Delivering advanced therapies to transform the lives of patients
Phase 2/3 AAVance Trial Topline Results Webcast

November 23, 2022
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Opening remarks
Karen Aiach
Chairman and Chief Executive Officer
Our story

‘Founded in 2009 by Karen Pignet-Aiach, whose own child was affected by a neurodegenerative disease, Lysogene is rooted in a deep and compassionate understanding of the impact these diseases have on patients and families. Karen’s personal experience fuels her determination to deliver real solutions that will improve patient outcomes and enhance quality of life for both patients and caregivers.’

OUR VISION

Delivering advanced therapies to transform the lives of patients suffering from devastating CNS diseases
Lysogene is focused on treating devastating neurodegenerative and neurodevelopmental diseases to achieve efficient therapeutic outcomes for patients.

- **Current CNS disease indications** in the pipeline, including rare and more prevalent conditions.
- **End-to-End Gene Therapy technology platform** with direct to CNS delivery.
- **5** current CNS disease indications in the pipeline, including rare and more prevalent conditions.
- **>10** Peer-Reviewed Scientific Publications.
- **4 ODDs, 2 RPDDs, 2 Fast track designations, 1 Innovation Passport**
- **Strong know-how in AAV manufacturing up to commercial-grade**

*(Euronext listed; LYS)*
## A diversified and differentiated early to late-stage pipeline

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<tr>
<th>Program</th>
<th>Discovery</th>
<th>IND-Enabling</th>
<th>Phase 1/2</th>
<th>Phase 2/3</th>
<th>Innovation/Differentiation</th>
<th>Designations</th>
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</table>
| LYS–SAF302         |           |              |           |           | Direct to CNS               | ▪ ODD (FDA)  
▪ ODD (EC)  
▪ RPDD (FDA)  
▪ Fast Track (FDA) |
| MPS IIIA Sanfilippo syndrome |          |              |           |           |                             |                                                |
| LYS–GM101          |           |              |           |           | Direct to CNS               | ▪ ODD (FDA+EC)  
▪ MHRA Innovation Passport (UK)  
▪ RPDD (FDA)  
▪ Fast Track (FDA) |
| GMI Gangliosidosis |           |              |           |           |                             |                                                |
| LYS–PDG01          |           |              |           |           | Direct to CNS               | ▪ ODD (FDA+EC)  
▪ MHRA Innovation Passport (UK)  
▪ RPDD (FDA)  
▪ Fast Track (FDA) |
| Parkinson–Gaucher  |           |              |           |           | Improved transgene          |                                                |
| LYS–ALS01          |           |              |           |           | Direct to CNS               | ▪ ODD (FDA+EC)  
▪ MHRA Innovation Passport (UK)  
▪ RPDD (FDA)  
▪ Fast Track (FDA) |
| ALS                |           |              |           |           | Novel approach              |                                                |
| LYS–FXS01          |           |              |           |           | Direct to CNS               | ▪ ODD (FDA+EC)  
▪ MHRA Innovation Passport (UK)  
▪ RPDD (FDA)  
▪ Fast Track (FDA) |
| Fragile X Syndrome |           |              |           |           | Novel target                |                                                |

**Neuro degenerative disease**

**Neuro developmental disease**
Phase 2/3 AAVance Trial Topline Results

Ralph Laufer, Chief Scientific Officer
Marie Trad, Chief Medical Officer
LYS–SAF302 for MPS IIIA

Rare neurodegenerative disease with high unmet medical need

- Caused by mutations in SGSH gene - accumulation of heparan sulfate
- Cognitive decline, behavioral and motor dysfunction
- Incidence: 0.5–1.2/100,000 births
- Global prevalence: 2,500–3,000
- No approved treatment

Direct-to-CNS delivery

- Optimized 2\textsuperscript{nd} generation product
- Intraparenchymal delivery to directly target the brain
- Most efficient method to bypass the blood brain barrier
- Robust preclinical proof of concept
- Potential first and best in class
Snapshot of Phase 2/3 AAVance trial (NCT03612869)

| Dosing | • N=19 patients, 10–64 months at screening  
|        | • Dose 7.2x10^{12} vg |
| Inclusion criteria | • ≥ 6 months, DQ≥ 50%  
|                  | • Main cohort: ≥30m at screening  
|                  | • Ancillary cohort: <30m at screening |
| Primary Endpoint (Main Cohort, n=13) | • Change in DQ (BSID-III) at 24 months vs baseline  
|                                | • Comparator: Natural History cohort |
| Primary Endpoint (Ancillary Cohort, n=6) | • DA at age 48m vs Natural History Study (NHS) |
| Secondary Endpoints | • Evolution of DA and DQ  
|                     | • Behavior  
|                     | • Quality of life  
|                     | • Imaging Biomarkers  
|                     | • Fluid Biomarkers  
|                     | • Safety/tolerability |
| Efficacy Assessment | • Primary, secondary and exploratory endpoints  
|                     | • PROVide video study |

Note: 1. DQ: Developmental Quotient; 2. MPS Type III (Sanfilippo Syndrome): Developing Drugs for Treatment. Guidance for Industry. Draft guidance; FDA Feb 2020
Cognitive development in MPS IIIA Natural History

**Developmental Age (DA)**

- **Dotted straight line:** Normal development, DQ=100
- **Dotted curve:** Hand-drawn estimation of mean DA evolution

