

inventiva



**iMProves**  
I M P R O V E M P S T R E A T M E N T

***WEBCAST – iMProves Head Line Results***  
***19 December 2019***

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# Today's speakers

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**Frédéric Cren, MA/MBA, Chairman, CEO and Co-Founder**



**Pierre Broqua, Ph.D., CSO and Co-Founder**



**Marie-Paule Richard, MD, CMO**



**Chris Hendriksz, member of the iMProveS clinical study steering committee and extraordinary professor of Paediatrics and Child Health, University of Pretoria, South Africa**

## ▶ Introduction

## ▶ Mucopolysaccharidoses (MPS) diseases

## ▶ Odiparcil mechanism of action

## ▶ iMProveS trial

- Study design and objectives
- Patients disposition
- Baseline characteristics and MPS history
- Odiparcil pharmacokinetic profile
- Odiparcil pharmacodynamics: urinary GAGs
- Safety
- Efficacy

## ▶ Conclusions

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## Mucopolysaccharidoses (MPS) diseases

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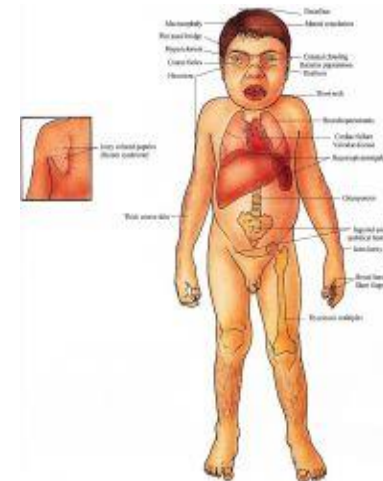
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# Mucopolysaccharidoses (MPS): rare genetic disorders caused by the absence or malfunctioning of lysosomal enzymes

## Pathology

- ▶ Lysosomes function as the primary digestive units within cells: enzymes within lysosomes break down or digest particular nutrients, such as certain carbohydrates and fats
- ▶ The absence or malfunctioning of lysosomal enzymes are responsible of metabolic disorders caused the abnormal degradation of glycosaminoglycans (GAGs) or mucopolysaccharides
- ▶ The progressive accumulation of GAGs in the lysosomes causes progressive damage throughout the body, including the heart, eyes, bones, joints, respiratory system and central nervous system
- ▶ MPS symptoms are first shown during early childhood and patient's life expectancy depends on the severity of symptoms: without treatment, severely affected individuals may survive only a few years, those with milder forms of the disorder usually live into adulthood, although their life expectancy may be reduced

## Clinical signs



## Epidemiology

- ▶ MPSs are autosomal recessive except X linked MPS II
- ▶ The prevalence of all forms of MPs combined is estimated to be 1 / 25 000 births
- ▶ However, because MPS, especially the milder forms of the diseases, often go unrecognized, these disorders are under-diagnosed or misdiagnosed, making it difficult to determine their true frequency in the general population

## Diagnosis based upon

- ▶ The clinical identification of characteristic findings (e.g., coarse facial features, skeletal malformations, hepatosplenomegaly)
- ▶ A variety of specialized tests including urine analysis to detect increased levels of GAGs
- ▶ Enzyme assays may be also performed to detect deficient levels of lysosomal
- ▶ Genotyping may be also performed to identify mutations

**Patient associations to help families with MPS can be found in almost all countries**

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## Odiparcil mechanism of action

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# Odiparcil: a GAG clearance therapy in MPS in which dermatan and chondroitin sulfates (DS, CS) accumulate

Odiparcil original mechanism of action could provide additive benefit to enzyme replacement therapies (ERT) in MPS I, II, IVA, VI and VII patients

