Pioneering gene therapies for CNS disorders

Advanced Therapies – Opportunities and Challenges
14th November, London
Michaël Hocquemiller
Michael Hocquemiller, PhD is a full time employee and shareholder of LYSOGENE.

The investigational use of AAVrh10-SGSH gene therapy for MPS IIA will be presented.

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Lysogene was founded in 2009 by Karen Aiach, the parent of an MPS IIIA (Sanfilippo A) child. Co-founded with the world-leading gene therapy expertise of Olivier Danos. Lead product candidate (LYS-SAF302) is entering a pivotal phase 2/3 trial in MPS IIIA patients.

### LYSOGENE FOCUS

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>PROGRAM</th>
<th>VECTOR</th>
<th>ENZYME</th>
<th>PRE-CLINICAL</th>
<th>PHASE I/II*</th>
<th>PIVOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sanfilippo A (MPS IIIA)</td>
<td>LYS-SAF302</td>
<td>AAVrh10</td>
<td>N-sulfoglycosamine sulphohydrolase</td>
<td></td>
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<td></td>
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<tr>
<td>GM1 Gangliosidosis</td>
<td>LYS-GM101</td>
<td>AAVrh10</td>
<td>Beta-galactosidase-1</td>
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**Comments**
- **Pivotal trial to begin by H1 2018 (FPI**)**
- **Phase I/II trial to begin in 2019 (FPI**)**

*FPI : « First Patient In », treatment of the first patient

*MPS IIIA Phase I/II: LYS-SAF301, first generation program
MPS IIIA (MUCOPOLYSACCHARIDOSIS TYPE IIIA /SANFILIPPO SYNDROME TYPE A)

Inheritance
Autosomal recessive lysosomal storage disease

Symptoms
First clinical symptoms occurring early in life
Severe behavioral, sleep and cognitive deficiencies and progressive loss of functions such as talking, eating, walking
Less than 15% patients survive beyond their teens

Population
Incidence: 0.5-1.2 / 100,000 live births \(^{(1)}\)
Point prevalence worldwide: 3000 \(^{(2)}\)

Burden of disease
Extremely deteriorating quality of life, devastating for patients and families \(^{(3)}\)
Massive social/economic costs

Treatment
No approved or curative treatments

Notes:
(1) Heron (2011); Poorthuis (1999)
(2) Average life expectancy: 15 years;
(3) Grant (2012)
To overcome the blood brain barrier hurdle, therapy must get to the CNS with a broad distribution throughout the brain so that the missing enzyme is sustainably produced where it is most needed.

- SGSH is a secreted enzyme and can therefore have an effect on cells distant from transfected cells via cross correction.

- AAV-mediated transfection of neurons is expected to express the transgene, SGSH, long-term, as supported by existing brain expression data e.g., long-term transgene expression (AAV2-NRTN) has been shown up to 11.5 years in human Parkinson patients (R. Bartus, personal communication).

- Lysogene has a unique expertise in gene therapy in MPS IIIA with 5 years safety data with LYS-SAF301 (1st generation product).

- Intense program optimization performed since the early Phase 1/2 LYS-SAF301 Study to support a Pivotal LYS-SAF302 Study.
# LYS-SAF302: An Optimized Second-Generation Program

**Product Candidate**

<table>
<thead>
<tr>
<th>LYS-SAF301</th>
<th>LYS-SAF302</th>
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<tbody>
<tr>
<td>mPGK</td>
<td>CAG</td>
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**Transgenes**

<table>
<thead>
<tr>
<th>LYS-SAF301</th>
<th>LYS-SAF302</th>
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<tbody>
<tr>
<td>SGSH cDNA &amp; SUMF-1 cDNA</td>
<td>SGSH cDNA</td>
</tr>
</tbody>
</table>

