



IMPROVING THE LIVES OF PEOPLE WITH NEURODEVELOPMENTAL DISABILITIES

14 March 2023



This presentation contains forward looking statements that involve risks and uncertainties. Although we believe that the expectations reflected in the forward looking statements are reasonable at this time, Neuren can give no assurance that these expectations will prove to be correct. Actual results could differ materially from those anticipated. Reasons may include risks associated with drug development and manufacture, risks inherent in the regulatory processes, delays in clinical trials, risks associated with patent protection, future capital needs or other general risks or factors.

Developing new therapies for debilitating neurodevelopmental disorders that emerge in early childhood and are characterised by impaired connections and signalling between brain cells



Clinical development in **5 more** neurodevelopmental disorders, all with **Orphan Drug** designation, with no existing approved therapies²

Neuren owns intellectual property, with **no royalties payable to 3rd parties**

Incorporated in New Zealand, based in Melbourne, Australia, listed on ASX (Code: NEU)

¹ Currently approved in US only ² Except growth hormone to treat some aspects of Prader-Willi syndrome neurer

pharmaceuticals

Highlights



DAYBUE [™] (trofinetide) approved by US FDA as the 1 st and only treatment for Rett syndrome, Acadia launching by end April 2023	Neuren's potential revenue for Rett syndrome in the US alone of US\$73m ¹ plus up to US\$350m sales milestones plus 10-15% royalties	Advancing partnering discussions for trofinetide outside North America
Accelerating Phase 2 development of NNZ-2591 in 4 indications, with potential markets 5x Rett syndrome	5 NNZ-2591 novel mechanism of action has many more potential applications	6 A\$40 million cash at 31 December 2022 – well funded to execute NNZ-2591 Phase 2 trials and preparation for Phase 3

¹ Assuming the product is launched in the US, US\$33m is received as one third share of the value of a Rare Pediatric Disease Priority Review Voucher

Seeking a ground-breaking impact on neurodevelopmental disorders



Rett	Fragile X	Phelan- McDermid	Angelman	Pitt Hopkins	Prader-Willi
MECP2	FMR1	SHANK3	UBE3A	TCF4	15q11-q13
dendrites soma myelin sheath nodes of Ranvier action potential		Impaired communication between neurons, abnormal formation/pruning of dendrites & chronic inflammation		f critical upstrea analogs	's drugs target the role of IGF-1 in this m process, using of peptides that can n orally as liquids
	Se	vere impact on near	rly every aspect of I	ife	
walking and b	alance issues	anxiety and h	nyperactivity	seiz	zures
speech im	pairment	intellectua	l disability	breathing i	rregularities
impaired	hand use	sleep dist	turbance	gastrointest	inal problems

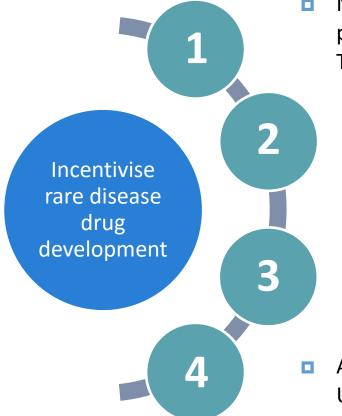
All programs have Orphan Drug designation and at Phase 2 or later



Compound	Indication	Preclinical	Phase 1	Phase 2	Phase 3	Registration	Commercial rights
	Rett NA					(trofinetide)	ACADIA
Trofinetide	Rett RoW						neuren
	Fragile X						NA: ACADIA RoW: neuren
	Phelan- McDermid						
	Angelman						politop
NNZ-2591	Pitt Hopkins						neuren
	Prader-Willi						