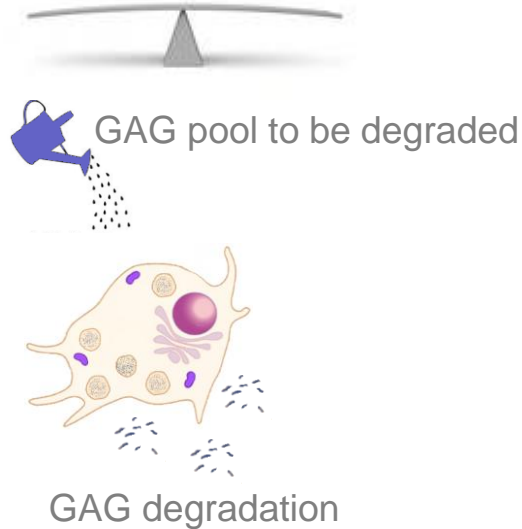
Odiparcil diverts endogenous protein-bound GAG to **soluble odiparcil-bound CS and DS synthesis**

Protein-bound GAG (HS, CS, DS, KS)

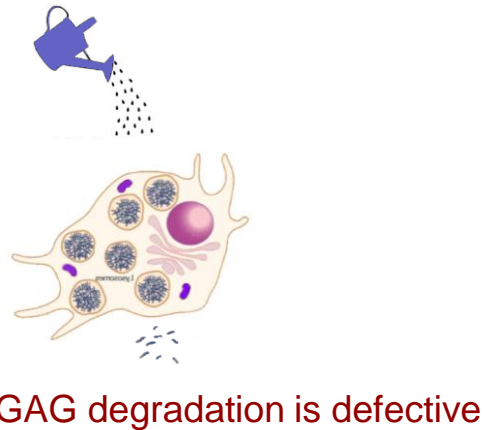


Odiparcil-bound GAGs (DS and CS)

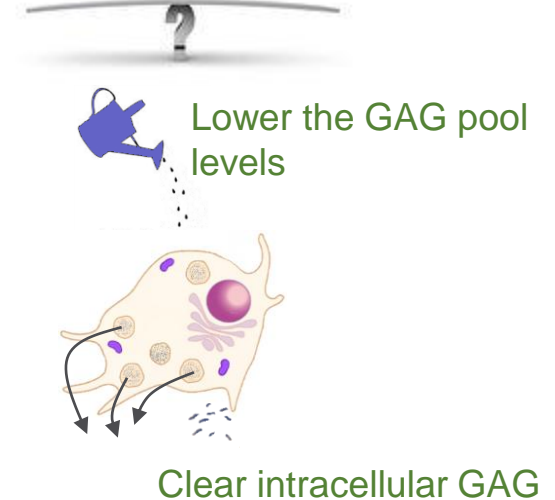
Healthy



MPS



GAG clearance therapy

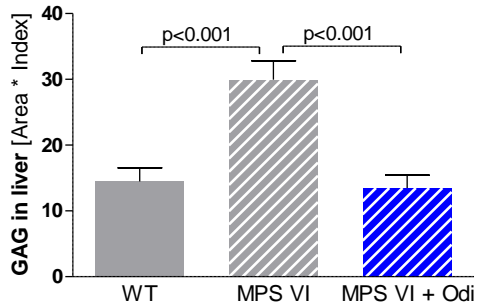




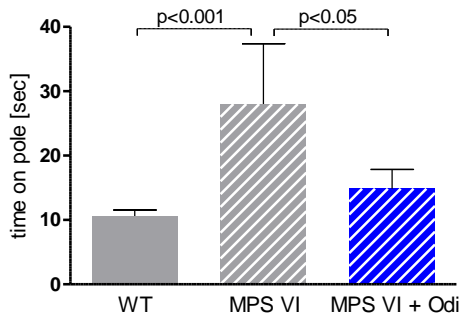
# Odiparcil GAG clearance mechanism of action observed in MPS VI mice



