

Enzyme replacement therapy for Mucopolysaccharidosis type II – where are we?

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Idursulfase (Elaprase – Shire HGT)

- Licensed in Europe since 2007
- Clinical trials showed significance in a composite end-point related to endurance
- Larger trial (96 Subjects)
- Longer placebo-controlled phase (12 months)

But.....

- All subjects able to 'co-operate with testing'
- Therefore all subjects attenuated (i.e. the minority of those with MPSII)
- Over the age of 5 years
- Relationship of endpoint to disease progression and quality of life unclear
- Many very important questions remain

How else can we learn?

- Extension phase to trial
- Published case reports and series
- Hunter Outcome Survey (HOS)

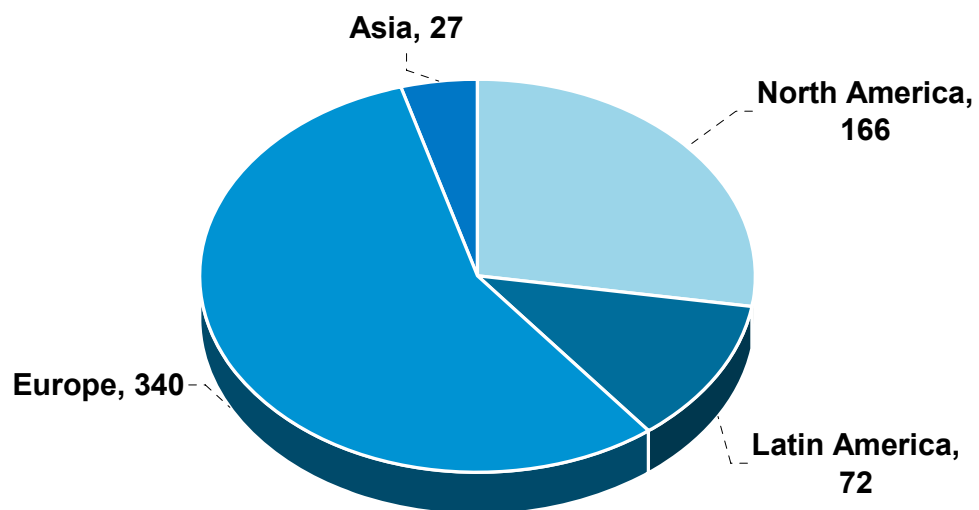
Hunter Outcome Survey - HOS

- Commenced 2005
- 765 patients globally
- Working groups
 - Natural history
 - Cardiac
 - CNS
 - Airway/ENT?