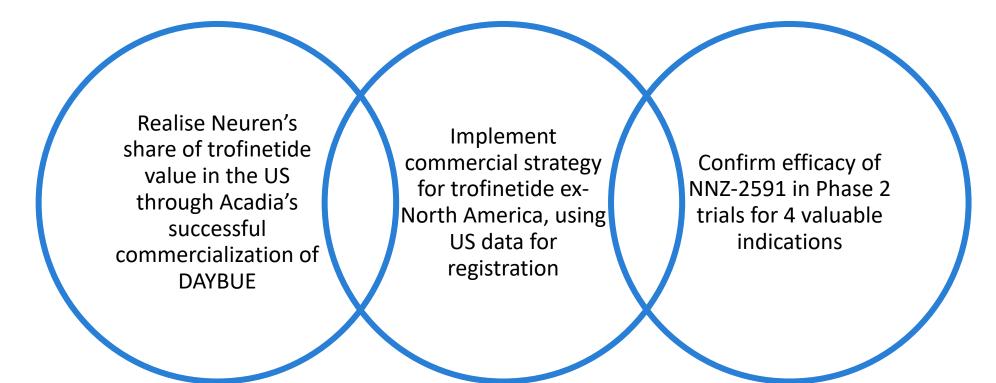
Neuren is targeting multiple "rare diseases", but they are not "ultra-rare"



- Marketing exclusivity periods protect against generics independent of patents (7.5 years in US, 12 years in EU, 10 years in Japan, South Korea and Taiwan, China has proposed to introduce 7 years)
 - Priority review by regulators (e.g. 6 months in US instead of 10 months) and higher probability of approval
 - Urgent unmet need results in strong engagement from patient community and leading physicians, and immediate access to known patients
- Attractive pricing environment (average US Orphan Drug price of US\$186,758 per patient p.a. in 2017¹)

Three key drivers transforming near term value





World's 1st and only approved therapy for Rett syndrome





US FDA approved for treatment of Rett Syndrome in patients 2 years and older

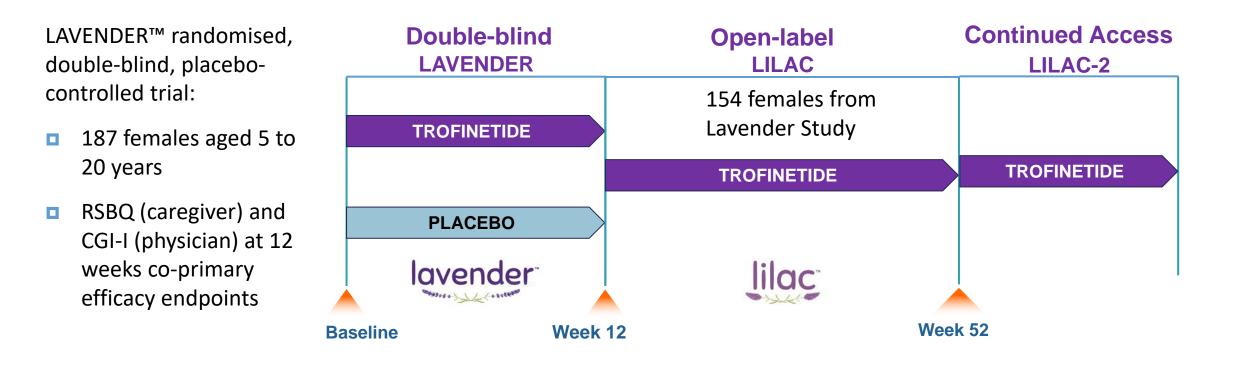
Rett Syndrome: a debilitating and complex, rare, neurodevelopmental disorder typically caused by a genetic mutation on the MECP2 gene, which strikes all racial and ethnic groups estimated at 1 in every 10,000 to 15,000 females born

- Acadia Pharmaceuticals has exclusive license from Neuren for development and commercialization of DAYBUETM (trofinetide) in North America (US, Canada and Mexico)
- US launch expected by end of April 2023
- Outside North America Neuren intends to pursue registration and commercialisation of trofinetide for Rett syndrome through partners and is currently in discussion with a number of third parties

