The disease course of untreated patients with thymidine kinase 2 deficiency (TK2d) aged ≤12 years at TK2d symptom onset: findings from the largest international TK2d dataset

2025 American Academy of Neurology (AAN) Annual Meeting; San Diego, CA, USA and online; April 5–9, 2025

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Introduction

- Thymidine kinase 2 deficiency (TK2d) is an autosomal recessive, mitochondrial disease associated with progressive proximal myopathy, bulbar weakness, respiratory insufficiency and premature death[1]
- The prevalence (25th percentile, 75th percentile) of TK2d is estimated at 1.64 (0.5, 3.1) patients per million people worldwide,[2] although many patients are not identified owing to underdiagnosis and misdiagnosis[3]
- TK2d presents as a continuous clinical spectrum with varying age of symptom onset[1]
  - Typically, the earlier symptoms appear, the faster the disease progresses; patients with age of TK2d symptom onset ≤12 years tend to experience rapid disease progression resulting in premature death[3]
  - TK2d in these patients is often characterized by a failure to attain or a loss of previously acquired developmental motor milestones, including the ability to stand and the ability to walk[3,4]
- The rapid progression of TK2d necessitates comprehensive management by a multidisciplinary team of healthcare professionals and imposes a significant burden on patients and caregivers[5]
  - Currently, there are no approved treatments for TK2d, and management is limited to supportive care[5]
  - Doxecitine and doxribtimine, an oral pyrimidine nucleoside therapy containing deoxycytidine and deoxythymidine, is under review by health authorities for use in TK2d
  - In patients with age of TK2d symptom onset ≤12 years, pyrimidine nucleos(t)ide therapy was generally well tolerated, significantly decreased the risk of mortality by 87–95% and increased survival time[6]
- Given the ultra-rare nature of TK2d, data on natural disease progression are scarce, and no TK2d-specific registries are in existence

Objective

- The aim of this study is to describe the characteristics and survival of and disease progression in untreated patients with TK2d and age of symptom onset ≤12 years
  - Results in patients with age of TK2d symptom onset >12 years are reported separately (poster number 020)

Methods

Study design

- A global Comprehensive Disease Course dataset of untreated patients with TK2d was generated from various data sources (**Figure 1**)
  - The Comprehensive Disease Course dataset comprised data from untreated patients (Integrated Summary of Efficacy [ISE]-Untreated Patient Database [UPD]) and pretreatment data from patients with TK2d later treated with pyrimidine nucleosides (ISE-pretreatment)
  - The ISE-UPD contained data from a comprehensive literature review for case studies conducted in June 2019 and updated in October 2021, as well as data from a retrospective chart review study (MT-1621-107 [NCT05017818])
  - The ISE-pretreatment dataset incorporated pretreatment data from three clinical trials (MT-1621-101 [NCT03701568], TK0102 [NCT03845712], MT-1621-107) and company-supported Expanded Access Programs (EAPs)
- Data were collected either prospectively (some patients from TK0102; company-supported EAPs) or retrospectively (MT-1621-101; MT-1621-107); data were cross-checked to remove duplicates to the greatest extent possible

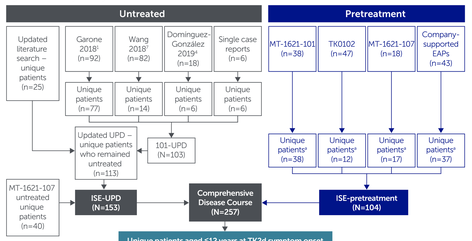
Outcomes

- Outcomes included survival; attainment, loss and regain of key developmental motor milestones; ventilatory support; and enteral feeding tube (nasogastric tube, gastrostomy tube) support

Statistical analysis

- Kaplan–Meier analysis was used to estimate the median (95% confidence interval [CI]) time from birth and from TK2d symptom onset to death, to first developmental motor milestone loss and to first use of ventilatory and feeding support
  - Patients with no event data or missing dates were censored at time point zero
  - In time-to-event analyses, patients who did not experience the event were censored at age last known alive, treated (if applicable) or died (only for endpoints without death as the event of interest), whichever occurred first
- Missing or partial dates were imputed; no other imputation was performed

Figure 1. Study analysis populations



[a]Individuals who participated in multiple studies are counted only once, although their data across studies is included.
EAP, Expanded Access Program; ISE, Integrated Summary of Efficacy; TK2d, thymidine kinase 2 deficiency; UPD, Untreated Patient Database.

Results

Patient characteristics

- In total, 199 patients (77.4%) from the Comprehensive Disease Course dataset had an age of TK2d symptom onset ≤12 years and were included in this study (**Table 1**); a further 49 patients (19.1%) had an age of TK2d symptom onset >12 years (9 patients [3.5%] had missing data for age of TK2d symptom onset)
  - In the Comprehensive Disease Course dataset, 54.3% of patients were male and 45.7% were White

Survival

- Among patients with age of TK2d symptom onset ≤12 years, 66/117 patients (56.4%) from the ISE-UPD dataset died, with a median (first quartile [Q1], third quartile [Q3]) age at death of 1.9 (1.0, 3.5) years
- In the ISE-UPD, Kaplan–Meier estimates of median (95% CI) time from birth and from TK2d symptom onset to death were 4.0 (2.8, 10.0) years and 2.6 (1.3, 6.4) years, respectively (**Figure 2**)

