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

2025 Muscular Dystrophy Association (MDA) Clinical & Scientific Conference; Dallas, TX, USA; March 16–19, 2025

Caterina Garone[1,2]*, Michio Hirano[3], Richard Haas[4,5], Carmen Paradas[6,7], Fernando Scaglia[8,9,10], Cynthia Beller[11], Carl Chiang[11], Anny-Odile Colson[12], Susan VanMeter[11], Cristina Domínguez-González[13,14,15]

[1]Department of Medical and Surgical Sciences, Alma Mater Studiorum, University of Bologna, Bologna, Italy; [2]Scientific Institute for Research, Hospitalization and Healthcare (IRCCS) Istituto delle Scienze Neurologiche, Unità Operativa Complessa (UOC) Neuropsichiatria dell'età Pediatrica di Bologna, Bologna, Italy; [3]The H. Houston Merritt Center for Neuromuscular and Mitochondrial Disorders, Department of Neurology, Columbia University Irving Medical Center, New York, NY, USA; [4]Department of Neurosciences, University of California, San Diego, CA, USA; [5]Rady Children's Hospital, San Diego, CA, USA; [6]Neuromuscular Disorders Unit, Neurology Department, Instituto de Biomedicina de Sevilla (IBiS), Hospital Universitario Virgen del Rocío, Consejo Superior de Investigaciones Científicas, University of Seville, Seville, Spain; [7]Center for Biomedical Network Research on Neurodegenerative Diseases (CIBERNED), Instituto de Salud Carlos III, Madrid, Spain; [8]Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, USA; [9]Texas Children's Hospital, Houston, TX, USA; [10]Baylor College of Medicine (BCM)–Chinese University of Hong Kong (CUHK) Joint Centre for Medical Genetics, Prince of Wales Hospital, Shatin, Hong Kong SAR, China; [11]UCB, Morrisville, NC, USA; [12]UCB, Colombes, France; [13]Neuromuscular Diseases Unit, Neurology Department, Hospital Universitario 12 de Octubre, Madrid, Spain; [14]Research Institute Hospital 12 de Octubre (i+12), Madrid, Spain; [15]Centre for Biomedical Network Research on Rare Diseases (CIBERER), Instituto de Salud Carlos III, Madrid, Spain

***Presenting author:** Caterina Garone (caterina.garone@unibo.it)

Introduction

- Thymidine kinase 2 deficiency (TK2d) is an ultra-rare, autosomal recessive, mitochondrial disease associated with progressive, life-threatening proximal myopathy[1,2]
  - Pathogenic variants of the thymidine kinase 2 gene (*TK2*) result in mitochondrial DNA (mtDNA) depletion and/or multiple mtDNA deletions[3]
  - Patients experience proximal muscle weakness and respiratory insufficiency, often losing the ability to walk, eat and breathe independently. Given the progressive nature of TK2d, there is typically no spontaneous recovery of lost functional abilities [1,4]
- There are no approved treatments for TK2d, with current management across the world focused on supportive care. This may include use of ventilatory support and feeding tubes to assist with daily living[2,5]
- 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]
- The age of TK2d symptom onset varies widely; however, patients with earlier symptom onset typically tend to experience more rapid disease progression[1,2]
  - Using a threshold of ≤12 years versus >12 years for the age of TK2d symptom onset is largely considered a clinically meaningful approach to disease categorization[1,2]

Objective

- To assess functional outcomes and safety in pediatric and adult participants 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 participants treated with pyrimidine nucleos(t)ides were pooled from retrospective (MT-1621-101 [NCT03701568], MT-1621-107 [NCT05017818]) and prospective (TK0102 [NCT03845712]) sources and company-supported expanded access programs (EAPs) to form the ISE treated group (**Figure 1**)
- The ISS pooled safety population included participants from MT-1621-101, TK0102 and MT-1621-107
- Subgroups were stratified by age of TK2d symptom onset categories; here, we report data from participants with symptom onset ≤12 years of age
  - Functional analyses in participants with symptom onset at >12 years of age are presented in poster P256

