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Trofinetide for the Treatment of Girls Aged Two to Four Years With Rett Syndrome: Final Results From the Open-Label DAFFODIL Study

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Disclosures

- Dr Percy has received funding for **consulting from Acadia Pharmaceuticals Inc.**, Anavex Life Sciences Corp., AveXis, and GW Pharmaceuticals, and is an adviser to the International Rett Syndrome Foundation.
- Dr Percy **does not own any assets (stocks, options, etc.) in Acadia Pharmaceuticals Inc.**

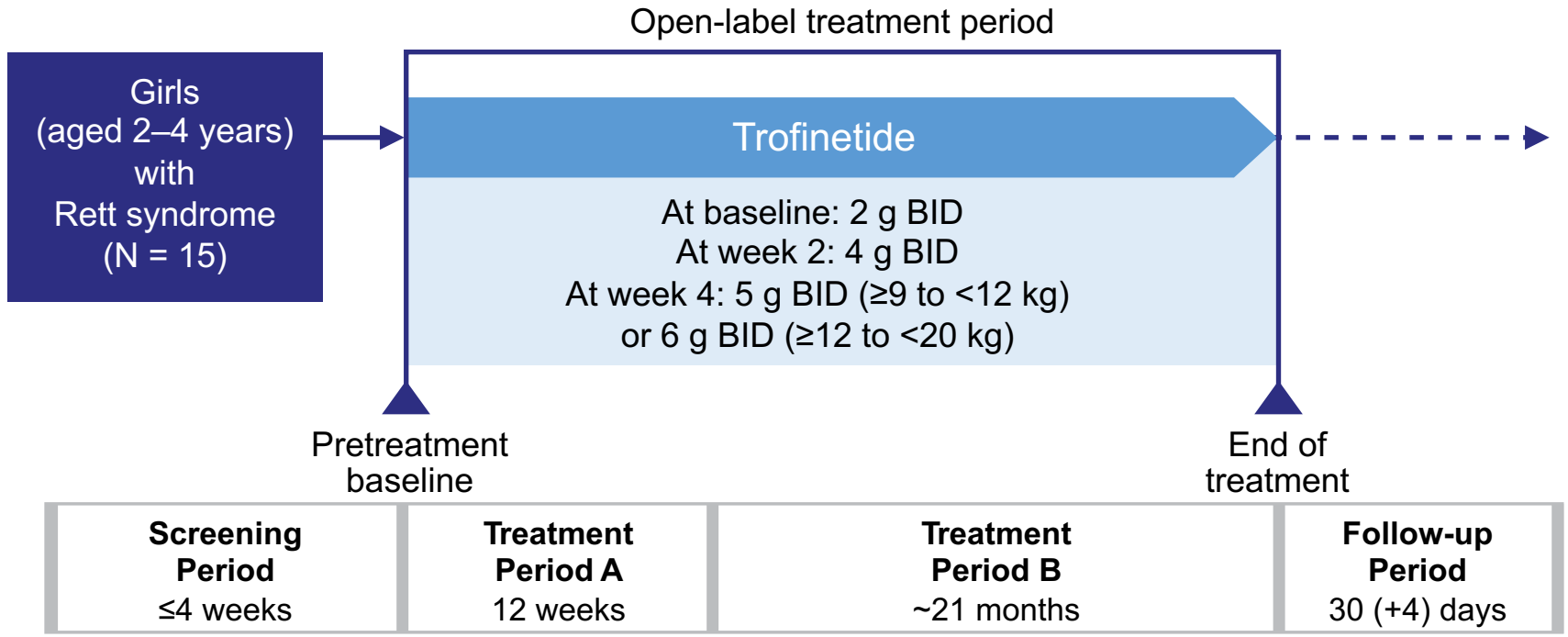
Introduction

- Rett syndrome (RTT) is a rare, debilitating, neurodevelopmental disorder that mostly affects females[1]
- Trofinetide is the first available treatment for RTT and is approved in adults and pediatric patients aged 2 years or older
- US Food and Drug Administration (FDA) approval was based on the positive efficacy and safety findings from the phase 3 12-week LAVENDER study in females aged 5–20 years[2] with RTT
- The findings of this phase 2/3 DAFFODIL study in younger girls with RTT (aged 2–4 years) contributed to the indication being inclusive of ages 2 years and older