**Developmental Quotient (DQ=DA/Age)**

Note: Data from Shapiro et al. 2016; Wijburg et al. 2022
DA: Developmental Age; DQ: Developmental Quotient
Statistical analysis shows no treatment effect in main cohort (subjects enrolled at age ≥30 m)

First evidence for treatment benefit in the youngest subjects (ancillary cohort enrolled at age <30m). Primary endpoint analysis at 48m of age (2Q 2023)

Gray lines: Natural history patients
Colored lines: Treated patients

Note: 1. Data from Shapiro et al. 2016; Wijburg et al. 2022
Positive evolution of cognitive DA in the ancillary cohort (subjects enrolled at less than 30 months of age, n=6)

- 2 subjects with cognitive DA at 24 months post-treatment above the highest value (DA=35) seen in NH cohort\(^1\), with DA of 41 (CA=38) and 42 (CA=55), respectively
- 4 out the 6 have severe mutations on both alleles
- Notably, the 2 subjects with the highest DA have biallelic deletions or duplications (ie express no functional enzyme)

Note: 1. Data from Shapiro et al. 2016; Wijburg et al. 2022
DA: Developmental Age
All Subjects enrolled at less than 30 months of age also have increasing or stable motor and language DA and VABS–II scores

- Persistent increase or stabilization in the main cognitive, language and motor domains over a period of at least 24 months post-treatment
- No deterioration of VABS–II scores between baseline and M24
- Consistency of effect across outcome measures

Note: 1. Assessment by BSID–III
DA: Developmental Age; DQ: Developmental Quotient

Colored lines: P4–SAF–302 subjects
Green dotted line: DQ=100 (normal development)
Red dotted line: DQ=50
Mean cognitive DA at 40 months of age is higher in treated subjects of the ancillary cohort vs NHS

- Initial analysis of 5 subjects in the ancillary cohort who have reached the age of 40±3 months
- Comparison to NHS patients with DA measurement at 40±3 months

*P value (P4-LYS-SAF302 versus NHS)
DA: Developmental Age; NHS: Natural History Study
Treatment slows decline of cognitive DQ in the ancillary cohort

NHS <30m at inclusion (n=6)  P4-SAF-302 mAC (n=6)  Linear regression slope

- P value (LYS-SAF302 versus NHS)
- DQ: Developmental Quotient; mAC: modified Ancillary Cohort; NHS: Natural History Study

*P value (LYS-SAF302 versus NHS)
No decline in cortical gray matter volume in the ancillary cohort in line with preservation of cognitive function

NHS patients\(^1\)

Cortical gray matter volume decreases in children with MPS IIIA and is closely associated with cognitive decline\(^1\)

P4-SAF-302 mAC

Cortical gray matter volume relative to baseline \([\text{mean} \pm \text{SD} (n); \text{p value}]\)

- M12: 12 ± 126 (5); P=0.8
- M24: 27 ± 148 (5); P=0.7
Positive biomarker data confirm biological activity

**Heparan sulfate (HS; disease biomarker)**
- Statistically significant and persistent ~20% decrease in CSF HS at M6, M12 and M24 relative to baseline; no significant change in serum HS
- Consistent with the fact that LYS- SAF302 affects only HS coming from the brain

**Neurofilament light chain (NF-L; axonal damage biomarker)**
- Elevated at baseline in CSF and serum relative to healthy controls
- Transient increase from baseline to M6 & return to baseline at M12 consistent with stabilization/decrease of lesions from M12
- 30–40% decrease below baseline at M24 (serum and CSF)
- Extent of NF-L decrease comparable to multiple sclerosis and CLN2 drugs (30–50% reduction per year¹).

**Note:** 1. Delcoigne et al, 2020, Ru et al, 2019
LYS–SAF302 safety profile – SAEs

35 SAEs (at database lock)

13 SAEs not related to IMP
22 SAEs reported by the PIs as IMP related

1 death 18 months post-treatment, at 5 years of age
1 seizure episode and 1 non-convulsive seizure
19 white matter lesions reported in all 19 study subjects

- Death considered to be due to disease progression; early fatal outcomes reported in patients with MPS IIIA
- Seizure with EEG abnormalities (hypsarrhythmia) in the same patient with history of febrile seizures, which is a common disease manifestation in MPS IIIA
- Other AEs are common disease manifestations in MPS IIIA


EEG, electroencephalogram
All treated subjects developed post-treatment white matter lesions at injection sites.

Lesion decrease or stabilization after M12.

No definite clinical symptoms that could be directly attributed to white matter lesions.

A biopsy of one of the brain lesions, 8 months after surgery, suggests self-limiting toxic SGSH overexpression in glial cells close to injection sites, without inflammatory changes.
Closing remarks
Karen Aiach
Chairman and Chief Executive Officer
Closing remarks

Major breakthrough in bringing a therapeutic option to MPS IIIA patients

- AAVance clinical results delineate the patient population that would benefit from treatment with LYS-SAF302
- LYS-SAF302 has a beneficial effect in the youngest patient population with MPS IIIA
- Early-dosing of patients in neurodegenerative diseases is crucial to provide therapeutic benefit
- Urgent need for a therapeutic option in a progressive, devastating neurodegenerative pediatric disorder without any treatment option
Q&A

Karen Aiach, Chairman and Chief Executive Officer
Ralph Laufer, Chief Scientific Officer
Marie Trad, Chief Medical Officer
Marie Deneux, Chief Regulatory Officer