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RARE DISEASE WORKSHOP SERIES

Improving the Clinical Development Process



Section 1:

Introduction to the Clinical Studies

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Description of the three drug studies

- All enzyme replacement therapies to treat mucopolysaccharidoses (I, II, IV)
- All three studies measured timed walk test distance, either for 6 or 12 minutes (6MWT or 12MWT)
- Two studies measured % predicted forced vital capacity (%FVC), one measured absolute FVC
- All multi-system diseases



Study Summary Information

	MPS I Aldurazyme	MPS II Elaprase	MPS VI Naglazyme
# of patients	45	96	39
Age range	6 to 43 yrs	5 to 31 yrs	5 to 29 yrs
Randomization scheme	1:1 weekly or placebo	1:1:1 every other week, weekly, or placebo	1:1 weekly or placebo
Study duration	26 weeks	53 weeks	24 weeks
Primary endpoint variable(s)	Coprietary 6MWT and %FVC	Composite 6MWT and %FVC	12MWT
Statistical method	Wilcoxon rank sum test	O'Brien rank sum test	Longitudinal analysis



High Variability in Baseline Walk Test Values

	MPS I Aldurazyme (6MWT)	MPS II Elaprase (6MWT)	MPS VI Naglazyme (12MWT)
Inclusion criteria (m)	≥ 5		≥ 5 , ≤ 270 in first 6 min, ≤ 400 in 12 min
Placebo group (m) Std Dev [range]	366.7 ± 113.7	392 ± 19	381 ± 202 [46-685]
Weekly treatment group (m) Std Dev [range]	319.1 ± 131.4	392 ± 19	227 ± 170 [9 - 623 m]



High Variability in Baseline % Predicted Forced Vital Capacity Values

	MPS I Aldurazyme	MPS II Elaprase
Inclusion criteria (%)	≤ 80	< 80
Placebo group (%)	54.2 ± 16.0	55.6 ± 2.2
Weekly treatment group (%)	48.4 ± 14.5	55.3 ± 2.8



High Variability in Baseline Absolute Forced Vital Capacity Values

	MPS II Elaprase	MPS VI Naglazyme
Inclusion criteria (%)	< 80	
Placebo group (L)	1.09 ± 0.09	0.50 ± 0.24
Weekly treatment group (L)	1.19 ± 0.10	0.65 ± 0.40



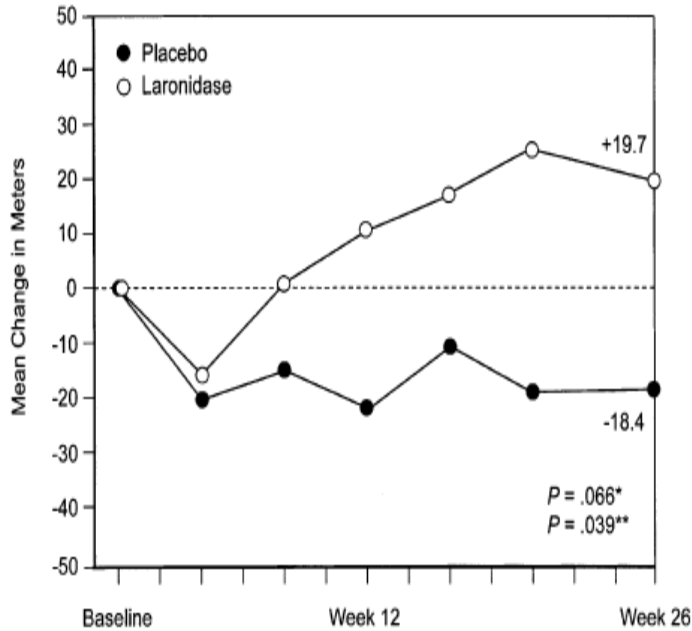
Results

		MPS I Aldurazyme	MPS II Elaprase	MPS VI Naglazyme	
Primary endpoint variable(s)		Coprimary 6MWT and %FVC	Composite 6MWT and %FVC	12MWT	
Statistical method		Wilcoxon rank sum test	O'Brien rank sum test	Longitudinal analysis	
Difference between weekly treatment group and placebo	Test	6MWT (m)	%FVC	Treatment difference	12MWT (m)
	Median	38.5	3.0	18.96 ± 6.47	92
	95% CI	(-2.0, 79.0)	(0.9, 8.6)		(11, 172)
	p-value	.066	.009	.0049	.025



Walk Test Results

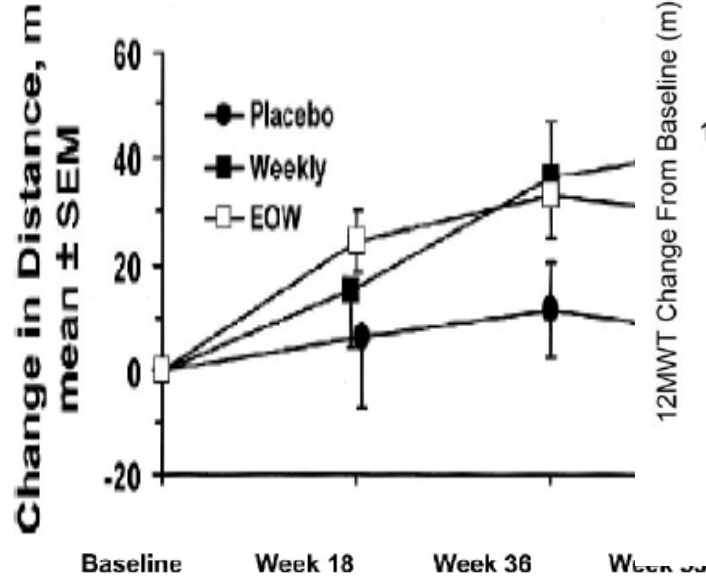
Aldurazyme, 6MWT



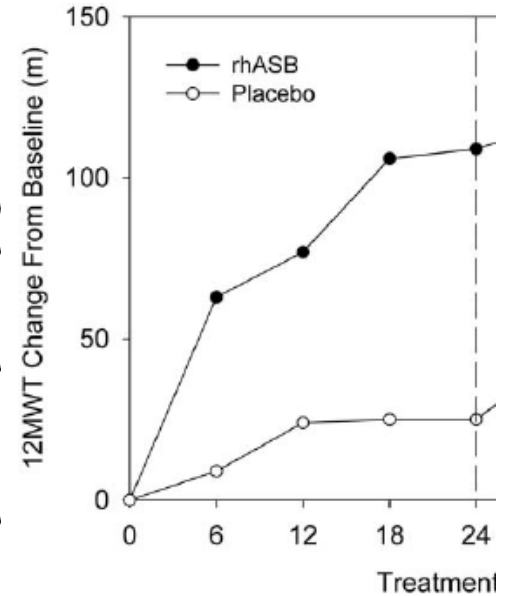
*Wilcoxon rank sum; **ANCOVA

$P = .066^*$
 $P = .039^{**}$

Elaprase, 6MWT



Naglazyme, 12MWT





% Predicted FVC Results

