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

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Introduction

- Thymidine kinase 2 deficiency (TK2d) is an ultra-rare, autosomal recessive, mitochondrial disease associated with progressive, life-threatening proximal myopathy[1,2]
  - Pathogenic variants of the thymidine kinase 2 gene (*TK2*) result in mitochondrial DNA (mtDNA) depletion and/or multiple mtDNA deletions[3]
  - Patients experience proximal muscle weakness and respiratory insufficiency, often losing the ability to walk, eat and breathe independently. Given the progressive nature of TK2d, there is typically no spontaneous recovery of lost functional abilities[1,4]
- There are no approved treatments for TK2d, with current management across the world focused on supportive care. This may include use of ventilatory support and feeding tubes to assist with daily living[2,5]
- Doxecitine and doxribtimine is a pyrimidine nucleoside therapy containing deoxycytidine (dC) and deoxythymidine (dT) currently in development for use in TK2d
  - Doxecitine and doxribtimine targets the underlying disease pathology of TK2d by utilizing residual thymidine kinase 2 activity in the mitochondria, as well as thymidine kinase 1 and dC kinase in the cytosol, to increase mtDNA quantity that supports increased energy metabolism in cells[6–9]
- The age of TK2d symptom onset varies widely; however, patients with earlier symptom onset typically tend to experience more rapid disease progression[1,2]
  - Using a threshold of ≤12 years versus >12 years for the age of TK2d symptom onset is largely considered a clinically meaningful approach to disease categorization[1,2]

Objective

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

Patient population

- Inclusion and exclusion criteria were specific to each source study
- The main eligibility criteria for treated patients were confirmed biallelic pathogenic *TK2* variants, absence of other genetic disease or polygenic disease, and treatment with nucleos(t)ides for TK2d (non-good manufacturing practice [GMP]-grade deoxycytidine monophosphate/deoxythymidine monophosphate, non-GMP-grade dC/dT or doxecitine and doxribtimine [GMP-grade dC/dT])
  - Available medical records or, at a minimum, information pertaining to survival, were required for retrospective studies

Outcomes

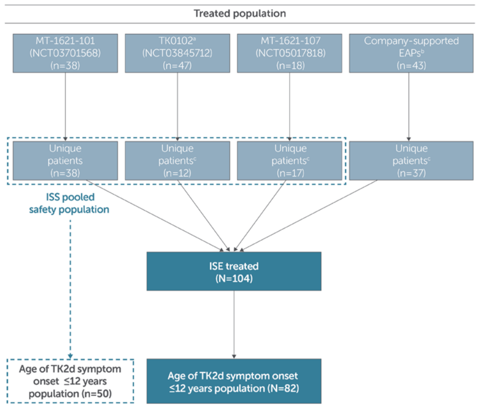
- Functional outcomes were assessed before and after treatment initiation, including the attainment, loss or regain of key developmental motor milestones, ventilatory support use (invasive or non-invasive) and enteral feeding tube use
  - Assessed motor milestones reflect those described by the World Health Organization:[10] ability to hold head upright, sit upright, stand (assisted and unassisted), walk (assisted and unassisted), climb stairs (assisted and unassisted) and run
  - Functional outcome data were not collected for treated patients in the EAPs
- The primary outcome was survival (poster 365)
- 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

Results

Patient baseline characteristics and demographics

- In total, 82 patients with age of TK2d symptom onset ≤12 years were treated with pyrimidine nucleos(t)ide therapy (**Table 1**)
  - There were more male (56.1%) than female patients (43.9%)
  - Most patients were White (81.7%), 32.9% resided in Europe and 67.1% were from the rest of the world
- Most patients had an age of TK2d symptom onset ≤2 years (56/82 [68.3%])
  - Median (quartile [Q]1, Q3) age of symptom onset was 1.50 (1.08, 2.41) years
- Median (Q1, Q3) age at first treatment was 4.26 (2.11, 10.49) years and duration of treatment was 54.8 (15.2, 78.4) months

Figure 1. Study analysis populations


Treated population
MT-1621-101 (NCT03701568) (n=38)
TK0102[a] (NCT03845712) (n=47)
MT-1621-107 (NCT05017818) (n=18)
Company-supported EAPs[b] (n=43)
Unique patients (n=38)
Unique patients[c] (n=12)
Unique patients[c] (n=17)
Unique patients[c] (n=37)
ISS pooled safety population
ISE treated (N=104)
Age of TK2d symptom onset ≤12 years population (n=50)
Age of TK2d symptom onset ≤12 years population (N=82)

Individual patient data described in each publication/source were cross-referenced with the aim of removing duplicates to obtain unique data. The untreated patient population used to assess survival in the ISE are not shown here.
[a]Data cutoff date: 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.
EAPs, expanded access programs; ISE, Integrated Summary of Efficacy; ISS, Integrated Summary of Safety; TK2d, thymidine kinase 2 deficiency.

