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DAYBUE™ (trofinetide): Possible Mechanism of Action in Rett Syndrome

This letter is provided in response to your specific request for information regarding the possible mechanism of action of trofinetide in Rett syndrome (RTT).

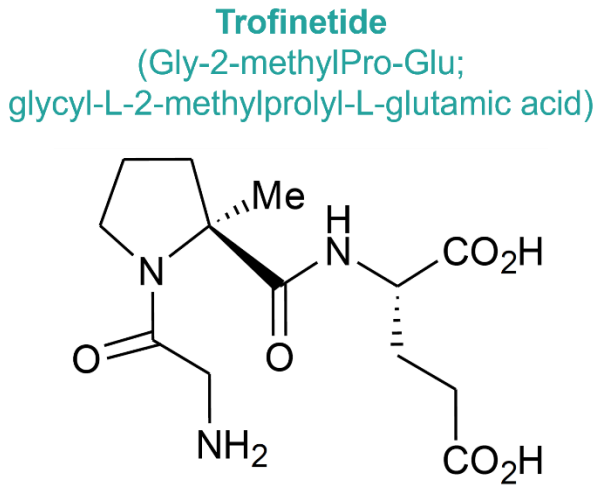
Summary

- The mechanism by which trofinetide exerts therapeutic effects in patients with RTT is unknown.[1]
- Trofinetide is thought to enhance neuronal synaptic function and morphology.[2] This hypothesis is supported by findings from studies of trofinetide in a methyl-CpG-binding protein 2 gene (*Mecp2*) mouse model of RTT, in which increased branching of the dendrites that form synapses and synaptic plasticity signals were observed.

Possible Mechanism of Action

Trofinetide (glycyl-L-2-methylprolyl-L-glutamic acid), formerly known as NNZ-2566, is a synthetic analog of the N-terminal tripeptide of insulin-like growth factor 1 (**Figure 1**).[3]

Figure 1. Chemical Structure of Trofinetide[4]



The mechanism by which trofinetide exerts therapeutic effects in patients with RTT is unknown.[1] However, trofinetide is thought to enhance neuronal synaptic function and morphology. This hypothesis is supported by findings from studies of trofinetide in a *Mecp2* mouse model of RTT, in which increased branching of the dendrites that form synapses and synaptic plasticity signals were observed.[2]

Preclinical Studies with Trofinetide

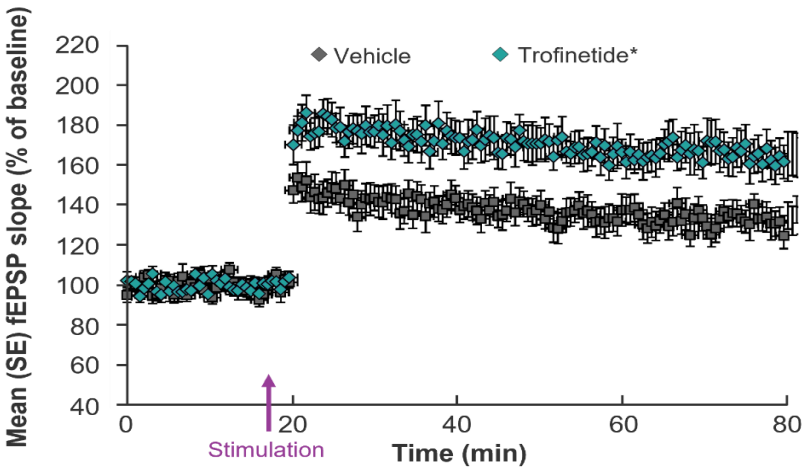
The effects of daily intraperitoneal (IP) administered trofinetide 20 mg/kg compared with vehicle control (saline) were investigated in male *Mecp2* knockout mice.[2] Treatment was started in the

mice at 4 weeks of age, hippocampal long-term potentiation (LTP) was assessed following 5 weeks of treatment, and dendritic morphology was assessed following 9 weeks of treatment (n=3 mice per treatment group). The clinical significance of these findings has not been established.