Clinical studies supported US approval



■ FDA approval supported by pivotal efficacy from positive LavenderTM Phase 3 trial, supportive safety and efficacy from LilacTM open-label extension trial, Neuren's positive Phase 2 trial, DaffodilTM safety/PK trial in children aged 2-5 years



Trofinetide North America Economics for Neuren



	<u>Rett Syndr</u>	ome only						
\checkmark	US\$10m	in 2022 follow	ving accep [.]	tance of NDA for re	eview	Rett Syndror	ne Patients	US
-	US\$40m	US\$40m following 1st commercial sale in the US (expected			Potential ¹		10,000	
		late Apr 2023)			Currently ide	ntified	5,000	
	US\$33m one third share of Priority Review Voucher awarded to Acadia (assuming market value US\$100m)			US annual average net realized cost of DAYBUE expected to be ~US\$375,000 ²				
	Aggregate	of all indicatio	<u>ns</u>			Orphan exclu	isivity plus patents to	o 2040
	Tiered Roy	alty Rates (% c	of net	Sales Milestone	Example calculations of royalty/s		ales milestones	
	sales) ³			Net Sales in one	!	Annual Net	Annual Royalty	Total Sales
	Annual Ne	et Sales	Rates	calendar year	US\$m	Sales in NA		Milestones
•	≤US\$250m	ו	10%	≥US\$250m	50			Earned
-	>US\$250m	n, ≤US\$500m	12%	≥US\$500m	50	US\$500m	US\$55m	US\$100m
-		, ≤US\$750m	14%	≥US\$750m	100	US\$750m	US\$90m	US\$200m
	>US\$750m	, .	15%	≥US\$1bn	150	US\$1bn	US\$128m	US\$350m

¹ Potential patient estimates derived by applying the mid-point of the published prevalence estimate range to the populations under 60 years

² Includes assumptions for average weight of expected patient population, compliance rates to therapy and mandatory government discounts; the list price will be US\$21.10 per mL

³ Royalty rates payable on the portion of annual net sales that fall within the applicable range



Rett Syndrome Patients	Europe	Japan	Israel	China urban	Other Asia
Potential ¹	13,000	3,000	300	28,000	6,000
Currently identified	4,000	1,000	200	2,000	'00s

- Advancing partnering discussions to secure optimum outcome
- Neuren has full access to US data for registration ex-North America
- Strong interest from families, advocacy groups and physicians
- Lower diagnosis rates expected to increase with awareness and accelerate with availability of a treatment

5x larger opportunity for NNZ-2591



Disorder Gene Published preval		Published prevalence estimates	Potential patients			
	mutation		US ¹	Europe ¹	Asia ^{1, 2}	
Phelan- McDermid	SHANK3	1/8,000 to 1/15,000 males and females	22,000	28,000	81,000	
Angelman	UBE3A	1/12,000 to 1/24,000 males and females	14,000	18,000	52,000	
Pitt Hopkins	TCF4	1/34,000 to 1/41,000 males and females	7,000	9,000	25,000	
Prader-Willi	15q11-q13	1/10,000 to 1/30,000 males and females	13,000	16,000	47,000	
			56,000	71,000	205,000	

- Current opportunity for NNZ-2591 is more than 5 times the Rett Syndrome opportunity³
- There are many other neurodevelopmental disorders potentially relevant for NNZ-2591 mechanism of action
- Neuren retains global rights

¹ Estimates derived by applying the mid-point of the prevalence estimate range to the populations under 60 years

² Asia comprises Japan, Korea, Taiwan, Israel and urban populations of China and Russia