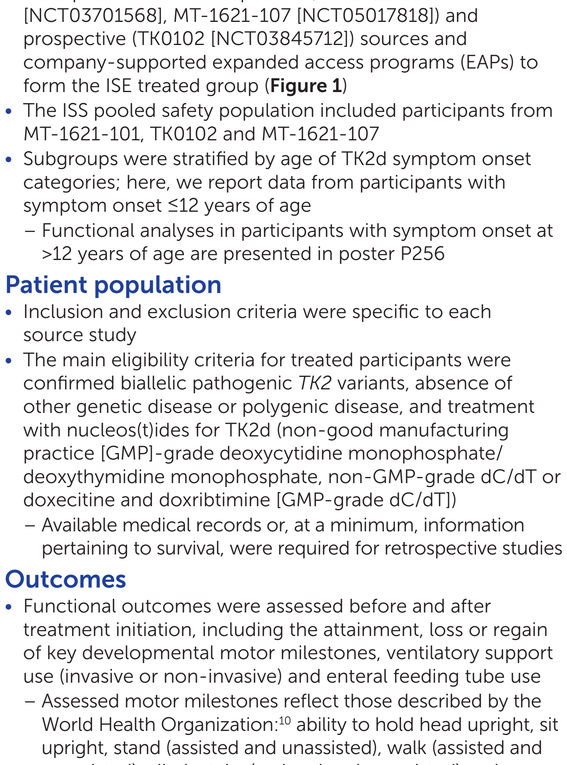
Patient population

- Inclusion and exclusion criteria were specific to each source study
- The main eligibility criteria for treated participants 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

Outcomes

- Functional outcomes were assessed before and after treatment initiation, including the attainment, loss or regain of key developmental motor milestones, ventilatory support use (invasive or non-invasive) and enteral feeding tube use
  - Assessed motor milestones reflect those described by the World Health Organization:[10] ability to hold head upright, sit upright, stand (assisted and unassisted), walk (assisted and unassisted), climb stairs (assisted and unassisted) and run
  - Functional outcome data were not collected for treated patients in the EAPs
- The primary outcome was survival (poster P257)
- Safety outcomes, including treatment-emergent adverse events (TEAEs), 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 participant data described in each publication/source were cross-referenced with the aim of removing duplicates to obtain unique data. The untreated patient population used to assess survival in the ISE are not shown here.
[a]Data cutoff date: March 15, 2024. [b]Data cutoff date: March 1, 2024. [c]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; TK2d, thymidine kinase 2 deficiency.

Results

Patient baseline characteristics and demographics

- In total, 82 participants with age of TK2d symptom onset ≤12 years were treated with pyrimidine nucleos(t)ide therapy (**Table 1**)
  - There were more male (56.1%) than female participants (43.9%)
  - Most participants were White (81.7%), 32.9% resided in Europe and 67.1% were from the rest of the world
- Most participants had an age of TK2d symptom onset ≤2 years (56/82 [68.3%])
  - Median (quartile [Q]1, Q3) age of symptom onset was 1.50 (1.08, 2.41) years
- 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

Developmental motor milestones

- Of participants with developmental motor milestone data collected, 49/52 (94.2%) achieved ≥1 milestone before treatment initiation (missing data, n=30)
- Before treatment initiation, in participants who had initially achieved ≥1 motor milestone, 83.7% of participants (41/49) lost ≥1 motor milestone and 40.8% of participants (20/49) lost ≥4 motor milestones (**Figure 2A**)
- After treatment initiation, 21.7% of participants (10/46) lost ≥1 motor milestone; only 2.2% of participants (1/46) lost ≥4 motor milestones (**Figure 2A**)
- Before treatment initiation, only 4.9% of participants (2/41) regained ≥1 previously lost motor milestone (**Figure 2B**); the ability to stand assisted and to run were both regained by 1 participant each
- After treatment initiation, 75.0% of participants (30/40) regained ≥1 previously lost motor milestone, and 22.5% (9/40) regained ≥4 previously lost motor milestones (**Figure 2B**)

