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 the true prevalence may be higher, given the underdiagnosis and misdiagnosis of this ultra-rare disease[2,3]
- TK2d manifests as a continuous clinical spectrum with varying age of symptom onset[1]
  - Patients with age of TK2d symptom onset >12 years tend to experience slower disease progression than patients with age of TK2d symptom onset ≤12 years[1,4]
  - A common feature of TK2d in patients with age of TK2d symptom onset >12 years is respiratory involvement, with most of these patients using ventilatory support while retaining the ability to walk[1,3]
- There are currently no approved treatments for TK2d, and management is limited to supportive care[5]
  - Research has shown that nucleos(t)ide therapy may stabilize disease progression in patients with age of TK2d symptom onset >12 years regarding the loss and regain of developmental motor milestones and use of ventilatory and feeding support[6]
  - Doxecitine and doxribtimine, an oral pyrimidine nucleoside therapy containing deoxycytidine and deoxythymidine, is under review by health authorities for use in TK2d
- Given the ultra-rare nature of TK2d, data on natural disease progression are scarce, particularly in those with age of TK2d symptom onset >12 years, 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 007)

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 either collected 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

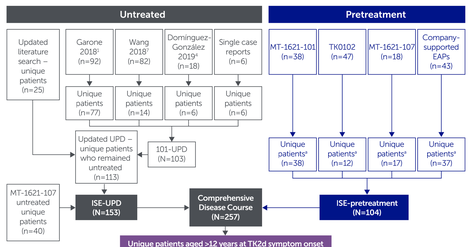
Outcomes

- 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 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, 49 patients (19.1%) 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 199 patients (77.4%) had an age of TK2d symptom onset ≤12 years (9 patients [3.5%] had missing data for age of TK2d symptom onset)
  - The majority of these patients were female (59.2%) and were White (61.2%); the most common geographic region of residence was Europe (57.1%)

Survival

- Among patients with age of TK2d symptom onset >12 years, 6/27 patients (22.2%) from the ISE-UPD dataset died (median [first quartile, third quartile] age at death, 64.0 [56.0, 67.0] years, n=5)
- In the ISE-UPD, Kaplan–Meier estimates of median (95% CI) time from birth and from TK2d symptom onset to death were 67.0 (56.0, not estimable) years and 24.0 (16.0, not estimable) years, respectively (**Figure 2**)

Developmental motor milestones

- In the Comprehensive Disease Course dataset, 96.4% of the 28 patients with available developmental motor milestone data initially achieved at least four developmental motor milestones (all of the 11 patients in the ISE-UPD and 94.1% of the 17 patients in the ISE-pretreatment dataset), consistent with what would be expected in this population of patients with TK2d, who had >12 years without TK2d symptom onset in which to initially achieve developmental motor milestones
- Loss of one and two developmental motor milestones was reported in seven patients (25.0%) and three patients (10.7%), respectively, in the Comprehensive Disease Course dataset (**Figure 3A**); ability to run was the most frequently lost developmental motor milestone (**Figure 3B**)
- Regain of developmental motor milestones lost was not reported in any patients