³ Based on number of potential patients globally

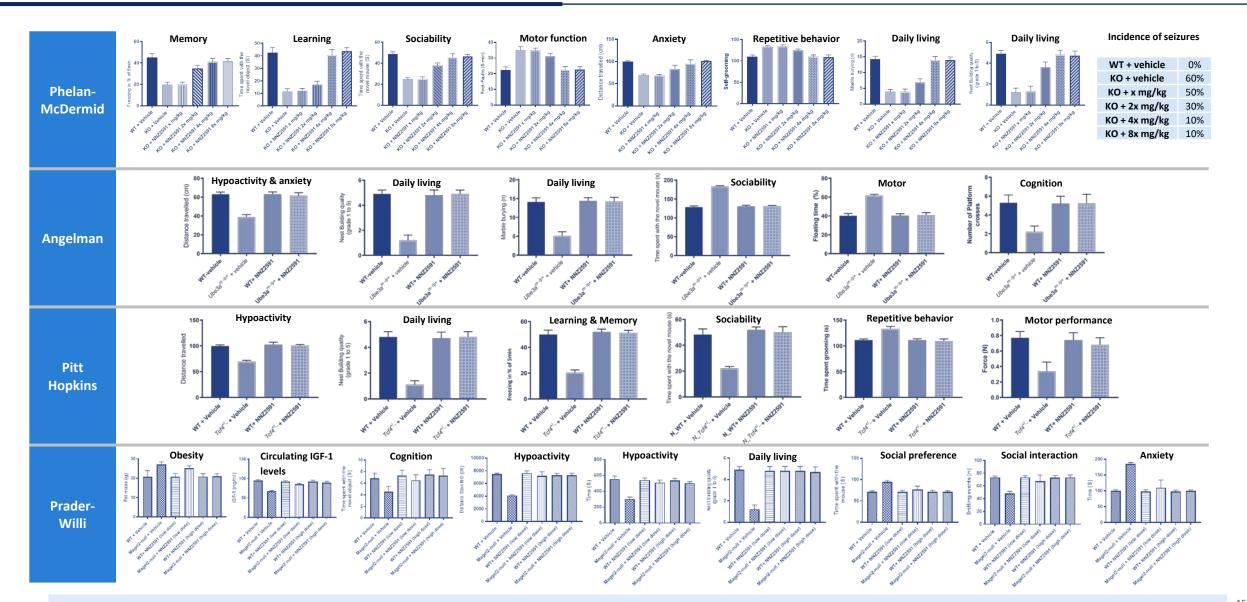
NNZ-2591 has ideal attributes leading into Phase 2



- Novel mechanism of action
- Clear and consistent efficacy in mouse models of each syndrome
- Biochemical effects in the brain confirmed
- Optimum dose identified
- Demonstrated high oral bioavailability and blood-brain barrier penetration
- ✓ IND-enabling program of non-clinical toxicology and CMC studies completed
- Proprietary drug substance manufacturing process with exceptional purity and high yield, administered as patient-friendly liquid dose
- ✓ Safe and well tolerated in Phase 1 trial
- Orphan designations from FDA and EMA
- ✓ INDs approved by FDA for Phelan-McDermid, Angelman, Pitt Hopkins and Prader-Willi syndromes

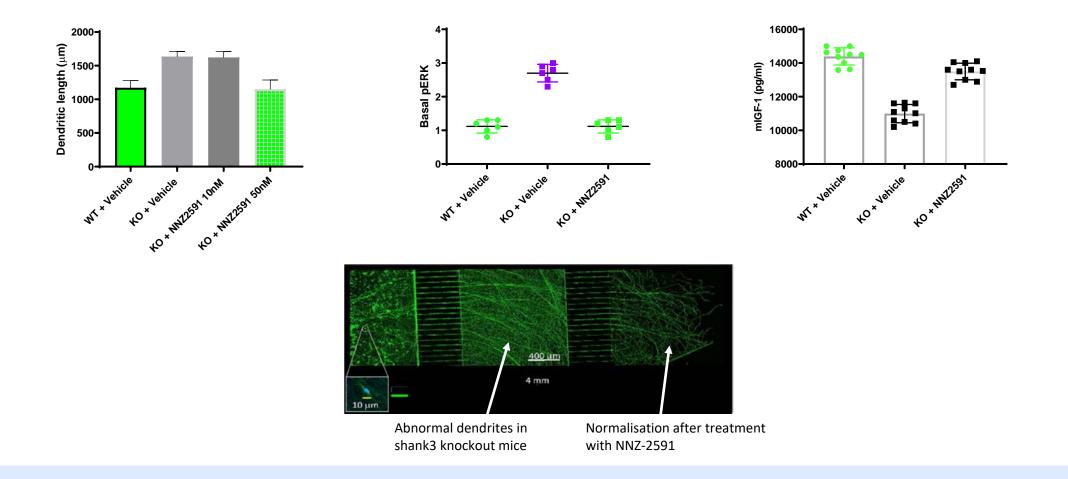
Clear and consistent efficacy in animal models







