A Phase 1/2, Multicenter, Open-Label, Dose-Escalation Study to Evaluate the Safety, Tolerability, and Efficacy of BMN 110 in Subjects with Mucopolysaccharidosis IVA (Morquio A Syndrome)

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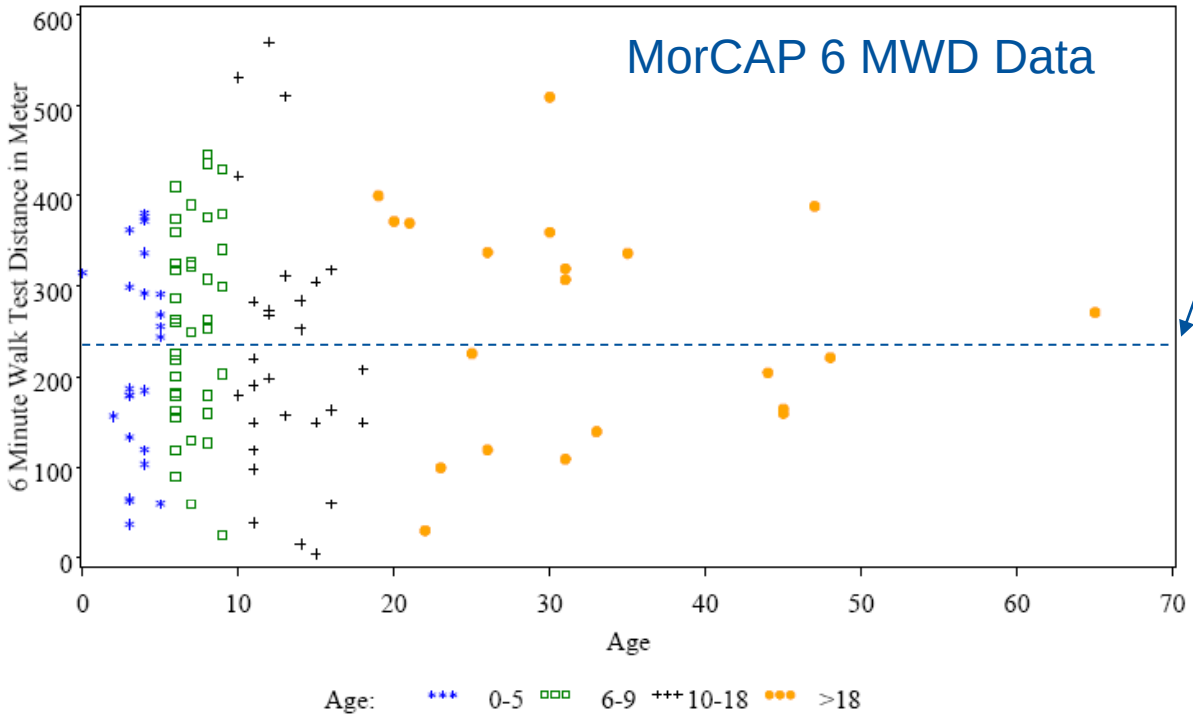
Survey Studies: MPS IVA and MPS VI Have Comparable Endurance



•Average 6MWD in Morquio Clinical Assessment Program **(MorCAP)** = 237 m

Other Studies

•Average 6MWD in **MPS VI survey** (non-drug study) = 273 m*

*Swiedler et al 2005

BMN110 RECOMBINANT HUMAN GALACTOSAMINE 6-SULFATASE (GALNS)

An Enzyme Replacement Therapy For Morquio Type IVA (MPS IVA)

Enzyme	N-acetyl-galactosamine 6 sulfate sulfatase (GALNS): No changes
Characteristics	High specific activity, naturally bone/cartilage targeted and optimized for high uptake
Intended Indication	Intravenous ERT for MPS IVA
Mechanism	Reduce the accumulation of keratan sulfate (KS) in affected tissues
Manufacturing	Specially modified CHO cell line to produce high uptake and properly activated enzyme

Phase 1/2 Study Design: Open-Label, Within Patient Dose Escalation

20* Patients
(age 5-18 y)

Key efficacy measurements

6 Minute Walk Test (6MWT)
3 Minute Stair Climb (3MSC)
Respiratory Function Tests:
- Forced Vital Capacity
- Maximum Voluntary Ventilation

Urine KS

*20 enrolled, 2 withdrawn approx. Week 12; 2 unable to perform endurance tests

Phase 1/2 Study: Baseline Demographics

- **Mean age 8 years**
- **Mean height approx. 102 cm, large variation (74 to 155 cm)**
- **Most patients below 3rd percentile for height**
- **80% use wheelchairs**
- **Average baseline 6MWD = 267 m**

Age at Enrollment, years	
n	20
Mean (SD)	8.0 (2.9)
Min , Max	4 , 16
Sex	
Male	12 (60%)
Female	8 (40%)
Height, cm	
n	19
Mean (SD)	102.3 (19.8)
Min , Max	74.3 , 154.9
Use of Wheelchairs	16 (80%)
Use of Walking Aids	2 (10%)