Developmental motor milestones

- In the Comprehensive Disease Course dataset, most patients (60/78 [76.9%]) initially achieved at least four developmental motor milestones (**Figure 3A**)
  - Ability to sit upright, stand and walk, unassisted, respectively, were initially achieved by 93.1%, 84.3% and 80.0% of patients (**Figure 3B**) and subsequently lost in 40.3%, 47.5% and 51.7% of patients who initially achieved them (**Figure 4B**)
- Among 75 patients in the Comprehensive Disease Course dataset who initially achieved at least one developmental motor milestone, 61 (81.3%) subsequently lost at least one developmental motor milestone and 28 (37.3%) subsequently lost at least four developmental motor milestones (**Figure 4**)
  - In the 53 patients with evaluable data, the median (Q1, Q3) age at first developmental motor milestone loss was 2.0 (1.2, 4.5) years
  - Regain of developmental motor milestones previously lost was reported in 3/61 patients (4.9%; ability to stand, assisted [n=1]; ability to walk, unassisted [n=1]; and ability to run [n=1])

Ventilatory and feeding support

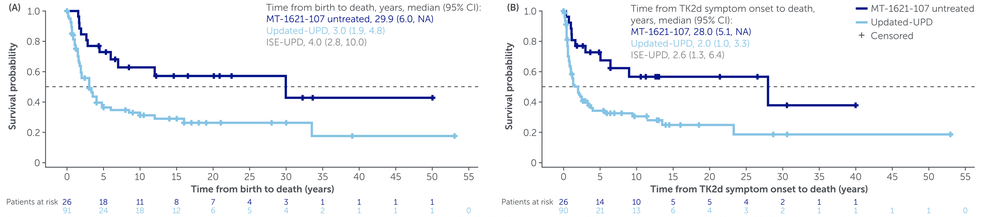
- In the Comprehensive Disease Course dataset, ventilatory support was used by 81/199 patients (40.7%; 50/117 patients [42.7%] and 31/82 patients [37.8%] in the ISE-UPD and ISE-pretreatment datasets, respectively) (**Table 2**)
  - Out of 81 patients who used ventilatory support, one (1.2%) discontinued for reasons other than death
  - Kaplan–Meier estimates for median (95% CI) time from birth and from TK2d symptom onset to first use of ventilatory support in the Comprehensive Disease Course dataset were 7.8 (3.5, 14.0) years and 6.2 (2.3, 9.7) years, respectively
- In the Comprehensive Disease Course dataset, feeding support was used by 28/199 patients (14.1%; 8/117 patients [6.8%] and 20/82 patients [24.4%] in the ISE-UPD and ISE-pretreatment datasets, respectively) (**Table 3**)
  - Out of 28 patients who used feeding support, one (3.6%) discontinued for reasons other than death
  - Kaplan–Meier estimates for median (95% CI) time from birth and from TK2d symptom onset to first use of feeding support in the Comprehensive Disease Course dataset were 16.3 (13.0, not estimable) years and 14.1 (10.3, not estimable) years, respectively

Table 1. Demographic and disease characteristics of patients with TK2d and age of symptom onset ≤12 years

	ISE-UPD (N=117)	ISE-pretreatment (N=82)	Comprehensive Disease Course (N=199)
Sex, n (%)			
Male	62 (53.0)	46 (56.1)	108 (54.3)
Female	53 (45.3)	36 (43.9)	89 (44.7)
Missing	2 (1.7)	0 (0)	2 (1.0)
Race,[a] n (%)			
White	24 (20.5)	67 (81.7)	91 (45.7)
Other	2 (1.7)	11 (13.4)	13 (6.5)
Missing or not reported	91 (77.8)	4 (4.9)	95 (47.7)
Ethnicity, n (%)			
Hispanic or Latino	12 (10.3)	30 (36.6)	42 (21.1)
Not Hispanic or Latino	14 (12.0)	41 (50.0)	55 (27.6)
Missing, unknown or not reported	91 (77.8)	11 (13.4)	102 (51.3)
Geographic region of residence,[a] n (%)			
Europe	20 (17.1)	27 (32.9)	47 (23.6)
Rest of world	48 (41.0)	55 (67.1)	103 (51.8)
Missing or unknown	49 (41.9)	0 (0)	49 (24.6)
Age of TK2d symptom onset, years			
Median (min, max)	1.2 (0.0, 11.0)	1.5 (0.0, 11.7)	1.4 (0.0, 11.7)
Q1, Q3	0.5, 2.0	1.1, 2.4	0.8, 2.3
Age at genetic confirmation, years	n=59	n=77	n=136
Median (min, max)	5.2 (0.0, 56.4)	3.2 (0.1, 35.3)	4.1 (0.0, 56.4)
Q1, Q3	2.0, 14.4	1.6, 8.3	1.7, 10.3
Time from TK2d symptom onset to genetic confirmation, months	n=59	n=77	n=136
Median (min, max)	38.1 (−5.9, 556.4)[b]	12.3 (−59.9, 359.9)[b]	24.7 (−59.9, 556.4)[b]
Q1, Q3	9.4, 129.1	4.3, 64.7	6.3, 90.1