1. Petriti U, et al. *Syst Rev.* 2023;12(1):5. 2. Neul JL, et al. *Nat Med.* 2023;29(6):1468–1475.

DAFFODIL study design

- Multicenter, open-label, long-term phase 2/3 study consisting of 2 treatment periods
- Twice-daily (BID) trofinetide was dosed by weight (after initial up-titration) and administered orally or by gastrostomy tube
- Twelve of 15 participants completed the study, which was terminated early when trofinetide was approved by the FDA (March 10, 2023) and became commercially available (**overall study duration was 78 weeks**)



DAFFODIL study assessments

- Safety (Treatment Periods A and B)
  - Treatment-emergent adverse events
- Pharmacokinetics (Treatment Period A)
  - Steady-state exposures calculated using population pharmacokinetic modeling and Bayesian estimation to confirm target exposure range ($AUC_{0–12,ss}$ = 800–1200 µg•h/mL)
- Exploratory efficacy (Treatment Periods A and B)
  - CGI-I
  - CGI-S
  - CaGI-I
  - ICND-QOL
- Optional caregiver exit interviews (study conclusion)

$AUC_{0–12,ss}$, area under the concentration-time curve for the 0- to 12-hour dosing interval at steady state; CaGI-I, Caregiver Global Impression–Improvement; CGI-I, Clinical Global Impression–Improvement; CGI-S, Clinical Global Impression–Severity; ICND-QoL, Overall Quality of Life Rating on the Impact of Childhood Neurologic Disability Scale.