Ventilatory and feeding support

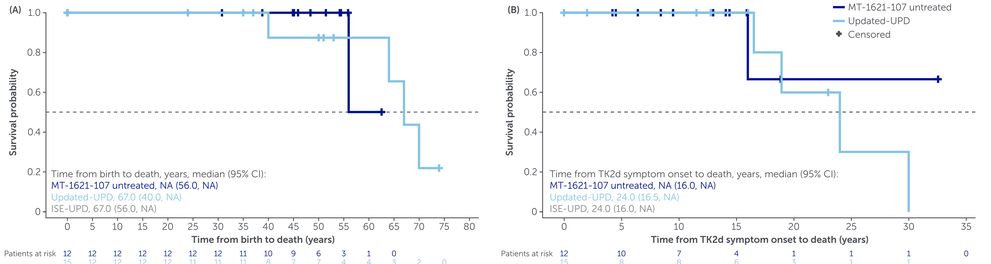
- In the Comprehensive Disease Course dataset, ventilatory support was used by 23/49 patients (46.9%; 14/27 patients [51.9%] and 9/22 patients [40.9%] in the ISE-UPD and ISE-pretreatment datasets, respectively) (**Table 2**)
  - Ventilatory support was predominantly noninvasive (69.6% of the 23 cases)
  - Out of the 23 patients who used ventilatory support, one patient (4.3%) 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 were 55.0 (49.0, 61.0) years and 14.0 (10.4, 31.0) years, respectively
- Feeding support was used by 4/22 patients (18.2%) in the ISE-pretreatment dataset (**Table 3**)
  - No patients discontinued feeding support for reasons other than death
  - In the Comprehensive Disease Course dataset, the Kaplan–Meier estimate for median (95% CI) time from birth to first use of feeding support was 63.0 (63.0, not estimable) years; median time from TK2d symptom onset to first use of feeding support was not estimable using the analysis

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

	ISE-UPD (N=27)	ISE-pretreatment (N=22)	Comprehensive Disease Course (N=49)
Sex, n (%)			
Male	9 (33.3)	9 (40.9)	18 (36.7)
Female	16 (59.3)	13 (59.1)	29 (59.2)
Missing	2 (7.4)	0 (0)	2 (4.1)
Race,[a] n (%)			
White	10 (37.0)	20 (90.9)	30 (61.2)
Other	0 (0)	2 (9.1)	2 (4.1)
Missing	17 (63.0)	0 (0)	17 (34.7)
Ethnicity, n (%)			
Hispanic or Latino	1 (3.7)	0 (0)	1 (2.0)
Not Hispanic or Latino	10 (37.0)	20 (90.9)	30 (61.2)
Missing	16 (59.3)	2 (9.1)	18 (36.7)
Geographic region of residence,[a] n (%)			
Europe	12 (44.4)	16 (72.7)	28 (57.1)
Rest of world	4 (14.8)	6 (27.3)	10 (20.4)
Missing	11 (40.7)	0 (0)	11 (22.4)
Age of TK2d symptom onset, years			
Median (min, max)	40.0 (12.0, 72.0)	27.1 (12.4, 60.3)	31.0 (12.0, 72.0)
Q1, Q3	23.5, 45.0	17.8, 40.0	20.0, 40.0
Age at genetic confirmation, years	n=16	n=22	n=38
Median (min, max)	44.9 (22.0, 75.5)	48.1 (15.0, 73.6)	46.3 (15.0, 75.5)
Q1, Q3	39.9, 53.7	29.6, 57.8	30.4, 56.8
Time from TK2d symptom onset to genetic confirmation, months	n=16	n=22	n=38
Median (min, max)	152.8 (17.4, 358.3)	172.5 (3.5, 524.0)	159.1 (3.5, 524.0)
Q1, Q3	80.6, 216.2	119.0, 311.1	97.0, 271.4

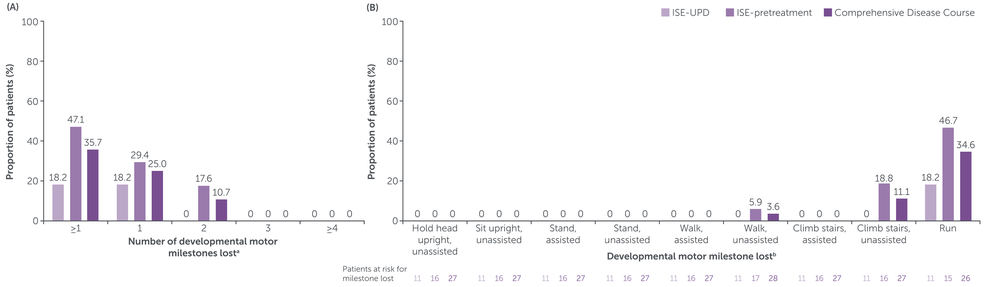
[a]Owing to the ultra-rare nature of TK2d and the small number of patients, some details relating to race and country of residence were grouped for reporting purposes to minimize risk of patient reidentification.
ISE, Integrated Summary of Efficacy; max, maximum; min, minimum; Q1, first quartile; Q3, third quartile; TK2d, thymidine kinase 2 deficiency; UPD, Untreated Patient Database.

