Survival analyses in patients with thymidine kinase 2 deficiency aged ≤12 years at symptom onset who received pyrimidine nucleos(t)ide therapy

16th European Paediatric Neurology Society (EPNS) Congress; Munich, Germany; 8–12 July 2025

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Poster number: 365

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Introduction

- Thymidine kinase 2 deficiency (TK2d) is an ultra-rare, autosomal recessive, mitochondrial disease manifesting as progressive, life-threatening myopathy[1,2]
  - Pathogenic variants of the thymidine kinase 2 gene (*TK2*) result in mitochondrial DNA (mtDNA) depletion and/or multiple mtDNA deletions,[3] leading to proximal, bulbar and axial muscle weakness[1,4]
  - TK2d frequently causes premature death, often from respiratory failure[1,2]
- There are no approved treatments for TK2d, with current management across the world focused on supportive care, which does not change the progressive disease trajectory[5]
- Doxecitine and doxribtimine is a pyrimidine nucleoside therapy containing deoxycytidine (dC) and deoxythymidine (dT) currently in development for use in TK2d
  - Doxecitine and doxribtimine targets the underlying disease pathology of TK2d by utilizing residual thymidine kinase 2 activity in the mitochondria, as well as thymidine kinase 1 and dC kinase in the cytosol, to increase mtDNA quantity that supports increased energy metabolism in cells[6–9]
- There is a wide spectrum of age of TK2d symptom onset. Generally, patients with earlier symptom onset have more rapid disease progression[1,2]
  - Using a threshold of ≤12 years versus >12 years for the age of symptom onset is largely considered a clinically meaningful approach to disease categorization[1,2]

Objective

- To assess survival and safety in paediatric and adult patients with an age of TK2d symptom onset ≤12 years who received pyrimidine nucleos(t)ide therapy

Methods

Pooled analysis

- The efficacy and safety of pyrimidine nucleos(t)ide therapy were assessed in the Integrated Summary of Efficacy (ISE) and Safety (ISS)
- Data from patients treated with pyrimidine nucleos(t)ides (**ISE treated group**) were pooled from retrospective (MT-1621-101 [NCT03701568], MT-1621-107 [NCT05017818]) and prospective (TK0102 [NCT03845712]) studies and company-supported expanded access programs (**Figure 1**)
- Data from untreated patients (**ISE-modified Untreated Patient Database [MUPD]**) were pooled from literature reviews and a retrospective chart review study (MT-1621-107; **Figure 1**)
- The ISS pooled safety population included patients from MT-1621-101, TK0102 and MT-1621-107
- Subgroups were stratified by age of TK2d symptom onset categories; here, we report data from patients with an age of symptom onset ≤12 years

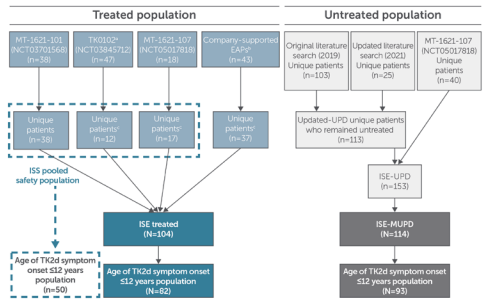
Patient population

- Inclusion and exclusion criteria were specific to each source study
- The main eligibility criteria for treated patients were confirmed biallelic pathogenic TK2 variants, absence of other genetic disease or polygenic disease, and treatment with nucleos(t)ides for TK2d (non-good manufacturing practice [GMP]-grade deoxycytidine monophosphate/deoxythymidine monophosphate, non-GMP-grade dC/dT or doxecitine and doxribtimine [GMP-grade dC/dT])
  - Available medical records, or at a minimum information pertaining to survival, were required for retrospective studies
- Untreated patients required individual-level patient data and genetic confirmation of biallelic pathogenic *TK2* variants

Outcomes

- The primary ISE outcome was survival, defined as time to death from TK2d symptom onset and from treatment start
- Functional outcomes were also assessed (poster 368)
- Safety outcomes were assessed in the ISS pooled safety population (**Figure 1**)
  - Some safety outcomes were not collected in MT-1621-107

Figure 1. Study analysis populations



Individual patient data described in each publication/source were cross-referenced with the aim of removing duplicates to obtain unique data. The ISE-MUPD is only used in comparative survival analyses.
*Data cutoff date: 15 March 2024. ‡Data cutoff date: 1 March 2024. †Individuals who participated in multiple studies are only counted once, although their data across studies are included.
EAPs, expanded access programs; ISE, Integrated Summary of Efficacy; ISS, Integrated Summary of Safety; MUPD, modified UPD; TK2d, thymidine kinase 2 deficiency; UPD, Untreated Patient Database.