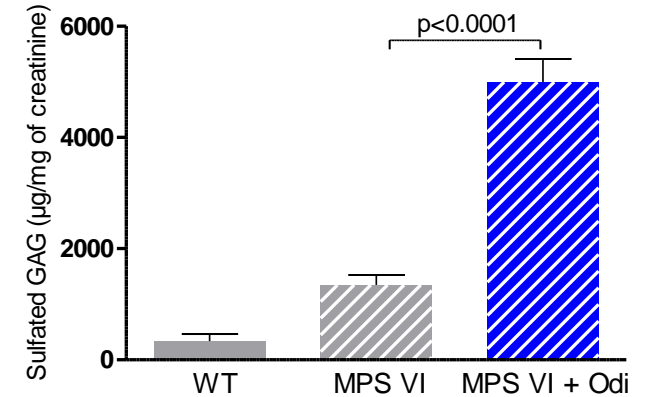
**Odiparcil decreases GAG accumulation in tissues**



**Odiparcil restores mobility**



**Soluble GAG produced from Odiparcil are excreted in urine**



**Wild-type and MPS VI mice**

# Odiparcil penetrates tissues that ERT cannot reach

Odiparcil is well distributed in tissues and organs poorly penetrated by recombinant enzymes

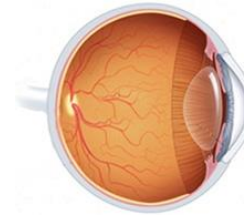
Heart



Bone



Cornea



Cartilage



Odiparcil<sup>(1)</sup>



rhASB<sup>(2)</sup>



Not tested

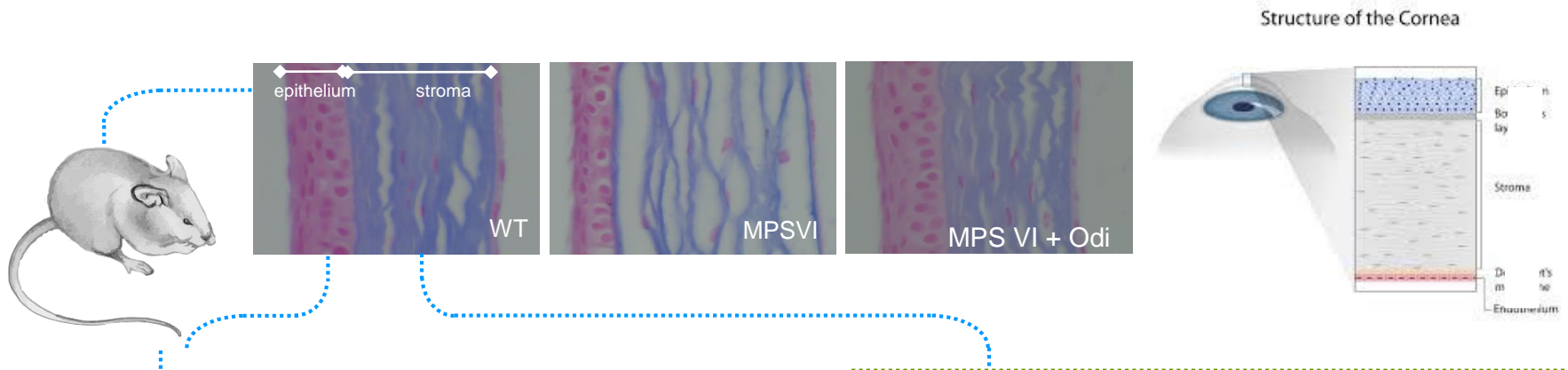
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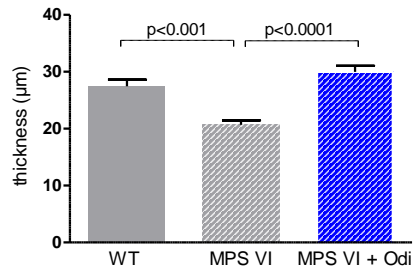
Meaningful concentrations of odiparcil observed also in tissues that are poorly vascularized or protected by a barrier: bone, corneal tissue and cartilage

