Neuren (NEU) – ASX Announcement **30 May 2023**

Chairman's Address at 2023 Annual Meeting of Shareholders

The recent approval by the US Food and Drug Administration (FDA) of DAYBUE™ as the first ever treatment for Rett syndrome was the most important milestone in Neuren's history. We are delighted that right now in the United States people suffering from Rett Syndrome are able to access the first ever medical treatment for this debilitating illness. With each week we hear and see more detailed stories directly from the families and carers of the of those who have had access to trofinetide via the clinical trials and now to DAYBUE™ as a commercial product on the market. It is very powerful to hear from the parents and carers as they share their unique journeys, the improvements they are seeing and how they have navigated any side effects.

It was ten years ago that Neuren embarked on the first ever multi-centre trial in Rett syndrome and painstakingly created the path forward with all stakeholders. Many people showed great determination over the journey but without doubt the greatest was shown by the Rett syndrome community and we are delighted for them to see the launch of DAYBUE™ in the United States last month.

On behalf of the Board I'd like to recognise the talent, dedication and perseverance of the team at Neuren, with special mention of Jon Pilcher who has led Neuren as CEO over the last three years but Jon has been an integral part of the senior leadership at Neuren for a decade. Without the calm tenacity of Jon and his team we would not be here today. I'd also like to mention Trevor Scott a non-executive Director of Neuren for some 21 years who has had an impact behind the scenes that few would understand and we are most fortunate to have had Trevor 's unbroken commitment, leadership and financial support over the years. Special mention also to Richard Treagus, former Executive Chair of Neuren, who like Jon and Trevor kept the faith and was pivotal in establishing the agreement with Acadia, which was not warmly welcomed by the market at the time it was announced. The passage of time has shown the deal to be the right decision and Acadia have put an incredible effort into trofinetide. Acadia is a very professional enterprise and they deserve high praise and reward for their commitment and focus to bring this product to the USA market. The resources, skill and effort required to take trofinetide beyond Phase 2 was at that time simply not plausible for us on our own and the choice to partner with Acadia was the right decision for all concerned.

The approval of DAYBUE™ has transformed our financial position and outlook, placing us in a very strong position to make the most of the opportunities ahead as we strive to make a difference to patients and families impacted by various neurodevelopmental disabilities.

The next payment from Acadia is US$40 million, payable following the first commercial sale, which should be received in June 2023. This will be followed by quarterly royalties, plus potential milestone payments of up to US$350 million on achievement of a series of four thresholds of total annual net sales. We are very pleased that Acadia was able to launch DAYBUE™ so soon after approval, made possible by the very extensive and sophisticated commercial preparations they made during the FDA review process and we are confident that they are very well placed for successful commercialisation. In addition to royalties and milestone payments from Acadia we will receive a one third share of the market value of the Rare Pediatric Disease Priority Review Voucher that was awarded to Acadia by the FDA.

In the meantime, we are advancing the discussions with potential partners for the registration and commercialisation of trofinetide outside North America. Our revenue from trofinetide partners will flow through to pre-tax profit, as no royalties or similar costs are payable by Neuren.

The first in a series of results from the Phase 2 trials of our second drug NNZ-2591 in four neurodevelopmental disorders are anticipated before the end of 2023. The number of potential patients targeted is more than five times the number for Rett syndrome and Neuren retains global rights, which means NNZ-2591 has the potential to generate larger value for shareholders than trofinetide. We are now carefully evaluating all options to maximize this value, preparing actively for Phase 3 studies while remaining receptive to partnering alternatives. There are other neurodevelopmental disorders potentially relevant for the NNZ-2591 mechanism of action and we will continue to evaluate further opportunities for the development of this important product.

As a result of increased trading volumes and a sharply higher share price we were promoted into the S&P/ASX 300 index in September 2022, and it is now quite possible that we may join the S&P/ASX 200 index in the near term. The institutional audience for our investor relations activities has continued to expand and Neuren is now covered actively by 6 broker analysts, which reflects the continued progression of your company as our prospects continue to grow.

Your Board is focused on assisting Management to achieve Neuren's full potential and we are excited about the opportunities in front of us. It is pleasing to report that we have an increasingly robust balance sheet, which affords us optionality as we carefully evaluate the multiple opportunities for future growth that are ahead of us.

In March we welcomed Joe Basile to the Neuren Board as a non-executive Director. Joe strengthens the Board and has excellent pharma industry experience in senior finance and commercial sales executive roles for over 30 years in Australia and Asia. Joe will assume the

role of Chair of the Audit Committee, which has been ably led by Trevor Scott over many years.

I'd like to express my sincere thanks to my fellow Directors for their contributions over the last year and it continues to be a pleasure to be involved with all of the people of Neuren.

