Disease Progression Modelling for an Ultra-Rare Disease: Lysosomal Acid Lipase Deficiency (LAL-D)

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BACKGROUND AND OBJECTIVE

- Lysosomal acid lipase deficiency (LAL-D) is an **ultra-rare, progressive, autosomal recessive disorder** caused by pathogenic variant in the LIPA gene that leads to a lack of the lysosomal acid lipase (LAL) enzyme activity [1-3].
- LAL activity deficiency or absence results in **disruption of intralysosomal degradation of cholesteryl esters and triglycerides and accumulation of relevant substrates** in organs like the liver and spleen, leading to liver disease, high cholesterol, and eventually cardiovascular issues [1,3,4].
- LAL-D has both severe, infantile-onset forms (formerly Wolman disease) that are often fatal, and less severe, progressive forms, **cholesteryl ester storage disease (CESD)**, often heralded by an abnormal lipid profile, liver function abnormalities or gallstones as incidental findings. **CESD can manifest in childhood or later years as an adult** [3].
- LAL-D guidelines focus on **enzyme replacement therapy (ERT)** with sebelipase alfa (Kanuma®) for patients with LAL-D, emphasizing **early and continuous treatment**, as well as the need for a low-fat diet, regular physical activity, and alcohol avoidance [4-6].
- The objective of this project was **to develop a disease progression model, specific for LAL-D, focused on the progressive form of the disease (excluding infantile onset disease)**, capturing clinical heterogeneity and the link between earlier onset and greater severity.

METHODS

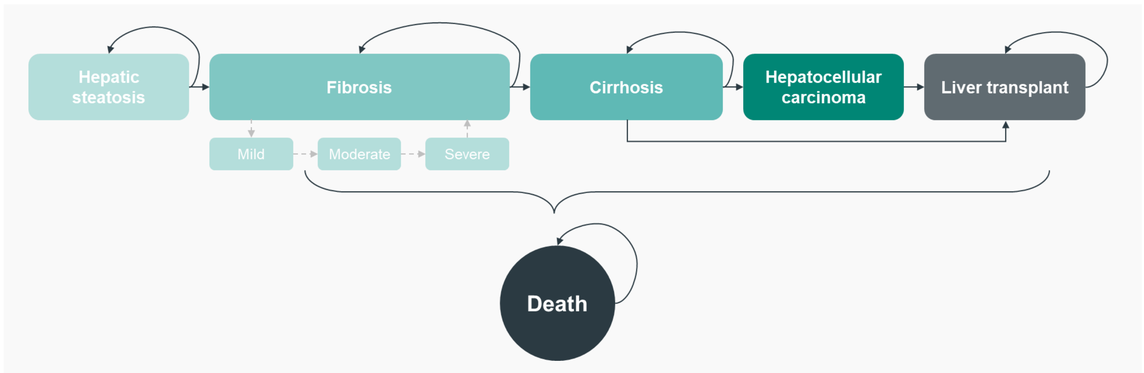
Model structure

- The disease progression model was developed in Excel to **characterize three scenarios of LAL-D progression (excluding infantile onset disease)**:
  1. **Untreated** patients with CESD (natural history),
  2. **Early initiation** of treatment with sebelipase alfa at diagnosis in patients with CESD,
  3. **Late initiation** of sebelipase alfa after diagnosis in patients with CESD, once organ damage is evidenced.
- Annual cycles were applied, and disease severity was adjusted to reflect the **greater burden associated with earlier onset**.
- For the three treatment scenarios, both the **hepatic and lipidic** disease trajectories were evaluated (Figure 1 and 2).
- The **treatment effect** was incorporated into the model by allowing **disease progression to halt, stabilize, or regress** to a milder state.
- **Mortality** was included from the fibrosis stage onward in the **hepatic profile**, and from myocardial infarction in the **cardiovascular profile**.

Hepatic progression

- A **six-state Markov model** was constructed to simulate progression from hepatic steatosis through fibrosis, advanced cirrhosis, and death (Figure 1).

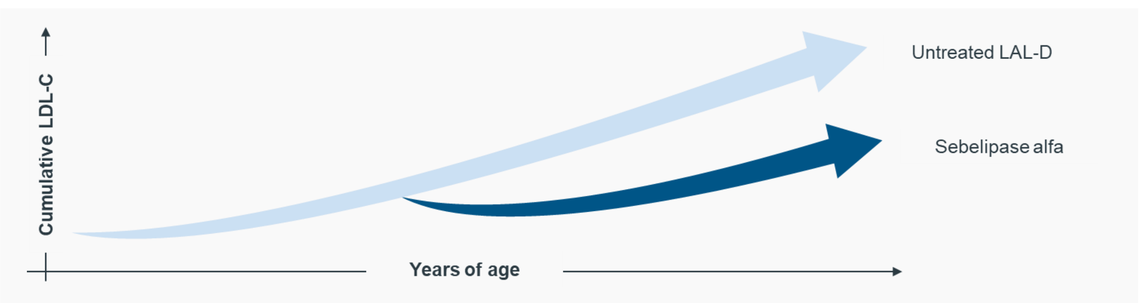
Figure 1. Model structure for the hepatic profile



Lipidic/cardiovascular progression

- An LDL-C accumulation model was designed to capture the progressive increase in cardiovascular risk (Figure 2).
- After reaching a **predefined LDL-C threshold**, the risk of myocardial infarction (MI) rose with continued lipid buildup.
- In the model, treatment effect was represented by **lowering LDL-C concentrations**, which in turn reduced the **rate of lipid accumulation** and consequential **cardiovascular risk**.

Figure 2. Model structure for the lipidic profile



Data Sources

- Efficacy inputs for SA were sourced from **clinical trials** (LAL-CL02 [7] and LAL-CL06 [8]), incorporating its effects on both **hepatic fibrosis stages** and **LDL-C levels**.
- **Natural history** of the disease and **epidemiological data** were sourced from the **literature** [9-13].

Base Case

- The base case was set at **baseline age** from the LAL-D international registry [9], and **severe organ damage,** e.g. liver failure, assumed to occur 27 years afterdiagnosis.

Model Validation

- Model assumptions, structure, and data sources were **validated by a panel of international lipidologists and hepatologists** with extensive experience in managing LAL-D*.
- The model was **not intended to predict individual patient outcomes** but to provide a **structured framework for exploring disease trajectories and supporting multidisciplinary clinical discussions**.

RESULTS & CONCLUSION

- **Hepatic profile:** in the base case, 70 years after disease onset, **early SA treatment resulted in a 31.6% reduction in the probability of death** compared to untreated patients and an 8.0% reduction compared to late SA treatment.
- **Lipidic profile:** in the base case, 70 years after disease onset, **patients treated with SA upon diagnosis had a 0.8% annual risk of MI due to lipid accumulation**, compared to 9.7% with delayed treatment and 30.3% without treatment.

Early diagnosis and treatment with sebelipase alfa improve survival and reduce cardiovascular events, highlighting the need for timely intervention in LAL-D.

LAL-D progression is heterogeneous, often involving both hepatic and cardiovascular complications, requiring a holistic, multidisciplinary approach to patient care.

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***NOTE:** Model assumptions, structure, data sources and panel of experts has shaped the outcomes of the study, any difference on the data analysis could derive on a variation of outcomes.

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