The use of RWD derived External Control Arm to assess the Benefit of New Therapies: The case of treatment of Thymidine Kinase 2 deficiency in patients under the age of 12 at symptom onset

Maurille Feudjo Tepie, Msc PhD

Global Head, Real World Evidence and Digital Sciences, UCB

HMA/EMA Big Data Steering Group Workshop on RWE Methods

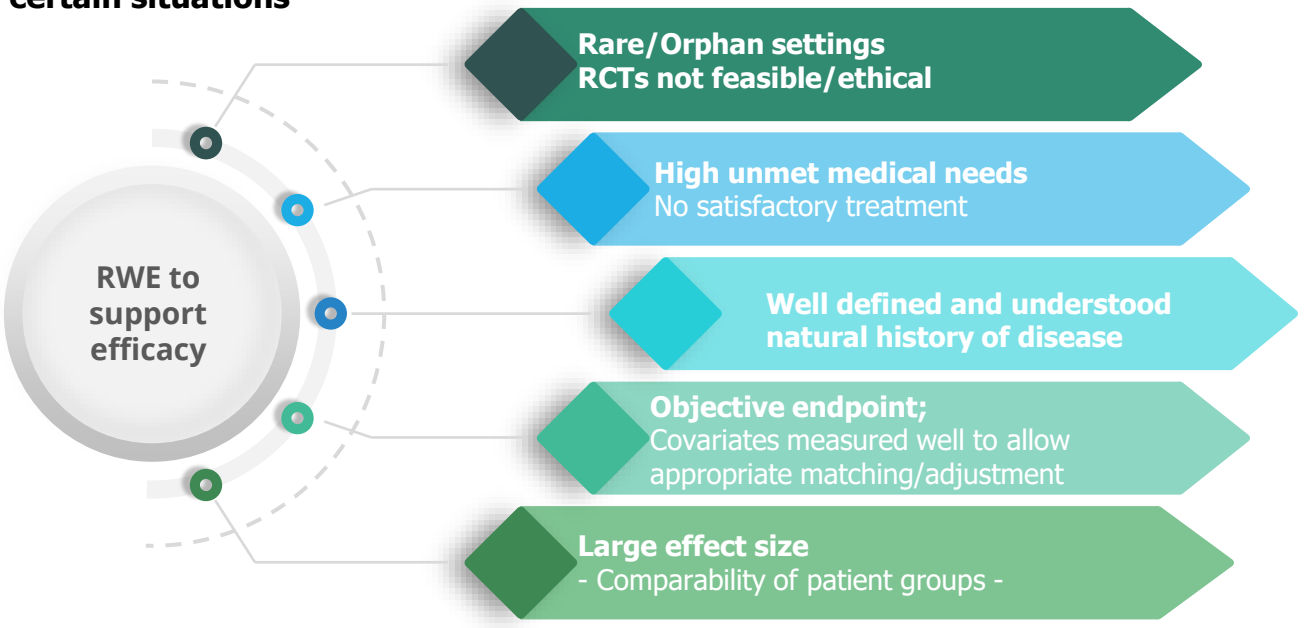
Amsterdam, 14th, June 2024

Outline

- Background
  - TK2d: Disease, Treatment options
- Clinical Program
  - Challenge for a phase 3 RCT;
  - Why an ECA would be the most ethical and viable alternative here
- External Control Arm
  - Sources of data, analytic and methodological considerations
- Key questions for discussions

