Survival, functional outcomes and safety in patients with thymidine kinase 2 deficiency (TK2d) and an age of TK2d symptom onset ≤12 years who received pyrimidine nucleos(t)ide therapy

European Human Genetics Conference (ESHG) 2025; Milan, Italy; 24–27 May 2025

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Introduction

- Thymidine kinase 2 deficiency (TK2d) is an ultra-rare, autosomal recessive, mitochondrial disease manifesting as progressive proximal myopathy, bulbar weakness and respiratory insufficiency, the latter often being responsible for premature death[1,2]
- There are no approved treatments for TK2d, with current management focused on supportive care, which does not change the progressive disease trajectory[3]
  - Doxecitine and doxribtimine is a pyrimidine nucleoside therapy containing deoxycytidine and deoxythymidine currently in development for use in TK2d[4,5]
- There is a wide spectrum of TK2d symptom onset; generally, patients with earlier symptom onset have more rapid disease progression[1,2]
  - A threshold of ≤12 years versus >12 years for the age of symptom onset is often considered a clinically meaningful approach to disease categorization[1,2]

Objective

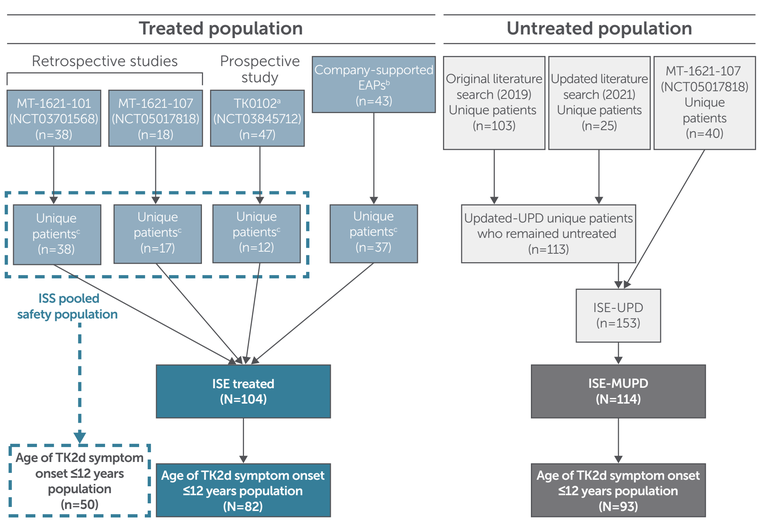
- To assess efficacy and safety in paediatric and adult patients with an age of TK2d symptom onset ≤12 years who received pyrimidine nucleos(t)ide therapy

Methods

Study design

- Data are presented for three groups of patients with TK2d and age of symptom onset ≤12 years (**Figure 1**)
  - The **Integrated Summary of Efficacy (ISE) treated group** (patients treated with pyrimidine nucleos[t]ides)
  - The **ISE-modified Untreated Patient Database (MUPD) group** (untreated patients)
  - The Integrated Summary of Safety (ISS) population (patients treated with pyrimidine nucleos[t]ides outside of company-supported expanded access programs [EAPs])
- Full details on inclusion/exclusion criteria can be found in the **Supplemental Methods**

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.
[a]Data cutoff date: 15 March 2024. [b]Data cutoff date: 1 March 2024. [c]Individuals who participated in multiple studies are only counted once, although their data across studies are included.
EAP, expanded access program; ISE, Integrated Summary of Efficacy; ISS, Integrated Summary of Safety; MUPD, modified UPD; TK2d, thymidine kinase 2 deficiency; UPD, Untreated Patient Database.