Ventilatory and enteral feeding tube support

- Before treatment, 31/82 participants (37.8%) were using ventilatory support (**Table 2**), most commonly non-invasive bilevel or continuous positive airway pressure (20/31 [64.5%])
  - Of these participants, 5/31 (16.1%) discontinued support after treatment and an additional 5/31 participants (16.1%) reduced their hours of use
- After starting treatment, 4/22 participants (18.2%) initiated ventilatory support, one of whom later discontinued support
- Before treatment, 20/82 participants (24.4%) had a feeding tube inserted (**Table 2**). One participant later had their feeding tube removed, leaving 19/82 participants (23.2%) using enteral feeding support at treatment initiation
  - Of these participants, 2/19 (10.5%) discontinued feeding support after treatment
- After starting treatment, 4/33 participants (12.1%) had a feeding tube inserted, two of whom later discontinued enteral feeding support
- Before treatment, the most common reason for enteral feeding tube insertion was to manage dysphagia (17/20 [85.0%]). After treatment, the most common reason for enteral feeding tube insertion was for supplemental oral intake (3/4 [75.0%])

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 participants (4.0%) experienced TEAEs leading to treatment discontinuation (**Table 3**)
- Among participants with age of TK2d symptom onset ≤12 years and full safety data availability (MT-1621-107 not included; n=39):
  - all participants had at least one TEAE, most commonly diarrhea (33/39 [84.6%])
  - 59.0% of participants (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 participants are presented in **Supplementary Table 1**

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

Baseline demographics and characteristics	ISE treated (N=82)
Sex, n (%)	
Male	46 (56.1)
Female	36 (43.9)
Race,[a] n (%)	
White	67 (81.7)
Other	11 (13.4)
Not reported	4 (4.9)
Ethnicity, n (%)	
Hispanic or Latino	30 (36.6)
Not Hispanic or Latino	41 (50.0)
Not reported	11 (13.4)
Geographic region of residence,[a] n (%)	
Europe	27 (32.9)
Rest of world	55 (67.1)
Not reported	0 (0)
Age of TK2d symptom onset, years	
Median (range)	1.50 (0.01–11.67)
Q1, Q3	1.08, 2.41
Age at first treatment (any treatment), years	
Median (range)	4.26 (0.69–35.52)
Q1, Q3	2.11, 10.49

[a]Owing to the ultra-rare nature of TK2d and the small number of participants, some details relating to race and geographic region of residence were grouped for reporting purposes to minimize risk of participant reidentification.
ISE, Integrated Summary of Efficacy; Q, quartile; TK2d, thymidine kinase 2 deficiency.

Table 2. Summary of use of ventilatory and enteral feeding tube support before and after treatment initiation in participants with age of TK2d symptom onset ≤12 years (N=82)

	Before treatment	After treatment
Summary of ventilatory support		
Initiated ventilatory support, n/N (%)	31/82 (37.8)	4/22[a] (18.2)
Discontinued ventilatory support, n/N (%)	0/31[b] (0)	6/35[c] (17.1)
Hours of ventilatory support per day (last observation)		
n	28	17
Median (range)	11.0 (8–24)	8.0 (0–24)
Q1, Q3	8.0, 24.0	0.0, 14.0
No ventilatory support data collected, n (%)	29 (35.4)	
Summary of enteral feeding tube support		
Feeding tube inserted, n/N (%)	20/82 (24.4)	4/33[a] (12.1)
Feeding tube removed, n/N (%)	1/20[b] (5.0)	4/23[c] (17.4)
No enteral feeding tube support data collected, n (%)	30 (36.6)	

[a]N is participants with available data not using support before treatment start who were at risk of initiating support after treatment start. [b]N is participants using support before treatment start who were at risk of discontinuing support. [c]N is participants using support at any time after treatment start who were at risk of discontinuing support.
Q, quartile; TK2d, thymidine kinase 2 deficiency.

Figure 2. Developmental motor milestone (A) loss and (B) regain before and after treatment initiation in participants with age of TK2d symptom onset ≤12 years (N=82)

In (A), 33 and 36 participants, respectively, before and after treatment initiation had missing data or were not at risk for motor milestone loss, so are not included in the graph. In (B), 41 and 42 participants, respectively, before and after treatment initiation had missing data or were not at risk for motor milestone regain, so are not included in the graph.
[a]N is the number of participants at risk for loss or regain of each individual motor milestone.
TK2d, thymidine kinase 2 deficiency.