# Odiparcil reverses corneal impairment in MPS VI mice

## Odiparcil restores a healthy corneal structure and decreases corneal GAG storage

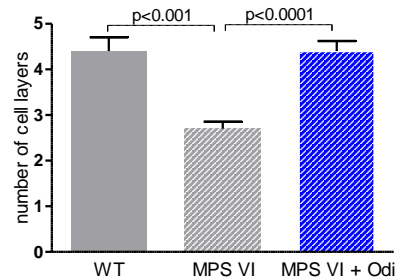


### Odiparcil restores corneal epithelium thickness



N=10 for all groups

### Odiparcil restores corneal epithelium cell layers



### Odiparcil decreases GAG storage in corneal stroma

#### Blinded corneal stroma vacuolation scoring

WT	0.0
MPS VI	2.9
MPS VI + Odi	0.5

#### scale (0-3)

0. no detectable vacuolation, no GAG accumulation
1. some large vacuolation with some distended cells
2. extensive area of large vacuolation with GAG accumulation
3. extensive area of large vacuolation with GAG accumulation and separate collagen fibers

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## *iMProveS trial*

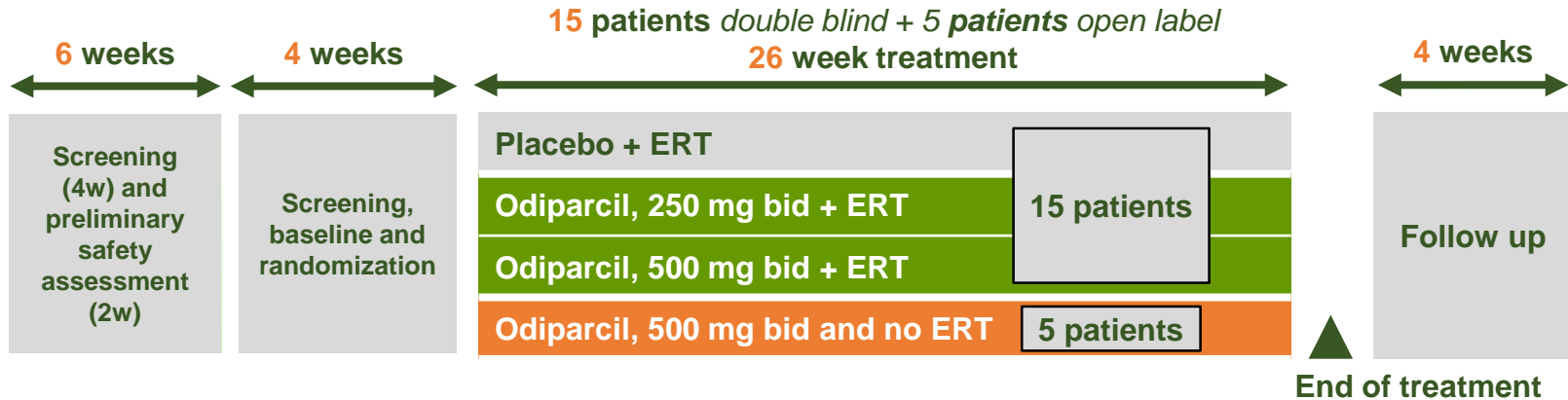
- Study design and objectives
- Patients disposition
- Baseline characteristics and MPS history
- Odiparcil pharmacokinetic profile
- Odiparcil pharmacodynamics: urinary GAGs
- Safety
- Efficacy

# Study design and objectives of iMProveS Phase IIa trial of odiparcil in MPS VI

## Phase IIa

- ▶ Phase III enabling study with evidence for dose selection and PK / PD response characterization
- ▶ **Clinicaltrials.gov identifier:** NCT03370653

## Population



## Objectives

### Safety

- ▶ Clinical and biological assessments (standard tests)

### Pharmacokinetics

- ▶ Odiparcil plasma levels

### Efficacy

- ▶ Leukocyte, skin and urinary GAG content
- ▶ Activity and mobility tests (6 minute walk test, upper limb function, shoulder mobility range)
- ▶ Cardiac, vascular and respiratory functions
- ▶ Eye impairment, hearing capacity, pain assessment, quality of life questionnaires