Hippocampal LTP

Daily IP administration of trofinetide 20 mg/kg led to a statistically significant increase in LTP in the hippocampi of *Mecp2* knockout mice compared to vehicle (**Figure 2**).[2]

Figure 2. Hippocampal LTP Following 5 Weeks of Treatment[2]

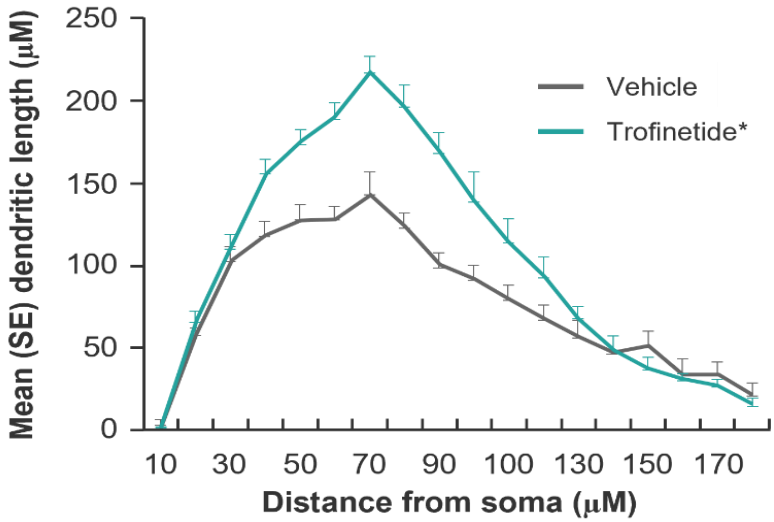


**Daily IP administration of trofinetide at 20 mg/kg/day starting at 4 weeks (n=3 mice per treatment group).*
Stimulus intensity was selected as 50–60% of the maximal response and baseline responses were collected every 30 seconds for 20 minutes. LTP was induced by theta-burst stimulation, after which, signals were recorded for 60 minutes.
Abbreviations: fEPSP=field excitatory postsynaptic potential; IP=intraperitoneal; LTP=long-term potentiation; SE=standard error.

Dendritic Morphology

With trofinetide vs vehicle, no significant changes were seen on the number of dendritic spines; however, a trend toward increased dendritic complexity (data not shown) and spine length (**Figure 3**) was observed.[2]

Figure 3. Dendritic Spine Length Following 9 Weeks of Treatment[2]



**Daily IP administration of trofinetide at 20 mg/kg/day starting at 4 weeks (n=3 mice per treatment group).*
Abbreviations: IP=intraperitoneal; SE=standard error.

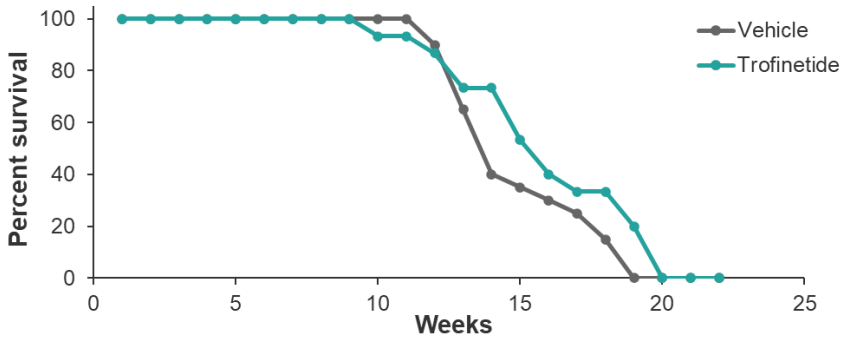
Functional Outcomes

Treatment of *Mecp2* knockout mice with daily IP administration of trofinetide 20 mg/kg had no functional effects comprising: motoric, respiratory, autonomic function, and general condition, compared with vehicle.

Survival Outcomes

Mecp2 knockout mice treated with daily IP administration of trofinetide 20 mg/kg had a 50% survival rate of 15.5 weeks compared to 13.5 weeks with vehicle (**Figure 4**).[2] The course of survival differed significantly over time (p=0.0375).

Figure 4. Survival in *Mecp*2 Knockout Mice with Daily Trofinetide or Vehicle Treatment[2]



Trofinetide (n=20), Vehicle (n=15)
Abbreviation: Mecp2=methyl-CpG-binding protein 2.

References

1. DAYBUE™ (trofinetide) [package insert]. San Diego, CA. Acadia Pharmaceutical Inc. **[Link]**
2. Acadia Pharmaceuticals Inc. Data on File. In. San Diego, CA.
3. Bickerdike MJ, Thomas GB, Batchelor DC, et al. NNZ-2566: a Gly-Pro-Glu analogue with neuroprotective efficacy in a rat model of acute focal stroke. *J Neurol Sci.* 2009;278(1-2):85-90. **[PubMed]**
4. Keam SJ. Trofinetide: First Approval. *Drugs.* 2023;83(9):819-824. **[PubMed]**