Survival and functional outcomes in patients with thymidine kinase 2 deficiency aged >12 years at symptom onset who received pyrimidine nucleos(t)ides

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Introduction

- Thymidine kinase 2 deficiency (TK2d) is an ultra-rare, progressive and often life-threatening, autosomal recessive, mitochondrial myopathy[1,2]
- Pathogenic variants in the TK2 gene (*TK2*) result in mitochondrial DNA (mtDNA) depletion and/or multiple mtDNA deletions[1]
- There are no approved treatments for TK2d.[3] Doxecitine and doxribtimine is a pyrimidine nucleoside therapy containing deoxycytidine (dC) and deoxythymidine (dT) currently in development to treat patients with an age of TK2d symptom onset ≤12 years
- TK2d manifests as a continuous clinical spectrum.[1,2] The prognosis for patients with later symptom onset is poor owing to progressive respiratory insufficiency and high risk of early death[4]
  - A threshold of >12 years of age at TK2d symptom onset is considered to be clinically meaningful in describing the form with the slowest progression[1,4]

Objective

- To assess efficacy and safety in 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**)
- Data from untreated participants were pooled from literature reviews and a retrospective chart review study (MT-1621-107) to form the **ISE-modified Untreated Patients Database (MUPD; 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 age of TK2d symptom onset >12 years
  - Corresponding analyses in participants with age of TK2d symptom onset ≤12 years are presented in posters P255 and P257

Patient population

- 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 dC/dT or doxecitine and doxribtimine [GMP-grade dC/dT])
  - Available medical records, or at a minimum information pertaining to survival, were required for retrospective studies
- Untreated patients required individual-level patient data and genetic confirmation of biallelic pathogenic *TK2* variants

Outcomes

- The primary ISE outcome was survival, defined as time to death from TK2d symptom onset and from treatment start
- Functional outcomes were also assessed, including attainment, loss or regain of developmental motor milestones reflective of those described by the World Health Organization;[5] ventilatory support use; and enteral feeding tube use
  - Functional outcome data were not collected in the EAPs
- 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

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 participants 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 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 start)

Results

Patient baseline characteristics and demographics

- In total, 43 participants with age of TK2d symptom onset >12 years were included in the ISE analysis (ISE treated, n=22; ISE-MUPD, n=21; **Table 1**)
- In the ISE treated group, median (quartile [Q]1, Q3) age at first treatment was 50.9 (31.8, 58.7) years and duration of treatment was 27.2 (3.8, 78.0) months

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

Baseline demographics and characteristics	ISE treated (N=22)	ISE-MUPD (N=21)
Sex, n (%)		
Male	9 (40.9)	6 (28.6)
Female	13 (59.1)	15 (71.4)
Race,[a] n (%)		
White	20 (90.9)	10 (47.6)
Other	2 (9.1)	0 (0)
Not reported	0 (0)	11 (52.4)
Geographic region of residence,[a] n (%)		
Europe	16 (72.7)	12 (57.1)
Rest of world	6 (27.3)	4 (19.0)
Not reported	0 (0)	5 (23.8)
Age of TK2d symptom onset, years		
Median (range)	27.06 (12.36–60.30)	40.00 (12.04–72.00)
Q1, Q3	17.79, 39.98	23.49, 40.41
Age at first treatment (any treatment), years		
Median (range)	50.86 (17.30–74.01)	NA
Q1, Q3	31.78, 58.66	

[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 available; Q, quartile; TK2d, thymidine kinase 2 deficiency.

Survival

- There were four deaths (18.2%) in the ISE treated group and five deaths (23.8%) in the ISE-MUPD group, with median (Q1, Q3) age at death of 57.4 (44.6, 65.8) years and 64.0 (56.0, 67.0) years, respectively
- Cox models showed no significant difference in the risk of death for treated compared with untreated participants (**Figure 2**)
  - Analyses included 17 matched pairs, of which 3 and 4 informative pairs were used to estimate time to death from TK2d symptom onset and from treatment initiation, respectively
- RMST estimates were calculated for treated and untreated participants (**Figure 2**)

Developmental motor milestones

- Loss of ≥1 previously acquired motor milestone was more frequent before treatment initiation than after (8/17 [47.1%] vs 2/16 [12.5%] participants, respectively; **Figure 3A**)
- Before treatment, no participants spontaneously regained motor milestones. Following initiation of treatment, 3/9 participants (33.3%) regained ≥1 motor milestone (**Figure 3B**)
- Motor milestone loss and regain was seen for more advanced abilities such as climbing stairs and running (**Supplementary Figure 1**)