Figure 2. Product-limit survival estimates of time to death from (A) birth and (B) TK2d symptom onset in the MT-1621-107 untreated and updated-UPD populations with age of TK2d 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 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=11; ISE-pretreatment, n=17; Comprehensive Disease Course, n=28). [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=27)	ISE-pretreatment (N=22)	Comprehensive Disease Course (N=49)
Ventilatory support used at any time,[a] n (%)	14 (51.9)	9 (40.9)	23 (46.9)
Mode of ventilatory support (first occurrence),[b,c] n (%)			
Invasive (tracheostomy or no tracheostomy)	0 (0)	0 (0)	0 (0)
Noninvasive (e.g. BiPAP, CPAP)	7 (50.0)	9 (100)	16 (69.6)
Missing	7 (50.0)	0 (0)	7 (30.4)
Age at first ventilatory support,[b] years			
Median (min, max)	50.0 (12.0, 74.0)	49.0 (24.0, 73.6)	49.5 (12.0, 74.0)
Q1, Q3	38.0, 55.0	40.6, 55.9	38.0, 55.9
Amount of ventilatory support used (first occurrence),[b] hours/day			
Median (min, max)	8.0 (7.0, 10.0)	9.0 (7.0, 24.0)	8.0 (7.0, 24.0)
Q1, Q3	8.0, 8.0	8.0, 10.0	8.0, 10.0
Duration of ventilatory support,[d] days			
Median (min, max)	435.8 (26.8, 8401.0)	1138.0 (134.0, 7052.8)	954.5 (26.8, 8401.0)
Q1, Q3	301.5, 3287.5	882.0, 2426.0	325.3, 3287.5

[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=27)	ISE-pretreatment (N=22)	Comprehensive Disease Course (N=49)
Feeding tube (gastrostomy or nasogastric) support used at any time,[a] n (%)	0 (0)	4 (18.2)	4 (8.2)
Age at first feeding support, years			
Median (min, max)	NA	35.2 (27.0, 63.0)	35.2 (27.0, 63.0)
Q1, Q3	NA	29.2, 51.0	29.2, 51.0
Tube insertion reason for first occurrence, n (%)			
Dysphagia	NA	4 (100)	4 (100)
Other	NA	0 (0)	0 (0)
Missing	NA	0 (0)	0 (0)
Total duration on feeding support,[b] days			
Median (min, max)	NA	1634.8 (102, 6912)	1634.8 (102, 6912)
Q1, Q3	NA	716.1, 4425.6	716.1, 4425.6

[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; NA, not applicable; 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

In patients with TK2d who were aged >12 years at symptom onset, outcomes were broadly comparable between Integrated Summary of Efficacy (ISE)-Untreated Patient Database and ISE-pretreatment groups

- Outcomes indicated substantial disease burden, manifesting as loss of previously achieved developmental motor milestones; use of ventilatory support; and death
- 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

A greater understanding of the disease course of TK2d may inform strategies for effective management in clinical practice

- There is an urgent need for new treatments for TK2d to manage the high disease burden, and these natural history data could help to inform study designs by identifying key outcome measures of importance in different subpopulations of patients 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, November 12–15, 2023; Copenhagen, Denmark. 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/NBK514628/ (Accessed February 4, 2025). 6. Scaglia F, *et al.* Survival and functional outcomes in patients with thymidine kinase 2 deficiency aged >12 years at symptom onset who received pyrimidine nucleosides [poster]. Presented at 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: 11-020