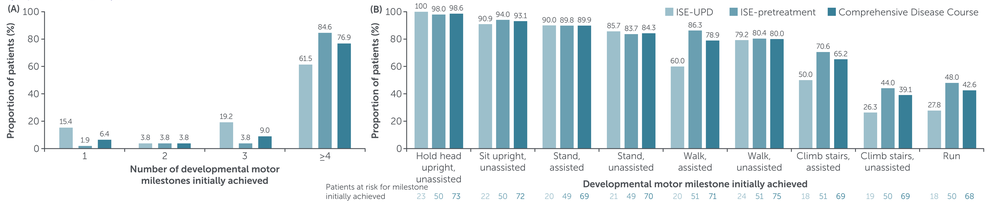
[a]Owing to the ultra-rare nature of TK2d and the small number of patients, some details relating to race and country of residence were grouped for reporting purposes to minimize risk of patient reidentification. [b]Negative values for time from TK2d symptom onset to genetic confirmation indicate that genetic confirmation took place before onset of disease symptoms.
ISE, Integrated Summary of Efficacy; max, maximum; min, minimum; Q1, first quartile; Q3, third quartile; TK2d, thymidine kinase 2 deficiency; UPD, Untreated Patient Database.

Figure 2. Product-limit survival estimates of time from (A) birth and (B) TK2d symptom onset to death in the MT-1621-107 untreated and updated-UPD populations with age of symptom onset ≤12 years.



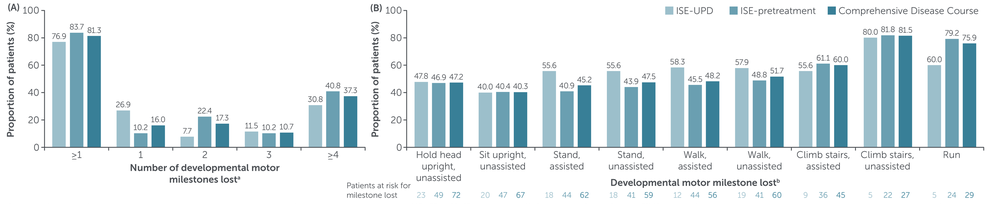
Patients censored at time point zero (event data not collected, no dates or missing period start or end dates) or at a later point in time (last known alive). The MT-1621-107 untreated and updated-UPD datasets are subpopulations of the ISE-UPD dataset. ISE-UPD and Comprehensive Disease Course population datasets are not plotted, given that they aggregate already plotted population datasets. To avoid the introduction of immortal time bias, the ISE-pretreatment group was not included in survival analyses.
CI, confidence interval; ISE, Integrated Summary of Efficacy; NA, not available; TK2d, thymidine kinase 2 deficiency; UPD, Untreated Patient Database.

Figure 3. Summary of (A) number of developmental motor milestones initially achieved and (B) individual developmental motor milestones initially achieved in patients with age of TK2d symptom onset ≤12 years



ISE, Integrated Summary of Efficacy; TK2d, thymidine kinase 2 deficiency; UPD, Untreated Patient Database.

Figure 4. Summary of (A) number of developmental motor milestones lost and (B) individual developmental motor milestones lost in patients with age of TK2d symptom onset ≤12 years



[a]Percentages for number of developmental motor milestones lost calculated based on number of patients initially achieving a milestone (ISE-UPD, n=26; ISE-pretreatment, n=49; Comprehensive Disease Course, n=75). [b]Percentages for individual developmental motor milestones lost calculated based on number of patients initially achieving each specific milestone.
ISE, Integrated Summary of Efficacy; TK2d, thymidine kinase 2 deficiency; UPD, Untreated Patient Database.

Table 2. Summary of ventilatory support for patients with TK2d and age of symptom onset ≤12 years

	ISE-UPD (N=117)	ISE-pretreatment (N=82)	Comprehensive Disease Course (N=199)
Ventilatory support used at any time,[a] n (%)	50 (42.7)	31 (37.8)	81 (40.7)
Mode of ventilatory support (first occurrence),[b,c] n (%)			
Invasive (tracheostomy or no tracheostomy)	6 (12.0)	9 (29.0)	15 (18.5)
Noninvasive (e.g. BiPAP, CPAP)	7 (14.0)	21 (67.7)	28 (34.6)
Missing	37 (74.0)	1 (3.2)	38 (46.9)
Age at first ventilatory support,[b] years			
Median (min, max)	3.0 (0.0, 44.0)	4.0 (0.4, 35.2)	3.0 (0.0, 44.0)
Q1, Q3	1.1, 9.0	1.3, 14.5	1.3, 10.0
Amount of ventilatory support used (first occurrence),[b] hours/day			
Median (min, max)	24.0 (10.0, 24.0)	11.0 (8.0, 24.0)	12.0 (8.0, 24.0)
Q1, Q3	16.0, 24.0	10.0, 24.0	10.0, 24.0
Duration of ventilatory support,[d] days			
Median (min, max)	730.6 (0.0, 6594.0)	218.0 (14.0, 9490.0)	499.8 (0.0, 9490.0)
Q1, Q3	152.1, 3287.1	61.0, 1215.6	105.0, 2633.0

[a]For treated patients, any time refers to the time up to treatment start. [b]In patients with at least one record of ventilatory support. [c]Percentages are based on the number of patients with ventilatory support at any time. [d]Total duration of all ventilatory support used per patient during the pretreatment or nontreatment phase.
BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; ISE, Integrated Summary of Efficacy; max, maximum; min, minimum; Q1, first quartile; Q3, third quartile; TK2d, thymidine kinase 2 deficiency; UPD, Untreated Patient Database.

