A combined fertility, embryofetal development, AAV integration and germline transmission risk study in mice with ST-920 (isaralgagene civaparvovec) for Fabry disease

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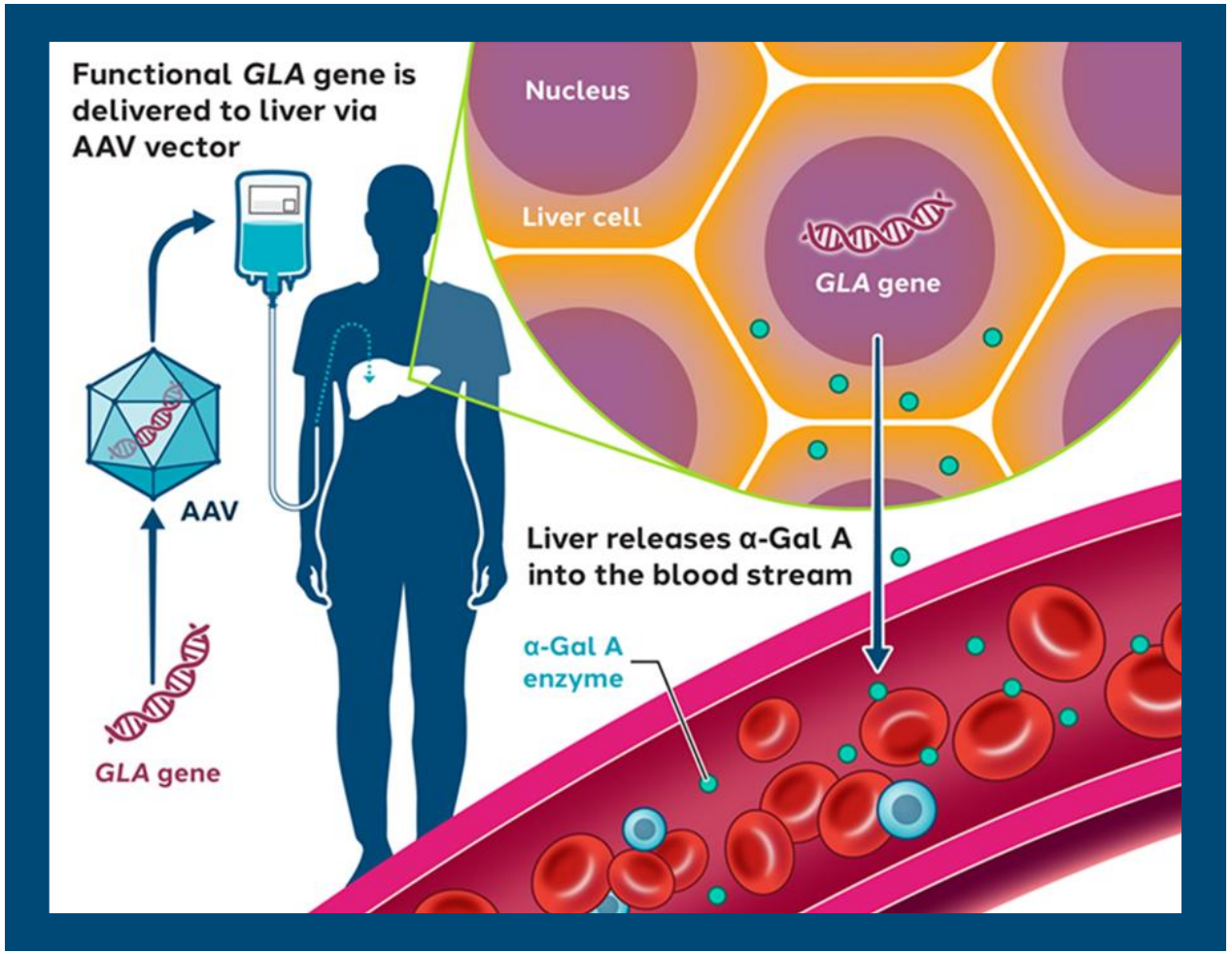
Isaralgagene civaparvovec (ST-920) for Fabry disease



