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RARE DISEASE WORKSHOP SERIES

Improving the Clinical Development Process



Section 1: Single Variable Methods of Analysis

Naglazyme Phase 3 Study Optimizing Power in a Tiny Study in an Ultra-Rare Disease using a Very Variable Clinical Endpoint

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Challenges for designing a study in Maroteaux Lamy Syndrome

- Extremely rare at about 1:300,000 births
- Highly variable phenotype and progression
- Large age range necessary to enroll a study
- Minimal existing information on clinical endpoints
 - Phase 1 and Phase 2 study with 16 patients



Phase 3 study for Naglazyme in MPS VI

- Randomized double-blind placebo controlled study with 1:1 randomization
- 39 patients with MPS VI, 5 - 27 years old
- Treated with IV weekly for 24 wks
- Primary Endpoint Variable:
 - 12 min. walk test
- Inclusion criteria: maximum walk distance
 - < 270m in 6min and <400 m in 12 min
- Baseline 12MWT with huge variation
- Baseline Range ~600m = 10 x 55m minimal clinically meaningful result
- Wide range despite selection criteria

Table III. 12MWT, Summary

	Baseline (m)
rhASB/rhASB	
Observed (raw)	
N	19
Mean \pm SD	227 \pm 170
Median	210
%iles (25, 75)	(90, 330)
Min, Max	(9, 623)
Fitted (predicted)	
Mean \pm SE	213 \pm 48
p value	—
Placebo/rhASB	
Observed (raw)	
N	20
Mean \pm SD	381 \pm 202
Median	365
%iles (25, 75)	(256, 560)
Min, Max	(46, 685)
Fitted (predicted)	
Mean \pm SE	375 \pm 49
p value	—

*A separate longitudinal model was fit for each differences.



Managing variation in rare diseases

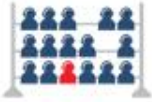
- Inclusions criteria have limitations
 - Not enough patients
- Enrolling study requires wide age ranges
 - Mixing of severity and stage of progression
- Walk test has substantial “effort-based” challenges in execution
- *Need powerful method to assure capture of benefit*



Benefits of Longitudinal Model with Categorical Time

(statistical analysis plan by Janet Wittes)

- Reduces unexplained variability in the response by using repeated measurements
 - Reduction in variability by adding information
- Increased power to detect differences in the effects of treatment
 - The 39 patient Naglazyme trial comparable to 80 pt trial
- Uncertainty about model to use & risks of mistake
 - Decision to use categorical time axes
- The model uses interim measurements to help refine the estimate of the difference in walk distance at 24 weeks



MPS VI Phase 3 Primary Analysis

12 Minute Walk test

	Observed			Estimated*	
	Baseline (m)	Week 24 (m)	Change (m)	Δ rhASB minus Placebo	P-value
rhASB (n=19)	227 \pm 170	336 \pm 227	109 \pm 154	92 \pm 40	0.025
Placebo (n=19)	381 \pm 202	407 \pm 214	26 \pm 119		