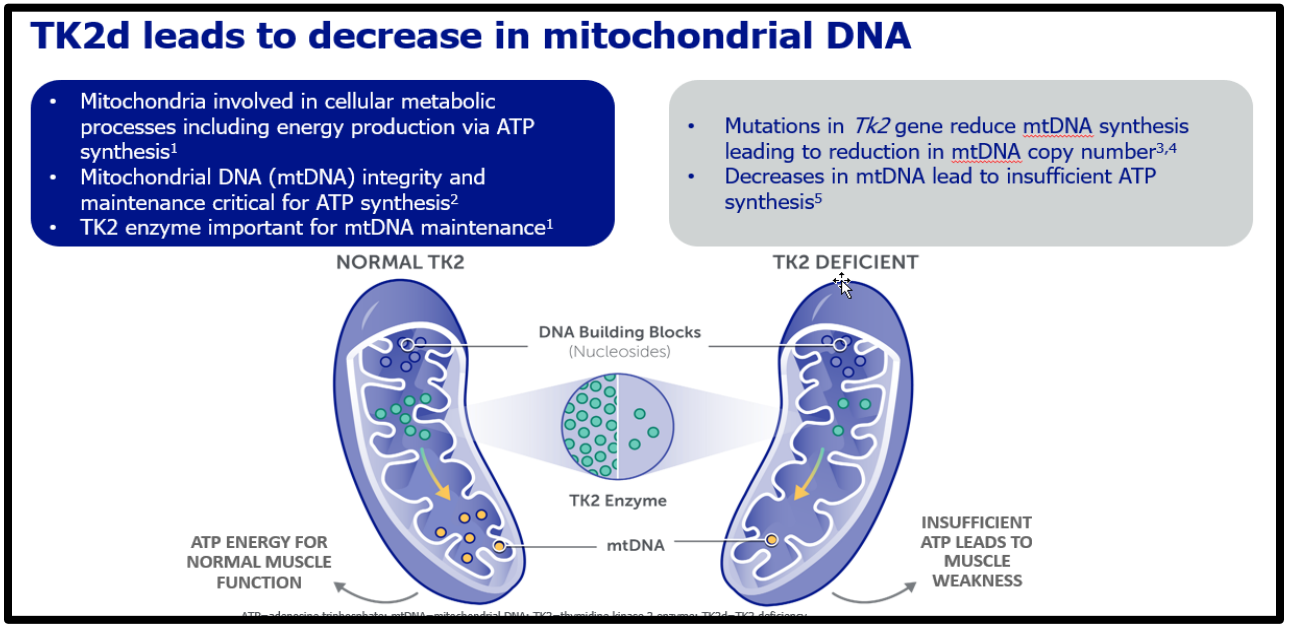
Regulatory Decision-Making using RWE to support efficacy/ effectiveness

Generally Limited to certain situations



Background: TK2d Disease

- Thymidine kinase 2 deficiency (TK2d): A mitochondrial deletion and depletion syndrome with substantial morbidity (progressive muscle weakness) and high mortality [1,2];
  - First cases described in 2001[3], in 4 children, with different mutations;
  - More than 50 TK2 mutations linked to TK2D
  - The **similarity in presentation** to other neuromuscular conditions (i.e spinal muscular atrophy) leads **underdiagnosis** and/or misdiagnosis [2]
  - Limited knowledge of disease natural course beyond mutated genes, age and progressive muscles weakness
  - Most patients have **childhood onset** (84% between 0 to 4 years [4]; or 0 to 12 years [1]).



References: 1. Garone C, et al. J Med Genet. 2018;55:515–521. 2. Domínguez-González C, et al. Orphanet J Rare Dis. 2021;16:407. 3. Berardo A, et al. J Neuromuscul Dis. 2022;9:225–235. 4. Wang J, et al. Mol Genet Metab. 2018;124(2):124-30

Background: TK2d Disease

- Thymidine kinase 2 deficiency (TK2d):
  - **An ultra-rare condition:**
    - Although some estimates suggest there could be **between 600 and 2700 cases in the USA** [1], there is limited knowledge on the prevalence of TK2d
    - Recently, **estimated prevalence of ~ 1-2/1000,000 people** [2]