More information on: <http://www.improves-mpsvi-trial.com/>

	ERT blinded cohort			Non-ERT open-label cohort	Total N = 26
	Placebo	Odiparcil 250mg bid	Odiparcil 500mg bid	Odiparcil 500mg bid	
<b>Screened patients</b>					26
<b>Included patients</b>					20
<b>FAS population [a]</b>	5	5	5	5	20
<b>Safety population [b]</b>	5	5	5	5	20
<b>End of treatment</b>					
• <b>Treatment period completed</b>	4	3	3	3	13
• <b>Treatment premature discontinuation</b>					
<b>Adverse Event</b>	1*	2	2	1	6
<b>Patient's decision</b>	0	0	0	1	1

[a] FAS: Randomised patients in double-blind cohort or included in open-label cohort receiving at least one dose of study treatment

[b] Safety: Patients who received at least one dose of study treatment

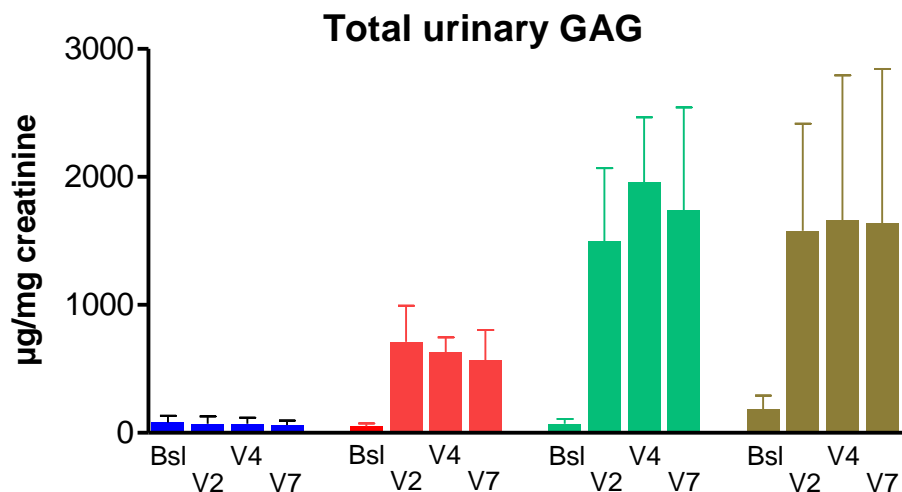
\* Death due to bronchopneumopathy

# Baseline characteristics and MPS history – FAS population

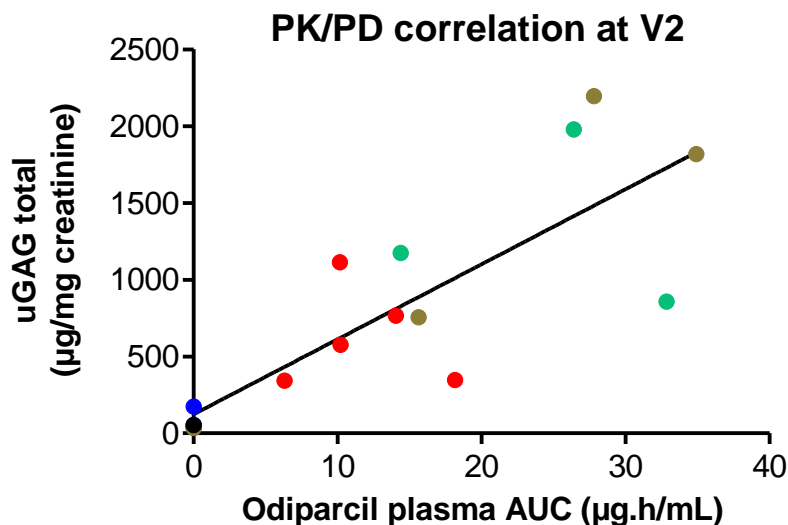
		Placebo N = 5	Odiparcil 250mg bid N = 5	Odiparcil 500mg bid N = 5	Odiparcil 500mg bid N = 5
<b>Gender</b>	Female	2	3	2	2
	Male	3	2	3	3
<b>Age (years)</b>	Median	18.0	24.0	25.0	28.0
	Min ; Max	16.0 ; 31.0	18.0 ; 64.0	17.0 ; 33.0	20.0 ; 39.0
<b>Height at baseline (cm)</b>	Median	130.0	147.0	122.0	140.0
	Min ; Max	111.0 ; 155.0	132.0 ; 150.0	108.0 ; 148.0	111.0 ; 165.0
<b>Age at diagnosis (years)</b>	Median	3.24	7.30	1.05	17.10
	Min ; Max	1.3 ; 6.5	4.4 ; 59.0	0.3 ; 6.9	5.3 ; 34.3
<b>Time elapsed of MPS diagnosis (years)</b>	Median	15.7	10.7	19.7	5.9
	Min ; Max	11.5 ; 27.8	5.0 ; 20.6	16.4 ; 28.5	2.0 ; 31.7
<b>Duration of ERT treatment (years)</b>	Median	13.42	12.07	13.87	
	Min ; Max	11.2 ; 16.8	4.4 ; 15.1	12.4 ; 17.0	