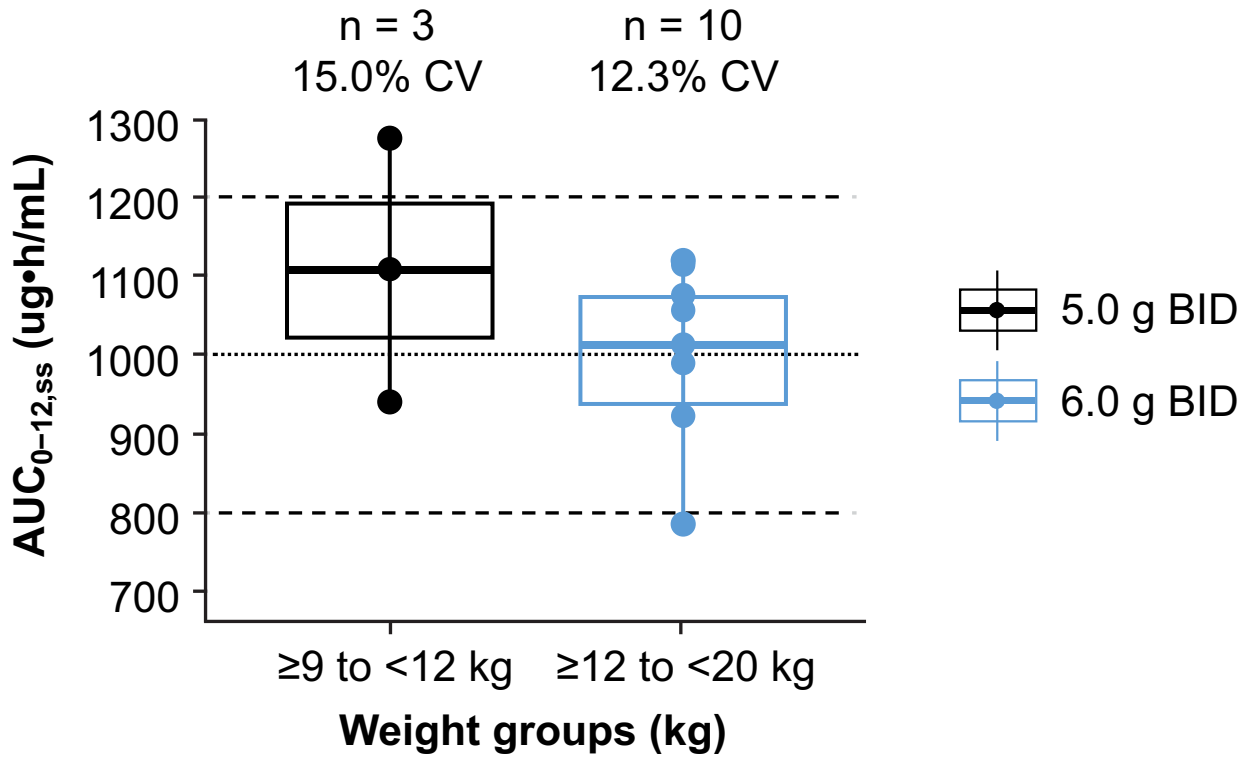
Treatment-emergent adverse events

Preferred term	Treatment Period A (N = 15) n (%)	Overall (Treatment Periods A and B) (N = 15) n (%)
Any TEAE	13 (86.7)	14 (93.3)
TEAEs reported in ≥5 participants overall		
Diarrhea	11 (73.3)	12 (80.0)
Vomiting	7 (46.7)	8 (53.3)
COVID-19	4 (26.7)	7 (46.7)
Gastroenteritis	2 (13.3)	5 (33.3)
Pyrexia	4 (26.7)	5 (33.3)
Seizure	3 (20.0)	5 (33.3)
Any serious TEAE*	1 (6.7)	4 (26.7)
Any TEAE leading to drug discontinuation or study termination	1 (6.7)	2 (13.3)
Any severe TEAE	1 (6.7)	2 (13.3)
Any fatal TEAE	—	—

*Serious TEAEs were unrelated to treatment.
TEAE, treatment-emergent adverse event.

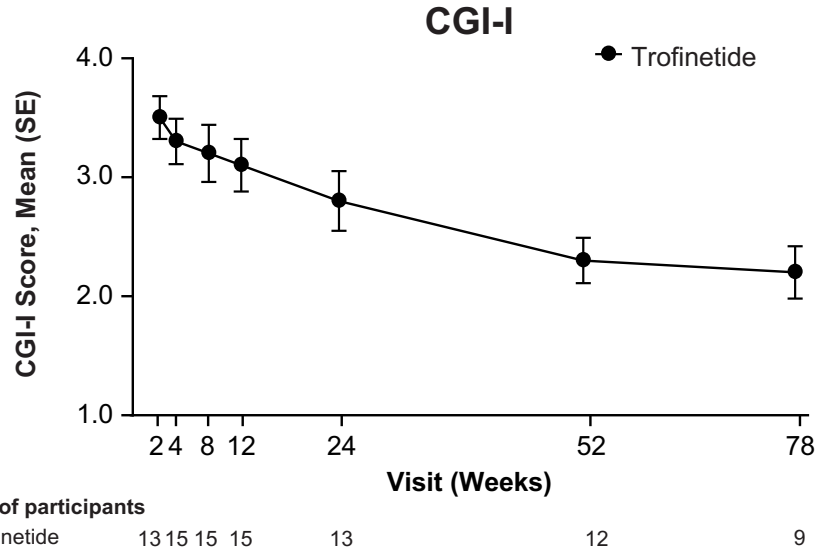
Pharmacokinetic analysis

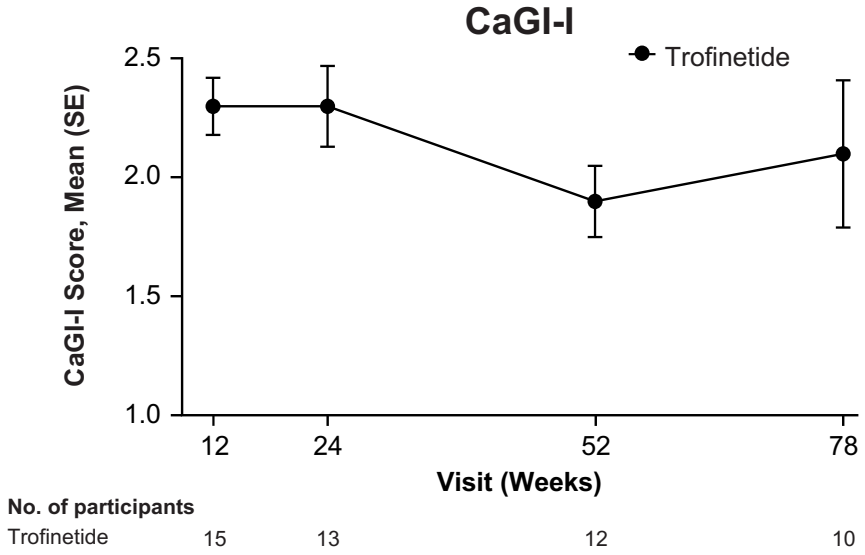
- Trofinetide exposure in study participants fell within the target exposure range



