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Substrate Enhancement Therapy With Deoxycytidine and Thymidine in Patients With Thymidine Kinase 2 Deficiency

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Disclosures

- Drs. Quan and Ms. Moors: Employment, ownership interest in Modis Therapeutics, a wholly owned subsidiary of Zogenix, Inc.
- Drs. D'Souza and Thompson: Paid consultants to Modis Therapeutics, a wholly owned subsidiary of Zogenix, Inc.
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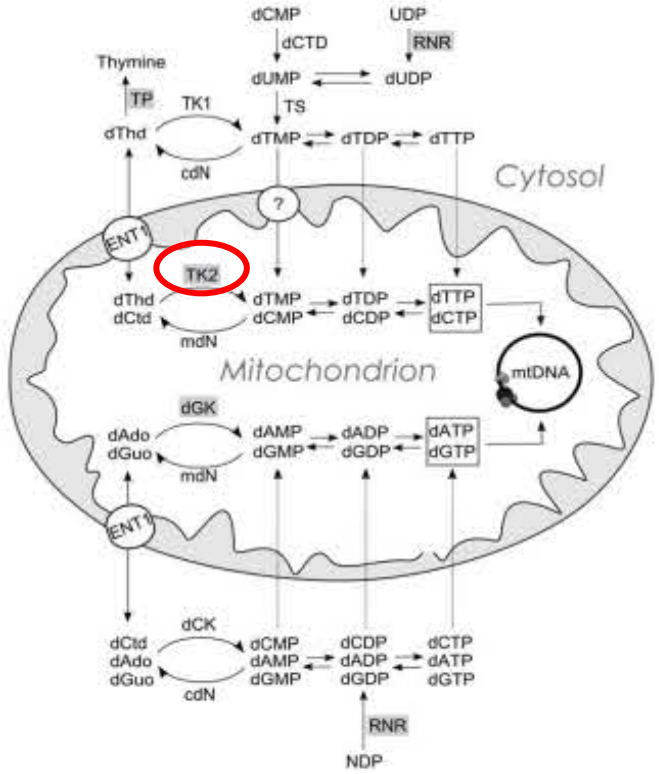
Thymidine Kinase 2 (TK2) Deficiency

- Autosomal recessive, encoded in nuclear DNA
- Deficiency of TK2 enzyme critical for phosphorylation of dC/dT in mitochondria, leading to:
  - Reduction of mitochondrial DNA in tissues and in components of electron transport chain necessary for energy metabolism within cells
- Ultra-rare; no ethnic or geographic predilection
- Clinical presentations vary in rate of progression
  - Young onset (most common) associated with severe course
    - Rapid progression to hypotonia/tetraparesis, ventilatory requirement, and death if untreated
  - Late onset is associated with a slower disease course
    - Progressive muscle weakness, need for noninvasive ventilatory support
- Treatment with pyrimidine nucleos(t)ide combination therapy restores mitochondrial function by working through the cytosolic salvage pathway and/or residual TK2 activity