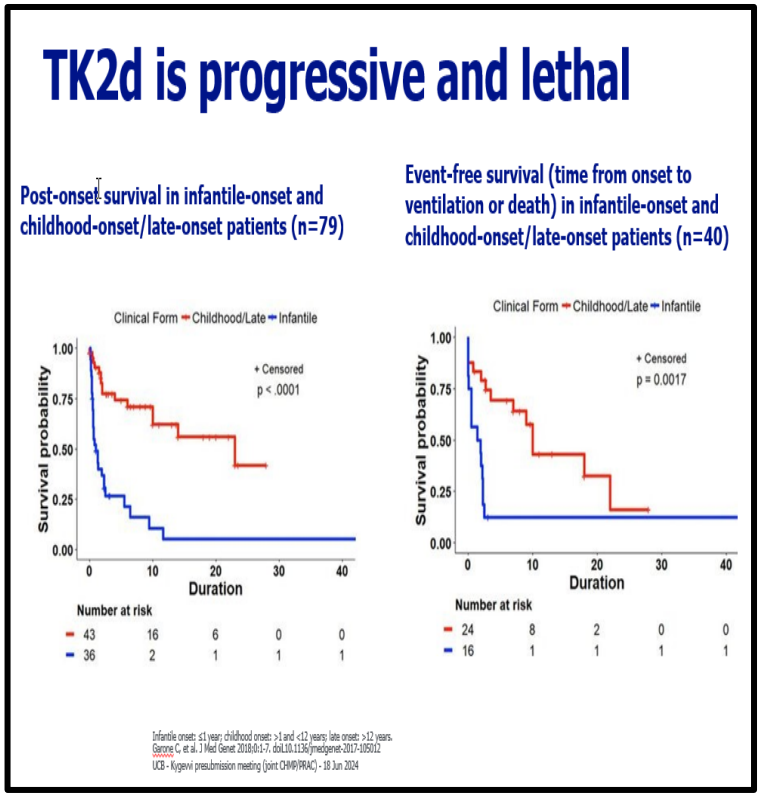
References: 1. Berardo A, et al. J Neuromuscul Dis. 2022;9:225–235. 2. Yuanjun Ma et al; ISPOR Europe 2023, Copenhagen, Denmark; 12–15 November

Background: TK2d Treatment Options

- No approved medicinal products indicated for TK2d in the EU
  - Management is limited to supportive care;
  - Palliative care approaches have remained largely unchanged since TK2d was first recognized as a disease in 2001
- dCT an investigational compound;
  - Granted **orphan drug designation** in 2017
  - Subsequently, dCT deemed eligible for **priority medicines (PRIME)** scheme in 2018
- Preliminary data suggests a **substantial reduction in mortality** in patients with early onset of disease symptoms (<12yo);
- Plan to submit a **MAA in near future** for dCT

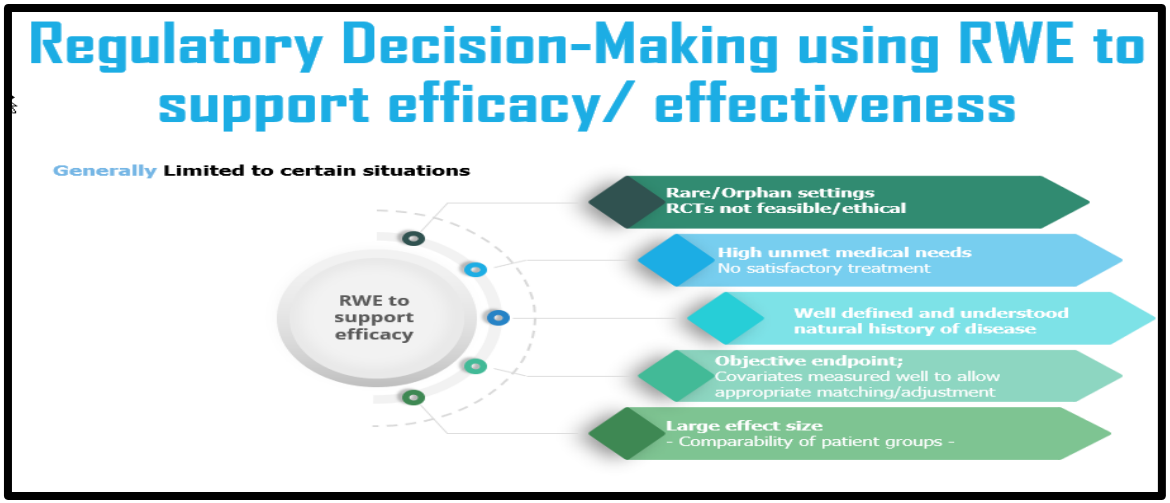
Clinical Program: Challenge of Phase 3 RCT