Table 3. Summary of feeding support for patients with TK2d and age of symptom onset ≤12 years

	ISE-UPD (N=117)	ISE-pretreatment (N=82)	Comprehensive Disease Course (N=199)
Feeding tube (gastrostomy or nasogastric) support used at any time,[a] n (%)	8 (6.8)	20 (24.4)	28 (14.1)
Age at first feeding support, years			
Median (min, max)	2.5 (1.0, 13.0)	1.7 (0.5, 16.3)	1.9 (0.5, 16.3)
Q1, Q3	1.3, 13.0	1.1, 4.1	1.2, 5.2
Tube insertion reason for first occurrence, n (%)			
Supplemental oral intake	2 (25.0)	2 (10.0)	4 (14.3)
Dysphagia	4 (50.0)	9 (45.0)	13 (46.4)
Dysphagia, supplemental oral intake	0 (0)	6 (30.0)	6 (21.4)
Other	2 (25.0)	3 (15.0)	5 (17.9)
Missing	0 (0)	0 (0)	0 (0)
Total duration on feeding support,[b] days			
Median (min, max)	1154.0 (49.0, 5844.0)	140.5 (6.0, 3855.0)	156.0 (6.0, 5844.0)
Q1, Q3	194.0, 3318.0	44.0, 219.0	45.0, 1154.0

[a]For treated patients, any time refers to the time up to treatment start. [b]Total duration of all feeding support received per patient during the pretreatment or nontreatment phase.
ISE, Integrated Summary of Efficacy; max, maximum; min, minimum; Q1, first quartile; Q3, third quartile; TK2d, thymidine kinase 2 deficiency; UPD, Untreated Patient Database.

Summary and Conclusions

The Comprehensive Disease Course dataset represents the largest single source of natural history data for patients with thymidine kinase 2 deficiency (TK2d), capturing data from a substantial proportion of the known global population of patients with TK2d

Our findings demonstrate a high and clinically meaningful degree of morbidity and mortality in patients with TK2d and age of symptom onset ≤12 years, with patients facing a high risk of premature death in the 3 years after TK2d symptom onset

- High levels of motor function loss and use of ventilatory and feeding tube support highlighted the heavy, progressive disease burden in these patients and were comparable between Integrated Summary of Efficacy (ISE)-Untreated Patient Database and ISE-pretreatment groups
- Loss of a developmental motor milestone is never considered to be normal and prompts further workups and attention

Study limitations included the high proportion of missing data for some variables, owing to the retrospective nature of the study in this ultra-rare disease, and the possibility for bias introduced by the requirement for genetic confirmation of pathogenic thymidine kinase gene variants excluding patients who died before genetic testing was available

- Analyses of developmental motor milestones initially achieved should be interpreted with caution owing to the nonlongitudinal nature of the data and the fact that some patients reached a state of disability that precluded achievement of subsequent developmental motor milestones

There is an urgent need for new treatments for TK2d to manage the high disease burden, and understanding the natural disease course of TK2d may aid management strategies and inform the development of studies to investigate new treatment options

- The diversity and widespread geographic locations covered by these data suggest that the current standard of care remains insufficient to meaningfully affect mortality and morbidity associated with TK2d

References: 1. Garone C, *et al. J Med Genet* 2018;55:515–21. 2. Ma Y, et al. Prevalence estimation of thymidine kinase 2 deficiency, an ultra-rare autosomal recessive mitochondrial disease [poster]. Presented at ISPOR 2023, Copenhagen, Denmark; November 12–15, 2023. 3. Berardo A, *et al. J Neuromuscul Dis* 2022;9:225–35. 4. Domínguez-González C, *et al. Orphanet J Rare Dis* 2019;14:100. 5. Wang J, *et al.* 2018. In: Adam MP, Feldman J, Mirzaa GM, *et al.*, editors. GeneReviews® [internet]. Seattle (WA): University of Washington, Seattle; 2018. Available from: https://www.ncbi.nlm.nih.gov/books/NBK114628/ (Accessed February 4, 2025). 6. Hirano M, *et al.* Survival analyses in patients with thymidine kinase 2 deficiency aged ≤12 years at symptom onset who received pyrimidine nucleos(t)ide therapy [poster]. Presented at the 2025 Muscular Dystrophy Association (MDA) Clinical & Scientific Conference, Dallas, TX, USA; March 16–19, 2025. 7. Wang J, *et al. J Genet Metabol* 2018;124:124–30.