By any measure it has been a huge year for your company and I know you will enjoy hearing more from Jon Pilcher who I'd now invite to make his presentation. Thanks for your attention.

About Neuren

Neuren is developing new drug therapies to treat multiple serious neurological disorders that emerge in early childhood and have no or limited approved treatment options.

DAYBUE™ (trofinetide) is approved by the US Food and Drug Administration (FDA) for the treatment of Rett syndrome in adult and pediatric patients two years of age and older. Neuren has granted an exclusive licence to Acadia Pharmaceuticals Inc. for the development and commercialisation of trofinetide in North America, while retaining all rights outside North America.

Neuren is conducting Phase 2 trials of its second drug candidate, NNZ-2591, for each of Phelan-McDermid syndrome, Angelman syndrome, Pitt Hopkins syndrome and Prader-Willi syndrome.

Recognising the urgent unmet need, all programs have been granted "orphan drug" designation in the United States. Orphan drug designation provides incentives to encourage development of therapies for rare and serious diseases.

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ASX Listing Rules information

This announcement was authorized to be given to the ASX by the board of directors of Neuren Pharmaceuticals Limited, Suite 201, 697 Burke Road, Camberwell, VIC 3124

Forward-looking Statements

This announcement contains forward-looking statements that are subject to risks and uncertainties. Such statements involve known and unknown risks and important factors that may cause the actual results, performance or achievements of Neuren to be materially different from the statements in this announcement.

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IMPROVING THE LIVES OF PEOPLE WITH NEURODEVELOPMENTAL DISABILITIES

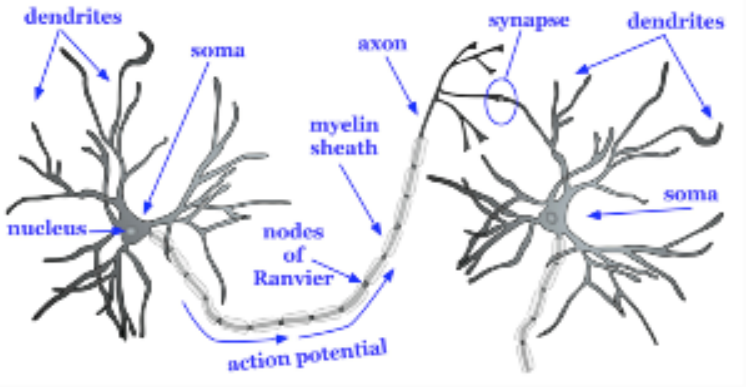
Annual Meeting of Shareholders 30 May 2023

Forward looking statements

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.

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*



Impaired communication between neurons, abnormal formation/pruning of dendrites & chronic inflammation

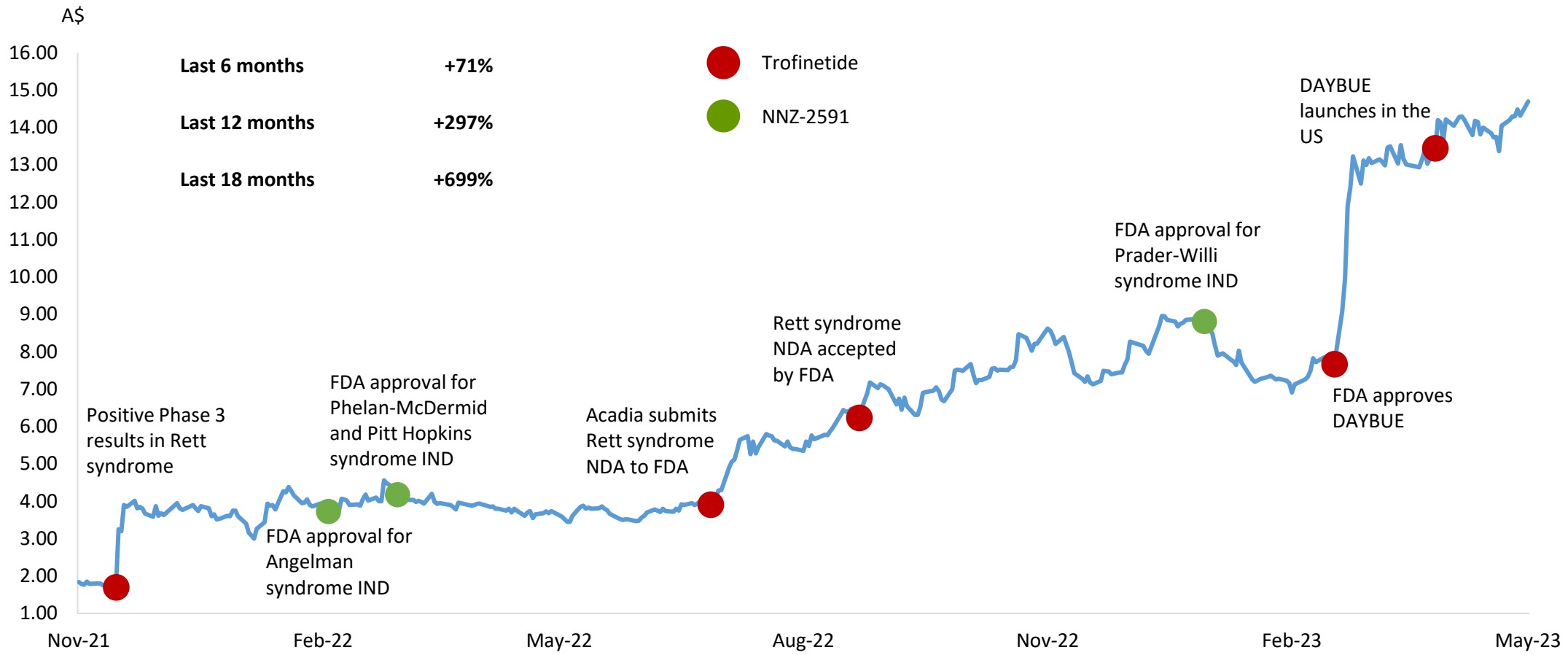
Neuren's drugs target the critical role of IGF-1 in this upstream process, using analogs of peptides that can be taken orally as liquids

