Lessons Learned from the Front Lines of Mitochondrial Disease Drug Development

Matthew B. Klein, MD, MS
CEO & Chief Medical Officer

September 6, 2019

Objective

- Share key learnings collected from the conduct of controlled clinical trials worldwide in patients with primary mitochondrial disease

Ideal disease attributes for drug development

- Homogeneous: shared genotype, phenotype, constellation of symptoms, rate of progression
- Natural history: well understood from onset to end-stage including rate or progression
- Objective metrics of disease: easily measured, correlate with disease severity
- Accessible population: sufficient number of subjects who meet criteria, able to participate in trials
- Precedent for drug approval: there is a clear and established path for drug approval

Ideal disease attributes for drug development

- *To what extent does mitochondrial disease meet these criteria?*

Ideal disease attributes for drug development

- Homogeneous
- Natural history
- Objective metrics of disease/validated endpoints
- Accessible patient population
- Precedent for drug approval in disease area

Mitochondrial disease drug development challenges

- No previous approved therapies
  - no established pathway forward
  - no validated endpoints
  - no model for clinical trial design
  - limited culture of clinical trial participation
  - education needed for patients and investigators
    - clinical trial is not clinical care

Key lessons learned

1. Don’t confuse rare with homogeneous
2. Accurate and comprehensive natural history critical
3. Engage FDA/EMA early and often
4. Biomarkers needed to facilitate all stages of development
5. Objective metrics of disease better endpoints than composite scales
6. Short trials, long delays
7. Aggregated patient community critical to patient recruitment
8. Challenges exacerbated by disease rarity and barriers to travel to study sites

Lesson 1: Don’t confuse fare with homogeneous

- Genetic heterogeneity
  - mtDNA mutations
  - nDNA mutations
  - Heteroplasmy
- Phenotypic heterogeneity
  - same genotype, different disease course
  - organ systems affected
  - severity of symptoms
  - rate of progression

Lesson 2: Accurate and comprehensive natural history

- Anecdotal or case series reports do not provide true natural history of disease
- Ideally understand disease progression in context of optimal care
- Absence of natural history prevents identification of suitable endpoints that could be reasonably targeted
- Waxing and waning in particular needs to be understood

Lesson 3: Engage regulatory authorities early & often

- Education is often needed regarding rare diseases
- Aligning on how you are thinking about clinical development plan is crucial
  - Not only for clinical, but non-clinical and CMC
- EMA & FDA may hold different views on endpoints, trial designs
- As more data are collected, views may evolve

Lesson 4: Biomarkers needed to for all development stages

- Preclinical
  - identify drug candidates
  - establish pk/pd models
- Clinical
  - identify candidate responder populations
  - demonstrate drug target engagement
  - allow for identification of subgroups

Lesson 5: Objective metrics better than composite scales

- Rating scales include both signs and symptoms
- Clinical scales not typically designed for clinical trials
  - suitable for longitudinal assessment (over many years)
- Issues of inter-rater variability (and sometimes intra-rater variability)

Lesson 6: Short trials, long delays

- Rationale for short trials is clear
  - minimize duration of exposure to placebo
  - shorter path to approval
  - less expensive
- Reality
  - 6 months too short to demonstrate change in disease progression
  - can’t affect heterogeneity so longer study time can help account for variability in rate of disease progression
  - time to organize a subsequent trial is much longer than the time it would take to complete a longer study
    - net delay in advancing therapeutic towards approval

Lesson 7: Aggregated patient community critical

- Culture of clinical trials helps in recruitment and understanding of the trial process
  - clinical trial vs. clinical care
  - inclusion criteria
  - placebo phases
  - travel to study sites
- Ability to inform patients/families about clinical trials

Lesson 8: Challenges exacerbated by disease rarity

- In trying to achieve homogeneity, the number of eligible subjects becomes even smaller
- Tradeoff between time to fully enroll and statistical power
- Infirmed patients may be unable to travel to study sites
  - creates a selection bias for trial enrollment

Conclusion

- Significant challenges to developing drugs for mitochondrial disease
- Education of community and regulators necessary to facilitate development
- Clinical trial designs that incorporate key learnings