Enzyme Replacement Therapy for Mucopolysaccharidosis Type IVA:

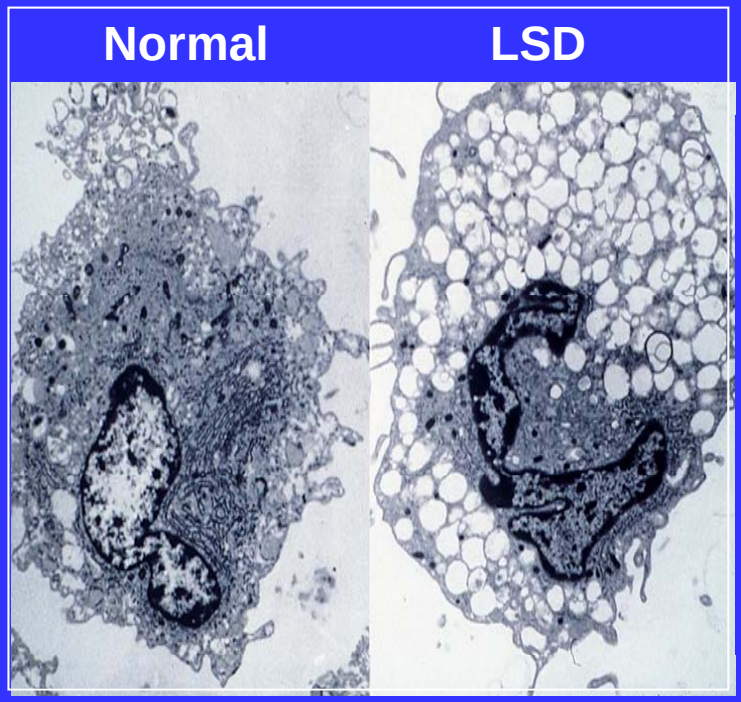
Update on Clinical Trials

Christian Hendriksz, MBChB, MSc, FRCPCH, MRCP,
Consultant in Metabolic Disorders, Birmingham
Children's Hospital, UK

MPS IVA (MORQUIO TYPE A)

Biochemistry

- Deficiency in a single enzyme **(GALNS)**
  - N-acetyl-galactosamine-6-sulfate sulfatase
- Results in inability to degrade keratan sulfate (KS)
- Accumulation of KS in many tissues throughout the body
  - “Stored” in cellular lysosomes
- Progressive storage leads to lysosomal enlargement, eventually causing cellular dysfunction



Classification of MPS Disorders

- 11 known enzyme deficiencies cause 7 main MPS types

MPS Type	Eponym(s)	Enzyme Deficiency	GAG Affected
MPS I	Hurler, Hurler-Scheie, or Scheie	α-L-iduronidase	DS,HS
MPS II	Hunter	iduronate sulfatase	DS,HS
MPS III	Sanfilippo A Sanfilippo B Sanfilippo C Sanfilippo D	Heparan-N-sulfatase α-N-acetylglucosaminidase acetyl CoA:α-glucosaminide acetyltransferase N-acetylglucosamine-6-sulfatase	HS HS HS HS
MPS IV	**Morquio A** Morquio B	**N-acetyl-galactosamine-6-sulfatase** β-galactosidase	**KS,CS** KS
MPS VI	Maroteaux-Lamy	N-acetylgalactosamine-4-sulfatase (arylsulfatase B or ASB)	DS
MPS VII	Sly	β-glucuronidase	DS,HS,CS
MPS IX	Hyaluronidase Def.	Hyaluronoglucosaminindase-1	HA

DS = dermatan sulfate, HS = heparan sulfate, CS = chondroitin sulfate, KS = keratan sulfate, HA= Hyaluronan

MPS IVA (MORQUIO TYPE A)