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Poster number: 6-007

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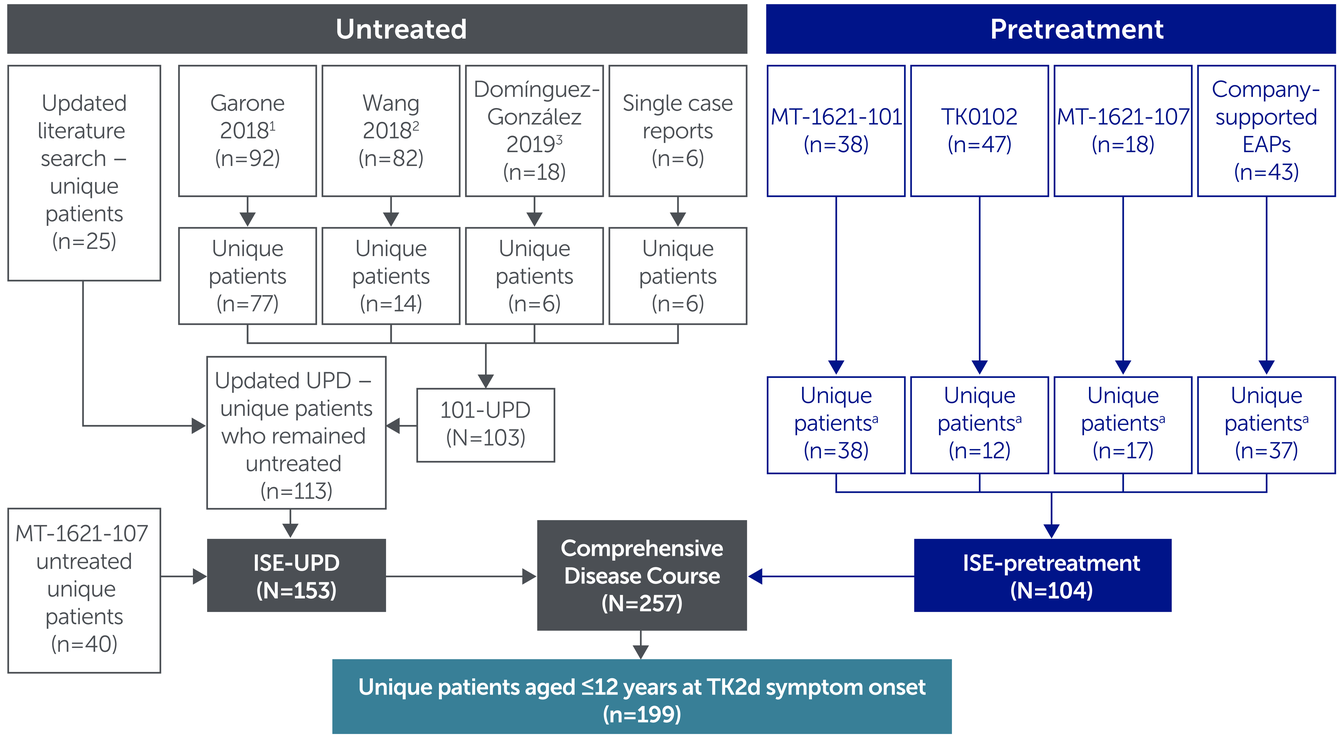
Figure 1. Study analysis populations



[a]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; TK2d, thymidine kinase 2 deficiency; UPD, Untreated Patient Database.

- The Comprehensive Disease Course dataset used in this study was formed by pooling untreated patient data from literature searches, clinical trials and company-supported Expanded Access Programs (EAPs)
- Two main subpopulations, the Integrated Summary of Efficacy (ISE)-Untreated Patient Database (UPD) and ISE-pretreatment datasets, were pooled to create the Comprehensive Disease Course dataset
  - The ISE-UPD comprised data from an updated literature search (conducted in June 2019; updated in October 2021) and untreated patients in MT-1621-107 (NCT05017818), a multicenter noninterventional chart review of untreated patients with thymidine kinase 2 deficiency (TK2d) and patients with TK2d who received pyrimidine nucleos(t)ide therapy outside of the company-sponsored clinical development program
  - The ISE-pretreatment dataset comprised pretreatment data from patients later treated in MT-1621-107 and pretreatment data sourced from two phase 2 studies of patients with TK2d who received nucleos(t)ide therapy as part of the company-sponsored clinical development program (MT-1621-101 [NCT03701568] and TK0102 [NCT03845712]) and also from company-supported EAPs that enable patients with TK2d at risk of death or major disability to receive doxecitine and doxribtimine
  - Data were cross-checked against all sources to remove duplicates to the greatest extent possible to ensure that only unique patient data were included

1. Garone C, *et al. J Med Genet* 2018;55:515–21.
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Geographic region of residence,[a] n (%)			
Europe	20 (17.1)	27 (32.9)	47 (23.6)
Rest of world	48 (41.0)	55 (67.1)	103 (51.8)
Missing or unknown	49 (41.9)	0 (0)	49 (24.6)
Age of TK2d symptom onset, years			
Median (min, max)	1.2 (0.0, 11.0)	1.5 (0.0, 11.7)	1.4 (0.0, 11.7)
Q1, Q3	0.5, 2.0	1.1, 2.4	0.8, 2.3
Age at genetic confirmation, years	n=59	n=77	n=136
Median (min, max)	5.2 (0.0, 56.4)	3.2 (0.1, 35.3)	4.1 (0.0, 56.4)
Q1, Q3	2.0, 14.4	1.6, 8.3	1.7, 10.3
Time from TK2d symptom onset to genetic confirmation, months	n=59	n=77	n=136
Median (min, max)	38.1 (–5.9, 556.4)[b]	12.3 (–59.9, 359.9)[b]	24.7 (–59.9, 556.4)[b]
Q1, Q3	9.4, 129.1	4.3, 64.7	6.3, 90.1

[a]Owing to the ultra-rare nature of TK2d and the small number of patients, some details relating to race and country of residence were grouped for reporting purposes to minimize risk of patient reidentification. [b]Negative values for time from TK2d symptom onset to genetic confirmation indicate that genetic confirmation took place before onset of disease symptoms.
ISE, Integrated Summary of Efficacy; max, maximum; min, minimum; Q1, first quartile; Q3, third quartile; TK2d, thymidine kinase 2 deficiency; UPD, Untreated Patient Database.