- **Ultra Rare disease** – recruitment, achieving sufficient sample size would be challenging, heterogeneous disease presentation
- **High Unmet medical need** - poor disease prognosis
- **Limited or no treatment options** – Unethical to allocate patients to "standard of care"
- **New therapy** – initial promise, might offer hope
- **Some control data better than no information** – To help put results into appropriate perspective/context



Clinical Program: WHY an ECA is the most ethical and viable option here? [1]

- Strong belief that the most ethical and feasible approach/studies to show efficacy and safety of the investigational compound is to consider a single-arm study; complemented with an external control arm, with mortality as the primary outcome



- **Objective**:
  - Characterize the clinical course (including survival, loss/gain/regain of motor milestones, respiratory and feeding support) in treated and untreated patients
  - Describe the safety/tolerability of investigational compound

Clinical Program: WHY an ECA is the most ethical and viable option here? [2]

- **Challenges**:
  - Ultra-rare disease, large multi-purpose RWD sources may not be appropriate
  - There is no existing patient registry for the disease from which an ECA can easily be extracted

An External Untreated Control Arm that help provide context to the treated single arm

- Build a new disease registry/repository dataset, using retrospective data, but with no prospective follow-up
  - Systematic literature reviews to identify cases series, natural history studies and case studies
  - Supplemented through direct contact with specialist center and networks
  - Compile core data (patients' history, patients characteristics and patients' outcomes) in a single database;
- Treated arm is made of integrated datasets:
  - Treated patients with retrospective and prospective data, through sponsored clinical studies
  - Patients receiving dCT as part of sponsor supported **compassionated use programs**