Advantages

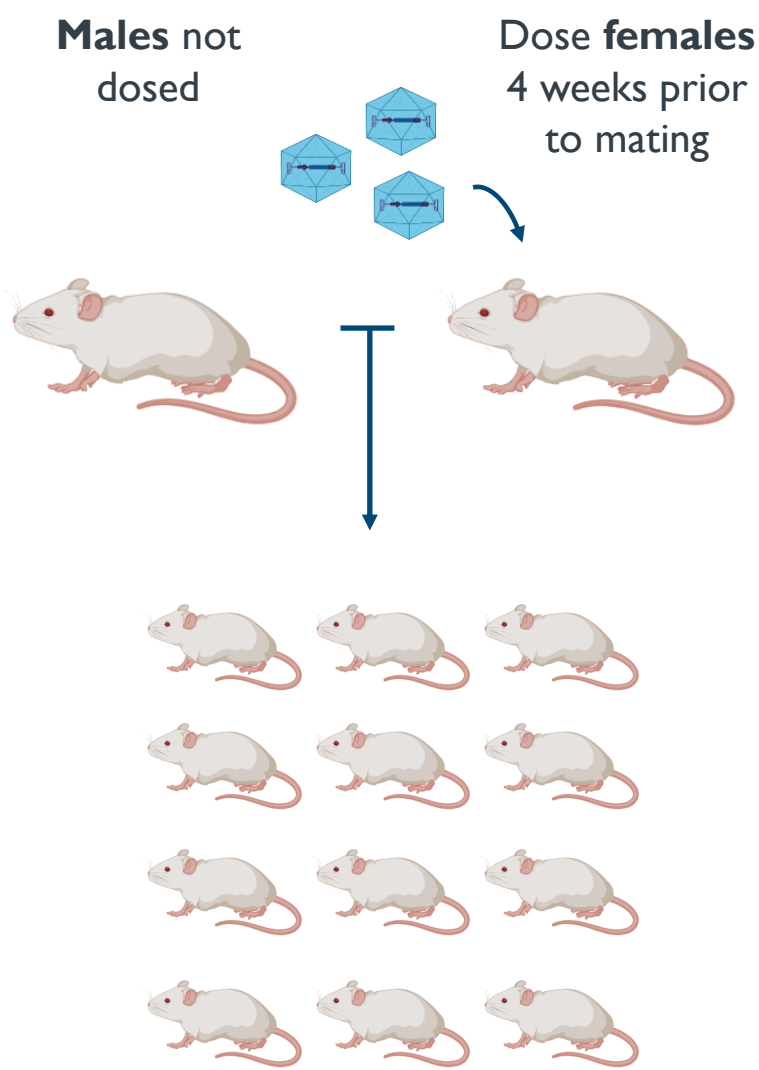
- Convenient one-time administration
- Potential to eliminate ERT infusions
- Durable efficacy
- Low immunogenicity
- No prophylaxis with steroids or other immunomodulating agents required
- Rolling submission of BLA in progress

α-Gal A, alpha galactosidase A; AAV, adeno-associated virus; ERT, enzyme replacement therapy; GLA, galactosidase alpha; BLA, Biologics License Applicarion.

DART, AAV integration & germline transmission risk study in mice

- GLP study
- ST-920 (2.63E+13 vg/kg; clinical dose; IV)
- C57BL/6 mice
- Dosed only female mice as no AAV vector detected in mouse semen (n=30/group for treated females and untreated males)
- FDA requested review of study protocol

Combination study design



F0 generation (parental animals)

- Female GD18 necropsy
- Maternal fertility assessments
- Maternal liver DNA for AAV integration analysis

F1 generation (pups)

- Embryofetal development assessments
- Liver DNA for germline transmission risk assessment

No ST-920-related toxicological findings in DART parameters and no evidence of vertical germline transmission

F0 (Parental) In-life Evaluations

- In-life Observations:
  - Clinical observation
  - Body weights
  - Estrous cycle patterns

F0 (Parental) Terminal Evaluations

- Necropsy
- Organ Weights:
  - Ovaries
- Vector Distribution:
  - vg levels in ovaries and liver (qPCR)

F0 (Parental) Terminal Evaluations

- Fertility Assessments:
  - Females
    - Number of corpora lutea
    - Number of pre- and post-implantation losses
    - Live and dead fetuses counts
    - Early and late resorptions counts
- AAV Integration Site Analysis:
  - Target Enrichment Sequencing and NGS of maternal liver DNA

F1 (Fetal) Postpartum Evaluations

- Fetal Observations:
  - Fetal weight
  - Sex ratio
  - External examination
  - Visceral examination (internal organs)
  - Skeletal examination
- Germline Transmission:
  - vg in offspring liver (qPCR)

DART/AAV integration/germline transmission study endpoints

Targeted enrichment sequencing and NGS for AAV integration site analysis

Characterize potential risk of oncogenesis

Mouse genomic DNA with integrated AAV vector

Integrated AAV vector sequences

- Identification of integration sites
- IS analysis
- Common integration site (CIS) (risk of clonal growth)
- Proximity to cancer genes

AAV integration profile does not raise concerns of risk of liver tumor formation

ST-920

- Total of 1,056 unique and exactly mappable integration sites were detected in ~19 million sequencing reads
- Low levels of vector integration
  - Range of 1.71E-4 to 5.18E-4 per cell
  - 0.35 +/- 0.14 IS per1000 cells (mean ± SD)
- Polyclonal vector integration profile
- 9.94% of integration sites were found in 44 common integration sites (CIS)
- No integration sites in *Rian* locus
- No evidence for clonal expansion

ST-920 conclusions

- **DART assessments**
  - No adverse findings in fertility, reproductive and embryofetal development parameters in parental or fetal mice
- **Germline transmission risk assessment**
  - No evidence of germline transmission of AAV vector from parents to offspring
- **AAV integration assessment**
  - Low levels of integration into mouse genome (similar to reported in literature)
  - Polyclonal integration profile (no signs of clonal outgrowth)
  - No expanded clones detected in vicinity of cancer-associated genes
  - No integration into cancer-associated *Rian* locus
  - AAV integration profile does not raise concerns about risk of liver tumor formation

Safety profile supportive of treating broad populations of adult patients

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