In biochemical testing, NNZ-2591 was shown to normalise the abnormal length of dendrite spines between brain cells, the excess activated ERK protein (pERK) and the depressed level of IGF-1 in *shank3* knockout mice





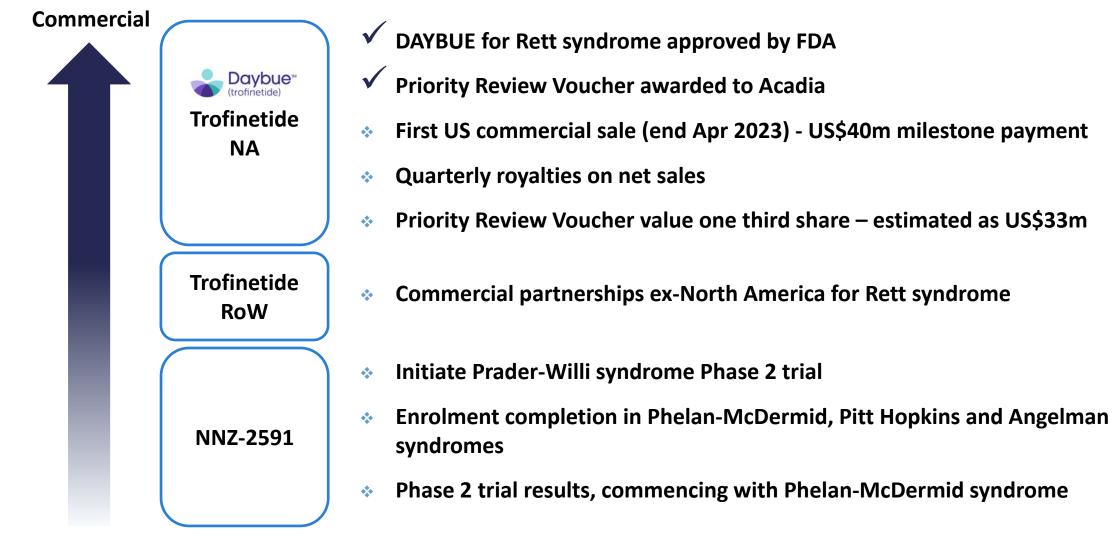
Overall aim – expedite data that enables subsequent trials to be designed as registration trials and prepare for Phase 3 in parallel

- Prioritising speed to data
- Maximising opportunity to demonstrate effects
- Confirm safety and PK in pediatric patients
- Assess treatment impact across multiple efficacy measures to select primary endpoint for registration trial
- Series of Phase 2 trial results, commencing with Phelan-McDermid syndrome in H2 2023

	Angelman	Phelan-McDermid	Pitt Hopkins		
n subjects	Up to 20	Up to 20	Up to 20		
Age range	3 to 17	3 to 12	3 to 17		
	(Sequential enrolm	nent in three age groups follo	wing DSMC review	()	
Location	Australia	US	US		
Baseline observation	n NN2	Z-2591 treatment	Follow-u	up	
	Up-titration				
eek 0	Week 4	Week 10	Week 17	Week 19	
Phase 3 preparation Non-clinical toxicity studies and optimisation of drug product and drug substance manufacturing					