# Odiparcil pharmacodynamics: urinary GAGs

## Total GAG levels in urine and PK/PD correlation



- uGAG (total) is increased after 4 week of Odiparcil
- uGAG increase reaches a steady state after 4 weeks of treatment
- At 1000 mg/day increased is comparable in ERT and non-ERT cohorts



Urinary GAG (total) is correlated with odiparcil exposure in plasma

● Placebo

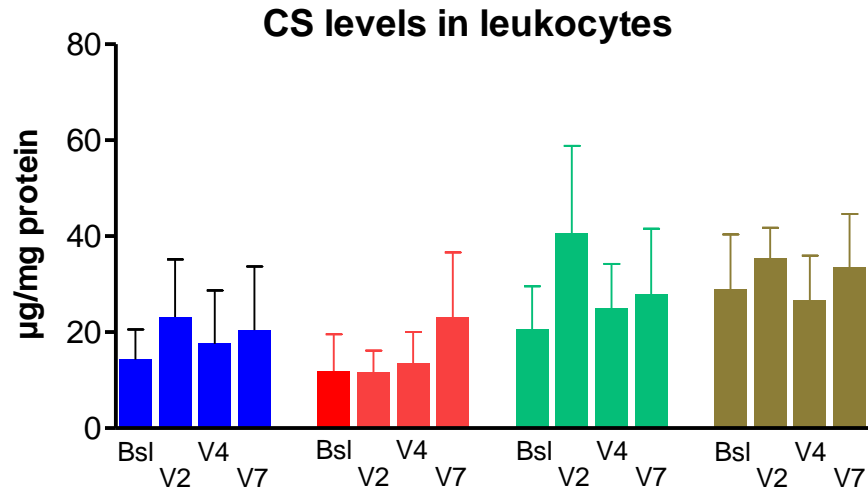
● odiparcil 500mg

● odiparcil 1000mg

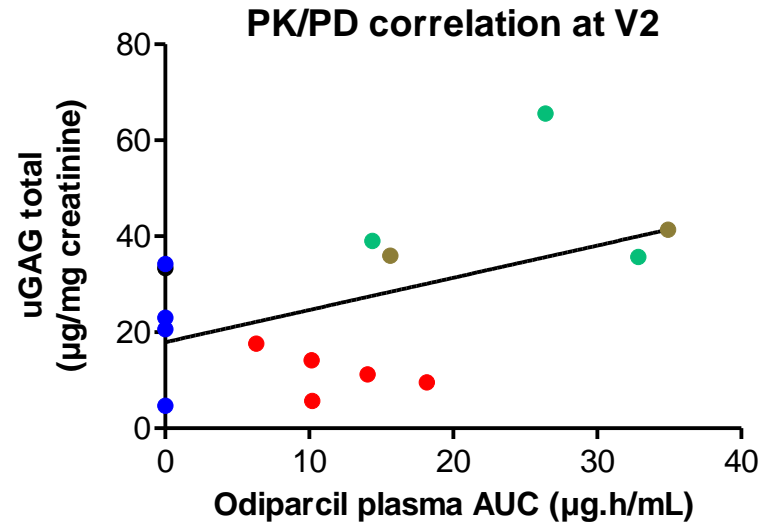
● Non-ERT, odiparcil 1000mg

**Consistent with odiparcil's mechanism of action, a dose-dependent urinary GAGs clearance, used as an activity biomarker, was clearly demonstrated in the entire patient population treated with odiparcil**