Severe impact on nearly every aspect of life

walking and balance issues	anxiety and hyperactivity	seizures
speech impairment	intellectual disability	breathing irregularities
impaired hand use	sleep disturbance	gastrointestinal problems

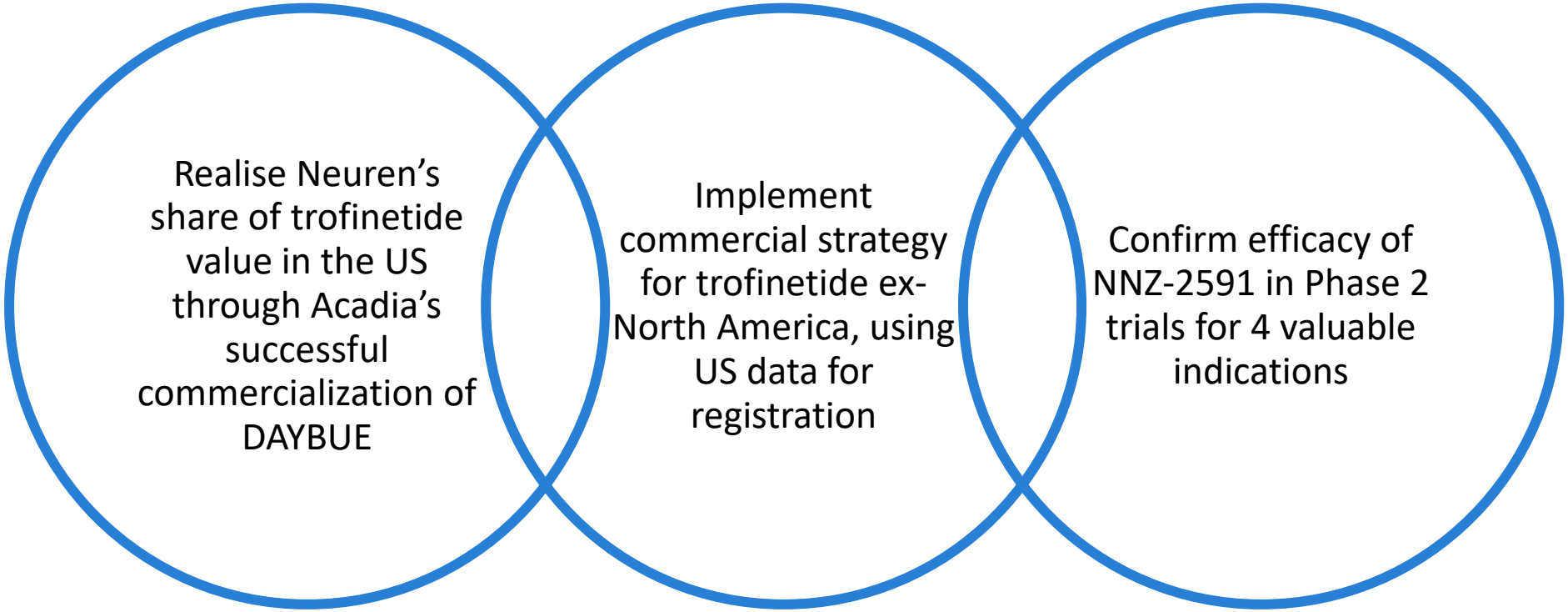
Value added in last 18 months

Last 18 Months NEU Share Price Performance



As of 22 May 2023

Three key drivers transforming near term value



World's first 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

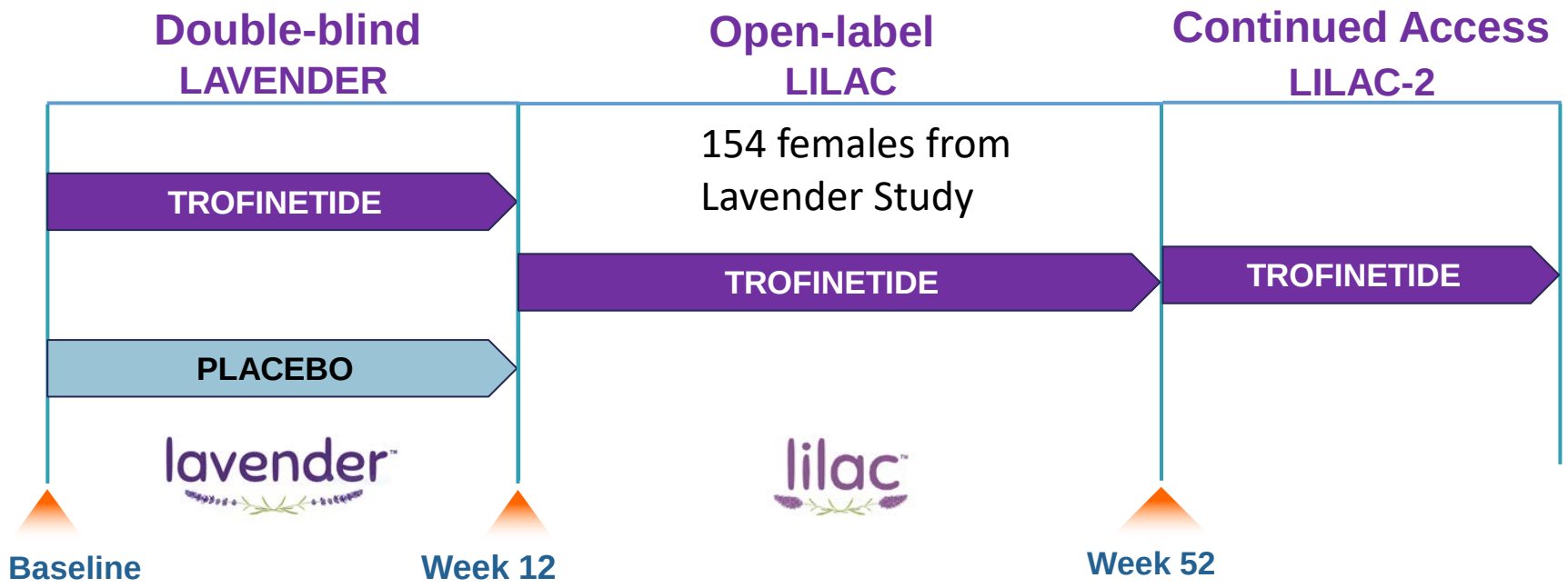
- Acadia Pharmaceuticals has exclusive license from Neuren for development and commercialization of DAYBUE™ (trofinetide) in North America (US, Canada and Mexico)
- Commercial launch in US on 17 April 2023
- Outside North America Neuren intends to pursue registration and commercialisation of trofinetide for Rett syndrome through partners and is currently in discussion with a number of third parties

Clinical studies supported US approval with broad label

- FDA approval for all people with Rett syndrome aged 2 years and older was supported by pivotal efficacy from positive Lavender™ Phase 3 trial, supportive safety and efficacy from Lilac™ open-label extension trial, Neuren's positive Phase 2 trial, Daffodil™ safety/PK trial in children aged 2-5 years

LAVENDER™ randomised, double-blind, placebo-controlled trial:

- 187 females aged 5 to 20 years
- RSBQ (caregiver) and CGI-I (physician) at 12 weeks co-primary efficacy endpoints



Sustained and continued improvement observed in Lilac

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LAVENDER (12 weeks) Placebo-controlled

LILAC (40 weeks) Open-label extension

RSBQ

Baseline

Dose Group	RSBQ mean change (12 wks)
Trofinetide	-5.1
Placebo	-1.7

Dose Group	RSBQ mean change from Lavender baseline to end of Lilac (52 wks)
Trofinetide	-7.3
	n/a
Trofinetide	-7.0

RSBQ scores improved **≥7 points** from Lavender baseline

CGI-I

Lavender Baseline

Dose Group	CGI-I Score (at 12 wks)
Trofinetide	3.5
Placebo	3.8

New Lilac Baseline

Dose Group	CGI-I Score (at 40 wks)
Trofinetide	3.1
	n/a
Trofinetide	3.2

CGI-I improvements:
- ❖ Trofinetide group: 0.5 improvement in Lavender, then 0.9 improvement in Lilac
- ❖ Trofinetide crossovers: 0.8 improvement 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.