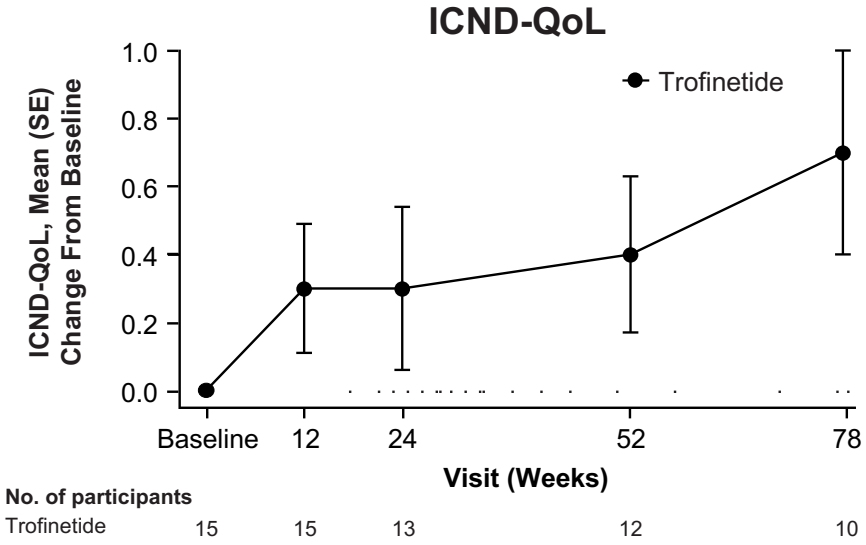
Dashed lines represent the target exposure range ($AUC_{0–12,ss}$= 800–1200 µg•h/mL). The dotted line represents the median target exposure ($AUC_{0–12,ss}$= 1000 µg•h/mL).
%CV, coefficient of variation expressed as a percent.

Exploratory efficacy





- Symptoms were improved throughout the study as measured by the CGI-I, CaGI-I, and change from baseline in the ICND-QoL
- No change in the CGI-S at each visit