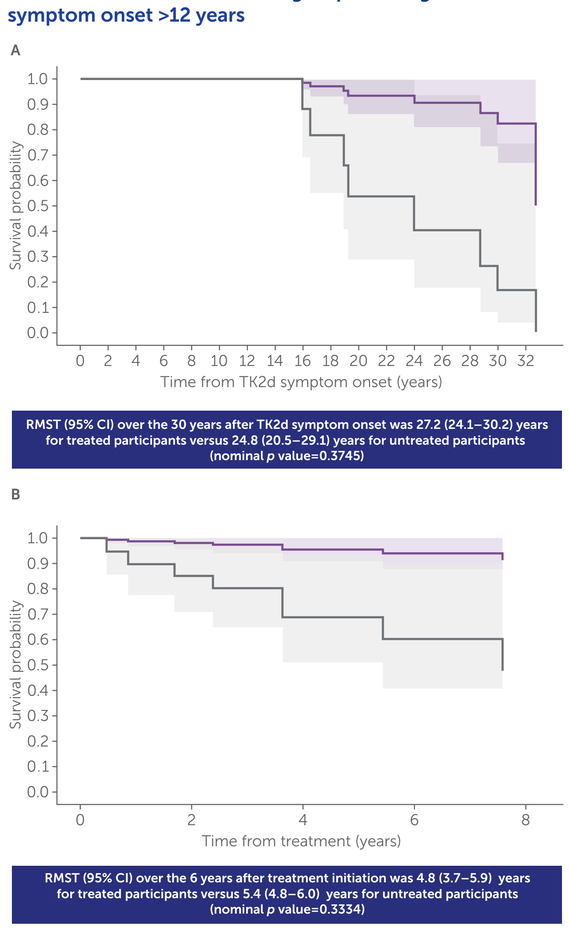
Ventilatory and enteral feeding tube support

- Nine of the 22 treated participants (40.9%) were using ventilatory support at treatment initiation (**Table 2**); all nine participants were using non-invasive bilevel or continuous positive airway pressure
  - None of these participants discontinued ventilatory support after treatment initiation, although 1/9 participants (11.1%) reduced their hours of use
- Three participants started using ventilatory support after treatment initiation, one of whom later discontinued support
- Four of the 22 treated participants (18.2%) were using enteral feeding support at treatment initiation and none discontinued support after treatment (**Table 2**)
- After treatment, one participant had an enteral feeding tube inserted to manage dysphagia

Safety and tolerability

- In the pooled safety population (MT-1621-101, TK0102, MT-1621-107; n=17 with age of TK2d symptom onset >12 years), seven participants (41.2%) 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=11):
  - all participants had at least one TEAE, most commonly diarrhea (10/11 [90.9%])
  - TEAEs reported in ≥10% of participants are presented in **Supplementary Table 1**
  - 45.5% of participants (5/11) experienced at least one serious TEAE over the duration of their treatment, none of which were considered treatment-related

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



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

Table 2. 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=22)

	Before treatment	After treatment
Summary of ventilatory support		
Initiated ventilatory support, n/N (%)	9/22 (40.9)	3/8[a] (37.5)
Discontinued ventilatory support, n/N (%)	0/9[b] (0)	1/12[c] (8.3)
Hours of ventilatory support per day (last observation)		
n	9	6
Median (range)	9.0 (7–24)	8.0 (0–13)
Q1, Q3	8.0, 10.0	7.0, 11.0
No ventilatory support data collected, n (%)	5 (22.7)	
Summary of enteral feeding tube support		
Feeding tube inserted, n/N (%)	4/22 (18.2)	1/12[a] (8.3)
Feeding tube removed, n/N (%)	0/4[b] (0)	0/5[c] (0)
No enteral feeding tube support data collected, n (%)	6 (27.3)	

[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.

Conclusions and Outlook

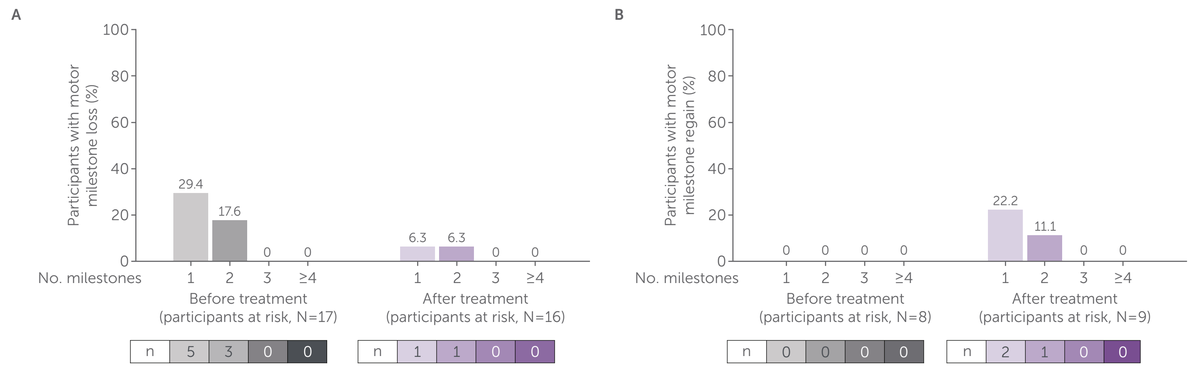
- Although there was no significant difference in risk of death between treated and untreated participants with age of TK2d symptom onset >12 years, a lower proportion of participants died in the treated group
  - Survival analyses were limited by the number of available matched-pairs, available observation period and long latency between TK2d symptom onset and treatment initiation or death in patients with later symptom onset
- Pyrimidine nucleos(t)ide therapy may stabilize or ameliorate disease progression in patients with age of TK2d symptom onset >12 years regarding the loss and regain of motor milestones, the use of ventilatory support and the use of enteral feeding support; further research is needed to fully determine the treatment impact
- Few TEAEs led to dose reductions or treatment discontinuation in the overall ISS safety population, suggesting that treatment with pyrimidine nucleos(t)ides was well tolerated