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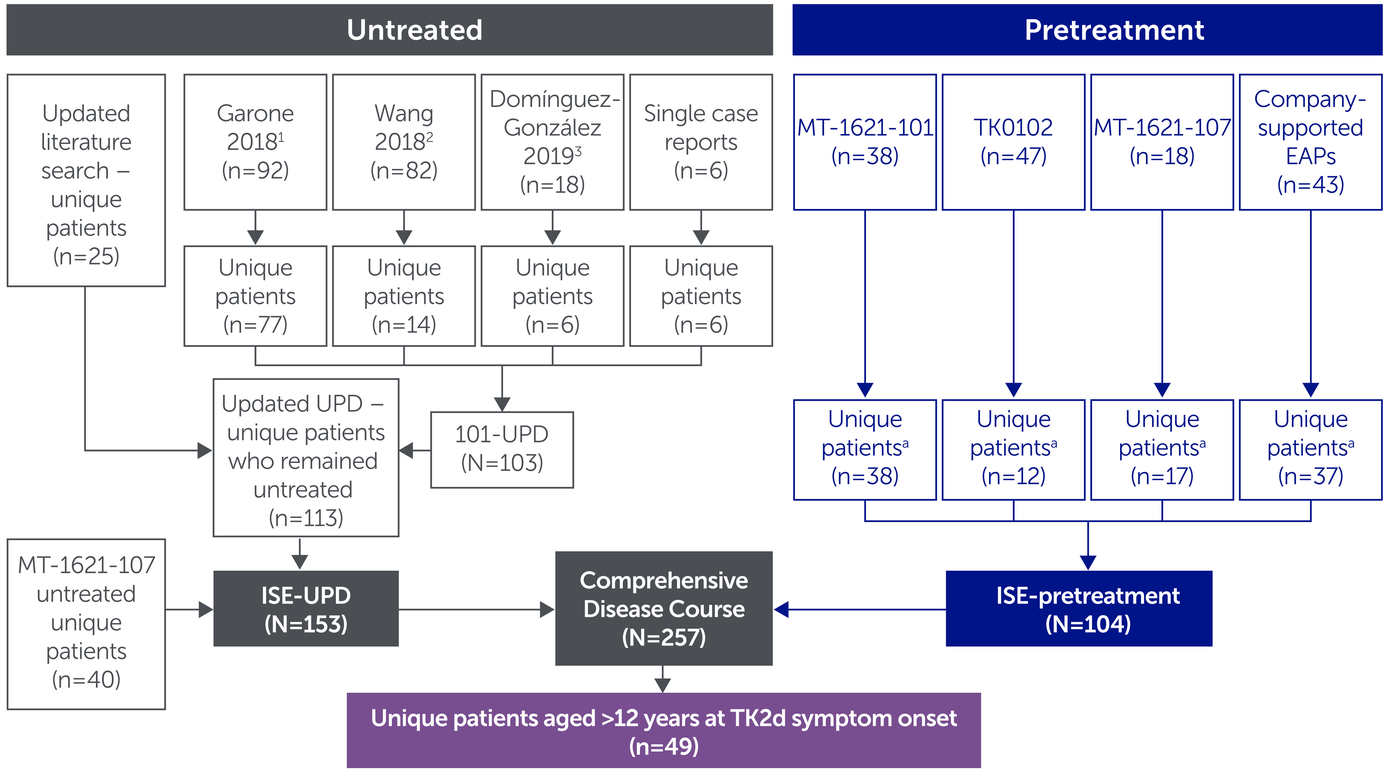
Figure 1. Study analysis populations



