Neurotech International Ltd

NTI.AX

MST Access
A research platform of MST Financial

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Positive data & commercial pathway NTI the next approved Cannabinoid?

Positive trial data in neuroinflammatory disorders,

Rational, phased strategy to launch approved therapy

- **Large neurological syndrome markets with unmet need**
- **Precedent is cannabinoid 'Epidiolex' now at >US$1b sales**
- **Trial data positive to date; sensible launch Aust 1st; then USA**

Investment Thesis

Neurotech International (ASX: NTI) is focused on treating rare paediatric neuroinflammatory disorders with attainable TAM of >A$12b across: (1) Autism Spectrum Disorder (ASD) (2) Rett Syndrome (3) Cerebral Palsy (CP) and (4) Paediatric Autoimmune Neuropsychiatric Disorders (PANDAS) / Paediatric Acute-onset Neuropsychiatric Syndrome (PANS).

Its primary drug 'NTI164' is a cannabis-derived therapy. Australian Ph2/3 clinical trial data in ASD at 12wks has shown a 56% improvement from baseline on a standard scale used to rate severity of illness. The common pathological factor underlying each of NTI's target syndromes is neuroinflammation. If NTI164 can demonstrate efficacy and safety in one indication it supports the prospect of a cascade of success in others.

Clinicians, patients & regulators are calling for full clinical trial-proven cannabinoid drugs – as distinguished from risky untested whole medicinal cannabis to provide certainty of outcomes for patients. Regulators have also acted to de-schedule medical cannabis with low THC.

NTI's approval strategy looks to parallel the pathway of 'Epidiolex' the first & only US FDA-approved cannabinoid drug, with sales now approaching >US$1b in epilepsy.

NTI has a two-stage launch strategy for Australia & ROW, using a 'Cash flow light' approach. Management describes themselves as "balance sheet aware. Commercialisation in Australia will help fund the clinical trials alongside a likely partnership to conduct full US trials. MST expects commercialisation in the US in late FY29.

Valuation & Risks

MST values NTI at A$0.60ps using an NPV on future earnings (current share price of A$0.07ps). Further details on valuation methodology and assumptions at page 56.

Key Assumptions: (1) FCF generating by FY29 2yrs post Australian launch; market penetration a subset of attainable TAM of >$12b. **(2)** Proforma cash balance of A$13.6m, qtrly cash burn ~$1.7m, implies a runway of ~8 qtrs of cash. **(3)** MST assumes NTI will raise capital in the future.

Key Risks: (1) Investment case for NTI hinges on successful clinical trials for NTI164, reimbursement & adoption. **(2)** Medicinal cannabis carries risk of positive & negative regulatory change, often moving at slow pace. **(3)** Further details on risk can be found in the Valuation and Risks section of this report.

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Neurotech International

Neurotech International Limited (NTI) is a clinical-stage biopharmaceutical development company focused predominantly on paediatric neurological disorders. It engages in the development and commercialisation of innovative neurological therapies that improve quality of life. The Group is dedicated to advancing research, developing innovative treatments, and providing compassionate care to improve the lives of children affected by neurological disorders.

Valuation	**A$0.60**
Current price	**A$0.07**
Market cap	**A$76.3m**
Cash on hand	**A$11.6m**

Upcoming Catalysts / Next News

Period	
2HCY24	Commence PhI/II CP Clinical Trial
1HCY25	IND approval in US/EMA
2HCY25	TGA provisional reg submission

Share Price (A$)

Source: FactSet, MST Access

Contents

Figure 1: Neurotech International Ltd (ASX: NTI): Financial Summary

Year end Dec	Units	FY22	FY23	FY24E	FY25E	FY26E
PE	**x**	**nm**	**-7.5**	**-14.7**	**-12.7**	**-12.6**
EV/EBITDA	x	nm	-8.3	-14.6	-10.8	-10.0
EV/EBIT	x	nm	-8.3	-14.6	-10.8	-10.0
Div yield	%	0.0%	0.0%	0.0%	0.0%	0.0%
FCF yield	%	-3.9%	-8.3%	-6.1%	-7.9%	-8.5%