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=11)	MT-1621-101, TK0102 and MT-1621-107 (n=17)
Participants with ≥1 TEAE	11 (100)	NC[a]
TEAE related to study drug	11 (100)	NC[a]
TEAE leading to study drug discontinuation	3 (27.3)	7 (41.2)
TEAE leading to dose reduction	5 (45.5)	6 (35.3)
Participants with ≥1 serious TEAE	5 (45.5)	NC[a]
Serious TEAE related to study drug	0 (0)	NC[a]
TEAEs reported in ≥20% of participants, by preferred term		
Diarrhea	10 (90.9)	NC[a]
Arthralgia	4 (36.4)	
Pneumonia	3 (27.3)	
Muscular weakness	3 (27.3)	
Myalgia	3 (27.3)	
Alanine aminotransferase increased	3 (27.3)	
Gamma-glutamyltransferase increased	3 (27.3)	
Dysphagia	3 (27.3)	
Upper respiratory tract infection	3 (27.3)	
Serious TEAEs reported in ≥10% of participants, by preferred term		
Pneumonia	2 (18.2)	NC[a]
Restrictive pulmonary disease	2 (18.2)	

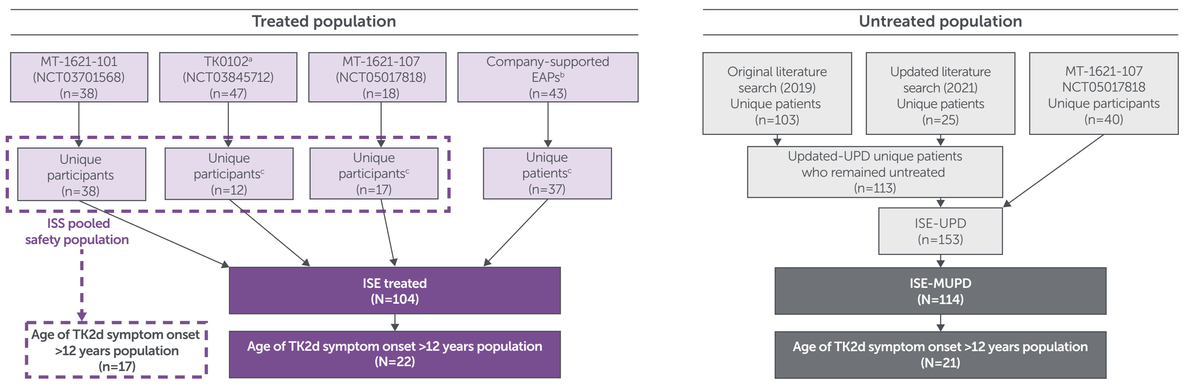
[a]Some safety outcomes were not collected in MT-1621-107.
NC, not calculable; TEAE, treatment-emergent adverse event; TK2d, thymidine kinase 2 deficiency.

Figure 3. Developmental motor milestone (A) loss and (B) regain before and after treatment initiation in participants with age of TK2d symptom onset >12 years (N=22)



In (A), 5 and 6 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), 14 and 13 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.
TK2d, thymidine kinase 2 deficiency.

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 ISE-MUPD is only used in comparative survival analyses.
[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; MUPD, modified UPD; TK2d, thymidine kinase 2 deficiency; UPD, Untreated Patient Database.

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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. Domínguez-González C, *et al. Orphanet J Rare Dis* 2019;14:100. 5. Wijnhoven TM, *et al. Food Nutr Bull* 2004;25:S37–45.