Conclusions and Outlook

In participants with an age of TK2d symptom onset ≤12 years, treatment with pyrimidine nucleos(t)ides resulted in a positive change in disease trajectory for functional outcomes

- After treatment initiation, the frequency of motor milestone loss was reduced and three-quarters of participants regained previously lost motor milestones
- 17% of participants discontinued use of ventilatory support after treatment initiation, while other participants reduced their level of support
- A smaller proportion of participants had a feeding tube inserted after treatment initiation than before treatment initiation

Treatment with pyrimidine nucleos(t)ides was generally well tolerated, with few TEAEs leading to treatment discontinuation in the overall ISS safety population

Considering the relentlessly progressive nature of TK2d, the stabilization or improvement of functional outcomes seen following treatment with pyrimidine nucleos(t)ides in this study is clinically important for addressing the severe unmet need for patients living with TK2d

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

Participants with TEAEs, n (%)	MT-1621-101 and TK0102 (n=39)	MT-1621-101, TK0102 and MT-1621-107 (n=50)
Participants 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)
Participants 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 participants, by preferred term		
Diarrhea	33 (84.6)	NC[a]
Pyrexia	18 (46.2)	
COVID-19	17 (43.6)	
Upper respiratory tract infection	16 (41.0)	
Rhinorrhea	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 participants, 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.
NC, not calculable; TEAE, treatment-emergent adverse event; TK2d, thymidine kinase 2 deficiency.

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 MSci 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.

References: 1. Berardo A, *et al. J Neuromuscul Dis* 2022;9:225–35. 2. Garone C, *et al. J Med Genet* 2018;55:515–21. 3. Lopez-Gomez C, *et al. EBioMedicine* 2019;46:356–67. 4. Dominguez-Gonzalez C, *et al. Orphanet J Rare Dis* 2019;14:100. 5. de Barcelos IP, *et al. Curr Opin Neurol* 2019;32:715–21. 6. Lopez-Gomez C, *et al. Ann Neurol* 2017;81:641–52. 7. Tsurada L, *et al. Neuromuscul Disord* 2020;30:S139. 8. Lopez-Gomez, C *et al. EBioMedicine* 2019;46:356–67. 9. Ramon J, *et al. Int J Mol Sci* 2021;22:6447. 10. Wijnhoven TM, *et al. Food Nutr Bull* 2004;25:S37–45.

Disclosures: Caterina Garone serves on an advisory board of 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. **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, Taysha 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, Saol 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. **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.

Please use this QR code to access the supplementary data and download a PDF of this poster.

Poster number: P255 (supplementary data)

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

Supplementary Table 1. Summary of TEAEs reported in ≥10% of participants in the pooled safety population[a] with age of TK2d symptom onset ≤12 years

Preferred term, n (%)	MT-1621-101 and TK0102 (n=39)
Diarrhea	33 (84.6)
Pyrexia	18 (46.2)
COVID-19	17 (43.6)
Upper respiratory tract infection	16 (41.0)
Rhinorrhea	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)
Ear infection	7 (17.9)
Pneumonia	7 (17.9)
Influenza	7 (17.9)
Oropharyngeal pain	7 (17.9)
Rash	7 (17.9)
Anion gap increased	7 (17.9)
Blood lactic acid increased	7 (17.9)
Femur fracture	5 (12.8)
Acute respiratory failure	5 (12.8)
Influenza-like illness	5 (12.8)
Dyspnea	5 (12.8)
Basophil count increased	5 (12.8)
Dysphagia	5 (12.8)
Platelet count increased	5 (12.8)
Pain in extremity	4 (10.3)
Urinary tract infection	4 (10.3)
Abdominal pain upper	4 (10.3)
Depression	4 (10.3)
Muscular weakness	4 (10.3)
Carbon dioxide decreased	4 (10.3)
Gastroesophageal reflux disease	4 (10.3)
Nasopharyngitis	4 (10.3)
Scoliosis	4 (10.3)
Tachycardia	4 (10.3)

[a]Data were not collected in MT-1621-107.
TEAE, treatment-emergent adverse event; TK2d, thymidine kinase 2 deficiency.