Stock information	
Ticker	**NTI.AX**
Share Price ($)	0.07
Target price ($)	0.60
Enterprise value (A$m)	65
Market capitalisation (A$m)	76

Income statement	Units	FY22	FY23	FY24E	FY25E	FY26E	1H23	2H23	1H24	2H24E	1H25E	2H25E
Revenue (Incl other income)	**A$m**	**0.6**	**1.3**	**3.2**	**2.3**	**2.5**	**1.2**	**0.1**	**3.2**	**0.0**	**2.3**	**0.0**
growth y/y	%	*0.0%*	*106.2%*	*155.9%*	*-28.2%*	*10.0%*	*502.5%*	*-86.9%*	*167.5%*	*nm*	*-28.2%*	*nm*
EBITDA	**A$m**	**-3.4**	**-7.8**	**-4.4**	**-6.0**	**-6.5**	**-3.5**	**-4.3**	**-0.7**	**-3.7**	**-1.9**	**-4.1**
EBITDA margin	%	*-552.6%*	*-621.2%*	*-138.2%*	*-260.2%*	*-255.6%*	*-294.7%*	*-7923.7%*	*-22.7%*	*nm*	*-84.4%*	*nm*
EBIT	**A$m**	**-3.4**	**-7.8**	**-4.4**	**-6.0**	**-6.5**	**-3.5**	**-4.3**	**-0.7**	**-3.7**	**-1.9**	**-4.1**
EBIT margin	%	*-552.7%*	*-621.3%*	*-138.2%*	*-260.2%*	*-255.6%*	*-294.8%*	*-7925.9%*	*-22.7%*	*nm*	*-84.4%*	*nm*
PBT	**A$m**	**-3.4**	**-7.8**	**-4.4**	**-6.0**	**-6.5**	**-3.5**	**-4.3**	**-0.7**	**-3.7**	**-1.9**	**-4.1**
PBT margin	%	*-552.9%*	*-621.3%*	*-138.2%*	*-260.2%*	*-255.6%*	*-294.8%*	*-7925.9%*	*-22.7%*	*nm*	*-84.4%*	*nm*
NPAT	**A$m**	**-3.4**	**-7.8**	**-4.4**	**-6.0**	**-6.5**	**-3.5**	**-4.3**	**-0.7**	**-3.7**	**-1.9**	**-4.1**
NPAT margin	%	*-552.9%*	*-621.3%*	*-138.2%*	*-260.2%*	*-255.6%*	*-294.8%*	*-7925.9%*	*-22.7%*	*nm*	*-84.4%*	*nm*
Reported NPAT	**A$m**	**-3.3**	**-7.8**	**-4.4**	**-6.0**	**-6.5**	**-3.5**	**-4.3**	**-0.7**	**-3.7**	**-1.9**	**-4.1**
Reported NPAT margin	%	*-548.7%*	*-622.2%*	*-138.3%*	*-260.3%*	*-255.6%*	*-295.6%*	*-7927.7%*	*-22.7%*	*nm*	*-84.4%*	*nm*

Per share data	Units	FY22	FY23	FY24E	FY25E	FY26E	1H23	2H23	1H24	2H24E	1H25E	2H25E
Average diluted shares	m	697	799	893	1,044	1,114	736.6	861.0	876.8	931.8	1,044.3	1,101.8
EPS	**cps**	**-0.5**	**-1.0**	**-0.5**	**-0.6**	**-0.6**	**-0.5**	**-0.5**	**-0.1**	**-0.4**	**-0.2**	**-0.4**
growth y/y	%	*nm*	*nm*	*-49.1%*	*15.6%*	*1.3%*	*0.0%*	*0.0%*	*0.0%*	*-19.5%*	*124.0%*	*-7.6%*
Reported EPS	**cps**	**-0.5**	**-1.0**	**-0.5**	**-0.6**	**-0.6**	**-0.5**	**-0.5**	**-0.1**	**-0.4**	**-0.2**	**-0.4**
growth y/y	%	*nm*	*nm*	*-49.1%*	*15.5%*	*1.3%*	*0.0%*	*0.0%*	*0.0%*	*-16.4%*	*123.9%*	*-6.2%*
DPS	**cps**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**
Payout ratio	%	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*