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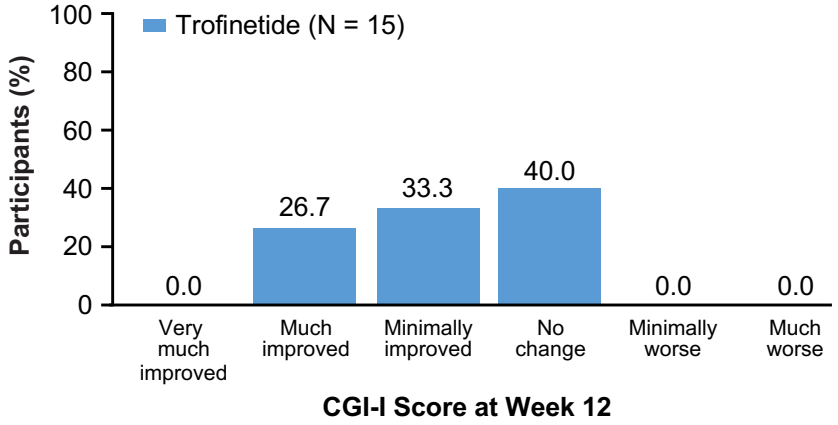
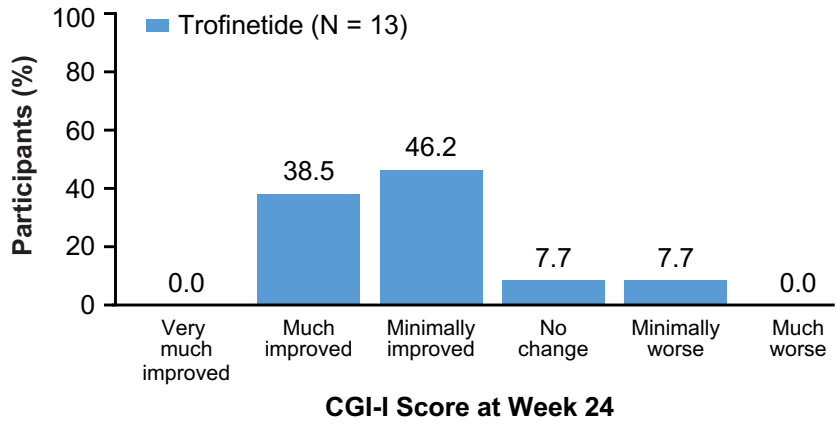
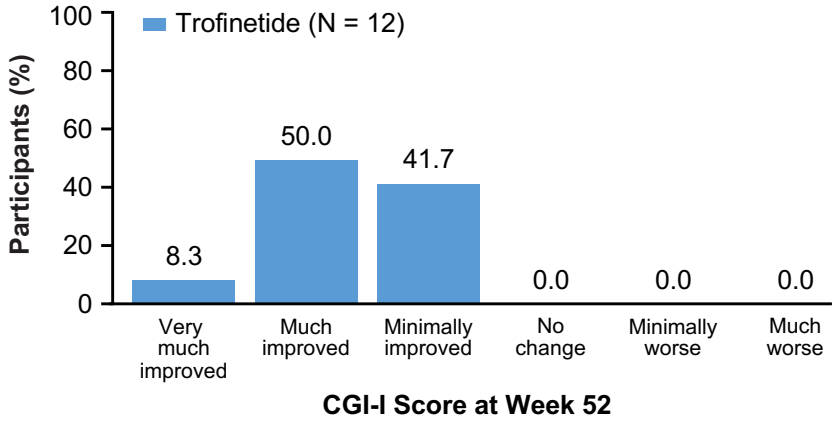
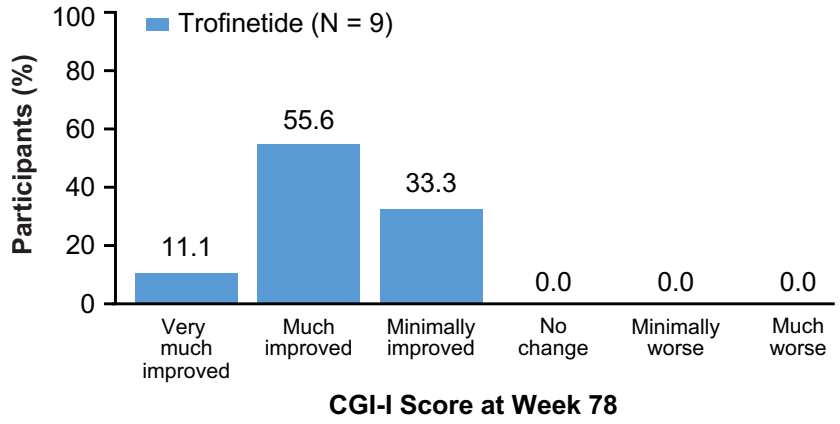
Post hoc CGI-I responder analysis

- The percentage of participants with a “much improved” CGI-I score of 2 increased throughout the study









