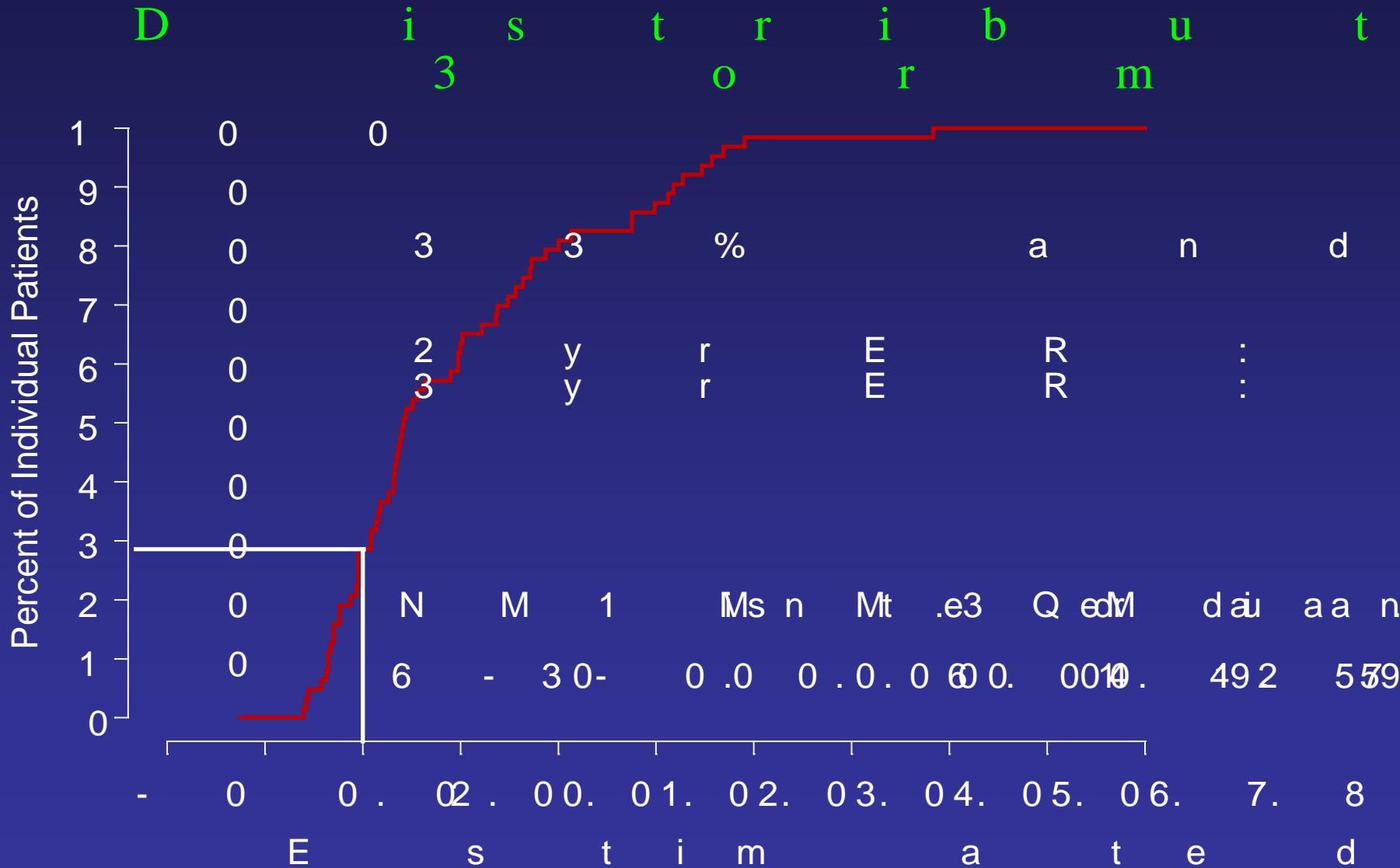
Three-Year Event Rate Estimates (50% Increase) Phase 3 Extension compared to Historical Control

	Estimated Event Rate		P-Value	Age-Adjusted Odds Ratio and CI	Risk Reduction
	Phase 3 Extension (Fabrazyme)	Historical Control			
All Observations	5.2% (3/58)	10.0% (19/190)	0.31	0.51 (0.14, 1.88)	49%
≥ 2 Observations	5.3% (3/57)	11.0% (17/153)	0.21	0.42 (0.11, 1.64)	58%
≥ 3 Observations	5.4% (3/56)	14.8% (16/108)	0.13	0.35 (0.09, 1.37)	65%

CI = 95% Confidence Interval

Risk Reduction = (1-Odds Ratio)×100

Natural History Fabry Disease Study (AGAL-014-01)



Three-Year Event Rate Estimates (50% Increase in Serum Creatinine) Phase 3 Extension Compared to Historical Control

Estimated Event Rate		P-Value	Odds Ratio and CI	Risk Reduction
Phase 3 Extension (Fabrazyme [®])	Historical Control			
7% (4/57)	13% (17/130)	0.234	0.502 (0.161, 1.564)	50%