- CS levels in leukocytes are variable in all groups
- Effect of treatment can not be assessed



No correlation between CS levels in leukocytes and odiparcil exposure in plasma

● Placebo

● odiparcil 500mg

● odiparcil 1000mg

● Non-ERT, odiparcil 1000mg

**In this study and similarly to ERT, leukoGAGs not confirmed as biomarkers for decrease of GAG accumulation**

- ▶ The **clinical study met its safety primary objective** further supporting the good overall safety profile of odiparcil already observed in previous Phase I and Phase II clinical studies
- ▶ **All 4 European investigators** of the iMProveS study **reported positive experience** with odiparcil in terms of safety
- ▶ The majority of adverse events were **mild or moderate**
- ▶ One death occurred in the placebo group
- ▶ Three serious adverse events (SAEs) were assessed as treatment-related in patients in the odiparcil groups.
  - Two SAEs were biological findings qualified as laboratory false-positive.
  - One SAE was a skin reaction, which is frequently observed in MPS patients.
- ▶ Compared to previous Phase I and II clinical studies conducted with odiparcil for the prevention of thrombosis, **no new safety findings were observed**

# Number of patients with at least one treatment-related Adverse Event (AE)

	Double blind (ERT)			Open label (non-ERT)
	Placebo N = 5	Odiparcil 250mg bid N = 5	Odiparcil 500mg bid N = 5	Odiparcil 500mg bid N = 5
AE	1	5	5	4
Serious AE	0	2	1	0
Severe AE	0	1	0	0
Moderate AE	0	3	1	1
Mild AE	1	5	5	4

AEs: occurred from first to last dose of the study treatment in the core study  
 Serious stands for hospitalisation or considered Important medical event by the investigator

	Double blind (ERT)			Open label (non-ERT)
	Placebo N = 5	Odiparcil 250mg Bid N = 5	Odiparcil 500mg Bid N = 5	Odiparcil 500mg Bid N = 5
Bronchopneumopathy	1, severe			
Proteinuria*		1	1	
Rash*		1, severe		
Acute Respiratory Failure				1, severe
Calculus Bladder	1			
Urinary Tract Infection			1	
Device Breakage**			1	
Venous Occlusion**			1	

SAEs: occurred from first to last dose of the study treatment ; Serious stands for hospitalisation or considered Important medical event by the investigator

\* Assessed treatment-related by the investigators ; \*\* Same patient

## 9 SAEs in 8 patients

- 2 patients in the placebo group including 1 death due to bronchopneumopathy
- 6 patients in the odiparcil groups including 3 treatment-related SAEs
  - *Proteinuria* further qualified as Laboratory false positive
  - *Rash* (skin exanthema) that recovered

- ▶ Number of evaluable patients at Visit 7 (26 weeks): N=13
  
- ▶ Main efficacy parameters at baseline and end-of-treatment (EOT):
  - Mobility: 6MWT, 9Hole Peg Test, Shoulder ROM,
  - Respiratory function: FEV1, FVC
  - Brief Pain Inventory (BPI): dimensions pain and interference,
  - Ophthalmological parameters: visual acuity, slit lamp examination, intra-optic pressure, corneal opacification measurement (COM), central cornea thickness
  - Cardiovascular parameters: Cardiac (ECG, echocardiogram), and Carotid Intima Media Thickness (CIMT)