Statistical analysis

- The primary analysis assessed survival for pair data from the ISE treated and ISE-MUPD groups matched using the 50th-percentile matching algorithm
  - Matched pairs from the same age-of-TK2d-symptom-onset group were selected after sorting untreated patients based on survival time, and treated patients based on treatment time
  - Cox proportional hazard models, with and without age of TK2d symptom onset as covariate, and marginal Cox models, were utilized to assess risk of death
  - Restricted mean survival time (RMST) analyses were used to summarize improvement in survival time with treatment over a prespecified number of years (30 years for RMST analyses after TK2d symptom onset; 6 years for RMST analyses after treatment start)

Results

Patient baseline characteristics and demographics

- In total, 175 patients with age of TK2d symptom onset ≤12 years were included in the ISE analysis (ISE treated, n=82; ISE-MUPD, n=93; **Table 1**)
  - Most patients in the ISE treated group were White (81.7%), 32.9% resided in Europe and 67.1% were from the rest of the world, with more male (56.1%) than female (43.9%) patients
- Most patients had an age of symptom onset ≤2 years (ISE treated, 56/82 [68.3%]; ISE-MUPD, 69/93 [74.2%])
  - Median (quartile [Q]1, Q3) age of symptom onset was 1.50 (1.08, 2.41) years and 1.33 (0.75, 2.49) years in the ISE treated and ISE-MUPD groups, respectively
- In the ISE treated group, median (Q1, Q3) age at first treatment was 4.26 (2.11, 10.49) years and duration of treatment was 54.8 (15.2, 78.4) months

Patient survival

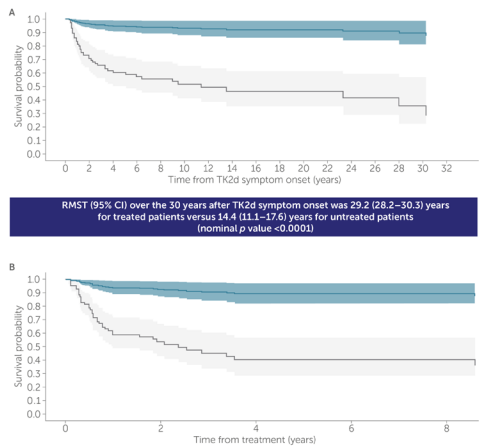
- There were three deaths (3.7%) in the ISE treated group and 53 deaths (57.0%) in the ISE-MUPD group, with median (Q1, Q3) age at death of 1.11 (0.94, 31.77) years and 2.64 (1.58, 4.00) years, respectively.
- The risk of death was reduced with treatment by 92–94% (hazard ratio [HR] = 0.06–0.08; $p<0.0001$) in the time from TK2d symptom onset and by 87–95% (HR = 0.05–0.13; $p<0.0001$) in the time from treatment initiation (HR ranges resulting from proportional hazard and marginal Cox models; **Figure 2**, **Table 2**)
- RMST estimates were increased for treated versus untreated patients (**Figure 2**)

Table 1. Baseline demographics and characteristics of patients with age of TK2d symptom onset ≤12 years

Baseline demographics and characteristics	ISE treated (N=82)	ISE-MUPD (N=93)
Sex, n (%)		
Male	46 (56.1)	49 (52.7)
Female	36 (43.9)	44 (47.3)
Race,[a] n (%)		
White	67 (81.7)	24 (25.8)
Other	11 (13.4)	2 (2.2)
Not reported	4 (4.9)	67 (72.0)
Ethnicity, n (%)		
Hispanic or Latino	30 (36.6)	12 (12.9)
Not Hispanic or Latino	41 (50.0)	14 (15.1)
Not reported	11 (13.4)	67 (72.0)
Geographic region of residence,[a] n (%)		
Europe	27 (32.9)	20 (21.5)
Rest of world	55 (67.1)	47 (50.5)
Not reported	0 (0)	26 (28.0)
Age of TK2d symptom onset, years		
Median (range)	1.50 (0.01–11.67)	1.33 (0.00–11.00)
Q1, Q3	1.08, 2.41	0.75, 2.49
Age at first treatment (any treatment), years		
Median (range)	4.26 (0.69–35.52)	NA
Q1, Q3	2.11, 10.49	

[a]Owing to the ultra-rare nature of TK2d and the small number of patients, some details relating to race and geographic region of residence were grouped for reporting purposes to minimize risk of patient reidentification.
ISE, Integrated Summary of Efficacy; MUPD, modified Untreated Patient Database; NA, not available; Q, quartile; TK2d, thymidine kinase 2 deficiency.