- 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.
2. Wang J, *et al. J Genet Metabol* 2018;124:124–30.
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Sex, n (%)			
Male	9 (33.3)	9 (40.9)	18 (36.7)
Female	16 (59.3)	13 (59.1)	29 (59.2)
Missing	2 (7.4)	0 (0)	2 (4.1)
Race,[a] n (%)			
White	10 (37.0)	20 (90.9)	30 (61.2)
Other	0 (0)	2 (9.1)	2 (4.1)
Missing	17 (63.0)	0 (0)	17 (34.7)
Ethnicity, n (%)			
Hispanic or Latino	1 (3.7)	0 (0)	1 (2.0)
Not Hispanic or Latino	10 (37.0)	20 (90.9)	30 (61.2)
Missing	16 (59.3)	2 (9.1)	18 (36.7)
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Europe	12 (44.4)	16 (72.7)	28 (57.1)
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Missing	11 (40.7)	0 (0)	11 (22.4)
Age of TK2d symptom onset, years			
Median (min, max)	40.0 (12.0, 72.0)	27.1 (12.4, 60.3)	31.0 (12.0, 72.0)
Q1, Q3	23.5, 45.0	17.8, 40.0	20.0, 40.0
Age at genetic confirmation, years	n=16	n=22	n=38
Median (min, max)	44.9 (22.0, 75.5)	48.1 (15.0, 73.6)	46.3 (15.0, 75.5)
Q1, Q3	39.9, 53.7	29.6, 57.8	30.4, 56.8
Time from TK2d symptom onset to genetic confirmation, months	n=16	n=22	n=38
Median (min, max)	152.8 (17.4, 358.3)	172.5 (3.5, 524.0)	159.1 (3.5, 524.0)
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- In total, 49 patients (19.1%) 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
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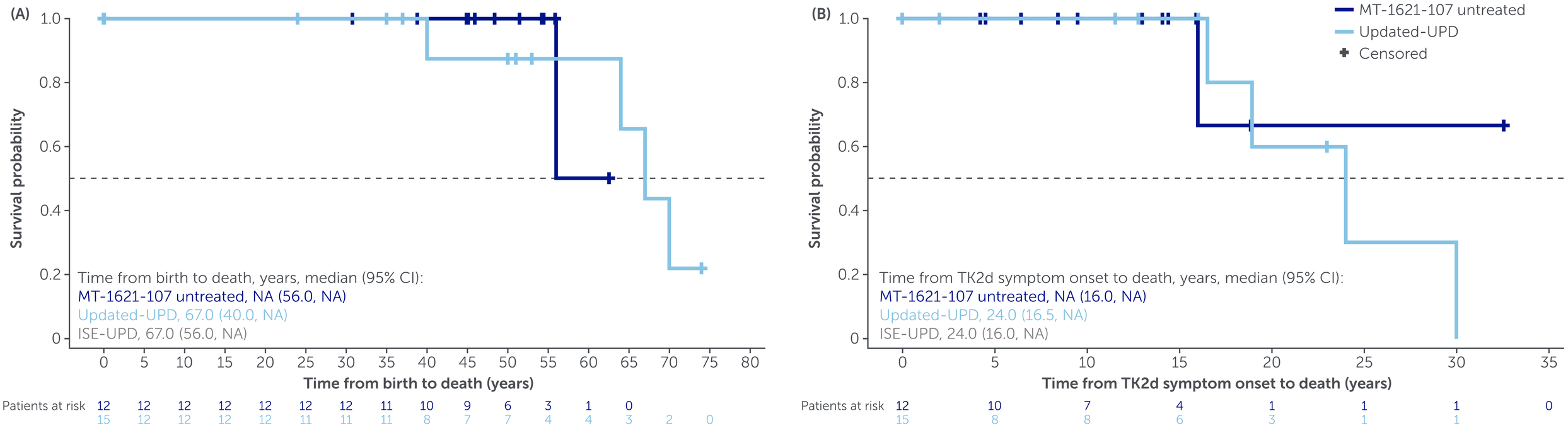
Figure 2. Product-limit survival estimates of time to death from (**A**) birth and (**B**) TK2d symptom onset in the MT-1621-107 untreated and updated-UPD populations with age of TK2d symptom onset >12 years



Patients censored at time point zero (event data not collected, no dates or missing period start or end dates) or at 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 median, 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, 6/27 patients (22.2%) from the ISE-Untreated Patient Database (UPD) dataset died (median [first quartile, third quartile] age at death, 64.0 [56.0, 67.0] years, n=5)
- In the ISE-UPD, Kaplan–Meier estimates of median (95% CI) time from birth and from TK2d symptom onset to death were 67.0 (56.0, not estimable) years and 24.0 (16.0, not estimable) years, respectively