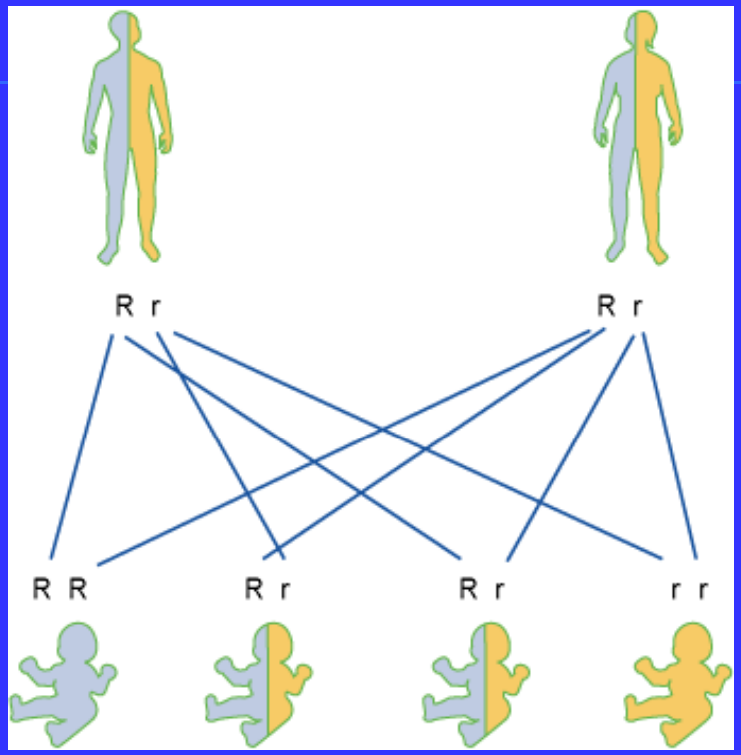
A progressive disease affecting multiple organ systems

- **Clinical Signs and Symptoms**
  - Systemic skeletal dysplasia (short stature)
  - Impaired endurance (ability to walk/climb stairs)
  - Cervical spine abnormalities and spinal cord compression
  - Respiratory disease (obstructive, restrictive, infections)
  - Hearing loss
  - Cataracts
  - Heart valvular disease
  - Normal intelligence

Wide variability in clinical presentation from slowly to very rapidly progressing forms

Autosomal-Recessive Inheritance

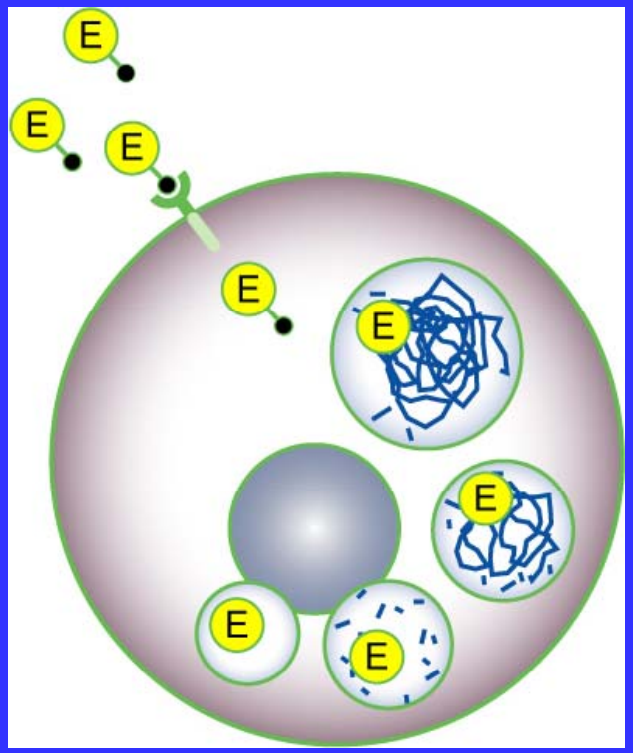
- Most MPS's are inherited as autosomal recessive conditions
- Males and females are equally affected



R, functional gene copy
r, non-functional gene copy

Enzyme Replacement Therapy (ERT)

- Provides recombinant (man-made) version of the deficient enzyme via regular intravenous (IV) infusion
- Corrects lysosomal storage in a number of tissues
- ERT is currently commercially available for 6 LSDs: MPS I, MPS II, MPS VI, Gaucher disease, Fabry disease, and Pompe disease



Clinical Trials - a series of "phases"

Rare disease clinical programs often start with survey/natural history study (no drug)

What are the phases of clinical trials?

Clinical trials are conducted in phases. The trials at each phase have a different purpose and help scientists answer different questions:

In Phase I Trials, researchers test an experimental drug or treatment in a small group of people for the first time to evaluate its safety, determine a safe dosage range, and identify side effects.

In Phase II Trials, the experimental study drug or treatment is given to a larger group of people to see if it is effective and to further evaluate its safety.