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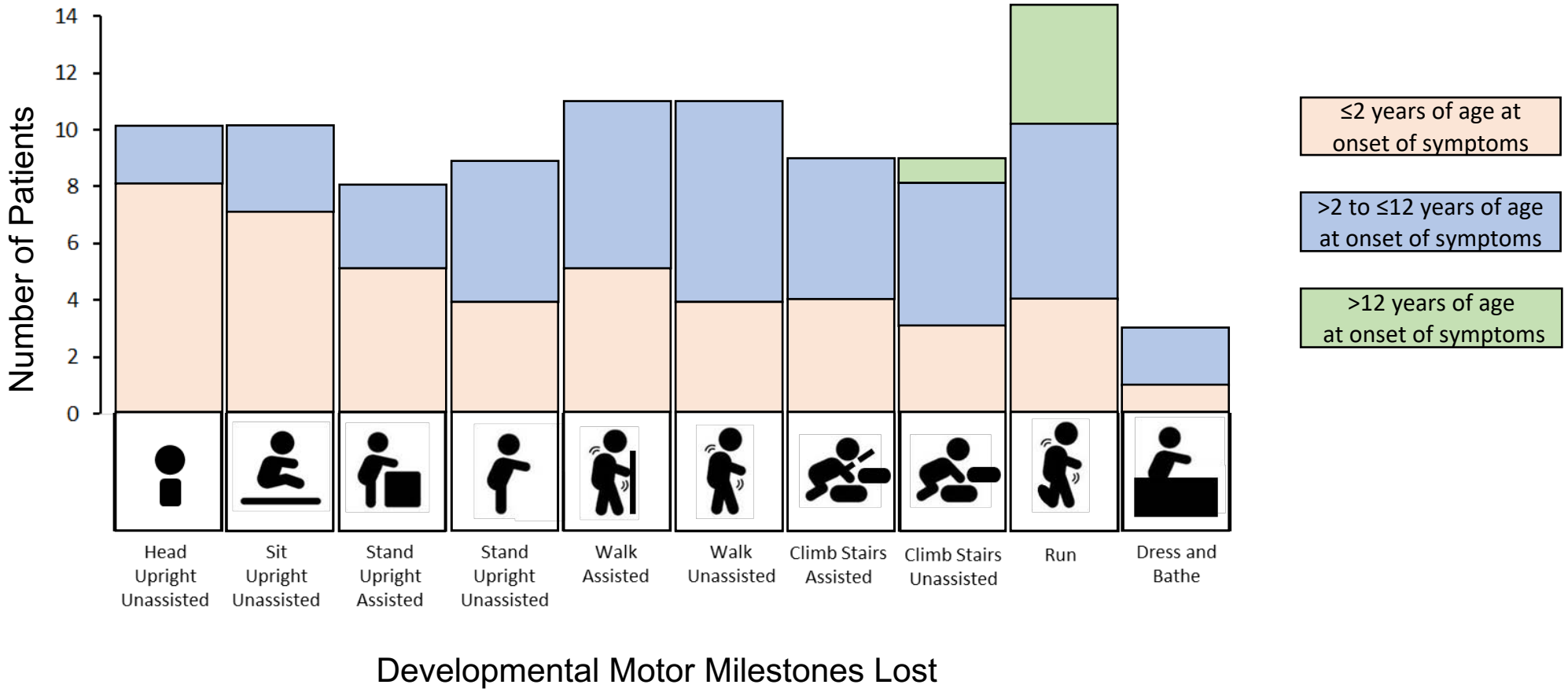
Motor Milestone Loss Shows Disease Progression in Untreated TK2



Untreated disease course illustrated from 38 patients enrolled in MT-1621-101 Retrospective Study. A single patient may be represented across multiple milestones, if multiple milestones were lost.

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Study Design and Patient Demographics

Study MT-1621-101 Retrospective Chart Review

- 38 pediatric and adult patients treated at 8 clinical sites in 3 countries (US, Spain, Israel)
- Genetically confirmed TK2 deficiency
- Treated with chemical-grade dCMP/dTMP and/or dC/dT for a median of 1.5 years (0.3– 7 years)

MT-1621-101 (N=38)	
Age of Onset, n (%)	
≤2 years	15 (39)
>2 to ≤12 years	14 (37)
>12 years	9 (24)
Male, n (%)	21 (55)
Deaths, n (%)	0 (0)

Untreated Patient Dataset

- Comprehensive literature review identified 103 unique patients with TK2 deficiency
- Survival and functional outcomes of untreated patients compared with those of treated patients from MT-1621-101

Untreated Patient Dataset (N=103)	
Age of Onset, n (%)[a]	
≤2 years	63 (61)
>2 to ≤12 years	19 (18)
>12 years	16 (16)
Male, n (%)[b]	57 (55)
Deaths, n (%)	58 (56)

[a]Age of onset missing for 5 patients.
[b]Gender missing for 2 patients.