Outcomes

- The primary ISE outcome was survival, defined as time to death from TK2d symptom onset and from treatment initiation (assessed in the ISE treated and ISE-MUPD groups)
- Functional outcomes were assessed before and after treatment initiation in patients in the ISE treated group and included the attainment, loss or regain of key developmental motor milestones (reflective of those described by the World Health Organization),[6] ventilatory support use and enteral feeding tube use
  - Functional outcome data were not collected for treated patients in the EAPs
- Safety outcomes, including treatment-emergent adverse events (TEAEs), were assessed in the ISS pooled safety population
  - Some safety outcomes were not collected in the MT-1621-107 study

Statistical analysis

- Survival in 50th-percentile treated and untreated patient matched pairs was assessed using proportional hazard and marginal Cox models, and restricted mean survival time analyses
  - Further details on statistical analyses can be found in the **Supplemental Methods**

Results

Patient characteristics

- 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 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) duration of treatment for the ISE treated group 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**; **Supplemental Table 1**])

Developmental motor milestones

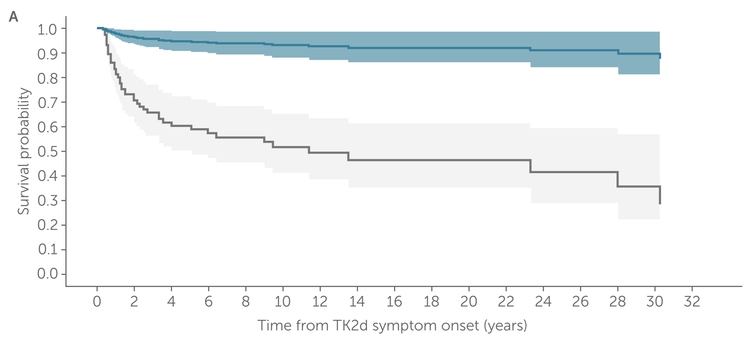
- Of the 52 patients with developmental motor milestone data collected, 49 (94.2%) initially achieved ≥1 milestone
- Before treatment initiation, in patients who had initially achieved ≥1 motor milestone, 41/49 (83.7%) lost ≥1 motor milestone; this proportion fell to 10/46 patients (21.7%) after treatment initiation (**Figure 3A**)
- Before treatment initiation, 2/41 patients (4.9%) regained ≥1 previously lost motor milestone; this proportion rose to 30/40 patients (75.0%) after treatment initiation (**Figure 3B**)
  - Details on individual developmental motor milestones lost and regained are presented in **Supplemental Figure 1**

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

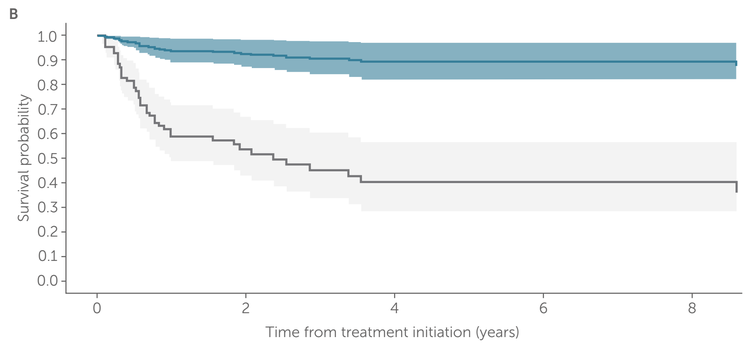
Baseline demographics and characteristics	ISE treated (N=82)	ISE-MUPD (N=93)
Sex, n (%)		
Male	46 (56.1)	49 (52.7)
Female	36 (43.9)	44 (47.3)
Race,[a] n (%)		
White	67 (81.7)	24 (25.8)
Other	11 (13.4)	2 (2.2)
Not reported	4 (4.9)	67 (72.0)
Ethnicity, n (%)		
Hispanic or Latino	30 (36.6)	12 (12.9)
Not 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 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; MUPD, modified Untreated Patient Database; NA, not applicable; Q, quartile; TK2d, thymidine kinase 2 deficiency.

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



RMST (95% CI) over the 30 years after TK2d symptom onset was 29.2 (28.2–30.3) years for treated patients versus 14.4 (11.1–17.6) years for untreated patients (nominal *p* value <0.0001)



RMST (95% CI) over the 6 years after treatment initiation was 5.8 (5.5–6.0) years for treated patients versus 2.8 (2.2–3.5) years for untreated patients (nominal *p* value <0.0001)

Treated — Untreated

Direct adjustment survival curves were estimated using a marginal Cox 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.