- In total, 199 patients (77.4%) from the Comprehensive Disease Course dataset were aged ≤12 years at the time of thymidine kinase 2 deficiency symptom onset and were included in this study
  - In the Comprehensive Disease Course dataset, 54.3% of patients were male and 45.7% were White

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The disease course of untreated patients with thymidine kinase 2 deficiency (TK2d) aged ≤12 years at TK2d symptom onset: findings from the largest international TK2d dataset

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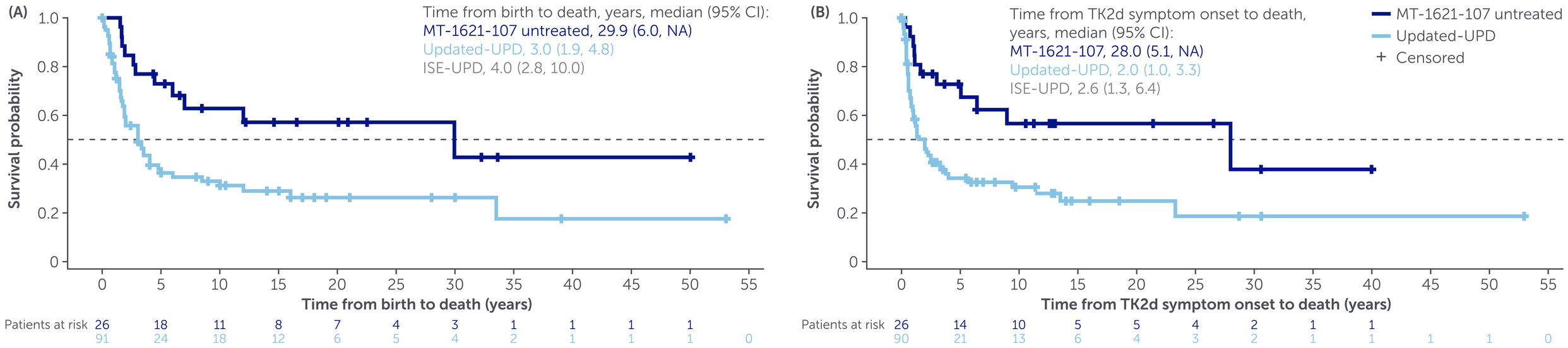
Figure 2. Product-limit survival estimates of time to death from (**A**) birth and (**B**) TK2d symptom onset in the MT-1621-107 untreated and updated-UPD populations



Patients censored at time point zero (event data not collected, no dates or missing period start or end dates) or at a later point in time (last known alive). The MT-1621-107 untreated and updated-UPD datasets are subpopulations of the ISE-UPD dataset. ISE-UPD and Comprehensive Disease Course population datasets are not plotted, given that they aggregate already plotted population datasets. To avoid the introduction of immortal time bias, the ISE-pretreatment group was not included in survival analyses.
CI, confidence interval; ISE, Integrated Summary of Efficacy; NA, not available; TK2d, thymidine kinase 2 deficiency; UPD, Untreated Patient Database

- Kaplan–Meier analyses were used to estimate, with respective 95% confidence intervals (CIs), time to death from birth (**Figure 2A**) and from thymidine kinase 2 deficiency (TK2d) symptom onset (**Figure 2B**)
  - Patients with no event data or missing dates were censored at time point zero
  - Patients still alive at last follow-up were censored at their age last known alive
  - To avoid immortal time bias, survival analyses were not performed in the Integrated Summary of Efficacy (ISE)-pretreatment dataset
- Among patients with age of TK2d symptom onset ≤12 years, 66/117 patients (56.4%) from the ISE-Untreated Patient Database dataset died (median [first quartile, third quartile] age at death, 1.9 [1.0, 3.5] years)
- Kaplan–Meier estimates of median (95% CI) time from birth and from TK2d symptom onset to death were 4.0 (2.8, 10.0) years and 2.6 (1.3, 6.4) years, respectively

Poster number: 6-007

The disease course of untreated patients with thymidine kinase 2 deficiency (TK2d) aged ≤12 years at TK2d symptom onset: findings from the largest international TK2d dataset

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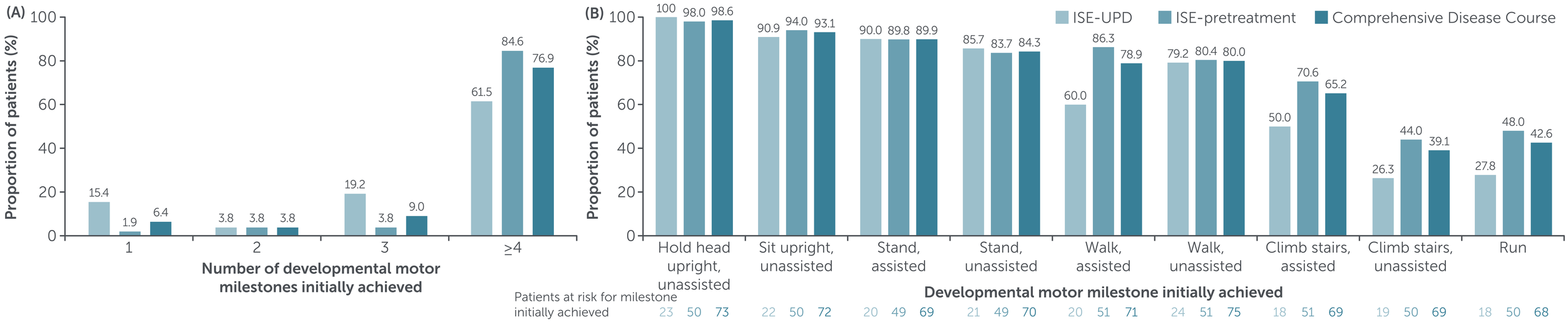
Figure 3. Summary of (**A**) number of developmental motor milestones initially achieved and (**B**) individual developmental motor milestones initially achieved in patients with age of TK2d symptom onset ≤12 years



ISE, Integrated Summary of Efficacy; TK2d, thymidine kinase 2 deficiency; UPD, Untreated Patient Database.