Poster number: 11-020

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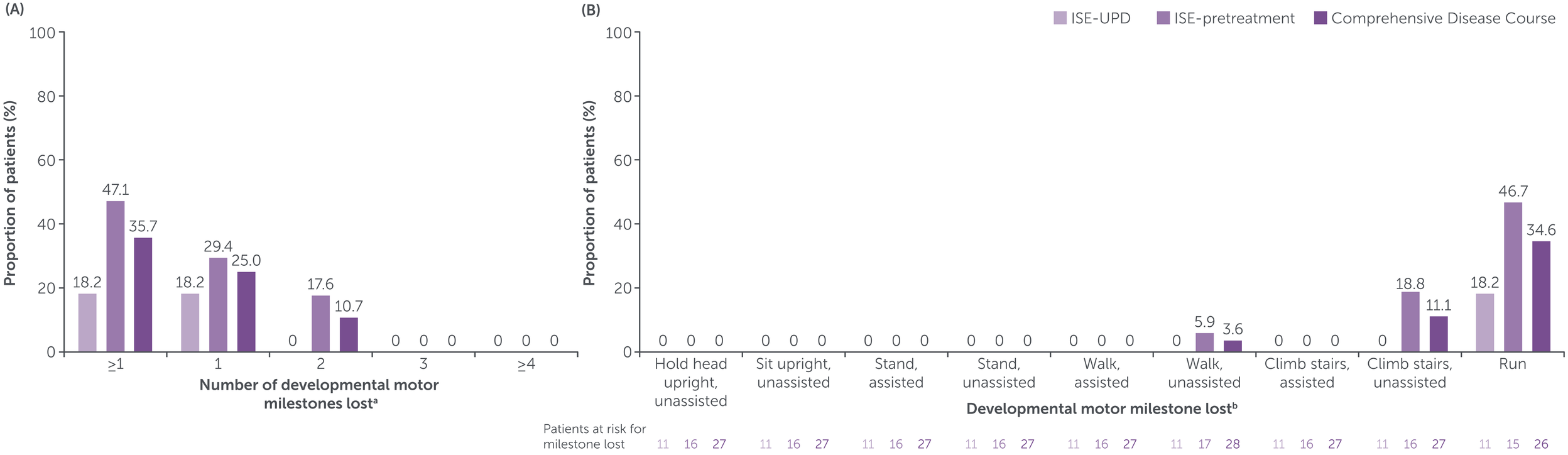
Figure 3. Summary of (**A**) number of developmental motor milestones lost and (**B**) individual developmental motor milestones lost in patients with age of TK2d symptom onset >12 years



[a]Percentages for number of developmental motor milestones lost calculated based on number of patients initially achieving milestone (ISE-UPD, n=11; ISE-pretreatment, n=17; Comprehensive Disease Course, n=28). [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.

- In the Comprehensive Disease Course dataset, 96.4% of the 28 patients with available developmental motor milestone data initially achieved at least four developmental motor milestones, consistent with what would be expected in this population of patients with thymidine kinase 2 deficiency (TK2d), who had >12 years without TK2d symptom onset in which to initially achieve developmental motor milestones
- Loss of one and two developmental motor milestones was reported in seven patients (25.0%) and three patients (10.7%), respectively, in the Comprehensive Disease Course dataset (**Figure 3A**)
  - The most frequently lost developmental motor milestones were ability to climb stairs, unassisted (3/27 patients [11.1%]) and ability to run (9/26 patients [34.6%]) (**Figure 3B**)
- Regain of developmental motor milestones lost was not reported in any patient