Figure 2. Direct adjustment survival curves and RMST estimates from (A) symptom onset and (B) treatment start for 50th-percentile matched-pairs of patients from the ISE treated and ISE-MUPD groups with age of TK2d symptom onset ≤12 years



Direct adjustment survival curves were estimated using a Cox marginal model with age of TK2d symptom onset as strata variable. RMSTs were estimated from Kaplan–Meier analyses; nominal *p* values are not multiplicity adjusted.
CI, confidence interval; ISE, Integrated Summary of Efficacy; MUPD, modified Untreated Patient Database; RMST, restricted mean survival time; TK2d, thymidine kinase 2 deficiency.

Table 2. Survival HRs for patients with age of TK2d symptom onset ≤12 years, estimated from Cox models using 50th-percentile matched-pair data from the ISE treated and ISE-MUPD groups

Model	HR (95% CI) for time from TK2d symptom onset to death	HR (95% CI) for time from treatment initiation to death
Cox proportional hazard model, match-pairs as strata variable, age of TK2d symptom onset as continuous covariate, with Firth correction	0.061 (0.006, 0.221); $p<0.0001$	0.134 (0.033, 0.362); $p<0.0001$
Cox proportional hazard model, match-pairs as strata variable, no covariate, with Firth correction	0.079 (0.016, 0.238); $p<0.0001$	0.127 (0.034, 0.340); $p<0.0001$
Marginal Cox model with age of TK2d symptom onset as strata variable	0.061 (0.019, 0.190); $p<0.0001$	0.052 (0.015, 0.179); $p<0.0001$

78 matched pairs were included in the analyses (deaths: ISE treated, n=3; ISE-MUPD, n=40), of which 33 and 30 informative pairs were used to estimate time to death from TK2d symptom onset and from treatment initiation, respectively. Firth correction was used to achieve convergence in Cox proportional hazard model estimates owing to the lack of events in the treated group.
CI, confidence interval; HR, hazard ratio; ISE, Integrated Summary of Efficacy; MUPD, modified Untreated Patient Database; TK2d, thymidine kinase 2 deficiency.

Safety and tolerability

- In the pooled safety population (MT-1621-101, TK0102, MT-1621-107; n=50 with age of TK2d symptom onset ≤12 years), two patients (4.0%) experienced treatment-emergent adverse events (TEAEs) leading to treatment discontinuation (**Table 3**)

Table 3. Summary of TEAEs in the pooled safety population with age of TK2d symptom onset ≤12 years

Patients with TEAEs, n (%)	MT-1621-101 and TK0102 (n=39)	MT-1621-101, TK0102 and MT-1621-107 (n=50)
Patients with ≥1 TEAE	39 (100)	NC[a]
TEAE related to study drug	32 (82.1)	NC[a]
TEAE leading to study drug discontinuation	0 (0)	2 (4.0)
TEAE leading to dose reduction	9 (23.1)	10 (20.0)
Patients with ≥1 serious TEAE	23 (59.0)	NC[a]
Serious TEAE related to study drug	4 (10.3)	NC[a]
TEAEs reported in ≥20% of patients, by preferred term		
Diarrhoea	33 (84.6)	NC[a]
Pyrexia	18 (46.2)	
COVID-19	17 (43.6)	
Upper respiratory tract infection	16 (41.0)	
Rhinorrhoea	15 (38.5)	
Vomiting	13 (33.3)	
Cough	11 (28.2)	
Headache	11 (28.2)	
Alanine aminotransferase increased	11 (28.2)	
Abdominal pain	10 (25.6)	
Gastroenteritis	9 (23.1)	
Aspartate aminotransferase increased	9 (23.1)	
Respiratory tract infection	8 (20.5)	
Blood creatine phosphokinase increased	8 (20.5)	
Serious TEAEs reported in ≥10% of patients, by preferred term		
Acute respiratory failure	5 (12.8)	NC[a]
Pneumonia	5 (12.8)	
Femur fracture	4 (10.3)	

[a]Some safety outcomes were not collected in MT-1621-107. Data for any TEAE or serious TEAE leading to treatment discontinuation, interruption or dose reduction were collected.
NC, not calculable; TEAE, treatment-emergent adverse event; TK2d, thymidine kinase 2 deficiency.