Summary of Endurance Data in Subjects With Evaluable Results Through Study Week 36

	Statistic	Week 24	Week 36
Change in 3 Minute Stair Climb from Baseline (stairs per minute)	N	15	15
	Mean (p-value)	6.9 (p=0.01)	8.9 (p=0.03)
	Median (p-value)	7.3 (p=0.01)	10.3 (p=0.06)
Change in 6 Minute Walk Test from Baseline (meters)	N	16	16
	Mean	17 (p=0.36)	15 (p=0.38)
	Median	38 (p=0.09)	19 (p=0.35)

T-test for mean comparison; Wilcoxon signed-rank test for median comparison

- **Median/mean improvement in 6MWT of 38 m/17 m at Week 24 and 19 m/15 m at Week 36**

- **Median/mean improvement in 3MSC of 7.3 /6.9 stairs/min at Week 24 and 10.3 /8.9 stairs/min at Week 36**

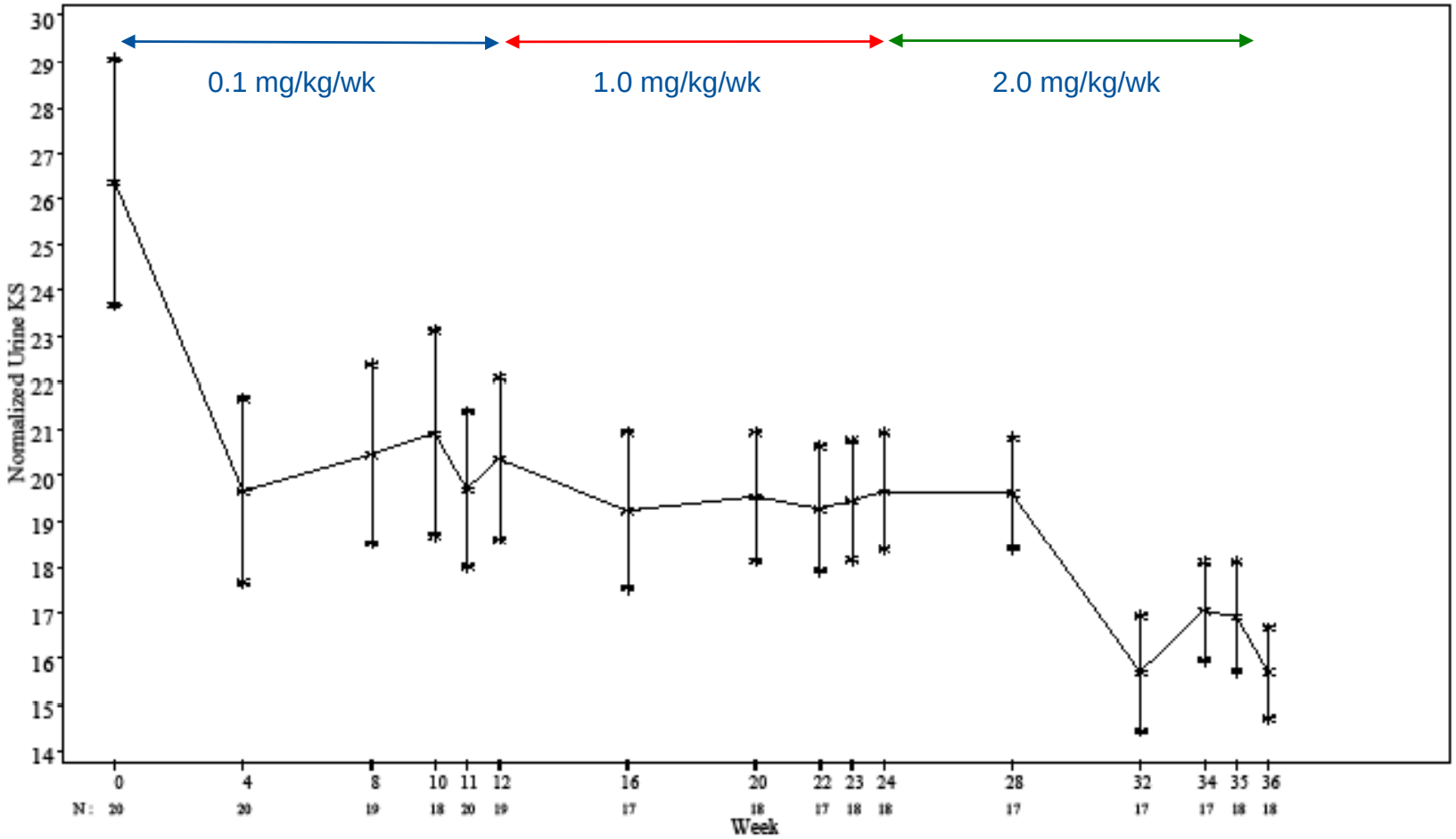
Summary of Respiratory Data in Subjects With Evaluable Results Through Study Week 36