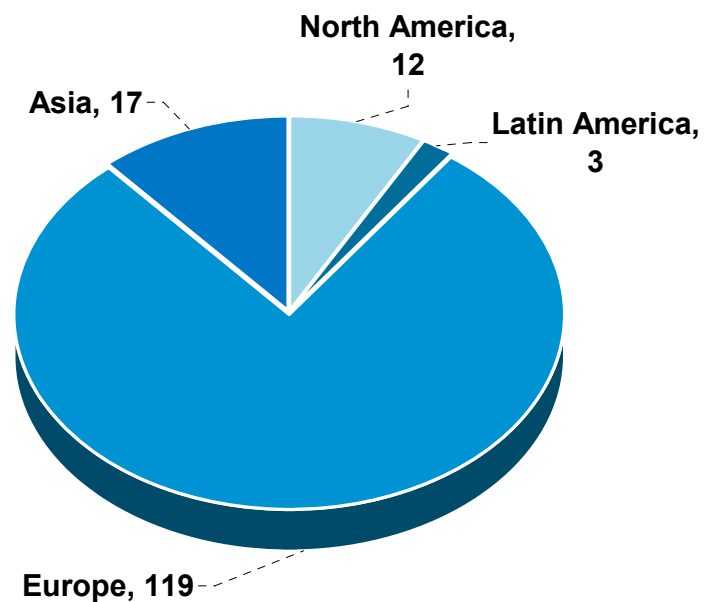
Regional Breakdown of HOS

Prospective vs Historical

Prospective Patients, N = 605

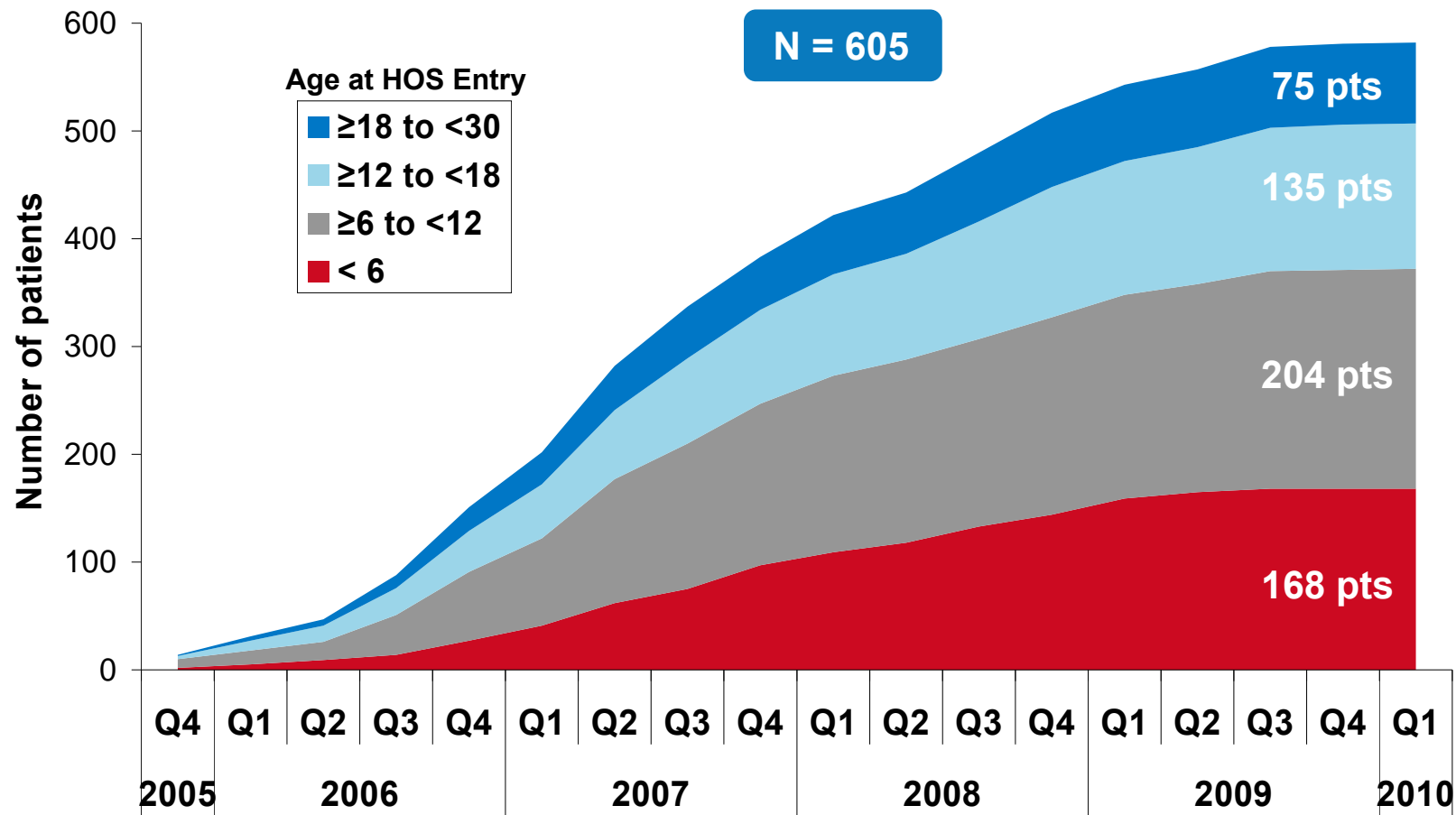


Historical Patients, N = 151



Enrollment over Time

Prospective Patients



HOS Data as of January 22nd
2010

What can ERT do well?

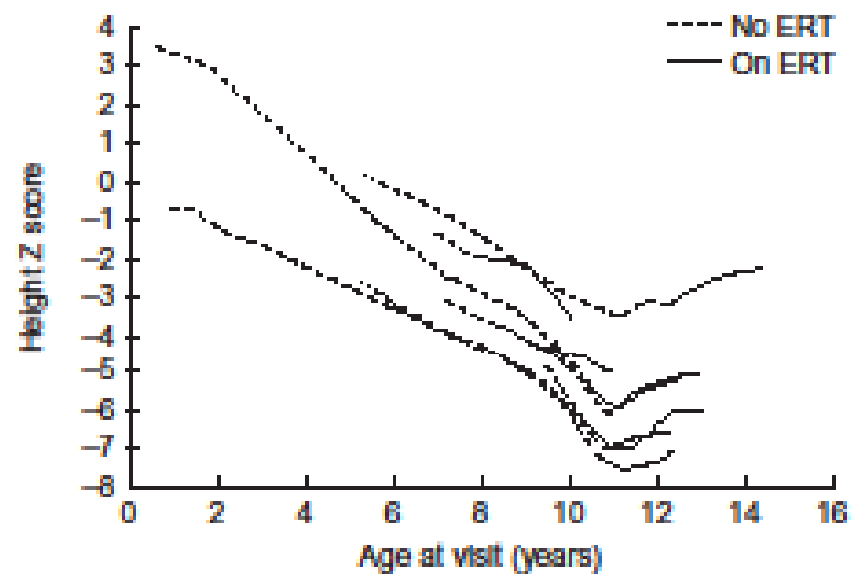
- Hepatosplenomegaly
- Skin rash and soft tissue deposits
- Reduce joint 'stiffness'
- Airway deposits

What can ERT NOT do?