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

	ISE-UPD (N=27)	ISE-pretreatment (N=22)	Comprehensive Disease Course (N=49)
Ventilatory support used at any time,[a] n (%)	14 (51.9)	9 (40.9)	23 (46.9)
Mode of ventilatory support (first occurrence),[b,c] n (%)			
Invasive (tracheostomy or no tracheostomy)	0 (0)	0 (0)	0 (0)
Noninvasive (e.g. BiPAP, CPAP)	7 (50.0)	9 (100)	16 (69.6)
Missing	7 (50.0)	0 (0)	7 (30.4)
Age at first ventilatory support,[b] years			
Median (min, max)	50.0 (12.0, 74.0)	49.0 (24.0, 73.6)	49.5 (12.0, 74.0)
Q1, Q3	38.0, 55.0	40.6, 55.9	38.0, 55.9
Amount of ventilatory support used (first occurrence),[b] hours/day			
Median (min, max)	8.0 (7.0, 10.0)	9.0 (7.0, 24.0)	8.0 (7.0, 24.0)
Q1, Q3	8.0, 8.0	8.0, 10.0	8.0, 10.0
Duration of ventilatory support,[d] days			
Median (min, max)	435.8 (26.8, 8401.0)	1138.0 (134.0, 7052.8)	954.5 (26.8, 8401.0)
Q1, Q3	301.5, 3287.5	882.0, 2426.0	325.3, 3287.5

[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 23/49 patients (46.9%; 14/27 patients [51.9%] and 9/22 patients [40.9%] in the Integrated Summary of Efficacy [ISE]-Untreated Patient Database and ISE-pretreatment datasets, respectively)
  - Ventilatory support was predominantly noninvasive (69.6% of the 23 cases)
  - Out of the 23 patients who used ventilatory support, one patient (4.3%) discontinued for reasons other than death
  - Kaplan–Meier estimates for median (95% confidence interval) time from birth and from TK2d symptom onset to first use of ventilatory support were 55.0 (49.0, 61.0) years and 14.0 (10.4, 31.0) years, respectively

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

	ISE-UPD (N=27)	ISE-pretreatment (N=22)	Comprehensive Disease Course (N=49)
Feeding tube (gastrostomy or nasogastric) support used at any time,[a] n (%)	0 (0)	4 (18.2)	4 (8.2)
Age at first feeding support, years			
Median (min, max)	NA	35.2 (27.0, 63.0)	35.2 (27.0, 63.0)
Q1, Q3	NA	29.2, 51.0	29.2, 51.0
Tube insertion reason for first occurrence, n (%)			
Dysphagia	NA	4 (100)	4 (100)
Other	NA	0 (0)	0 (0)
Missing	NA	0 (0)	0 (0)
Total duration on feeding support,[b] days			
Median (min, max)	NA	1634.8 (102, 6912)	1634.8 (102, 6912)
Q1, Q3	NA	716.1, 4425.6	716.1, 4425.6

[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; NA, not applicable; max, maximum; min, minimum; Q1, first quartile; Q3, third quartile; TK2d, thymidine kinase 2 deficiency; UPD, Untreated Patient Database.

- Feeding tube support was used by 4/22 patients (18.2%) in the Integrated Summary of Efficacy-pretreatment dataset
  - The median (first quartile, third quartile) age at first use of feeding support was 35.2 (29.2, 51.0) years
  - No patients discontinued feeding support for reasons other than death
  - Kaplan–Meier estimates for median (95% confidence interval) time from birth to first use of feeding support was 63.0 (63.0, not estimable) years; median time from thymidine kinase 2 deficiency symptom onset to first use of feeding support was not estimable

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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

In patients with TK2d who were aged >12 years at symptom onset, outcomes were broadly comparable between Integrated Summary of Efficacy (ISE)-Untreated Patient Database and ISE-pretreatment groups

- Outcomes indicated substantial disease burden, manifesting as loss of previously achieved developmental motor milestones; use of ventilatory support; and death
- 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

A greater understanding of the disease course of TK2d may inform strategies for effective management in clinical practice

- There is an urgent need for new treatments for TK2d to manage the high disease burden, and these natural history data could help to inform study designs by identifying key outcome measures of importance in different subpopulations of patients with TK2d