Consistent safety and tolerability findings

LAVENDER (12 weeks) Placebo-controlled

	Adverse Events (AEs) >10% observed in Trofinetide group
Diarrhea	80.7% (97% Mild and Moderate)
Vomiting	27.0% (96% Mild and Moderate)

LILAC (40 weeks) Open-label extension

	Adverse Events (AEs) >10% observed in Lilac
Diarrhea	74.7% (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

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

Trofinetide North America Economics for Neuren

Rett Syndrome only

✓	**US$10m**	**in 2022 following acceptance of NDA for review**
✓	**US$40m**	following 1st commercial sale in the US
	US$33m	one third share of Priority Review Voucher awarded to Acadia (assuming market value US$100m)

Aggregate of all indications

Tiered Royalty Rates (% of net sales)[3]

Annual Net Sales	Rates
≤US$250m	10%
>US$250m, ≤US$500m	12%
>US$500m, ≤US$750m	14%
>US$750m	15%

Sales Milestones

Net Sales in one calendar year	US$m
≥US$250m	50
≥US$500m	50
≥US$750m	100
≥US$1bn	150

Rett Syndrome Patients	US
Potential[1]	10,000
Currently identified	4,500

US annual average net realized cost of DAYBUE expected to be ~US$375,000[2]

Orphan exclusivity to 2030, patents to 2040

Example calculations of royalty/sales milestones

Annual Net Sales in NA	Annual Royalty	Total Sales Milestones Earned
US$500m	US$55m	US$100m
US$750m	US$90m	US$200m
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

Trofinetide ex North America

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

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

5x larger opportunity for NNZ-2591

Disorder	Gene mutation	Published prevalence estimates	Potential patients		
			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 opportunity[3]
- 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

Clear and consistent efficacy in animal models

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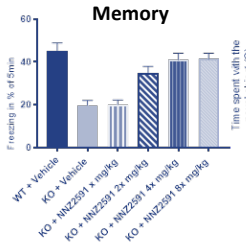
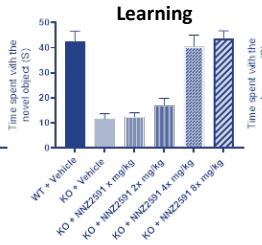
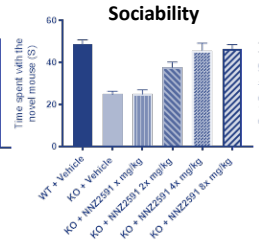
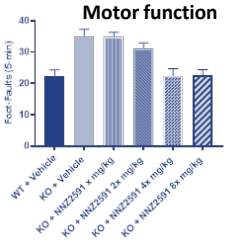
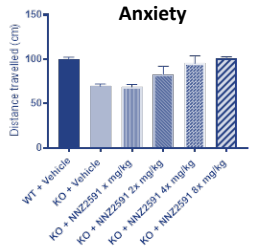
Phelan-McDermid