* Baseline walk distance and site included as covariates in the model



Phase 3 Observed /Adjusted means 12 Minute Walk test - Change over Time

Figure 11-1: Observed Means of 12-Minute Walk Test Over Time

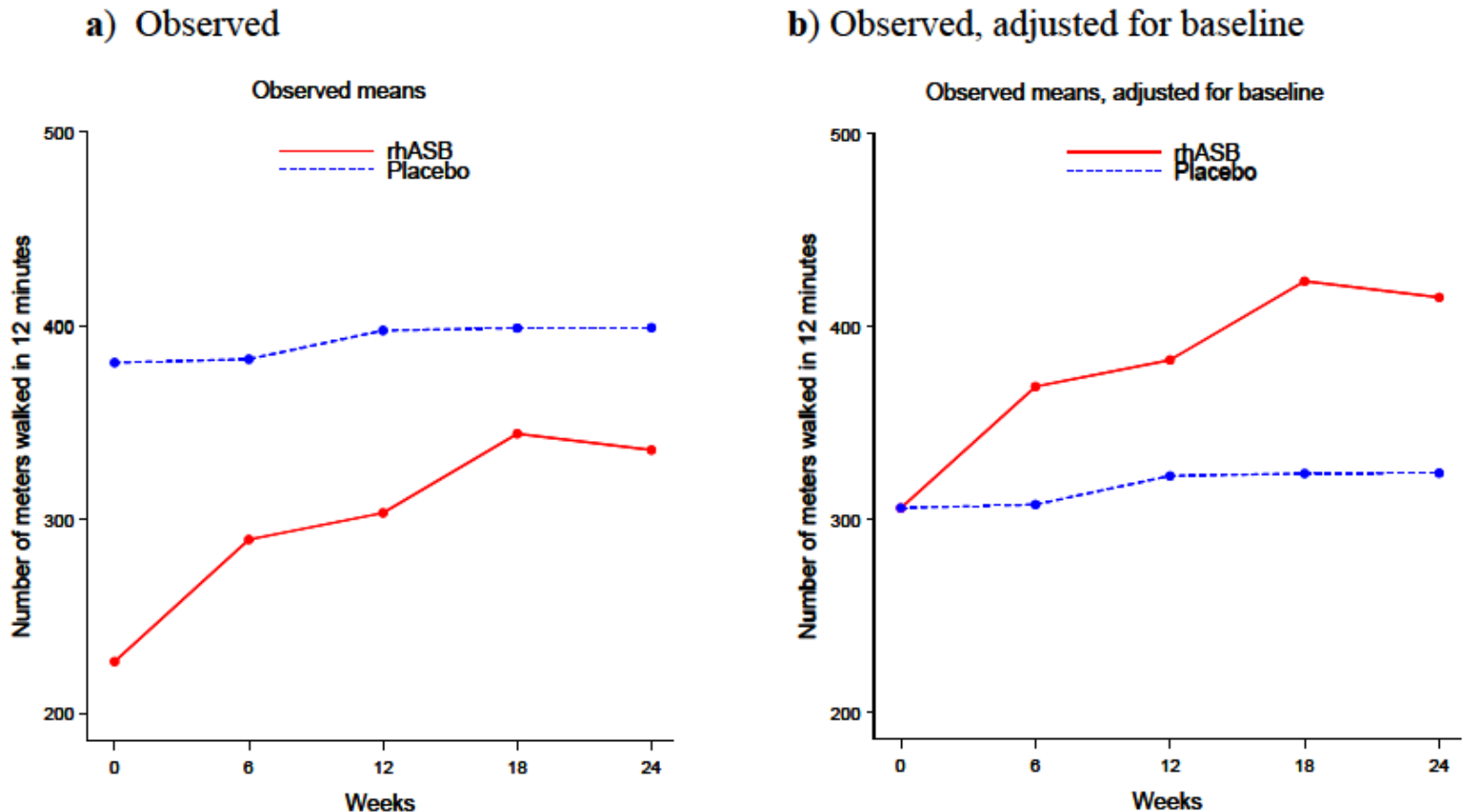
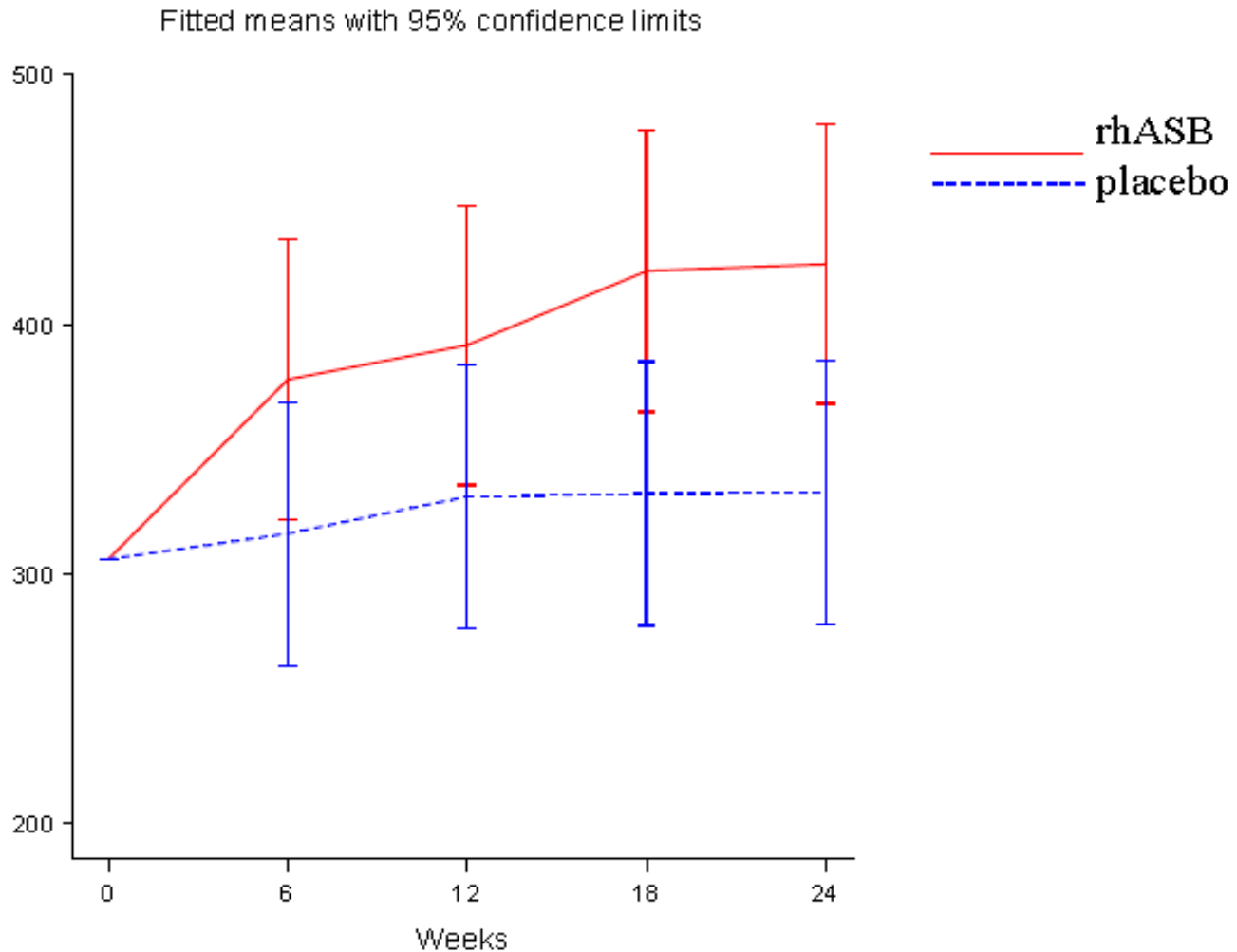