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

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

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

Developmental motor milestones

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

Ventilatory and enteral feeding tube support

- Before treatment initiation, 31/82 patients (37.8%) were using ventilatory support (**Table 2**), 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 initiation, 20/82 patients (24.4%) had a feeding tube inserted (**Table 2**). One patient later had their feeding tube removed, leaving 19/82 patients (23.2%) using enteral feeding support at treatment initiation
  - Of these patients, 2/19 (10.5%) discontinued feeding support after treatment initiation
- After starting treatment, 4/33 patients (12.1%) had a feeding tube inserted, two of whom later discontinued enteral feeding support
- Before treatment initiation, the most common reason for enteral feeding tube insertion was to manage dysphagia (17/20 [85.0%]). After treatment initiation, the most common reason for enteral feeding tube insertion was for supplemental oral intake (3/4 [75.0%])

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)

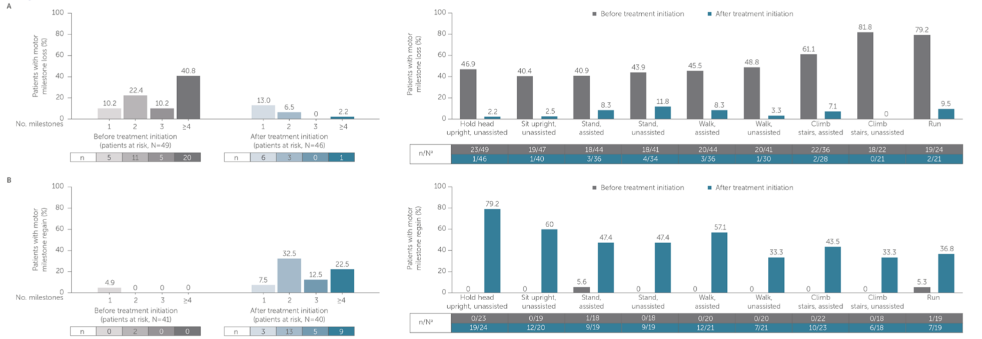
	Before treatment initiation	After treatment initiation
Summary of ventilatory support		
Initiated ventilatory support, n/N (%)	31/82 (37.8)	4/22[a] (18.2)
Discontinued ventilatory support, n/N (%)	0/31[b] (0)	6/35[c] (17.1)
Hours of ventilatory support per day (last observation)		
n	28	17
Median (range)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

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

Safety and tolerability

- In the pooled safety population (MT-1621-101, TK0102, MT-1621-107; n=50 with age of TK2d symptom onset ≤12 years), two patients (4.0%) experienced TEAEs leading to treatment discontinuation (**Table 3**)
- Among patients with age of TK2d symptom onset ≤12 years and full safety data availability (MT-1621-107 not included; n=39):
  - all patients had at least one TEAE, most commonly diarrhoea (33/39 [84.6%])
  - 59.0% of patients (23/39) experienced at least one serious TEAE over the duration of their treatment, most of which were not considered treatment-related TEAEs reported in ≥10% of patients are presented in **Supplementary Table 1**

Figure 2. 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)


A
Patients with motor milestone loss (%)
No. milestones
1 2 3 ≥4
Before treatment initiation (patients at risk, N=49)
After treatment initiation (patients at risk, N=46)
Before treatment initiation
After treatment initiation
Hold head upright, unassisted
Sit upright, unassisted
Stand, assisted
Stand, unassisted
Walk, assisted
Walk, unassisted
Climb stairs, assisted
Climb stairs, unassisted
Run
n/N[a]
B
Patients with motor milestone regain (%)
Before treatment initiation (patients at risk, N=41)
After treatment initiation (patients at risk, N=40)

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.

Conclusions and Outlook

- In patients with an age of TK2d symptom onset ≤12 years, treatment with pyrimidine nucleos(t)ides resulted in a positive change in disease trajectory for functional outcomes
  - After treatment initiation, the frequency of motor milestone loss was reduced and three-quarters of patients regained previously lost motor milestones
  - 17% of patients discontinued use of ventilatory support after treatment initiation, while other patients reduced their level of support
  - A smaller proportion of patients had a feeding tube inserted after treatment initiation than before treatment initiation
- Treatment with pyrimidine nucleos(t)ides was generally well tolerated, with few TEAEs leading to treatment discontinuation in the overall ISS safety population
- Considering the relentlessly progressive nature of TK2d, the stabilization or improvement of functional outcomes seen following treatment with pyrimidine nucleos(t)ides in this study is clinically important for addressing the severe unmet need for patients living with TK2d

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

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 ≥20% of patients, by preferred term		
Diarrhoea	33 (84.6)	NC[a]
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)	
Serious TEAEs reported in ≥10% of patients, by preferred term		
Acute respiratory failure	5 (12.8)	NC[a]
Pneumonia	5 (12.8)	
Femur fracture	4 (10.3)	

[a]Some safety outcomes were not collected in MT-1621-107. 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.

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

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