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

Poster number: P256 (supplementary data)

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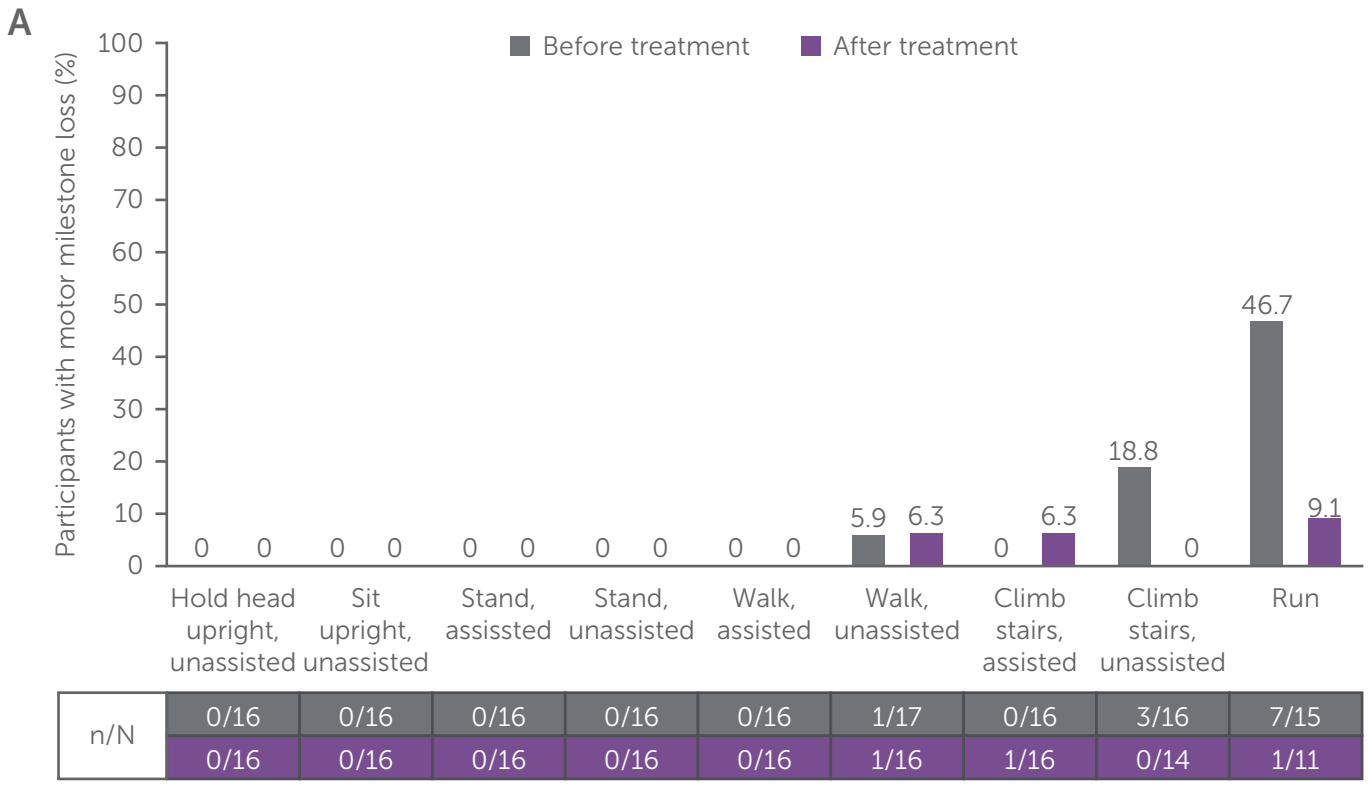
Supplementary Figure 1. Developmental motor milestone (A) loss and (B) regain before and after treatment initiation in participants with age of TK2d symptom onset >12 years, by motor milestone (N=22)



N is the number participants at risk for loss or regain of each individual motor milestone; no denominator indicates that no participants had previously lost that milestone, so no participants were at risk for regaining that milestone.
TK2d, thymidine kinase 2 deficiency.

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=11)
Diarrhea	10 (90.9)
Arthralgia	4 (36.4)
Pneumonia	3 (27.3)
Muscular weakness	3 (27.3)
Myalgia	3 (27.3)
Alanine aminotransferase increased	3 (27.3)
Gamma-glutamyltransferase increased	3 (27.3)
Dysphagia	3 (27.3)
Upper respiratory tract infection	3 (27.3)
Headache	2 (18.2)
Aspartate aminotransferase increased	2 (18.2)
Restrictive pulmonary disease	2 (18.2)
Hepatic enzyme increased	2 (18.2)
Respiratory tract infection	2 (18.2)
Back pain	2 (18.2)
Blood creatine phosphokinase increased	2 (18.2)
Constipation	2 (18.2)
Facial paresis	2 (18.2)
Fall	2 (18.2)
Gastroesophageal reflux disease	2 (18.2)
Hypoventilation	2 (18.2)
Lymphopenia	2 (18.2)
Pyrexia	2 (18.2)

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