Figure 11-2: Fitted Means of the 12-Minute Walk Test Over Time





Sensitivity analyses using other methods for the primary variable

**Table 11-17: Sensitivity Analyses for the 12-Minute Walk:
Methods using only Baseline and Week 24 Data**

Method	Mean \pm SE (m)	95% CI	p-value
Change from baseline			
t-test	85 \pm 44	(-4, 174)	0.062
Wilcoxon test	Not applicable	Not applicable	0.29
Analysis of variance with baseline 12-Minute Walk Distance as a covariate			
Site as additional covariate	103 \pm 49	(3, 204)	0.044
No additional covariate	72 \pm 48	(-25, 170)	0.14

Reference: [Table 14-71](#).



Longitudinal model with categorical time axis

- Robust: makes no assumption about the nature of the temporal relationship between distance walked and number of weeks on study
- Simply posits a correlational structure (compound symmetry) of the repeated measures of walk distance within a person and treats time as a categorical variable.
- The study results are insensitive to the choice of model
- Remained essentially unchanged under a wide range of assumptions about the correlation within patient and the underlying longitudinal relationships



Conclusion for Naglazyme Phase 3

- Small samples sizes and large variation challenging
- Using more data via a longitudinal model can help
- Risks of choosing a model large
- Categorical X-axis method, leads to more robust analysis
- Successfully used in Naglazyme
- Other common methods would have failed to capture the obvious improvement observed

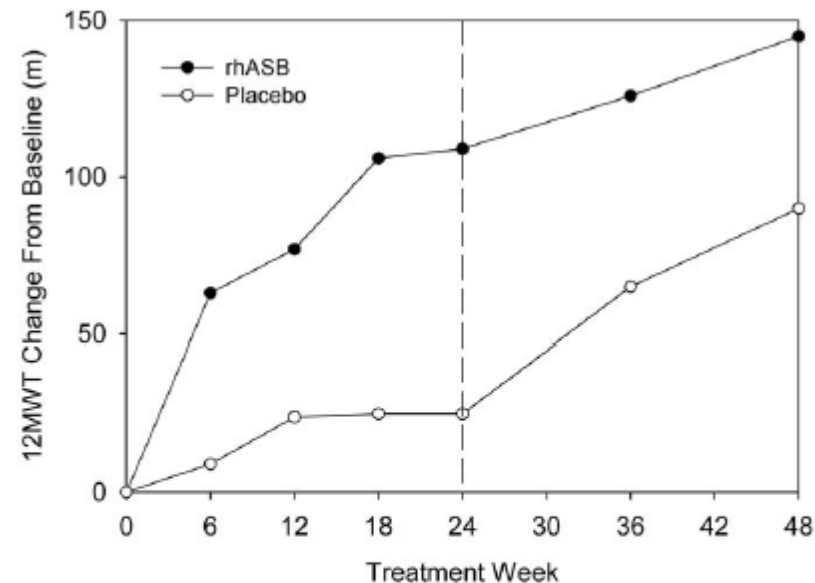


Figure 1. 12MWT vs treatment week. The fitted means from the longitudinal model for the change from baseline in the distance walked in 12 minutes for the rhASB group (filled circles) and placebo group (open circles) were estimated for each treatment week. The dotted line at Week 24 denotes the last timepoint of the double-blind study after which all patients received weekly infusions of rhASB.



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Discussion of Single Variable Methods