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Safety of pyrimidine nucleos(t)ide therapy in thymidine kinase 2 deficiency: an integrated analysis from a pooled dataset

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Introduction

- Thymidine kinase 2 deficiency (TK2d) is an ultra-rare, autosomal recessive, mitochondrial disease that manifests with progressive proximal myopathy, bulbar weakness and respiratory insufficiency, often leading to early death[1–3]
  - Pathogenic variants in the thymidine kinase 2 gene result in mitochondrial DNA depletion and/or multiple deletions[2]
- Estimates suggest a TK2d prevalence of 1.64 per million people worldwide (first quartile, third quartile [Q1, Q3]: 0.5, 3.1)[4]
- There are no approved treatments for TK2d, with management focused on supportive care that does not change the progressive disease trajectory[5]
- Doxecitine and doxribtimine is an oral pyrimidine nucleoside therapy containing deoxycytidine and deoxythymidine and is currently in development for the treatment of TK2d

Objective

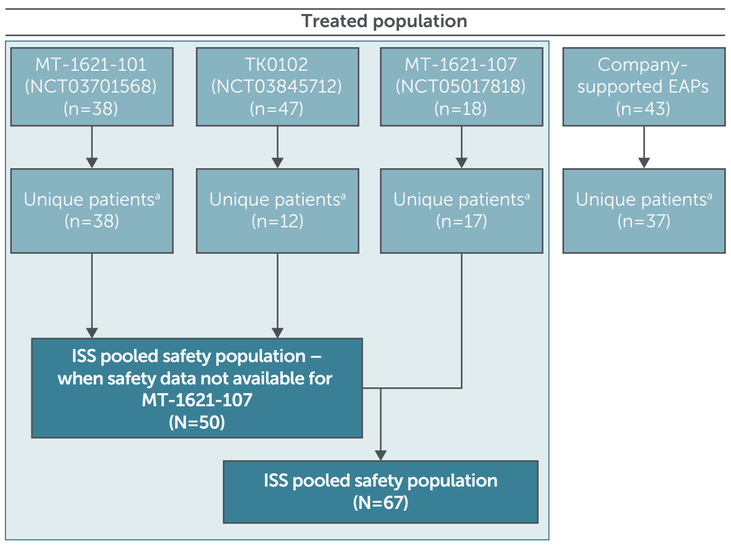
- To assess the safety and tolerability of pyrimidine nucleos(t)ide therapy in patients with TK2d

Methods

Pooled analysis

- The safety profile of pyrimidine nucleos(t)ide therapy was assessed in the Integrated Summary of Safety (ISS)
- Data from treated patients were pooled from retrospective (MT-1621-101 [NCT03701568], MT-1621-107 [NCT05017818]) and prospective (TK0102 [NCT03845712]) studies (**Figure 1**); there was no untreated control arm
  - Data collection in the retrospective chart review study MT-1621-107 was limited; therefore, some ISS analyses only include data from the MT-1621-101 and TK0102 studies
- The ISS pooled safety population constitutes a subset of the treated arm, as part of a wider Integrated Summary of Efficacy pooled analysis that aimed to characterize the efficacy of doxecitine and doxribtimine in patients with TK2d[6–8]

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.
[a]Individuals who participated in multiple studies are only counted once.
EAP, Expanded Access Program; ISS, Integrated Summary of Safety.

Outcomes

- Safety outcomes included treatment-emergent adverse events (TEAEs), safety topics of interest and serious TEAEs

Statistical analysis

- Data for patient demographics and clinical characteristics were summarized with descriptive statistics

Results

Patient demographics and treatment characteristics

- In total, 67 patients from the ISS pooled safety population were included in this analysis (**Figure 1**); certain safety outcomes are reported for only 50 patients, when data for the 17 patients in MT-1621-107 were not available (**Table 1**)
  - Overall, there were more male patients (38/67 [56.7%]) than female patients (29/67 [43.3%]) and most patients were White (61/67 [91.0%])
- Median (Q1, Q3) age of TK2d symptom onset was 2.05 (1.21, 12.36) years (**Table 1**)
  - Median (Q1, Q3) age at first treatment was 6.79 (2.52, 28.97) years and median (Q1, Q3) treatment duration was 5.45 (3.90, 6.72) patient-years, with an overall cumulative exposure of 345.0 patient-years