ECA: Analytical / Methodological considerations – Overall

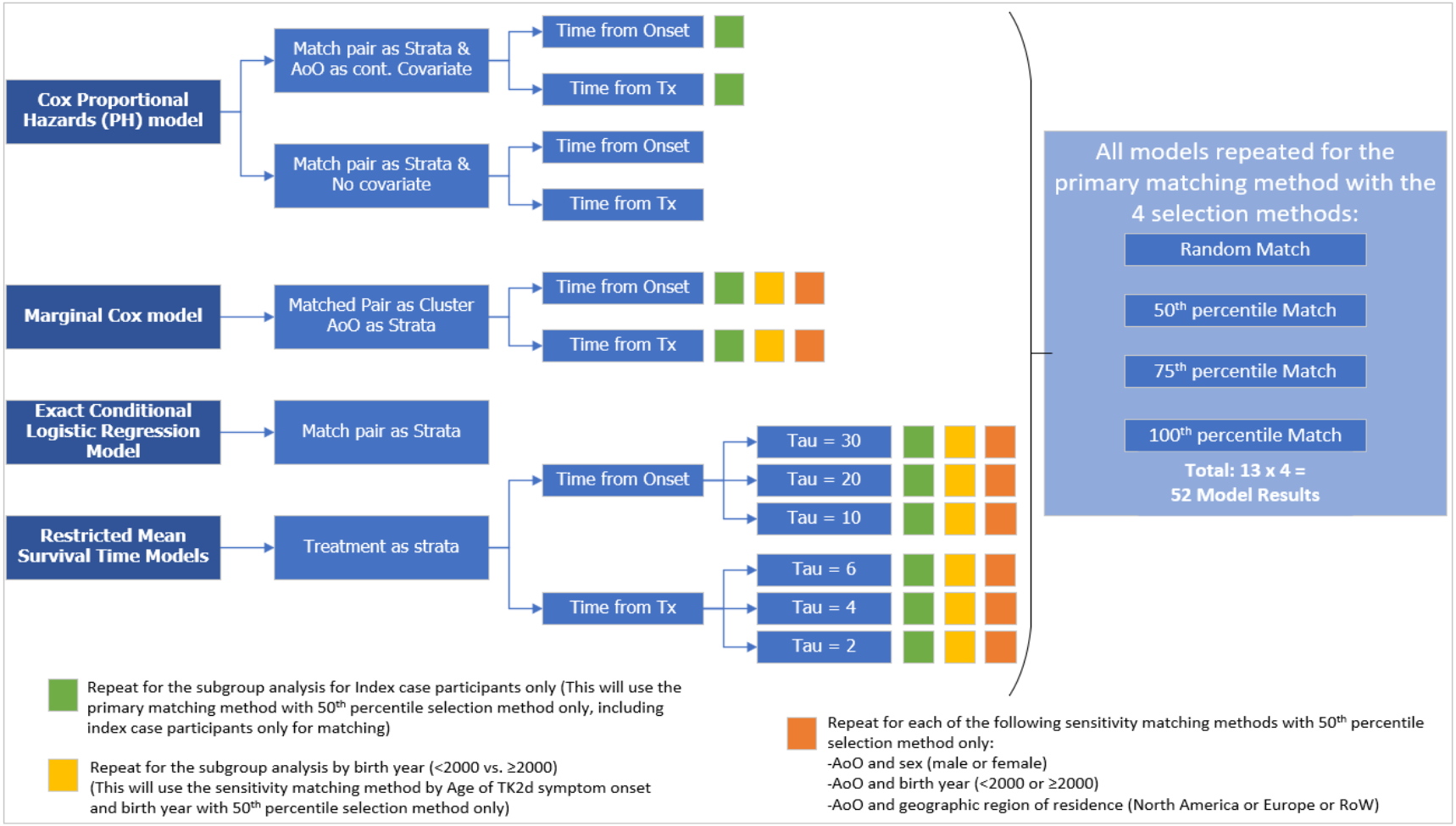
- Choice of objective endpoint(s):
  - **Survival**
- Ensure comparability and appropriate control for potential bias
  - Selection bias
  - Immortal time bias
  - Confounding bias
  - Lead time bias
  - Current knowledge of natural course of the disease points to age at disease symptoms onset as the key prognostic factor:
  - Similarity between groups will be improved using matching methodology;
  - Considered analytical approaches:
    - Stratified Cox PH; Marginal Cox Model
    - Exact Conditional Logistic Regression
    - Restricted Mean Survival Time models
- A batterie of sensitivity analyses

Key Questions for Discussion

- What steps should the sponsor take to demonstrate the validity and robustness of the data and data sources that are proportionate to the potential patient benefit of the new treatment?
- When the ethical and clinical criteria to pursue and explore an ECA strategy are clearly met, how can the sponsor best structure the engagement with regulator, including the extent of clarity and details they can offer up front on design and analytical approaches to considered ECA?

Thank You!

Considered Overall Survival Analyses Models



Sensitivity Analysis Matching Methods

1. **Sensitivity - Age of TK2d symptom onset and sex (male or female)**

   Each treated participant and the corresponding match will come from the same age of TK2d symptom onset group and sex.

2. **Sensitivity - Age of TK2d symptom onset and birth year (<2000 or ≥2000)**

   Each treated participant and the corresponding match will come from the same age of TK2d symptom onset group and birth year group.

3. **Sensitivity - Age of TK2d symptom onset and geographic region of residence (North America or Europe or ROW)**

   Each treated participant and the corresponding match will come from the same age of TK2d symptom onset group and geographic region of residence group.

Matching algorithm – Step by Step process