	Statistic	Week 24	Week 36
Percent Increase in FVC[(1)]	N	16	16
	Mean	<1% (p=0.98)	11% (p=0.06)
	Median	<1% (p=0.85)	11% (p=0.01)
Percent Increase in MVV[(2)]	N	13	14
	Mean	11% (p=0.09)	11% (p=0.04)
	Median	6.4% (p=0.15)	10% (p=0.06)

(1) forced vital capacity; (2) maximum voluntary ventilation
T-test for mean comparison; Wilcoxon signed-rank test for median comparison

- **MVV shows approximate 11 % mean increase from baseline at Week 24 (10% change at Week 12)**
- **FEV1, FVC and MVV are increased from baseline at Week 36**

Urine KS Decreases in Response to ERT



- Significant decrease between Baseline and Week 4 (0.1 mg/kg/wk dose), further decrease between Week 28 and Week 32 (2 mg/kg/wk dose)
- 41% mean and 47% median decrease between Baseline and Week 36

Antibody and Additional Biomarkers

- All patients developed drug specific antibody response by Week 18 of treatment
- Preliminary analysis shows no apparent relationship between total antibody level and safety or efficacy outcomes
- Changes in biomarkers of inflammation, matrix factors, metabolism, and growth were measured during ERT; data analysis is ongoing

Safety

Category	0.1 mg/kg/week (n=20)	1.0 mg/kg/week (n=18)	2.0 mg/kg/week (n=18)	Continuation Period (n=18)	Entire Study (n=20)
AEs	18 (90.0%)	18 (100.0%)	17 (94.4%)	15 (83.3%)	20 (100.0%)
Drug-Related AEs	12 (60.0%)	10 (55.6%)	7 (38.9%)	5 (27.8%)	14 (70.0%)
SAEs	6 (30.0%)	2 (11.1%)	8 (44.4%)	3 (16.7%)	13 (65.0%)
Drug-Related SAEs	2 (10.0%)	1 (5.6%)	2 (11.1%)	1 (5.6%)	4 (20.0%)
AEs During Infusion	15 (75.0%)	13 (72.2%)	10 (55.6%)	9 (50.0%)	17 (85.0%)
SAEs During Infusion	5 (25.0%)	0	1 (5.6%)	1 (5.6%)	6 (30.0%)
AEs Causing Study Discontinuation	1 (5.0%)	0	0	0	1 (5.0%)

- **Number of patients experiencing drug related AEs decreases over time**
- **Most SAEs not drug related**
- **2 patients withdrew, one due to severe type I hypersensitivity accompanied by drug specific IgE at low dose, other for personal reasons (sibling)**
- **One patient suspended treatment after Week 45 due to recurrent infusion reactions but remains enrolled in study**

6 Minute Walk Distance, Median Change From Baseline, Phase 1/2 Morquio ERT Trial Compared to Other MPS Trials

Trial (Treatment Period)	Median Baseline 6MWD	Median Change at End of Treament Period
Phase 1/2 Morquio (24 Weeks)	258 m	38 m
Phase 1/2 Morquio (36 Weeks)	258 m	19 m
Phase 3 MPS VI treated (24 Weeks)	123 m	19 m
Phase 3 MPS VI placebo (24 Weeks)	204 m	6 m
Phase 3 MPS I treated (26 Weeks)	349 m	28 m
Phase 3 MPS I placebo (26 Weeks)	360 m	- 11 m

- Morquio Phase 1/2 trial median change at Week 24 (38 m) compares favorably with median improvements in other Phase 3 MPS trials
- Other MPS trials showed minimal increase or decrease in placebo group

Notes:

- **Morquio data represent n = 16 subjects that had evaluable data at baseline through Week 36.**
- **Naglazyme data represents average of 2 values at each point, 6 minute time point of 12 MWT.**

3 Minute Stair Climb, Median Change From Baseline, Phase 1/2 Morquio ERT Trial Compared to Other MPS Trials

Trial (Treatment Period)	Median Baseline 3MSC (stairs/min)	Median Change at End of Treament Period (stairs/min)
Phase 1/2 Morquio (24 Weeks)	32	7
Phase 1/2 Morquio (36 Weeks)	32	10
Phase 3 MPS VI treated (24 Weeks)	17	5
Phase 3 MPS VI placebo (24 Weeks)	25	4

- Morquio Phase 1/2 trial median improvements at Week 24 and at Week 36 greater than improvement in MPS VI trial

Notes:

- **Morquio data represent n = 15 subjects that had evaluable data at baseline through Week 36.**
- **MPS VI data represents average of 2 values at each point.**

Morquio Phase 1/2 Trial Summary

- Morquio A patients have impaired endurance and respiratory function similar to other MPS disorders
- Walk and stair climb improved (comparable to other ERTs)
- Urine KS reduced, largest decrease occurs in 2 mg/kg dose interval
- Respiratory function improved (comparable to other ERTs)
- Overall safety profile is favorable
- These data support conducting a Phase 3, randomized trial