- Among 78 patients with at least one response for developmental milestone achievement, 60 patients (76.9%) in the Comprehensive Disease Course dataset initially achieved at least four motor development milestones (**Figure 3A**)
- Ability to sit upright, stand and walk, unassisted, respectively, were initially achieved by 93.1%, 84.3% and 80.0% of patients (**Figure 3B**), and these developmental motor milestones were subsequently lost in 40.3%, 47.5% and 51.7% of patients who initially achieved them

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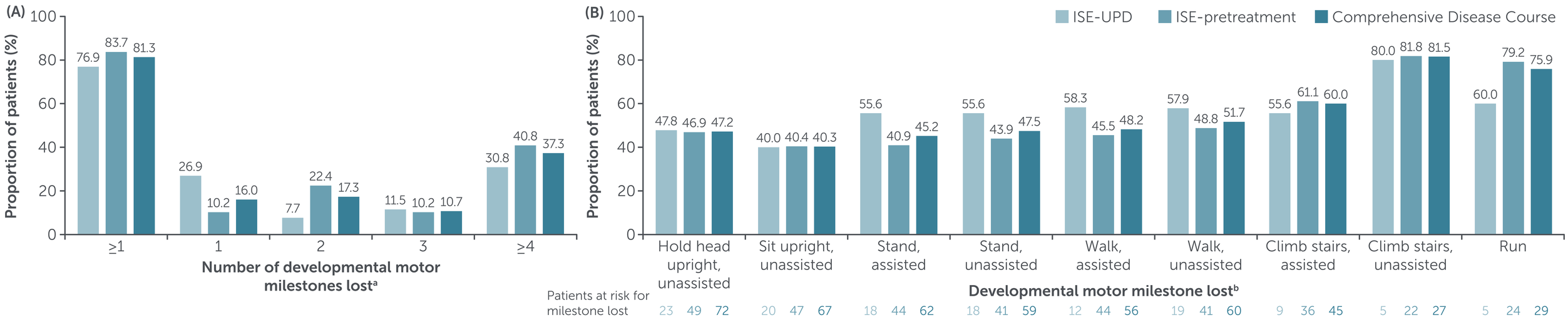
Figure 4. Summary of (**A**) number of developmental motor milestones lost and (**B**) individual developmental motor milestones lost in patients with age of TK2d symptom onset ≤12 years



[a]Percentages for number of developmental motor milestones lost calculated based on number of patients initially achieving milestone (ISE-UPD, n=26; ISE-pretreatment, n=49; Comprehensive Disease Course, n=75). [b]Percentages for individual developmental motor milestones lost calculated based on number of patients initially achieving each specific milestone.
ISE, Integrated Summary of Efficacy; TK2d, thymidine kinase 2 deficiency; UPD, Untreated Patient Database.

- Among 75 patients in the Comprehensive Disease Course dataset who initially achieved at least one developmental motor milestone, 61 (81.3%) subsequently lost at least one developmental motor milestone and 28 (37.3%) subsequently lost at least four developmental motor milestones (**Figure 4A**)
- More than half of patients in the Comprehensive Disease Course dataset lost the ability to walk, unassisted; the ability to climb stairs, assisted and unassisted; and the ability to run (**Figure 4B**)
  - In the 53 patients with evaluable data, the median (first quartile, third quartile) age at first developmental motor milestone lost was 2.0 (1.2, 4.5) years
  - Regain of developmental motor milestones lost was reported in 3/61 patients (4.9%; ability to stand, assisted [n=1]; ability to walk, unassisted [n=1]; and ability to run [n=1])

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Table 2. Summary of ventilatory support for patients with TK2d and age of symptom onset ≤12 years

	ISE-UPD (N=117)	ISE-pretreatment (N=82)	Comprehensive Disease Course (N=199)
Ventilatory support used at any time,[a] n (%)	50 (42.7)	31 (37.8)	81 (40.7)
Mode of ventilatory support (first occurrence),[b,c] n (%)			
Invasive (tracheostomy or no tracheostomy)	6 (12.0)	9 (29.0)	15 (18.5)
Noninvasive (e.g. BiPAP, CPAP)	7 (14.0)	21 (67.7)	28 (34.6)
Missing	37 (74.0)	1 (3.2)	38 (46.9)
Age at first ventilatory support,[b] years			
Median (min, max)	3.0 (0.0, 44.0)	4.0 (0.4, 35.2)	3.0 (0.0, 44.0)
Q1, Q3	1.1, 9.0	1.3, 14.5	1.3, 10.0
Amount of ventilatory support used (first occurrence),[b] hours/day			
Median (min, max)	24.0 (10.0, 24.0)	11.0 (8.0, 24.0)	12.0 (8.0, 24.0)
Q1, Q3	16.0, 24.0	10.0, 24.0	10.0, 24.0
Duration of ventilatory support,[d] days			
Median (min, max)	730.6 (0.0, 6594.0)	218.0 (14.0, 9490.0)	499.8 (0.0, 9490.0)
Q1, Q3	152.1, 3287.1	61.0, 1215.6	105.0, 2633.0