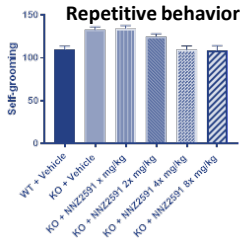


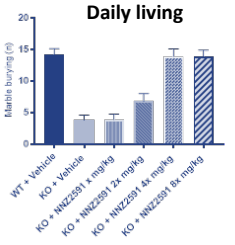


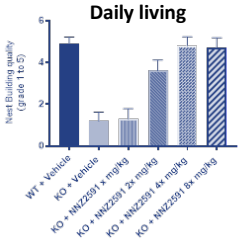








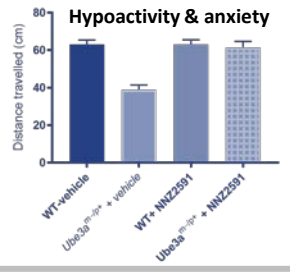


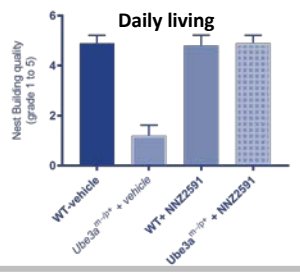


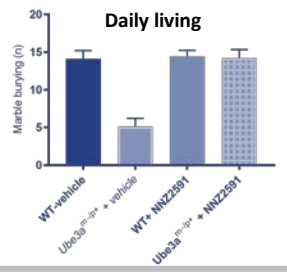
Incidence of seizures

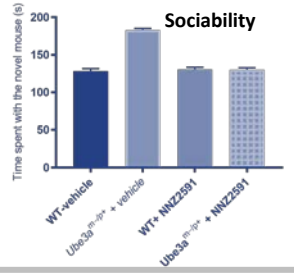
WT + vehicle	0%
KO + vehicle	60%
KO + x mg/kg	50%
KO + 2x mg/kg	30%
KO + 4x mg/kg	10%
KO + 8x mg/kg	10%

