**Supplementary Table 1. Summary of Sebelipase Alfa trials in LALD patients.**

Abbreviations: CESD, cholesteryl ester storage disease; LAL, lysosomal acid lipase; ADA, anti-drug antibodies; TC, total cholesterol; LDL, low density lipoprotein cholesterol; HDL, high density lipoprotein cholesterol; TG, triglycerides; IAR, infusion-associated reaction; apo, apolipoprotein; ALT, alanine aminotransferase; DBS, dried blood spot; PBMC, peripheral blood mononuclear cells.

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| Patient characteristics | Number of participants | Dose and treatment period | Baseline LAL activity\* | Study conclusions | Citation |
| CESDAge 19-45 | 9 | 0.35, 1, or 3 mg/kg weekly for 4 weeks | 35+/- 15 umol/g/h in leukocytes (central lab lower limit of normal is 350) | * Well-tolerated
* No ADA
* Transaminases decreased, many to normal levels
* TC, LDL, and TG first increased then decreased
* Transaminases increased off-treatment
 | (Balwani et al., 2013) CL-01 |
|  | 7 | 0.35, 1, or 3 mg/kg weekly for 4 additional weeks with variable washout period, then 1 or 3 mg/kg biweekly for 8 weeks |  | * Well-tolerated
* No ADA
* Transaminases decreased further from baseline
* TC, LDL, TGs decreased, HDL increased
 | (Balwani et al., 2013)CL-04 extension of CL-01 |
|  | 7 | Continued 1 or 3 mg/kg biweekly for up to 52 weeks |  | * One patient with severe IAR but desensitized and resumed treatment
* Transaminases decreased further and normalized
* LDL decreased, HDL increased further
* Decreased liver fat content
 | (Valayannopoulos et al., 2014)further extension of CL-04  |
|  | 7 | Continued 1 or 3 mg/kg biweekly for up to 5 years total treatment |  | * One additional patient with severe IAR but resumed treatment
* One patient positive for ADA but later negative
* Transaminases normalized and all maintained low levels
* LDL remained low and HDL remained increased
* Liver volume and liver and spleen fat content decreased
 | (Malinová et al., 2020)further extension of CL-04 |
| CESDAge 4-58 | 66, (36 treatment, 30 placebo) | 1 mg/kg biweekly 20 weeks |  | * Well-tolerated: most patients experienced mild adverse events, one serious infusion reaction which resolved with diphenhydramine
* 5 patients with ADA, but did not affect safety or efficacy
* Transaminases decreased, some to normal levels
* Hepatic fat content reduced
* LDL initially increased then LDL, TG, and apoB decreased, HDL and apoA1 increased
 | (Burton et al., 2015a)double-blind period |
| CESDAge 4-58 | 65 | 1 mg/kg biweekly 16 additional weeks (=36 total) |  | * Transaminases in placebo patients switched to sebelipase alfa dropped
* LDL decreased further from baseline
 | (Burton et al., 2015a)partway through open-label period |
| CESDAge 4-58 | 65 open-label, 47 expanded | 1 mg/kg biweekly for 20 weeks, then 1 mg/kg or 3 mg/kg biweekly for an additional 130 weeks, for 104 weeks (= 256 weeks total). One patient received a few doses of 0.35 mg/kg. |  | * Most patients experienced mild-moderate adverse events, with one severe infusion reaction.
* 6 patients had ADAs, 3 also had high ALTs but 5/6 later tested negative for ADAs.
* Lowered transaminases sustained, many normalized
* Lowered TC, LDL, and TG and raised HDL were maintained
* Liver volume, liver fat content, and spleen volume reduced from baseline
* Reduced steatosis
 | (Burton et al., 2022)open-label and expanded open-label period |
| WD0-2 months | 5 | 3 or 5 mg/kg weekly or biweekly for 12-116 months | One patient 5.1 nmol/h/mg (control: 31.2), one 57 umol/h/g (normal: 350-200) in leukocytes, three had 0 by DBS (nmol/punch/h) | * One patient anaphylaxis on first infusion, but continued treatment
* Transaminases reduced but not statistically significant
* HDL increased but did not normalize, effect on other lipids unclear
* Digestive symptoms resolved in all patients, hepatosplenomegaly resolved in 4/5
* All patients survived, compared to natural history of 100% mortality
 | (Demaret et al., 2021) |
| WDAge 1-6 months | 9 | 0.35 mg/kg weekly, escalated to 1, 3, or 5 mg/kg | 5-65 umol/g/h in PBMCs, 0.004-0.018 nmol/punch by DBS. Not measured in all patients. | * 5 patients had infusion reactions, three severe, but continued treatment.
* Four patients developed ADAs but three later tested negative
* Decreased transaminases, normalization in most patients
* LDL decreased, TG decreased and normalized, HDL increased
* Digestive symptoms resolved
* Hepatosplenomegaly reduced
* Increased weight for age centile
* 67% survival (6/9) to 12 months, 56% (5/9) to 24 months, compared to 0% historical control. Patients who did not survive only received 1-4 infusions.
 | (Jones et al., 2017)VITAL |
| WD1-6 months | 9 | 3 or 5 mg/kg weekly |  | * Most patients had mild infusion reactions.
* Transaminases remained low
* LDL decreasing trend and HDL increased
* Weight and length for age z scores increased
* 56% survival to 4 years
 | (Vijay et al., 2021)VITAL extension |
| WD0.5-4 months | 10 | 1, 3, or 5 mg/kg weekly |  | * Most patients had mild infusion reactions.
* 5 serious adverse events related to treatment: 4 infusion reactions, but all continued treatment.
* 6 patients had ADA, 3 affected treatment efficacy
* Transaminases normalized in most patients
* TGs decreasing trend and HDL increased
* Weight and length for age z scores increased
* 79% survival to 12 months, 80% survival to 3 years
 | (Vijay et al., 2021)CL-08 |