Conclusions and Outlook

- In patients with an age of TK2d symptom onset ≤12 years, pyrimidine nucleos(t)ide therapy substantially decreased the risk of mortality by 87–95% and increased survival time
  - Potential bias resulting from the use of an external comparator was addressed by utilizing multiple survival analyses, strict matching methodology, covariate adjustment and stratification
- Treatment with pyrimidine nucleos(t)ides was generally well tolerated, with few TEAEs leading to treatment discontinuation in the overall ISS safety population
- The observed improvement in survival with pyrimidine nucleos(t)ide therapy may have important implications for addressing the severe unmet need for patients living with TK2d
- Among patients with age of TK2d symptom onset ≤12 years and full safety data availability (MT-1621-107 not included; n=39):
  - all patients had at least one TEAE, most commonly diarrhoea (33/39 [84.6%])
  - 59.0% of patients (23/39) experienced at least one serious TEAE over the duration of their treatment, most of which were not considered treatment-related
- TEAEs reported in ≥10% of patients are presented in **Supplementary Table 1**

This poster was previously presented at 2025 Muscular Dystrophy Association (MDA) Clinical & Scientific Conference, 16–19 March 2025, Dallas, TX, USA

Acknowledgments: This study was funded by UCB. The authors acknowledge Tamsin Chambers PhD of PharmaGenesis Cambridge, Cambridge, UK, for writing and editorial assistance, which was funded by UCB, in accordance with Good Publication Practice 2022 (GPP 2022) guidelines (https://www.ismpp.org/gpp-2022). The authors would like to thank Margarita Lens MSc CMPP of UCB for publication coordination. The authors thank the patients and their caregivers, in addition to the investigators and their teams who contributed to this study.

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Disclosures: Caterina Garone serves on an advisory board of UCB. **Cristina Domínguez-González** serves on an advisory board of UCB; has received funding from UCB to cover travel expenses to medical conferences and as a speaker; and has received funding from UCB for research projects related to TK2d. **Richard Haas** has consultant agreements with Stealth BioTherapeutics, Sun Pharma Advanced Research Company and UCB; and has received research funding from the NIH North American Mitochondrial Disease Consortium (Director Career Enhancement program), Stealth BioTherapeutics, Tiyotha Gene Therapies and Tisento Therapeutics, and for research projects related to mitochondrial disease. **Carmen Paradas** has nothing to disclose. **Fernando Scaglia** serves on advisory boards of Nestlé, UCB and Zevra Therapeutics (formerly Acer Therapeutics); has consultant agreements with Precision BioSciences and Tisento Therapeutics; has received research support from Astellas Pharma, the NIH (U54 NS078059 and U54 NS115198), PTC Therapeutics, Stealth BioTherapeutics and the US Food and Drug Administration's Office of Orphan Products Development (5R01-FD005407). He is also the Program Chair of the Mitochondrial Medicine Society. **Cynthia Beller**, **Carl Chiang**, **Anny-Odile Colson** and **Susan VanMeter** are employees of and stockholders in UCB. **Michio Hirano** serves on an advisory board of UCB; has received research support, honoraria or both from Entrada Therapeutics, Modis Therapeutics (a wholly owned subsidiary of Zogenix/UCB), Precision BioSciences and Stealth BioTherapeutics; and has received grant support from the Department of Defense (FPA W81XWH2010807), the J. Willard and Alice S. Marriott Foundation, the Muscular Dystrophy Association (577392) and the National Institutes of Health (NIH; U54 NS078059 and P01 HD32062). **Michio Hirano** is also on the scientific and medical advisory boards of the Barth Syndrome Foundation and the United Mitochondrial Disease Foundation, and he is on the Research Advisory Committee of the Muscular Dystrophy Association. Columbia University Irving Medical Center (CUIMC) has a patent for deoxynucleoside therapies for mitochondrial DNA depletion syndrome including TK2d, which is licensed to Modis Therapeutics, a wholly owned subsidiary of Zogenix/UCB; this relationship is monitored by an unconflicted external academic researcher. **Caterina Garone** and **Michio Hirano** are coinventors of this patent. CUIMC has received royalty payments related to the development and commercialization of the technology; **Caterina Garone** and **Michio Hirano** have received shares of the royalty payments following Columbia University policies.