CI = 95% Confidence Interval; Risk Reduction = (1-Odds Ratio)×100

Natural History Fabry Disease Study

(AGAL-014-01)

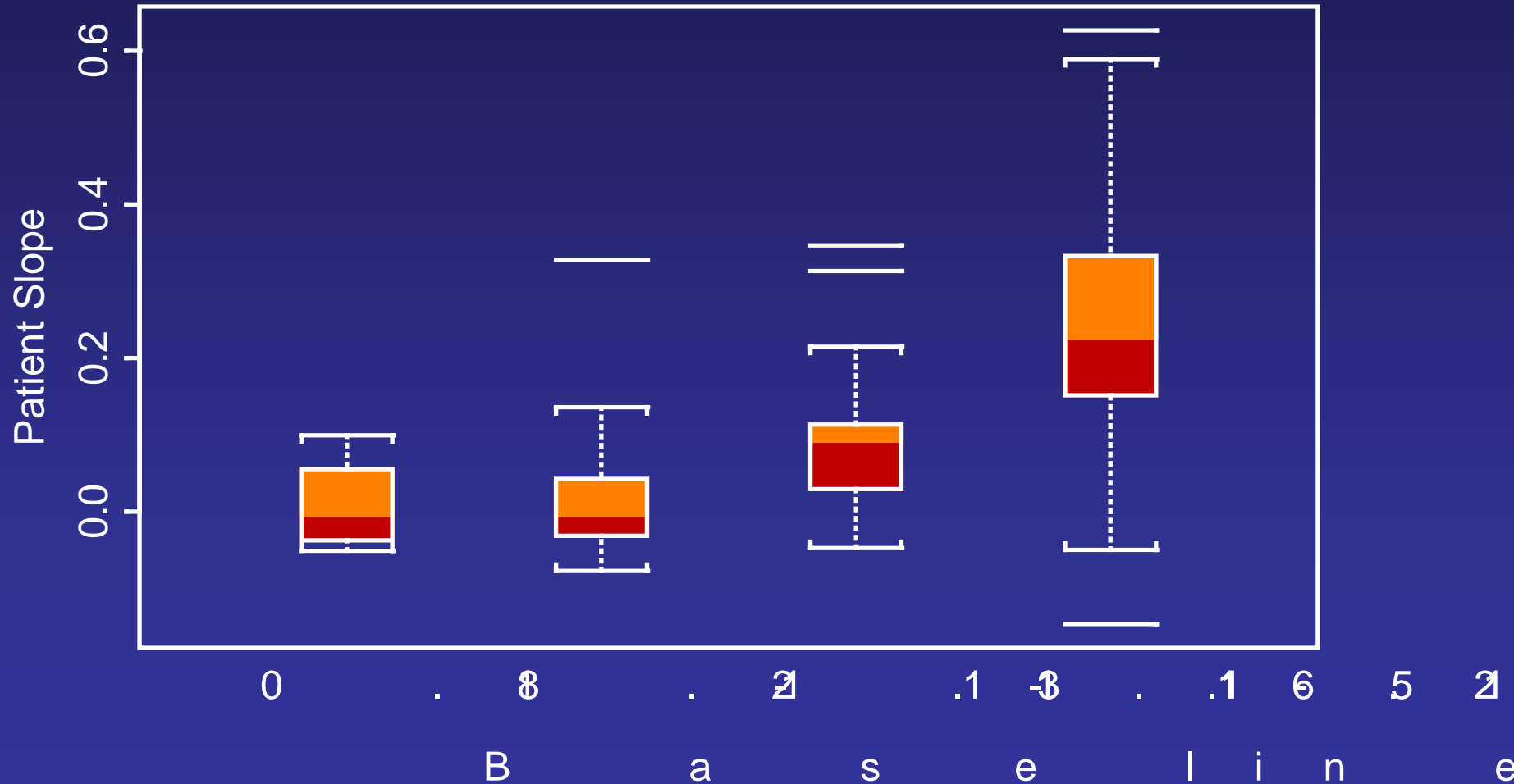
Confidence Intervals for Estimated 3-Year Renal Event Rates

		Confidence Intervals			
Population	Renal Event Rate Point Estimate*	95%	90%	84%	80%
All Qualifiers (N=103)	32%	(23, 47)	(24, 39)	(26, 36)	(26, 36)
N ≥ 2 Observations (N=85)	31%	(22, 42)	(24, 38)	(26, 36)	(26, 34)
N ≥ 3 Observations (N=63)	33%	(22, 41)	(24, 38)	(25, 35)	(27, 35)

* The estimated renal event rate is proportion of patients with an estimated slope of 0.135 or greater (corresponding to a 50% increase in serum creatinine over 3-years).

Natural History Fabry Disease Study (AGAL-014-01)

D i s t r i b u t



Natural History Fabry Disease Study (AGAL-014-01)

Estimated incidence