- ▶ A steering committee and Experts in Audiology, Cardiology and Ophthalmology **reviewed blindly all body systems measurements** and evaluations with their overall medical history and profile, and therefore assessed efficacy of each of them in a 5-point scale by body system:
  - Improved
  - Slightly improved
  - Stable
  - Slightly worsened
  - Worsened
- ▶ Body systems analyzed were Locomotor, Respiratory, Ophthalmologic, Cardiac, and Audiologic
- ▶ Body systems analyses included the usual descriptive statistical parameters, and both
  - the relative change from the reference value to the end of treatment (EOT)/V7 visit value
  - the absolute change from the reference value to the V7 value

Treatment	Respiratory (FVC)	Ophthalmology (COM)	Cardiology
ERT Placebo (N=4)	0	1 (slightly improved)  #Patient D: +12%, +24%	1 (slightly improved)  #Patient F: ↓ 30% LVMI
	3 (slightly improved)	2 (improved)	4 (3 slightly improved + 1 improved)
ERT ODI (N=6)	<u>250mg bid</u> #Patient A: + 5%	<u>250mg bid</u> #Patient E: +19%, +23%	<u>250mg bid</u> #Patient E: no longer mitral regurgitation #Patient A: ↓ 17% LVMI
	<u>500mg bid</u> #Patient B: + 4% #Patient C: +9%	<u>500mg bid</u> #Patient C: +42%(a)	<u>500mg bid</u> #Patient C: ↓ severity mitral regurgitation
			#Patient G: ↓ 14.5% LVMI, ↓ severity aortic regurgitation, ↓ CIMT both carotids

► Regarding locomotor function, no clear difference was observed among the different patient subgroups

(a) Corneal transplant of the other eye  
LVMI: left ventricular mass index (echocardiogram)  
CIMT: carotida intima media thickness

- ▶ Considering the short study duration, patients under long ERT duration, and the advanced status of the disease in adult patients included in the study, the iMProveS study showed positive results regarding the efficacy of odiparcil.
  - Improvements were observed in patients treated with odiparcil, in addition to ERT, with regards to corneal clouding as well as cardiac and respiratory functions.



Some initial signals of efficacy were also detected in the 3 non-ERT treated patients

Treatment	Respiratory (FVC)	Ophthalmology	Cardiology	Range of Motion	Other
Patient # 1	Improved FVC by +18%	NA	Stable	Improved range of motion on both shoulders (+17,8%/+21,0%)	Pain improved
Patient # 2	Stable	Stable	Slightly Worsened	Improved range of motion on both shoulders (+8,1%/+8,5%)	Pain improved
Patient # 3 <ul style="list-style-type: none"> <li>• Severe patient hospitalized</li> <li>• Poor compliance</li> </ul>	NA	Stable	Worsening	Worsening	Pain improved

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# Conclusions

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## Conclusions (1/2)

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- ▶ Safety primary objective further supports the **good overall safety profile of odiparcil** already observed in previous Phase I and Phase II clinical studies
  - **No new safety findings were observed**
- ▶ **Positive results regarding the efficacy** after 6 months of odiparcil in advanced stages of MPS VI disease
- ▶ Improvements in patients treated with odiparcil, in addition to ERT, with regards to **corneal clouding** as well as **cardiac** and **respiratory functions**
  - Regarding locomotor function, no clear difference among the different patient subgroups.
- ▶ Consistent with odiparcil's mechanism of action, **a dose-dependent urinary clearance of glycosaminoglycans** (GAGs), used as an activity biomarker, was clearly demonstrated in the entire patient population treated with odiparcil.
- ▶ Similarly to ERT, odiparcil did not induce a reduction of leukocyte GAGs, which is not confirmed as a biomarker for the decrease of GAG accumulation in this study.

## Conclusions (2/2)

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- ▶ The PK profile obtained in MPS VI patients treated with odiparcil is not impacted by ERT and is consistent with profiles previously observed in other Phase I and Phase II studies in prevention of thrombosis
- ▶ Inventiva will **continue the clinical development of odiparcil** for the treatment of MPS VI

**➡ Launch, as planned, a clinical study evaluating odiparcil in MPS VI children, the target population for this disease**

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**Q&A**

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