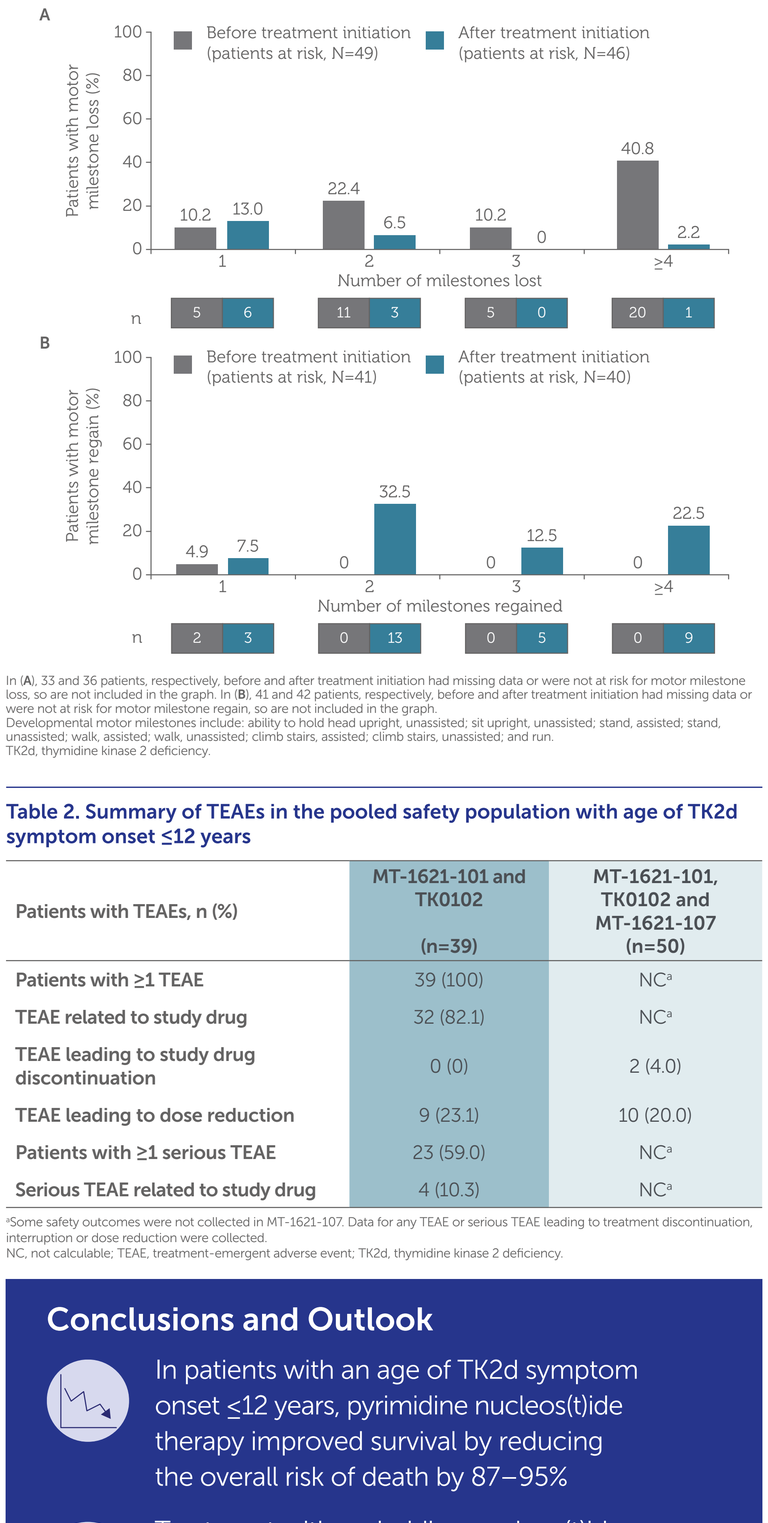
Ventilatory and enteral feeding tube support