Transforming catalysts in 2023





Development

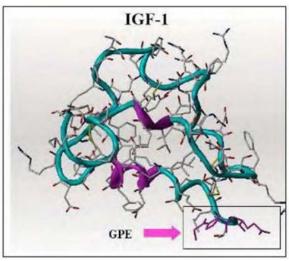
CONTACT

Jon Pilcher, CEO jpilcher@neurenpharma.com +61 438 422 271



Trofinetide

 Trofinetide is an investigational drug and a novel synthetic analog of GPE, the amino-terminal tripeptide of IGF-1



 $\mathsf{GPE}{=}\mathsf{glycine}{-}\mathsf{proline}{-}\mathsf{glutamate};$ IGF-1= Insulin-like growth factor 1

Proposed Mechanism of Action¹

Rett syndrome features:

- Insufficient formation of new synapses by neurons
- Excessive pruning of existing synapses by overactive microglia

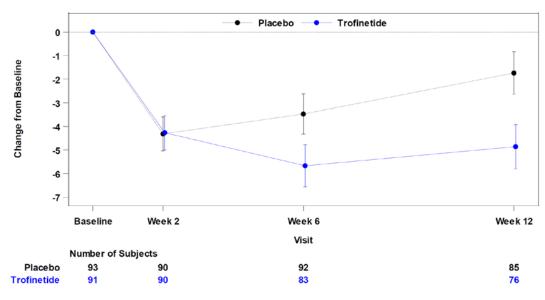
Trofinetide is thought to:

- Improve synaptic function and restore synaptic structure
- Inhibit overactivation of inflammatory microglia and astrocytes
- Increase the amount of IGF-1 in the brain

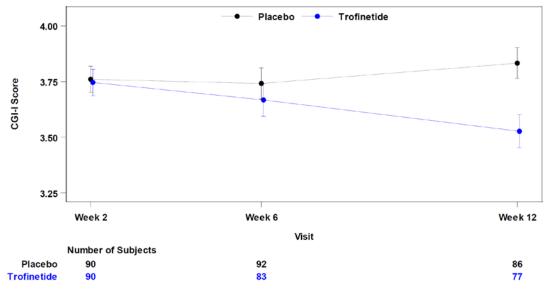
Positive Lavender Phase 3 results



Rett Syndrome Behavioural Questionnaire (RSBQ)



Clinical Global Impression – Improvement (CGI-I)



Change from Baseline	Placebo	Trofinetide*	
Mean	-1.7	-5.1	
p-value		0.0175	
Effect Size		0.37	

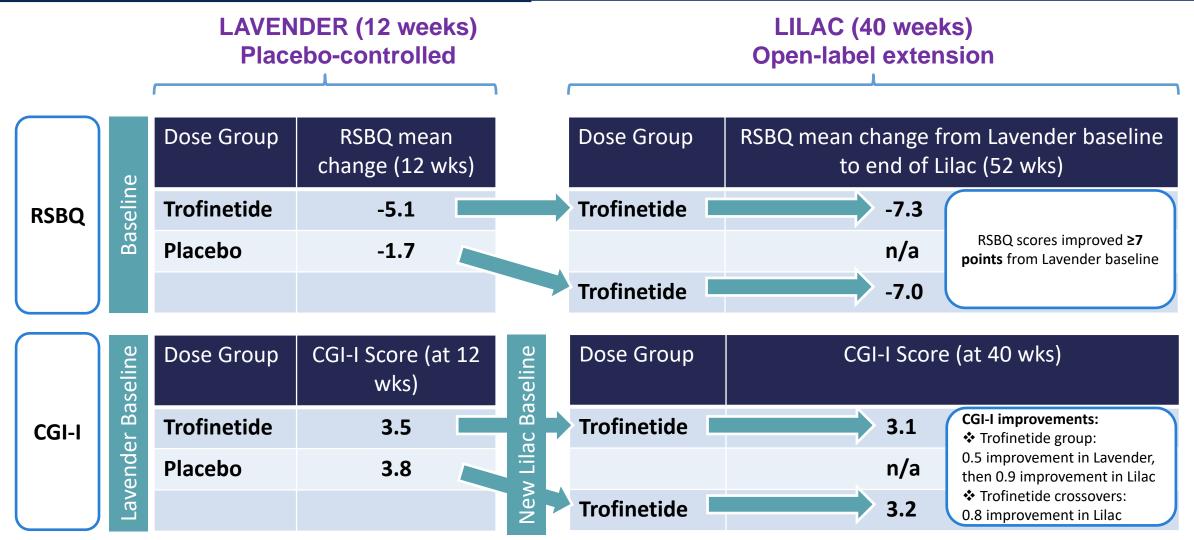
Week 12 Score	Placebo	Trofinetide*
CGI-I	3.8	3.5
p-value		0.0030
Effect Size		0.47