[a]For treated patients, any time refers to the time up to treatment start. [b]In patients with at least one record of ventilatory support. [c]Percentages are based on the number of patients with ventilatory support at any time. [d]Total duration of all ventilatory support used per patient during the pretreatment or nontreatment phase.
BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; ISE, Integrated Summary of Efficacy; max, maximum; min, minimum; Q1, first quartile; Q3, third quartile; TK2d, thymidine kinase 2 deficiency; UPD, Untreated Patient Database.

- In the Comprehensive Disease Course dataset, ventilatory support was used by 81/199 patients (40.7%; 50/117 patients [42.7%] and 31/82 patients [37.8%] in the Integrated Summary of Efficacy [ISE]-Untreated Patient Database and ISE-pretreatment datasets, respectively)
  - Out of 81 patients who used ventilatory support, one (1.2%) discontinued for reasons other than death
  - Kaplan–Meier estimates for median (95% confidence interval) time from birth and from thymidine kinase 2 deficiency symptom onset to first use of ventilatory support in the Comprehensive Disease Course dataset were 7.8 (3.5, 14.0) years and 6.2 (2.3, 9.7) years, respectively

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Table 3. Summary of feeding support for patients with TK2d and age of symptom onset ≤12 years

	ISE-UPD (N=117)	ISE-pretreatment (N=82)	Comprehensive Disease Course (N=199)
Feeding tube (gastrostomy or nasogastric) support used at any time,[a] n (%)	8 (6.8)	20 (24.4)	28 (14.1)
Age at first feeding support, years			
Median (min, max)	2.5 (1.0, 13.0)	1.7 (0.5, 16.3)	1.9 (0.5, 16.3)
Q1, Q3	1.3, 13.0	1.1, 4.1	1.2, 5.2
Tube insertion reason for first occurrence, n (%)			
Supplemental oral intake	2 (25.0)	2 (10.0)	4 (14.3)
Dysphagia	4 (50.0)	9 (45.0)	13 (46.4)
Dysphagia, supplemental oral intake	0 (0)	6 (30.0)	6 (21.4)
Other	2 (25.0)	3 (15.0)	5 (17.9)
Missing	0 (0)	0 (0)	0 (0)
Total duration on feeding support,[b] days			
Median (min, max)	1154.0 (49.0, 5844.0)	140.5 (6.0, 3855.0)	156.0 (6.0, 5844.0)
Q1, Q3	194.0, 3318.0	44.0, 219.0	45.0, 1154.0

[a]For treated patients, any time refers to the time up to treatment start. [b]Total duration of all feeding support received per patient during the pretreatment or nontreatment phase.
ISE, Integrated Summary of Efficacy; max, maximum; min, minimum; Q1, first quartile; Q3, third quartile; TK2d, thymidine kinase 2 deficiency; UPD, Untreated Patient Database.

- In the Comprehensive Disease Course dataset, feeding tube support was used by 28/199 patients (14.1%; 8/117 patients [6.8%] and 20/82 patients [24.4%] in the Integrated Summary of Efficacy [ISE]-Untreated Patient Database and ISE-pretreatment datasets, respectively)
  - Out of 28 patients who used feeding support, one (3.6%) discontinued for reasons other than death
  - Kaplan–Meier estimates for median (95% confidence interval) time from birth and from thymidine kinase 2 deficiency symptom onset to first use of feeding support in the Comprehensive Disease Course dataset were 16.3 (13.0, not estimable) years and 14.1 (10.3, not estimable) years, respectively

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Summary and Conclusions

The Comprehensive Disease Course dataset represents the largest single source of natural history data for patients with thymidine kinase 2 deficiency (TK2d), capturing data from a substantial proportion of the known global population of patients with TK2d

Our findings demonstrate a high and clinically meaningful degree of morbidity and mortality in patients with TK2d and age of symptom onset ≤12 years, with patients facing a high risk of premature death in the 3 years after TK2d symptom onset

- High levels of motor function loss and use of ventilatory and feeding tube support highlighted the heavy, progressive disease burden in these patients and were comparable between Integrated Summary of Efficacy (ISE)-Untreated Patient Database and ISE-pretreatment groups
- Loss of a developmental motor milestone is never considered to be normal and prompts further workups and attention

Study limitations included the high proportion of missing data for some variables, owing to the retrospective nature of the study in this ultra-rare disease, and the possibility for bias introduced by the requirement for genetic confirmation of pathogenic thymidine kinase gene variants excluding patients who died before genetic testing was available

- Analyses of developmental motor milestones initially achieved should be interpreted with caution, owing to the nonlongitudinal nature of the data and the fact that some patients reached a state of disability that precluded achievement of subsequent developmental motor milestones

There is an urgent need for new treatments for TK2d to manage the high disease burden, and understanding the natural disease course of TK2d may aid management strategies and inform the development of studies to investigate new treatment options

- The diversity and widespread geographic locations covered by these data suggest that the current standard of care remains insufficient to meaningfully affect mortality and morbidity associated with TK2d