- Reach tissues with slow turnover and poor blood supply
 - Cardiac valves
 - Cartilage
 - Bone
- Cross the BBB (currently used therapies)

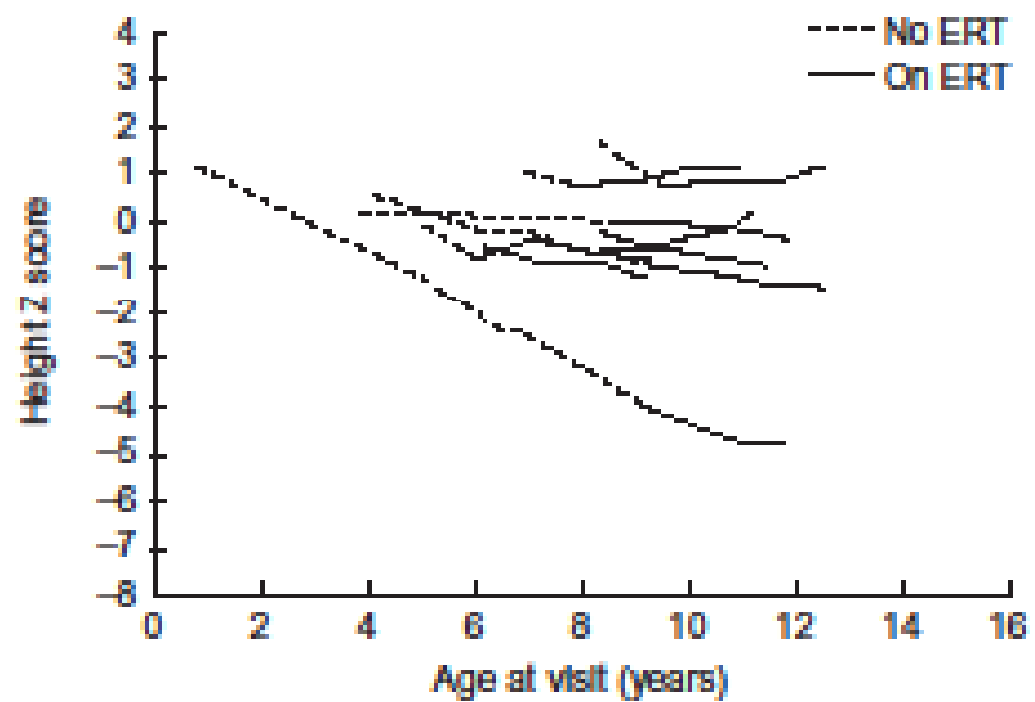
The question of bone and joint involvement?

- Once joints are heavily changed/ destroyed there may be no way back
- Early treatment may improve bone health
- Early treatment seems to impact on growth



The role of antibodies in ERT for Hunters?

- Complex relationship to infusion associated reactions
 - Occur at similar time in treatment course
 - Not a clear association with type or titre
- Impairment of efficacy unclear in a general sense
 - i.e. not all antibodies 'bad'
 - Some individual cases demonstrate a clear deleterious effect



What we don't know (much)..

- Intravenous ERT in:
 - Under 5 years (i.e. early treated)
 - Severe (CNS involved) Hunter patients
 - Well tolerated in most
 - Home therapy feasible
 - Most do well and derive 'benefit' at least initially
 - Does not prevent disease progression in CNS

Manchester severe Hunter patients

- 13 families offered treatment
- 1 refused
- 1 stopped after 6 weeks
- 1 stopped after 2 years
- 2 stopped after 3 years
- Ongoing discussions with rest of families
- No regrets....

What we don't know (at all)..

- How early in the course of the disease do we have to treat?
- Is there any effect on the brain of iv Idursulfase?
- Role of intra-thecal ERT in severe Hunter patients?
 - Trial just commenced in US

Acknowledgements

- Prof Ed Wraith
- Jane Roberts – MPS II nurse specialist
- Prof Beck and Dr Schulze-Frenking (Mainz)
- Yvonne Jangelind - Shire HGT (HOS)