Source: Acadia presentation (Acadia Corporate Presentation (4Q22 Earnings), Lavender Study Results (acadia.com))

* RSBQ mean (SE) baseline score placebo = 44.5 (1.26) and trofinetide = 43.7 (1.21). CGI-I no baseline score. CGI-I uses a 7-point Likert scale; with a score of 4 = no improvement; >4 = worsening and <4 = improvement. p-values based on least squares mean from the mixed-effects model for repeated measures analysis.

Sustained and continued improvement observed in Lilac





Source: Acadia presentation (Acadia Corporate Presentation (4Q22 Earnings), Lavender Study Results (acadia.com))

RSBQ: n=161 for Lavender at 12 weeks; n=88 for Lilac at 40 weeks.

CGI-I: n=163 for Lavender at 12 weeks; n=91 for Lilac at 40 weeks. CGI-I uses a 7-point Likert scale; a score of 4 = no improvement; >4 = worsening and <4 = improvement.



LAVENDER (12 weeks) Placebo-controlled

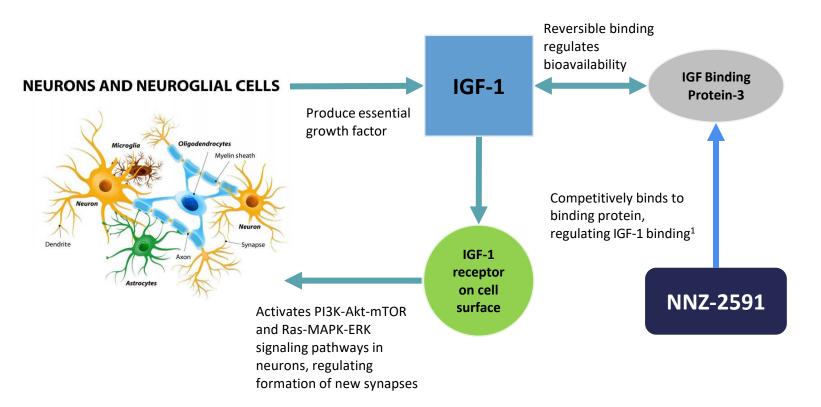
LILAC (40 weeks) Open-label extension

	Adverse Events (AEs) >10% observed in Trofinetide group		Adverse Events (AEs) >10% observed in Lilac	
Diarrhea	80.7% (97% Mild and Moderate)	Diarrhea	74.7% (96% Mild and Moderate)	
Vomiting	27.0% (96% Mild and Moderate)	Vomiting	28.6% (100% Mild and Moderate)	
		COVID-19	11%	
		Discontinuations due to AE of diarrhea: 21%		

No new safety or tolerability findings in Lilac

Novel mechanisms of action – NNZ-2591





- NNZ-2591 is a synthetic analog of cyclic glycine proline, a peptide that occurs naturally in the brain, designed to be more stable, orally bioavailable and readily cross the blood-brain barrier
- NNZ-2591 can regulate the amount of IGF-1 that is available to activate IGF-1 receptors
- The effects of NNZ-2591 are "state-dependent" – correcting impairment, but not impacting normal cells