- Before treatment, 31/82 patients (37.8%) were using ventilatory support, most commonly non-invasive bilevel or continuous positive airway pressure (20/31 [64.5%])
  - Of these patients, 5/31 (16.1%) discontinued support after treatment initiation and an additional 5/31 patients (16.1%) reduced their hours of use
- After starting treatment, 4/22 patients (18.2%) initiated ventilatory support, one of whom later discontinued support
- Before treatment, 20/82 patients (24.4%) had a feeding tube inserted; one patient later had their feeding tube removed, leaving 19/82 patients (23.2%) using enteral feeding tube support at treatment initiation
  - Of these patients, 2/19 (10.5%) discontinued feeding support after starting treatment
- After starting treatment, 4/33 patients (12.1%) had a feeding tube inserted, two of whom later discontinued feeding tube support
- Further details on ventilatory and enteral feeding tube support can be found in **Supplemental Table 2**

Safety and tolerability

- An overview of TEAEs is presented in **Table 2**
- Among patients with age of TK2d symptom onset ≤12 years and full safety data available (MT-1621-107 not included; n=39):
  - all patients had at least one TEAE, most commonly diarrhoea (33/39 [84.6%]), pyrexia (18/39 [46.2%]) and COVID-19 (17/39 [43.6%]); see **Supplemental Table 3** for further details on TEAEs
  - a total of 23 (59.0%) experienced at least one serious TEAE, with acute respiratory failure (12.8%), pneumonia (12.8%) and femur fracture (10.3%) occurring in ≥10% of patients
- Of the 67 patients in the ISS pooled safety population (regardless of age of TK2d symptom onset), three patients experienced a fatal serious TEAE
  - None of these deaths were considered related to treatment

Figure 3. Developmental motor milestone (A) loss and (B) regain before and after treatment initiation in patients with age of TK2d symptom onset ≤12 years (N=82)



In (**A**), 33 and 36 patients, 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 patients, 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.
Developmental motor milestones include: ability to hold head upright, unassisted; sit upright, unassisted; stand, assisted; stand, unassisted; walk, assisted; walk, unassisted; climb stairs, assisted; climb stairs, unassisted; and run.
TK2d, thymidine kinase 2 deficiency.

Table 2. 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]

[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 improved survival by reducing the overall risk of death by 87–95%

Treatment with pyrimidine nucleos(t)ides also resulted in positive changes in disease trajectory for functional outcomes, including reductions in the frequency of motor milestone loss, increased regain of previously lost motor milestones, discontinuation or reduction of ventilatory support in some patients, and a reduced frequency of feeding tube insertion

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 stabilization of functional outcomes and improvement in survival seen with pyrimidine nucleos(t)ide therapy have important implications for addressing the severe unmet need for patients living with TK2d

Data first presented at Muscular Dystrophy Association (MDA) Conference 2025; Dallas, TX, USA; 16–19 March 2025.

Acknowledgements: This study was funded by UCB. The authors acknowledge Bobby Thompson MSc(Res) of Oxford PharmaGenesis, Oxford, 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. de Barcelos IP, *et al. Curr Opin Neurol* 2019;32:715–21. 4. Tsuruda L, *et al. Neuromuscul Disord* 2020;30:S139. 5. Lopez-Gomez C, *et al. EBioMedicine* 2019;46:356–67. 6. Wijnhoven TM, *et al. Food Nutr Bull* 2004;25:S37–45.

Disclosures: **Caterina Garone** serves on an advisory board of UCB and has received funding from UCB for research projects related to TK2d. **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 National Institutes of Health (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. **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 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.

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

Poster number: P08.001.D (supplementary data)

Survival, functional outcomes and safety in patients with thymidine kinase 2 deficiency (TK2d) and an age of TK2d symptom onset ≤12 years who received pyrimidine nucleos(t)ide therapy

Supplemental Methods

Patient population

- The main eligibility criteria for treated patients were confirmed biallelic pathogenic thymidine kinase 2 gene (*TK2*) variants, absence of other genetic disease or polygenic disease, and treatment with nucleos(t)ides for thymidine kinase 2 deficiency (TK2d) (non-good manufacturing practice [GMP]-grade deoxycytidine monophosphate/deoxythymidine monophosphate, non-GMP-grade deoxycytidine/deoxythymidine [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
- 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]) studies and company-supported expanded access programs to form the Integrated Summary of Efficacy (ISE) treated group
- Data from untreated participants were pooled from literature reviews and a retrospective chart review study (MT-1621-107) to form the ISE-modified Untreated Patient Database (MUPD) group