In Phase III Trials, the experimental study drug or treatment is given to large groups of people to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the experimental drug or treatment to be used safely.

In Phase IV Trials, post marketing studies delineate additional information including the drug's risks, benefits, and optimal use.

Morquio Clinical Program Overview

October 2008

Initiated Natural History Study (MorCAP)

- Longitudinal (yearly visits over several days)
- Observational (non-drug)
- 200-300 subjects
  - 129 patients evaluated through 2009 (about equal numbers of males & females)
- 15 multi-national sites for enrollment
  - (US, UK, Canada, France, Germany, Italy, Netherlands, Taiwan, Brazil, Argentina)
- Phase 3 study participants will likely be identified from this study
- Goals:
  - To evaluate degree and variability of untreated clinical disease
  - To provide natural history data
  - Assessing growth, medical problems & their severity, daily functioning

Lessons from MorCAP (Part 1 of 2)

1. Surgeries for skeletal, joint and ENT problems are common
2. Wheelchairs (44%) are used more frequently than walk aids (24%)
3. Height in children usually below 3rd percentile, average adult height less than 120 cm
4. About 1/3 of pediatric and adult patients are at a healthy weight, the rest tending to be overweight (per CDC BMI norms)
5. Overall, MPS IVA patients have limited endurance
   - Distance walked and number of stairs per minute climbed are reduced compared to unaffected individuals

Lessons from MorCAP (Part 2 of 2)

6. Overall, MPS IVA individuals have impaired respiratory function

7. Urine KS (uKS) is better than plasma KS for tracking MPS IVA disease & differentiating between affected & unaffected peers
   - Individuals under age 20 tend to have uKS that's about 20 times higher than unaffected peers
   - Urine KS tended to be lower in older patients compared to younger patients

8. Generally, higher levels of urine KS reflect shorter stature and greater impairments in endurance and respiratory function

Morquio Clinical Program Overview

<u>April 2009</u>

Initiated Phase 1/2 ERT clinical study (M0R-002)

- First test of investigational therapy in patients
- Enrolled 20 subjects in 3 UK centers
  - Enrollment completed in July 2009
- 72 week total duration
  - Plan to file additional protocol for extension study

Goals: Phase 1/2 Clinical Study (MOR-002)

- **Establish safety**
  - Closely monitor adverse events
  - Measure antibody response
- **Determine optimal dose**
- **Establish treatment responsiveness of clinical endpoints**
  - Endurance
    - For example: 6 minute walk test, 3 minute stair climb
  - Respiratory function
    - For example: forced vital capacity (FVC), maximum ventilation volume (MVV)
  - Keratan sulfate levels

Phase 1/2 Study Design:

- Open Label
- 20* patients age 5-18 years
- 36 weeks, Dose escalation
- Treatment continuation after dose escalation

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**

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 Patients
(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 Preliminary Respiratory Data

Maximum Voluntary Ventilation (MVV)

The volume of air that can be breathed in 15 seconds when a person breathes as deeply and quickly as possible. Also called *maximum breathing capacity*.