Safety and tolerability

TEAEs

- All patients (50/50 [100%]) reported ≥1 TEAE and 43/50 patients (86.0%) experienced ≥1 study-drug-related TEAE (per Investigator assessment; **Table 2**); the severity of TEAEs reported by patients were as follows:
  - Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 (mild): 5/50 (10.0%); Grade 2 (moderate): 16/50 (32.0%); Grade 3 (severe): 21/50 (42.0%); Grade 4 (life-threatening or disabling): 7/50 (14.0%); Grade 5 (fatal): 1/50 (2.0%)
- The most common TEAE was diarrhoea (43/50 [86.0%]; **Table 3**); this was considered study-drug-related per the Investigator in 40/50 patients (80.0%)
  - Diarrhoea was reported as a serious single event (of mild intensity) in one patient (2.0%), who continued treatment with no further reported events
  - In 37/50 patients (74.0%), diarrhoea events occurred within the first 3 months of treatment initiation; most events resolved without dose changes or with temporary dose reduction
- Other TEAEs are listed in **Table 3**
- Since elevated liver enzymes and serum creatine kinase (CK) are among the ten most frequently reported clinical manifestations in patients with TK2d,[9] hepatic safety events were also investigated as safety topics of interest
  - At baseline, elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transferase (GGT), serum CK and total bilirubin values were reported in 28/50 (56.0%), 22/50 (44.0%), 6/50 (12.0%), 42/50 (84.0%) and 1/50 (2.0%) patients, respectively
  - The majority of patients who experienced ALT or AST elevations following treatment for ≥4 weeks had increases that were ≤3× the upper limit of normal; there were no potential drug-induced liver injury or Hy's Law events reported throughout the programme
  - Most events of ALT or AST elevations were mild or moderate, transient and not associated with direct bilirubin elevation; the majority resolved without the need for dose change (13/14 ALT [92.9%] and 9/11 AST [81.8%] elevation events)
  - The majority of patients with liver enzyme elevations CTCAE Grade ≥1 at baseline had post-baseline values lower than or equal to those at baseline (ALT: 26/28 [92.9%]; AST: 22/22 [100%]; GGT: 6/6 [100%]; serum CK: 31/42 [73.8%]; total bilirubin: 1/1 [100%])
- In total, 9/67 patients (13.4%) had ≥1 TEAE that resulted in treatment discontinuation and 16/67 patients (23.9%) had ≥1 TEAE that led to dose reduction (**Table 2**)
  - The most common events leading to treatment discontinuation were: non-serious events of liver enzyme elevations in 2/67 patients (3.0%; age of TK2d symptom onset >12 years) and non-serious events of diarrhoea in 2/67 patients (3.0%)

Table 1. Demographics and treatment characteristics of the ISS pooled safety population[a,b]

	MT-1621-101 and TK0102	MT-1621-101, TK0102 and MT-1621-107
N	50	67
Sex, n (%)		
Male	28 (56.0)	38 (56.7)
Female	22 (44.0)	29 (43.3)
Race,[c] n (%)		
White	47 (94.0)	61 (91.0)
Other	3 (6.0)	5 (7.5)
Not reported	0 (0)	1 (1.5)
Ethnicity, n (%)		
Hispanic or Latino	14 (28.0)	15 (22.4)
Not Hispanic or Latino	36 (72.0)	49 (73.1)
Not reported	0 (0)	1 (1.5)
Unknown	0 (0)	2 (3.0)
Geographic region of residence,[c] n (%)		
Europe	27 (54.0)	34 (50.7)
Rest of the world	23 (46.0)	33 (49.3)
Age of TK2d symptom onset, years		
Median (min, max)	2.37 (0.3, 60.3)	2.05 (0.0, 60.3)
Q1, Q3	1.34, 6.09	1.21, 12.36
Age of TK2d symptom onset category, n (%)		
≤12 years of age	39 (78.0)	50 (74.6)
>12 years of age	11 (22.0)	17 (25.4)
Age at first treatment (any treatment), years		
Median (min, max)	7.63 (0.7, 74.0)	6.79 (0.7, 74.0)
Q1, Q3	2.55, 26.59	2.52, 28.97
Total duration of treatment, patient-years		
Median (min, max)	6.02 (0.3, 12.1)	5.45 (0.1, 12.1)
Q1, Q3	5.18, 8.00	3.90, 6.72

[a]ISS pooled safety population includes patients with TK2d who received ≥1 dose of pyrimidine nucleos(t)ide therapy in MT-1621-101, TK0102 and MT-1621-107 (safety data from MT-1621-107 only included when available). [b]Data for one patient were reported in both MT-1621-101 and MT-1621-107 but the patient was counted only once in this table. [c]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 the risk of patient identification.
ISS, Integrated Summary of Safety; max, maximum; min, minimum; Q1, first quartile; Q3, third quartile; TK2d, thymidine kinase 2 deficiency.