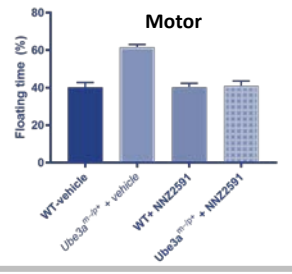
Angelman

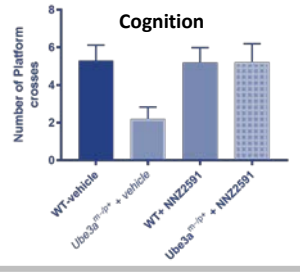




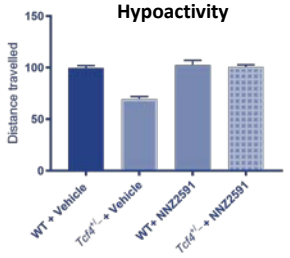


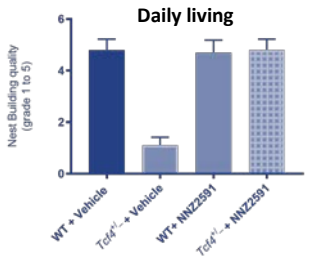


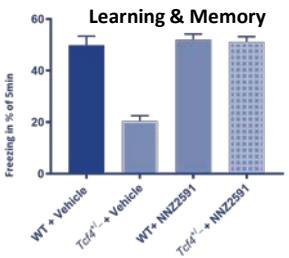


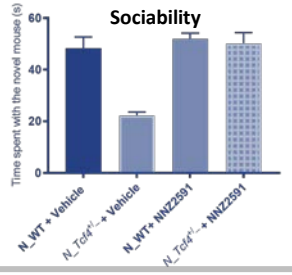


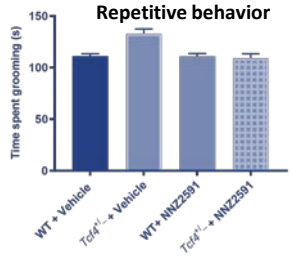
Pitt Hopkins

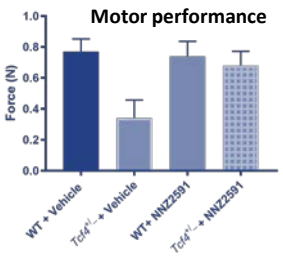




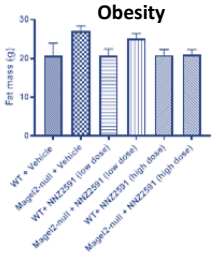


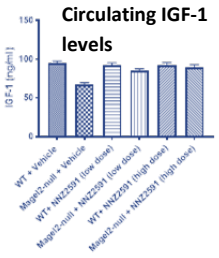


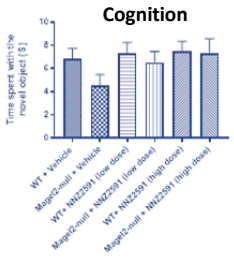


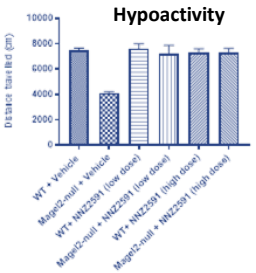


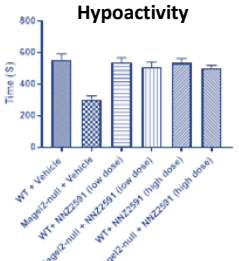
Prader-Willi

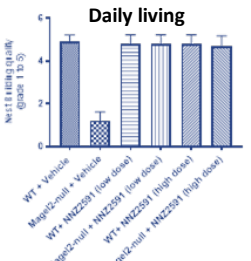


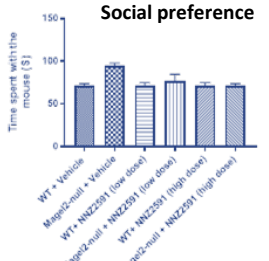


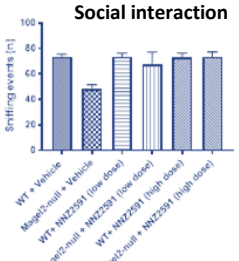


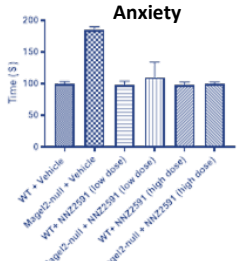






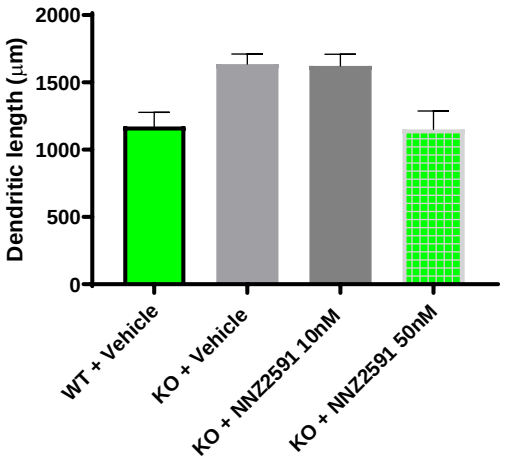


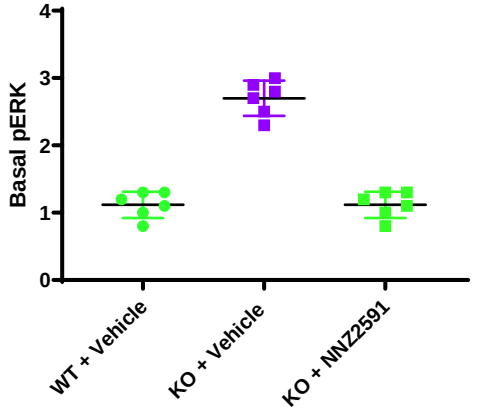