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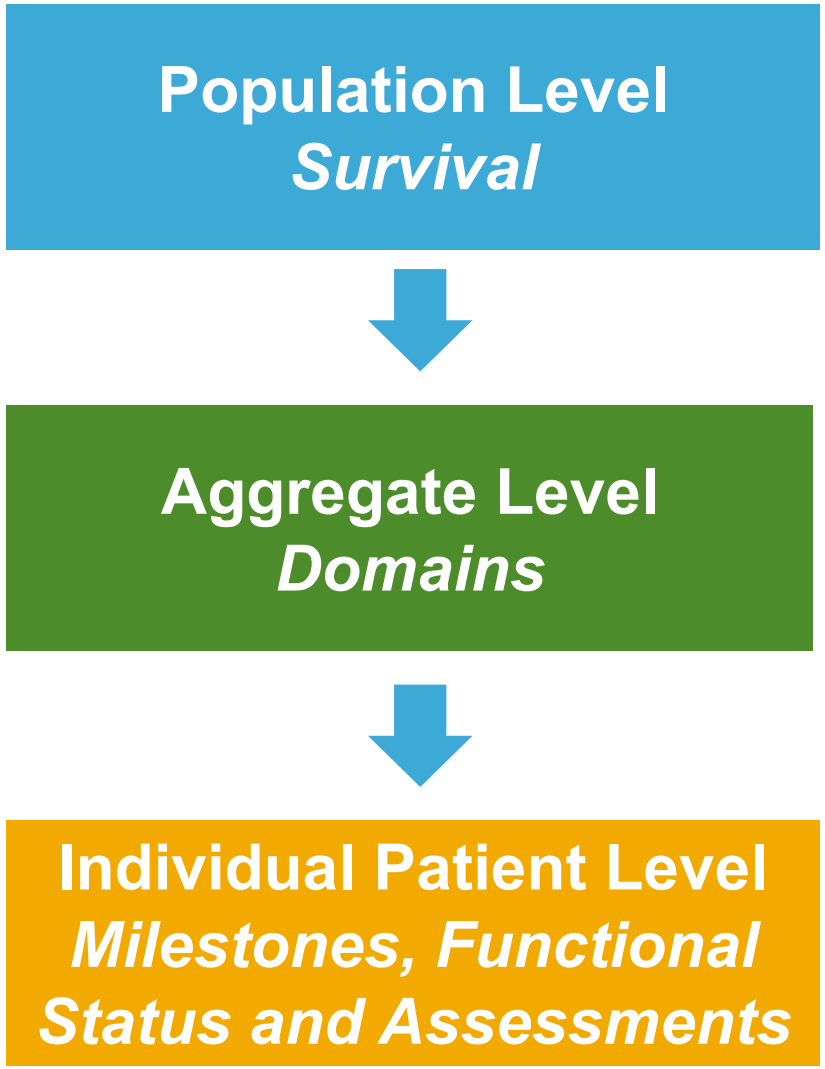
Approaches to Assessment of Efficacy



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Multiple Analytic Approaches Demonstrate Improved Survival

- **All 38 patients treated with dC/dT in the Retrospective Study are still alive**
- **Statistical analysis approaches**
  - **Whole population analyses**
    - Age of onset category as a strata variable
  - **Matched pair analyses**
    - Each treated patient is matched to an untreated (control) patient selected at random from possible matches in the upper half when untreated patients are sorted according to the last known age alive (conservative approach)
- **Highly significant difference in survival compared to the untreated natural history cohort**

Analysis Method	Hazard Ratio	95% CI	*P* Value
Age of Onset Category as a Strata Variable	0.0743	0.0006, 0.5320	0.0006
Matched Pair Analysis (Random Control)	0.1111	0.0000, 1.0405	0.0185

Note: age group statistics are estimated using a Cox Model within each individual age group.
Survival analysis set: contains all patients from the MT-1621-101 Retrospective Study and the MUPD. MUPD=modified untreated patient dataset (n=68) with known age of death/age last known alive and age at death > 1.3 years..
CI=confidence interval. CI will be calculated using exact method when the survival probability is 0 or 1. Likelihood p-values are presented.