Table 2. Summary of TEAEs and serious TEAEs in the ISS pooled safety population[a]

Patients with TEAEs, n (%)	MT-1621-101 and TK0102 (N=50)	MT-1621-101, TK0102 and MT-1621-107[b] (N=67)
Patients with ≥1 TEAE	50 (100)	–
TEAE related to study drug	43 (86.0)	–
TEAE leading to study drug discontinuation	3 (6.0)	9 (13.4)
TEAE leading to dose reduction	14 (28.0)	16 (23.9)
Patients with ≥1 serious TEAE	28 (56.0)	–
Serious TEAE related to study drug	4 (8.0)	–
Serious TEAE leading to study drug discontinuation	1 (2.0)	4 (6.0)
Serious TEAE leading to dose reduction	0 (0.0)	0 (0.0)
Serious TEAE leading to death	1 (2.0)	3 (4.5)[c]

All adverse event terms were coded to Medical Dictionary for Regulatory Activities Terminology version 26.0. Data for any TEAE or serious TEAE leading to treatment discontinuation or dose reduction were collected.
[a]Patients reporting ≥1 TEAE are only counted once. [b]Some safety outcomes were not collected in MT-1621-107. [c]In total, five deaths were reported in MT-1621-107; however, three of these occurred after treatment discontinuation and are therefore not included in this table.
ISS, Integrated Summary of Safety; TEAE, treatment-emergent adverse event.

Serious TEAEs

- Serious TEAEs were experienced by 28/50 patients (56.0%); although few had serious TEAEs related to the study drug (4/50 [8.0%]) (**Table 2**)
  - The most commonly reported included: pneumonia (7/50 [14.0%]), acute respiratory failure (5/50 [10.0%]), femur fracture (4/50 [8.0%]), dysphagia (3/50 [6.0%]) and pneumonia aspiration (3/50 [6.0%])
- In total, 4/67 patients (6.0%) discontinued treatment owing to serious TEAEs and none led to dose reduction (**Table 2**)
- 3/67 patients (4.5%) experienced a fatal serious TEAE; none of these deaths were considered study-drug-related; events leading to death were seizures, disease progression and unknown causes

Conclusions and outlook

- An acceptable safety profile was observed in the ISS analysis and treatment with pyrimidine nucleos(t)ides was well tolerated in patients with TK2d
  - While all treated patients had ≥1 TEAE, the majority of these TEAEs did not lead to treatment discontinuation or dose reduction
- Diarrhoea was the most commonly reported TEAE; most events resolved without dose changes or with temporary dose reduction
- These safety findings, alongside survival and functional outcome benefits previously reported (not shown here),[6–8] suggest that doxecitine and doxribtimine therapy may have important implications for addressing the severe unmet need of patients living with TK2d

Table 3. Summary of TEAEs reported in ≥10% of patients in the ISS pooled safety population[a]

TEAEs ordered by system organ class and preferred term, n (%)	MT-1621-101 and TK0102 (N=50)
Gastrointestinal disorders	46 (92.0)
Diarrhoea	43 (86.0)
Vomiting	14 (28.0)
Abdominal pain	10 (20.0)
Dysphagia	8 (16.0)
Gastro-oesophageal reflux disease	6 (12.0)
Abdominal pain upper	5 (10.0)
Constipation	5 (10.0)
General disorders and administration-site conditions	29 (58.0)
Pyrexia	20 (40.0)
Influenza-like illness	6 (12.0)
Infections and infestations	43 (86.0)
Upper respiratory tract infection	19 (38.0)
COVID-19	18 (36.0)
Pneumonia	10 (20.0)
Respiratory tract infection	10 (20.0)
Gastroenteritis	9 (18.0)
Influenza	8 (16.0)
Ear infection	7 (14.0)
Nasopharyngitis	5 (10.0)
Urinary tract infection	5 (10.0)
Injury, poisoning and procedural complications	20 (40.0)
Femur fracture	5 (10.0)
Investigations	35 (70.0)
ALT increased	14 (28.0)
AST increased	11 (22.0)
Blood creatine phosphokinase increased	10 (20.0)
Anion gap increased	7 (14.0)
Blood lactic acid increased	7 (14.0)
Basophil count increased	5 (10.0)
GGT increased	5 (10.0)
Platelet count increased	5 (10.0)
Musculoskeletal and connective tissue disorders	22 (44.0)
Muscular weakness	7 (14.0)
Arthralgia	6 (12.0)
Back pain	5 (10.0)
Pain in extremity	5 (10.0)
Nervous system disorders	22 (44.0)
Headache	13 (26.0)
Respiratory, thoracic and mediastinal disorders	34 (68.0)
Rhinorrhoea	15 (30.0)
Cough	11 (22.0)
Oropharyngeal pain	8 (16.0)
Acute respiratory failure	5 (10.0)
Dyspnoea	5 (10.0)
Skin and subcutaneous tissue disorders	17 (34.0)
Rash	7 (14.0)

All adverse event terms were coded to Medical Dictionary for Regulatory Activities Terminology version 26.0.
[a]Patients reporting ≥1 TEAE are only counted once.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase; ISS, Integrated Summary of Safety; TEAE, treatment-emergent adverse event.

Limitations

- A traditional randomized controlled trial was not possible owing to the limited pool of available patients and length of time needed to evaluate treatment benefit
- Pooled data from varied sources and retrospective studies carry bias risks, and not all safety outcomes were available for each patient

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