**Manufacture**

<table>
<thead>
<tr>
<th>LYS-SAF301</th>
<th>LYS-SAF302</th>
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<tbody>
<tr>
<td>Academic centres: Weill Cornell, University College London</td>
<td>Commercial CMO: Novasep, process development &amp; optimization</td>
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**Delivery**

<table>
<thead>
<tr>
<th>LYS-SAF301</th>
<th>LYS-SAF302</th>
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<tbody>
<tr>
<td>Physician-assembled device</td>
<td>Commercial device</td>
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**Improved construct increases enzyme activity**

MPS IIIA Mouse model

**SGSH Enzyme Activity**

- % of WT activity
  - **LYS-SAF301** vs WT: $p < 0.001$
  - **LYS-SAF302** vs WT: $p < 0.05$

4 weeks post injection
NORMAIZATION OF BEHAVIOR IN MPS IIIA MOUSE MODEL

Analysis of behavior: Open field test

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<tr>
<th>Condition</th>
<th>Frequency Speed, &gt;100mm/s (sec)</th>
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<tbody>
<tr>
<td>Wild Type</td>
<td>100 ± 20</td>
</tr>
<tr>
<td>MPS IIIA untreated</td>
<td>500 ± 30</td>
</tr>
<tr>
<td>AAVrh10-SGSH treated</td>
<td>200 ± 10</td>
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Shown as frequency of rapid exploration - 16 wks post-injection

- Wild Type
- MPS IIIA untreated
- MPS IIIA treated
Rostro-Caudal spread of Gadolinium, Vector and SGSH activity in Dog Brain Mapped onto Child’s Brain

3 injections/hemisphere planned in clinical trial
### Primary Objective

Assess the efficacy of direct to CNS delivery of LYS-SAF302 in improving or stabilizing the neurodevelopmental status of severe MPS IIIA patients after 12 months, compared with the natural history. Powered to demonstrate disease stabilization using Development Quotient as PEP\(^{(1)}\).

### Endpoints

- **Primary endpoints:** Neurocognitive and motor development (Development quotient)
- **Secondary endpoints:** Behavior, sleep, QOL\(^{(2)}\), MRI\(^{(3)}\), Biomarkers (CSF, blood, urine)

### Sample Size and Sites

- N=20 patients
- **US:** sites
- **EU:** sites

### First Patient Enrolled

By Q2-2018

### Study Duration

- 12-24 months (efficacy analysis)
- Study extension of additional 4 years, with secondary efficacy analysis at 24 months

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\(^{(1)}\): DQ= Development Age/Calendar age ;\(^{(2)}\): QOL= Quality Of Life; \(^{(3)}\): MRI= Magnetic Resonance Imaging
Inheritance
Lysosomal disease caused by mutations in the GLB1 gene, which encodes the β-galactosidase enzyme

Symptoms
Four clinical subtypes based on age of symptom onset and disease severity: early infantile, late infantile, juvenile and adult.
Severe neurodegeneration, seizures, coarse facial features.
100% lethal

Population
Incidence: 1/200 000 to 1/100 000 live births
Prevalence: 2,000

Burden of disease
Extremely deteriorating quality of life, devastating for patients, and families

Treatment
No approved or curative treatments

Notes
LYS-GM101: TRANSFORMATIONAL IMPROVEMENT OF SEVERE MOTOR DISTURBANCE AFTER TREATMENT WITH DIRECT TO BRAIN AAV GENE THERAPY

Direct to brain injections of an AAV prototype in GM1 cat model

6-7 month-old GM1 cat

5 year-old AAV-treated GM1 cat

Research Collaborations

Source: Douglas R. Martin lab, Scott-Ritchey Center at Auburn University School of Veterinary Medicine
CONCLUSION

• Intracerebral injection of AAV vector provides a durable therapeutic protein via a single administration.

• AAV serotype and route of administration choices are crucial and need to be supported by efficacy data in animal disease models of the disease and biodistribution studies in larger animals.

• Concerted efforts are required for gene therapy development to accelerate research through collaborations between academia, industry and patient organizations.