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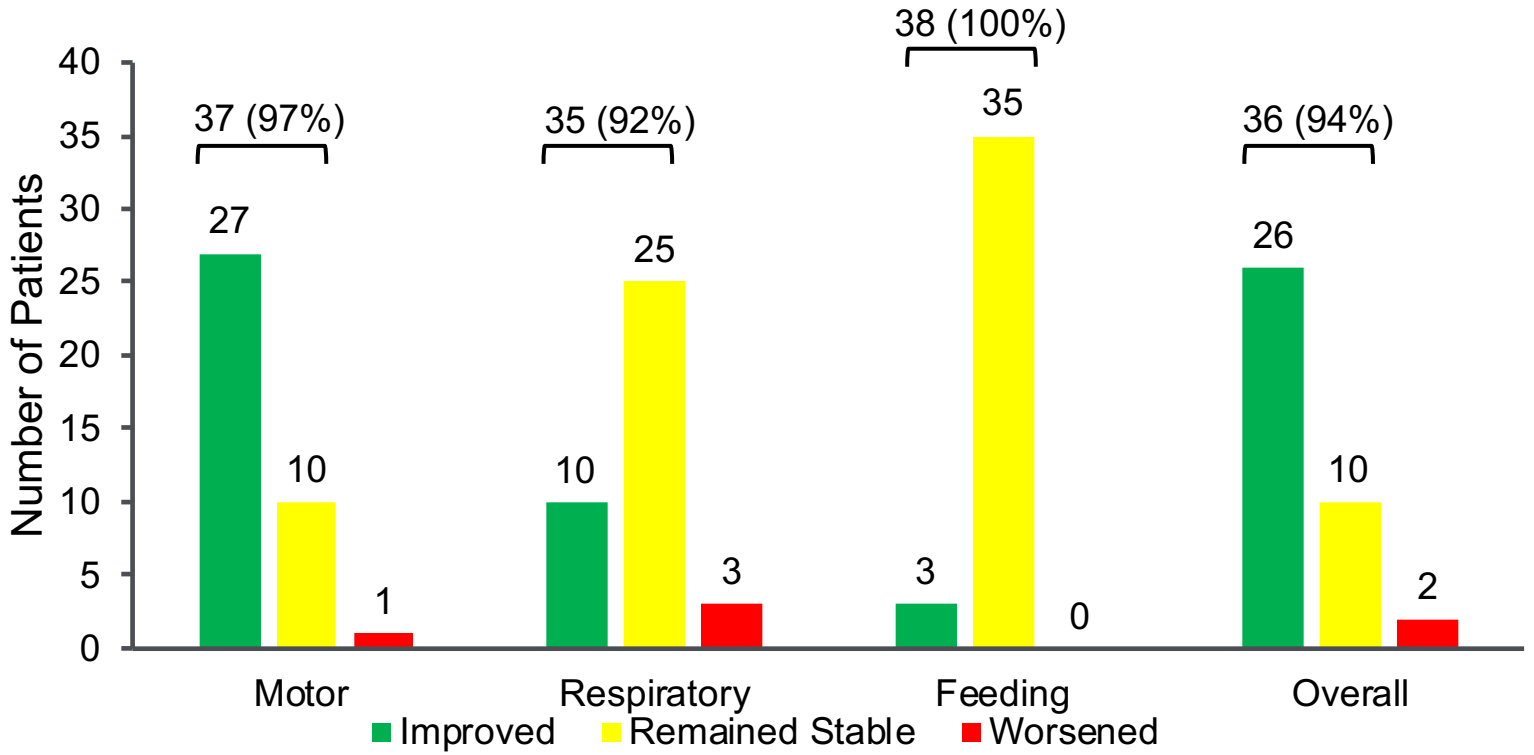
Results From Domain Analysis Support Treatment Benefit

- Approach integrates results from all assessments for a single patient
- Response thresholds based on gain/loss of motor milestones, minimal clinically important difference as defined in other neuromuscular diseases, or change in status (for respiratory and feeding)
- Majority of patients are stable or improved, reflecting benefit in a progressive disease



