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Trofinetide: A Pioneering Treatment for Rett Syndrome

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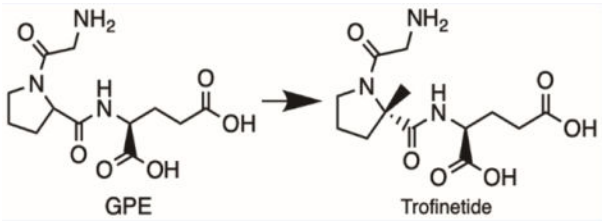
Graphical Abstract



STRUCTURE: Trofinetide ((2S)-2-{[(2S)-1-(2-aminoacetyl)-2-methylpyrrolidine-2-carbonyl]amino}pentanedioic acid) is derived from the tripeptide glycine-proline-glutamic acid (GPE), which is an endogenous tripeptide of the N-terminal domain of Insulin-like Growth Factor 1 (IGF-1). The compound differs from endogenous GPE by a methyl (-CH3) substitution at the α-carbon of the proline residue. This methyl substitution assists in resistance to protease cleavage and improves oral bioavailability. The molecular formula of trofinetide is C13H21N3O6, and the molecular weight is 315.33 g/mol.

Graphical Abstract

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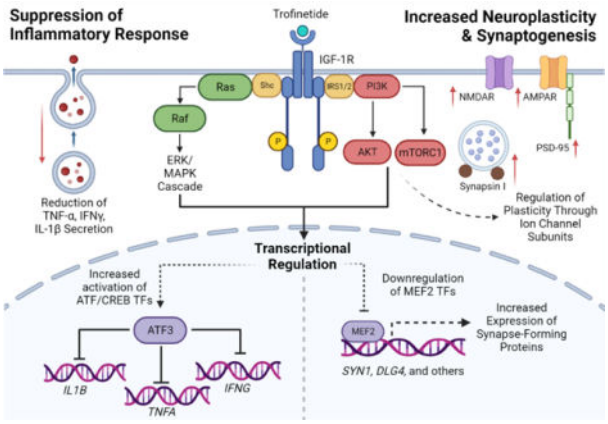

MECHANISM OF ACTION: Rett syndrome is a neurodevelopmental disease caused by mutations in the X-linked Methyl CpG Binding Protein 2 (*MECP2*) gene, affecting primarily females. *MECP2* mutations cause a diverse range of phenotypes and disrupt various cellular signalling pathways. While the mechanism of action of trofinetide has yet to be fully elucidated, due to its homology with the N-terminus of Insulin-Like Growth Factor-1 (IGF-1) it is hypothesized that it acts through the IGF-1 receptor on both neurons and glia. IGF-1 receptor activation stimulates downstream pathways including Mitogen-Associated Protein Kinase (MAPK), Phosphoinositide-3-Kinase (PI3K) and Mammalian Target of Rapamycin (mTOR) to induce transcriptional changes. Evidence suggests that trofinetide induces upregulation of Activating Transcription Factor 3 (ATF3), which attenuates expression of inflammatory cytokine genes encoding proteins such as Interleukin-1β (IL-1β), Interferon γ (IFNγ), and Tumor Necrosis Factor α (TNF-α). These cytokines are upregulated in Rett syndrome and contribute to aberrant systemic activation of the inflammatory response. IGF-1 has also been reported to be an essential component of synaptic formation, maturation, and neuroplasticity during CNS development, particularly through modulation of α-Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic Acid (AMPA) and N-methyl-D -aspartate (NMDA) receptor subunit composition and downregulation of the Myocyte Enhancer Factor-2 (MEF2) transcriptional repressor. Reduced activity of MEF2 increases expression of genes involved in synaptic formation and plasticity, such as SYN1 (Synapsin 1) and DLG4 (PSD-95) and trofinetide may also act through this pathway to enhance synaptic formation and plasticity. Trofinetide improved numerous psychomotor symptoms in Rett syndrome patients during clinical trials, which were quantified through clinician-assessed composite scores. Interestingly, clinical trials for recombinant human IGF-1 (mecasermin) in Rett syndrome patients yielded inconclusive results, which may reflect unique pharmacology or pharmacokinetics of trofinetide, warranting further investigation. Although the exact mechanism of action of the drug is still unknown, trofinetide's efficacy in clinical trials suggests that the drug is an important step forward in the management of patients with Rett syndrome.

Acknowledgments

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Declaration of interests

C.N. has received royalties and research funding from Acadia Pharmaceuticals for a program other than trofinetide. H.P. and A.F. have no interests to declare.

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NAME:

Trofinetide (brand name: Daybue; also known as NNZ-2566).

DRUG CLASS:

Trofinetide is a first-in-class drug to treat multiple psychomotor symptoms in Rett syndrome. It is an orally bioavailable small molecule and received orphan drug designation from the FDA in 2015.

CLINICAL USE:

Trofinetide is indicated to treat patients 2 years and older diagnosed with Rett syndrome, including males and patients with mutations in loci other than *MECP2*. It is the only FDA-approved drug for Rett syndrome. Dosing information for adults of 50 kg or more: 12,000 mg twice daily. Dosage for children is weight-dependent.

DEVELOPED BY:

Acadia Pharmaceuticals Inc and Neuren Pharmaceuticals Ltd.

ADVERSE EFFECTS:

Clinical trials reported the most common adverse effects as: diarrhea (82%), vomiting (29%), fever (9%), seizure (9%), anxiety (8%), decreased appetite (8%), fatigue (8%), and nasopharyngitis (5%). Trofinetide is also a weak CYP3A4 inhibitor.

TIMELINE:

2009: First publication of preclinical efficacy of trofinetide in traumatic brain injury (NNZ-556); first publication supporting the efficacy of IGF-1 in animal model of Rett syndrome.

2010–2012: Phase I trials for Multiple Sclerosis (NCT01420042, NCT00961779).

2013–2017: Phase II trials for use in Rett syndrome (NCT02715115, NCT01703533).

2015: Trofinetide receives orphan drug designation.

2018: Acadia Pharmaceuticals enters into licensing agreement with Neuren Pharmaceuticals.

2019-Present: Phase III trials conducted in females with documented *MECP2* mutations (NCT04181723, NCT04279314, NCT04776746, NCT04988867)

2022: NDA for approval in Rett Syndrome submitted.

March 2023: FDA approval granted for trofinetide.