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
- Firth correction was used to achieve convergence in the Cox proportional hazard model estimates owing to the lack of events in the treated group
- 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 initiation)

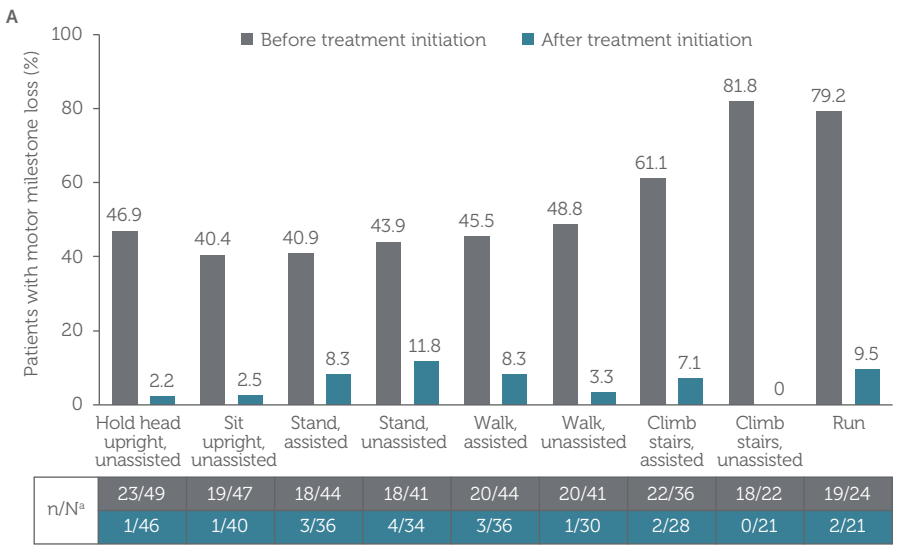
Supplemental Results

Supplemental Table 1. 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. Nominal *p* values are not multiplicity adjusted.
CI, confidence interval; HR, hazard ratio; ISE, Integrated Summary of Efficacy; MUPD, modified Untreated Patient Database; TK2d, thymidine kinase 2 deficiency.

Supplemental Figure 1. Individual developmental motor milestone (A) loss and (B) regain before and after treatment initiation in patients with age of TK2d symptom onset ≤12 years (N=82)



In (**A**), 33 and 36 patients, 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 patients, 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 patients at risk for loss or regain of each individual motor milestone.
TK2d, thymidine kinase 2 deficiency.

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

	Before treatment initiation	After treatment initiation
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 (8.0–24.0)	8.0 (0.0–24.0)
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[d] (24.4)	4/33[a,e] (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 patients with available data not using support before treatment initiation who were at risk of initiating support after treatment initiation. [b]N is patients using support before treatment initiation who were at risk of discontinuing support. [c]N is patients using support at any time after treatment initiation who were at risk of discontinuing support. [d]Before treatment, the most common reason for enteral feeding tube insertion was to manage dysphagia (17/20 [85.0%]). [e]After treatment initiation, the most common reason for enteral feeding tube insertion was for supplemental oral intake (3/4 [75.0%]).
Q, quartile; TK2d, thymidine kinase 2 deficiency.

Supplemental Table 3. Summary of TEAEs in the pooled safety population[a] 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 ≥10% of patients, by preferred term		
Diarrhoea	33 (84.6)	
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)	
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)	NC[a]
Blood lactic acid increased	7 (17.9)	
Femur fracture	5 (12.8)	
Acute respiratory failure	5 (12.8)	
Influenza-like illness	5 (12.8)	
Dyspnoea	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)	
Serious TEAEs reported in ≥10% of participants, by preferred term		
Acute respiratory failure	5 (12.8)	
Pneumonia	5 (12.8)	NC[a]
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.