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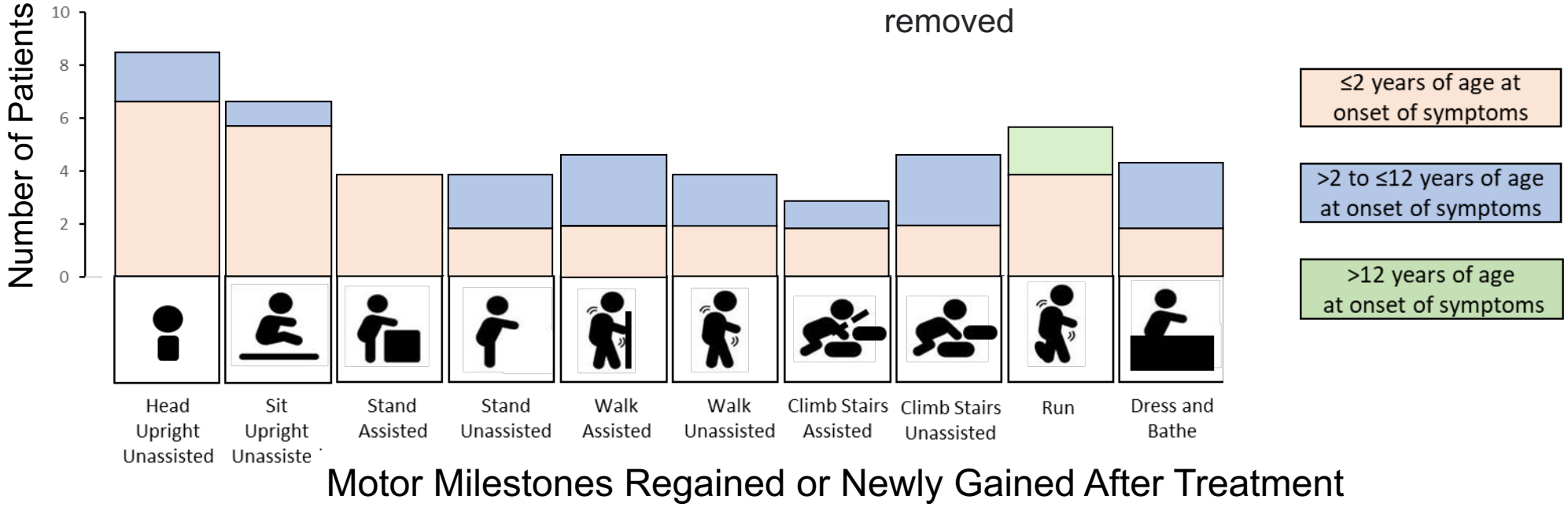
Treatment Is Associated With Improvements in Individual Patients

- Motor
  - No patient lost motor milestones
  - Patients demonstrated both regain of lost milestones and new gains in milestones
  - Supportive findings in functional assessments (6MWT, NSAA, EK, CHOP-INTEND, HFMSE)
- Respiratory
  - 1 patient with tracheostomy/full mechanical ventilation was able to discontinue ventilatory support and 3 patients decreased the number of hours of ventilatory support by at least 4 hours/day
- Feeding
  - 3 patients were able to have their feeding tubes removed



Motor Milestones Regained or Newly Gained After Treatment

A single patient may be represented across multiple milestones,

6MWT, 6-minute walk test; CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; EK, Egen Klassification; HFMSE, Hammersmith Functional Motor Scale Expanded; NSAA, North Star Ambulatory Assessment.

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Common Treatment-Emergent Adverse Events (TEAEs) in Overall Patient Population

- **Dose-related diarrhea is the most common AE**
  - Resolved over time with dose reduction and continued treatment
  - Most patients able to reach and maintain target dose of 400 mg/kg/day
- 2 adult patients discontinued drug due to elevated transaminases
  - Highest AST/ALT 5-10 × ULN, GGT 2-5 × ULN
  - No elevation in bilirubin or alkaline phosphatase
  - Resolved upon discontinuation
- Some patients had elevated transaminases prior to treatment, which decreased after treatment
  - Hepatic dysfunction is common in TK2 deficiency[1]

Treatment-Emergent Adverse Events (N=38)	
Patients With Any TEAE, n (%)	36 (95)
TEAEs in ≥10% of patients, n (%)	
Diarrhea	24 (63)
Blood CK increased	7 (18)
Pyrexia	6 (16)
ALT increased	6 (16)
AST increased	5 (13)
Vomiting	4 (11)
Influenza-like illness	4 (11)
Pneumonia	4 (11)
Cough	4 (11)

[1]Zhang S, et al. *Mol Genet Metab.* 2010;99:53-57.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; GGT, gamma-glutamyltransferase; ULN, upper limit of normal.

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Summary and Conclusions

- TK2 deficiency is a severe, progressive disease associated with loss of function and high rates of morbidity and mortality
- A retrospective chart review study of 38 patients with TK2 deficiency treated with dC/dT showed:
  - Improved survival, when compared to untreated patients
  - Clinically meaningful improvements in motor, respiratory, and feeding functions
- Stability and/or improvements were seen in patients with rapid as well as slower progressing disease
- Treatment was generally safe and well tolerated: dose-related diarrhea was the most common AE

Modis Therapeutics is developing substrate enhancement therapy as treatment for patients with TK2 deficiency

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