Background of Friedreich Ataxia (FRDA) cardiomyopathy

- Most common form of inherited ataxia, incidence 1/50,000 yr in Caucasians
- 10,500 FRDA patients in North America (US, Canada and Mexico), 13,000 FRDA patients in Europe
- FRDA is caused by a mutation in the FXN gene, which encodes a small mitochondrial protein called frataxin involved in energy homeostasis in cells
- Symptoms begin in childhood with impaired muscle coordination (ataxia) and worsens slowly over time
- Hypertrophic cardiomyopathy (HCM), leading to congestive heart failure and arrhythmia, death before age 30 occurs in 59% of FRDA patients
- No available therapy to alter progression of cardiac disease in FRDA patients: cardiac transplant is the only curative possibility (only 3 Canadian patients up to now)

Gene Therapy

- Pre-clinical study: AAVrh.10 vector carrying the human FXN gene (AAVrh.10-FXN) shows very promising data in the well-established MCK-frataxin mouse
  - 1 unique intravenous injection of AAVrh10-FXN vector completely reverses very rapidly the cardiomyopathy of MCK-frataxin mice
  - manuscript under review at Science
- AAVrh.10 vector technology is already being used in humans in Phase I/II Late Infantile Neuronal Ceroid Lipofuscinosis study to deliver the CLN2 gene in the brain of children; in Phase I/II metachromatic leukodystrophy to deliver the ARSA gene in the brain of children
- AAVrh.10-FXN plan can deliver BLA in 4 years

Next Steps

- Efficacy and Safety study in pigs — intracardiac delivery
  - Dose escalation
  - 6 months and follow-up for 18 mos.
- Toxicity Study in rats — intracardiac delivery
  - Concurrent with pig study
  - To be delivered in 18 months for IND
- Phase I/II Open label study in patients <21 years with evolutive cardiomyopathy
- Phase I: dose escalation in 12 patients in 3 groups of 4 patients
  - 2 sites: Paris, NY
  - Duration: 3 months
- Extend Phase II to registration study
  - Add additional 20-30 patients at MTD
  - Primary efficacy endpoint: composite clinical and echocardiographic endpoint that will be validated and agreed with agencies
  - Duration: 6 months
- Total duration of the trial up to analysis of results: 24 months

Summary

- FRDA cardiomyopathy indication has high commercial value
  - Potential revenue would be $500 million in US if only 50% of eligible US patients were treated under initial indication
- Robust pipeline for further indications

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