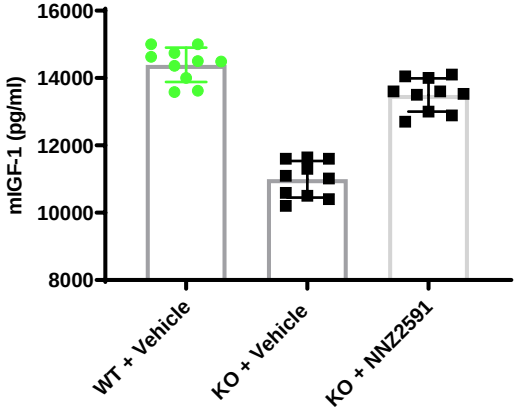


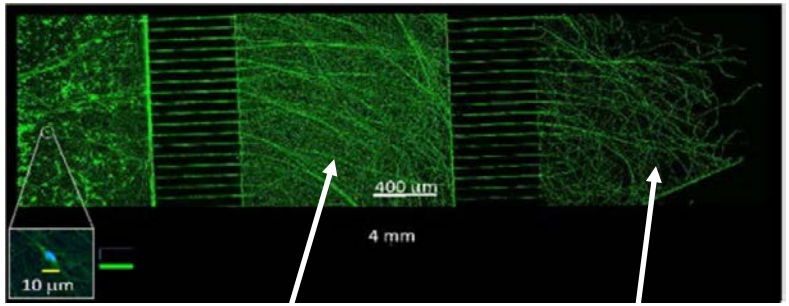
Biochemical effects confirmed

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









Abnormal dendrites in shank3 knockout mice

Normalisation after treatment with NNZ-2591

NNZ-2591 has ideal attributes leading into Phase 2

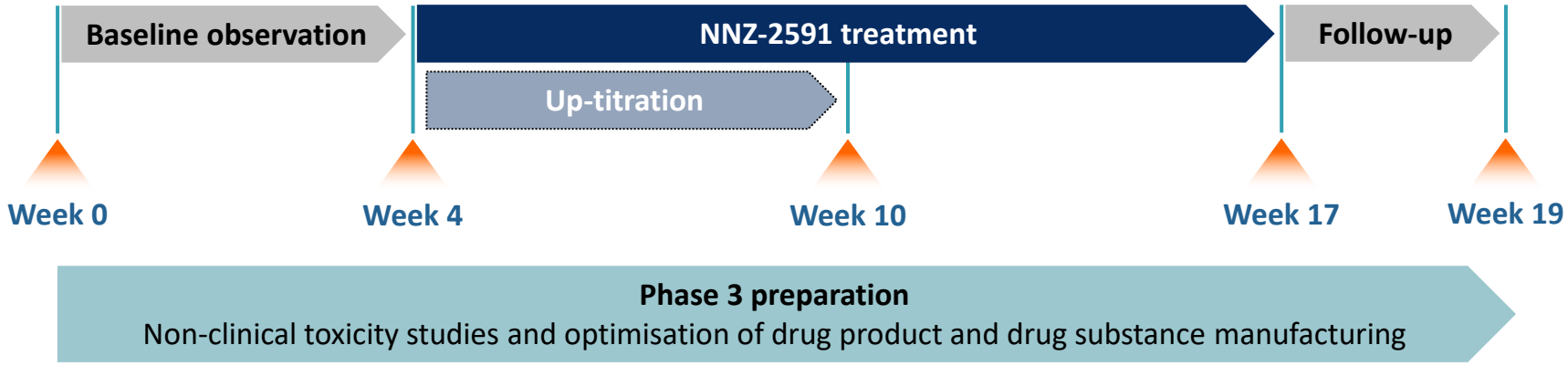
- ✓ Novel mechanism of action
- ✓ Clear and consistent efficacy in mouse models of each syndrome
- ✓ Biochemical effects in the brain confirmed
- ✓ Optimum dose identified
- ✓ Demonstrated high oral bioavailability and blood-brain barrier penetration
- ✓ IND-enabling program of non-clinical toxicology 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

Key features of first Phase 2 trials

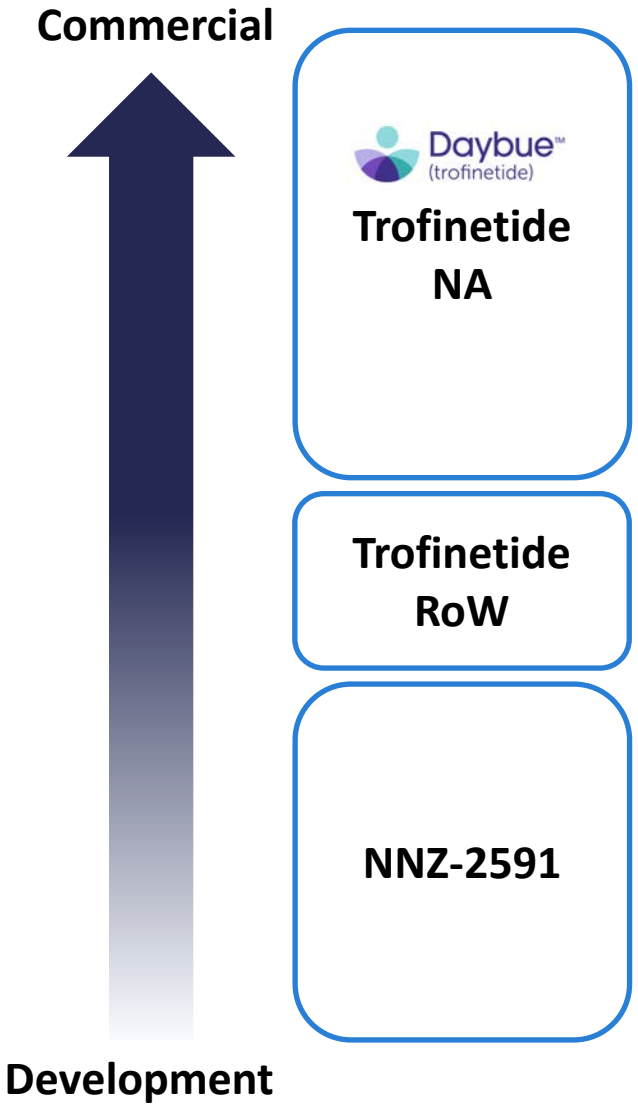
Overall aim – expedite data that enables subsequent trials to be designed as registration trials and prepare for Phase 3 in parallel

- 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 Q4 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 enrolment in three age groups following DSMC review)		
Location	Australia	US	US



Transforming catalysts in 2023



- ✓ DAYBUE for Rett syndrome approved by FDA
- ✓ Priority Review Voucher awarded to Acadia
- ✓ First US commercial sale - US$40m milestone payment
- ❖ Quarterly royalties on net sales
- ❖ Priority Review Voucher value one third share – estimated as US$33m
- ❖ Commercial partnerships ex-North America for Rett syndrome
- ❖ Initiate Prader-Willi syndrome Phase 2 trial
- ❖ Complete enrolment in Phelan-McDermid, Pitt Hopkins and Angelman syndrome Phase 2 trials
- ❖ Phase 2 trial results, commencing with Phelan-McDermid syndrome

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