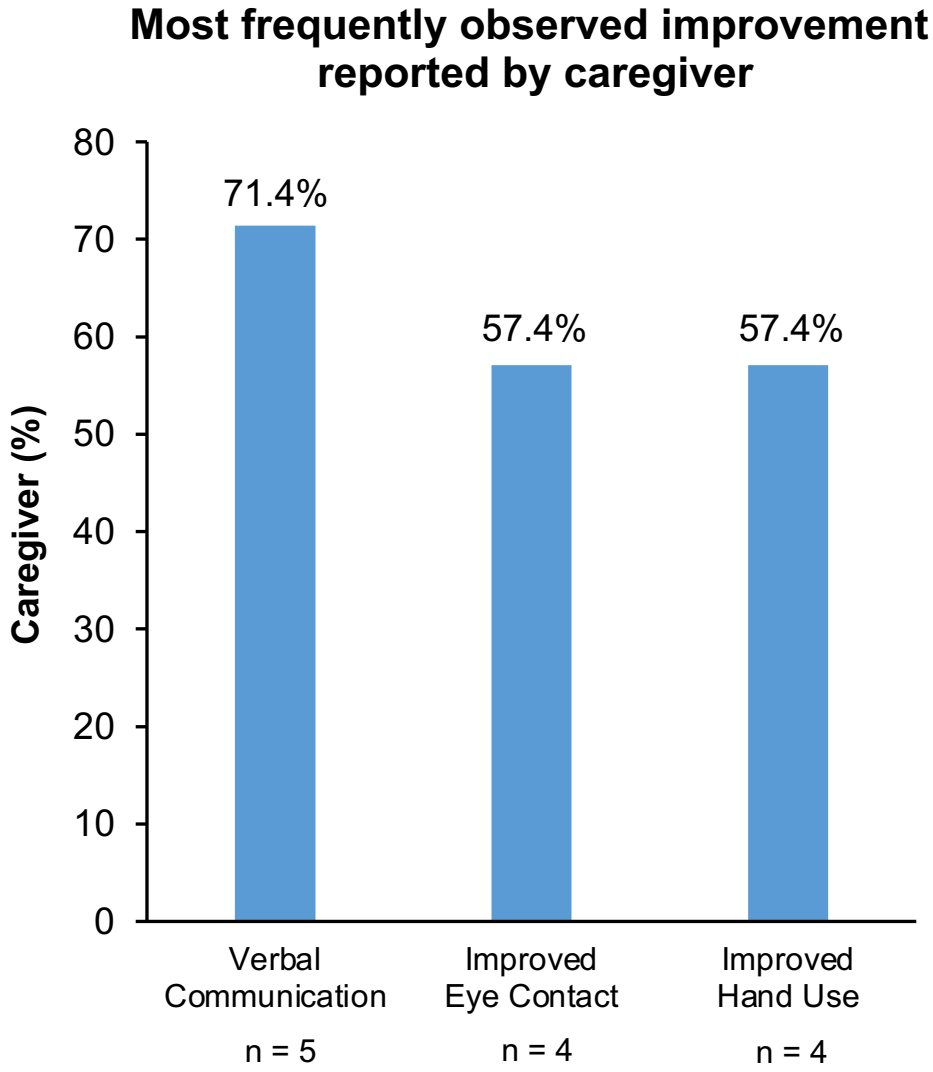
Caregiver exit interviews (n = 7)

Impact of RTT

- The inability to communicate was the most impactful symptom of RTT (n = 3; 42.9%)
- Improved communication was the most desired treatment effect (n = 5; 71.4%)

Trofinetide Benefit

- Verbal communication was the most frequently observed improvement (n = 5; 71.4%)
- All 7 caregivers were “satisfied” (n = 4) or “very satisfied” (n = 3) with the benefits of trofinetide



Conclusions

- Trofinetide had acceptable tolerability for up to 78 weeks in girls 2–4 years of age with RTT; safety results were consistent with the 12-week LAVENDER study[1] and the 40-week LILAC open-label extension study[2]
- The prescribed dosing in DAFFODIL achieved the target exposure and was similar to the range of exposure reported in pediatric and adult participants with RTT from the LAVENDER study
- Improvements in caregiver- and clinician-rated efficacy endpoints related to the global impression of RTT symptoms and quality of life were sustained up to 78 weeks
- All caregivers reported they were “satisfied” or “very satisfied” with the benefits provided by trofinetide
- These findings together with the LAVENDER results support the approval of trofinetide in adults and pediatric patients 2 years of age or older

1. Neul JL, et al. *Nat Med.* 2023;29(6):1468–1475. 2. Percy AK, et al. Poster presented at IRSF; June 5–7, 2023; Nashville, TN, USA.