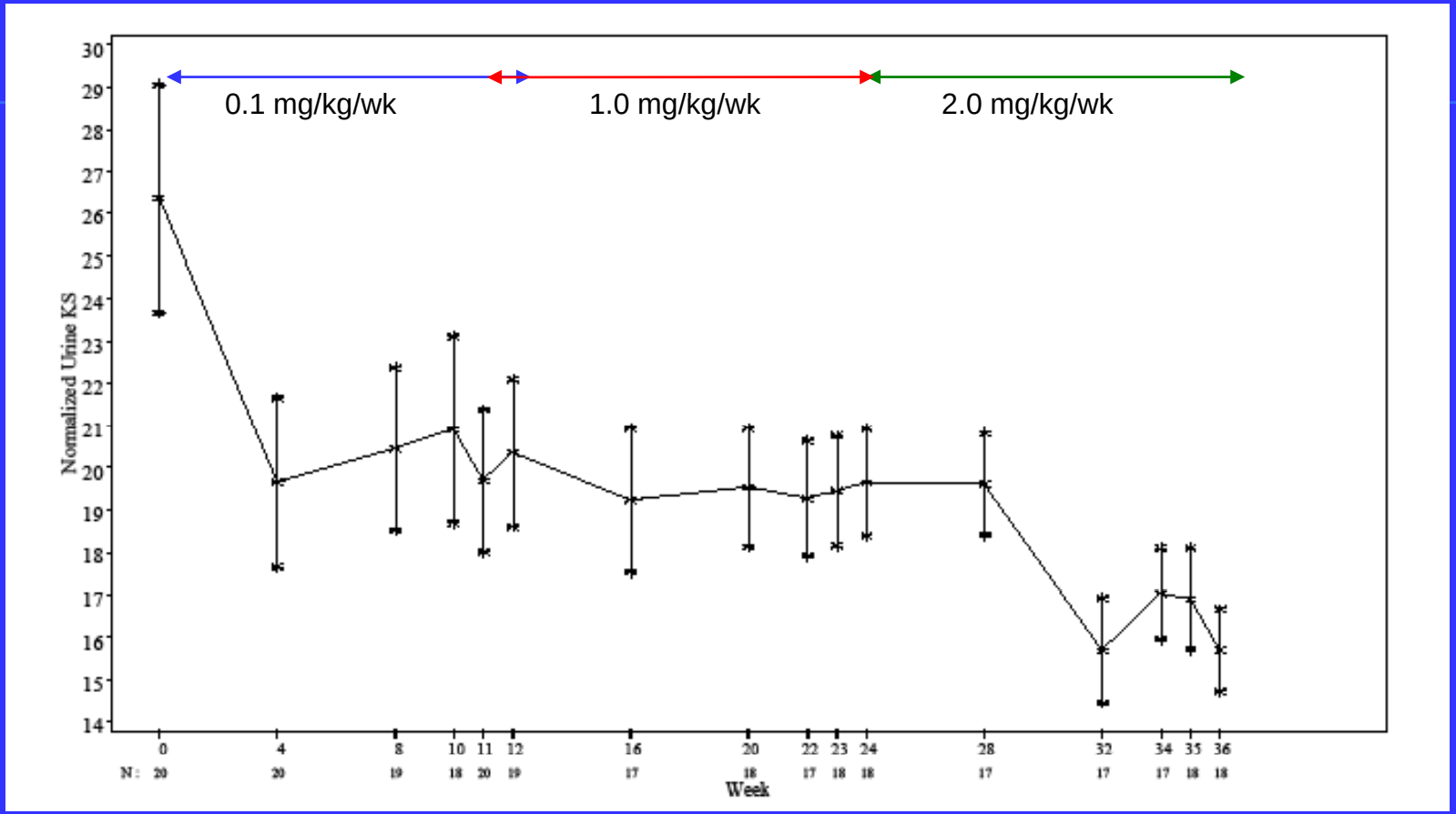
- MVV shows approximate 11 % increase from baseline at Week 24 and Week 36

Forced Vital Capacity (FVC)

The amount of air which can be forcibly exhaled from the lungs after taking the deepest breath possible.

- FVC show an approximate 11 % increase 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) 47% (median) decrease between Baseline and Week 36

Phase 1/2 Study: Safety

- The primary goal of the Phase 1/2 study is to determine safety

- Patients are continuously monitored for any reactions during a clinical study

Phase 1/2 Study: Safety

- Number of patients experiencing drug-related adverse events (AE's) decreases over time
- Most severe adverse events (SAE's) are not drug related
- Two patients withdrew
  - One due to severe type I hypersensitivity
  - One for personal reasons (sibling)
- One patient suspended treatment at week 45
  - Due to recurrent infusion reactions
  - Remains enrolled in study

Morquio Phase 1/2 Trial Summary

- Morquio A patients have impaired endurance and respiratory function similar to other MPS disorders
- Walk and stair climb show improvements comparable to other ERT trials
- Urine KS shows response to treatment, largest decrease occurs in 2 mg/kg dose interval
- Respiratory function tests show improvement
- Overall safety profile is favorable

Next Steps for Morquio Clinical Program

Phase 3 pivotal trial

- Analysis of MOR-002 will dictate trial endpoints and patient selection criteria
  - Likely endpoints: Endurance (6MWT), respiratory function

- **Goals for Phase 3 study:**
  - Confirm safety of therapy
  - Confirm that therapy provides benefit to individuals with MPS IVA
  - Larger patient enrollment than Phase 1/2
  - Many centers around the world

Possible other studies

- Under 5 years old
- Other individuals not eligible for pivotal trial