Balance sheet	Units	FY22	FY23	FY24E	FY25E	FY26E
Cash	A$m	2	5	12	17	11
Trade receivables	A$m	0	0	0	0	0
Inventories	A$m	0	0	0	0	0
Property, plant & equipment	A$m	0	0	0	0	0
Right-of-use assets	A$m	0	0	0	0	0
Goodwill	A$m	0	0	0	0	0
Intangibles	A$m	0	0	0	0	0
Other assets	A$m	0	0	0	0	0
Total assets	**A$m**	**2**	**5**	**12**	**18**	**11**
Trade payables	A$m	1	1	0	0	0
Provisions	A$m	0	0	0	0	0
Borrowings	A$m	0	0	0	0	0
Lease liabilities	A$m	0	0	0	0	0
Other liabilities	A$m	0	0	0	0	0
Total liabilities	**A$m**	**1**	**1**	**0**	**0**	**0**
Total equity	**A$m**	**1**	**4**	**12**	**18**	**11**
Invested capital	A$m	0	-1	0	0	0
Net debt (pos)	**A$m**	**-2**	**-5**	**-12**	**-17**	**-11**

Performance metrics	FY23	FY24E	FY25E	FY26E
ROE (%)	-393%	-56%	-41%	-45%
ROIC (%)	nm	1342%	-1489%	-1611%
Gearing (%)	472%	-2874%	-4250%	-2644%
Adj ND / EBITDA (x)	0.3	1.3	1.4	0.8
NWC (A$m)	-1	0	0	0
NWC % of sales (%)	-86%	0%	0%	0%
Gross OCF / EBITDA (%)	81%	105%	100%	100%
Capex / sales (%)	0.0%	0.0%	0.0%	0.0%
P/FCF (x)	-12.1	-16.4	-12.7	-11.8
P/BV (x)	19.3	6.4	4.4	6.9

Cash flow statement	Units	FY22	FY23	FY24E	FY25E	FY26E
EBITDA	A$m	-3	-8	-4	-6	-6
Change in NWC	A$m	0	1	-1	0	0
Other	A$m	0	1	1	0	0
Gross operating cash flow	A$m	-3	-6	-5	-6	-6
Net interest	A$m	0	0	0	0	0
Tax paid	A$m	0	0	0	0	0
Operating cash flow	**A$m**	**-3**	**-6**	**-5**	**-6**	**-6**
Capital expenditure	A$m	0	0	0	0	0
Acquisitions	A$m	0	0	0	0	0
Asset sales	A$m	0	0	0	0	0
Other	A$m	0	0	0	0	0
Investing cash flow	**A$m**	**0**	**0**	**0**	**0**	**0**
Net borrowings	A$m	0	0	0	0	0
Dividends paid	A$m	0	0	0	0	0
New shares issued / other	A$m	0	9	11	12	0
Financing cash flow	**A$m**	**0**	**9**	**11**	**12**	**0**
Net change in cash	**A$m**	**-3**	**3**	**7**	**6**	**-6**
Free cash flow	**A$m**	**-3**	**-6**	**-5**	**-6**	**-6**

Source: MSTe

Investment Thesis

Neurotech International (ASX: NTI) is an Australian-listed biopharmaceutical company focused on treating rare paediatric neurological disorders. Its primary drug 'NTI164' is a cannabis-derived therapy being developed for four indications.

Background - What is NTI164?

NTI164 is an Australian-grown medicinal cannabis-derived broad-spectrum oil-based biopharmaceutical that offers the benefits of medicinal cannabis without the psychoactive effects of high levels of tetrahydrocannabinol (THC). The drug uses a unique combination of cannabinoids with high levels of cannabidiolic acid (CBDA) and minor cannabinoids including cannabidiol (CBD), cannabigerol (CBG), cannabidiophenol (CBDP) and cannabinol (CBN). THC levels are below 1%, making NTI164 suitable for children.

Investment Case

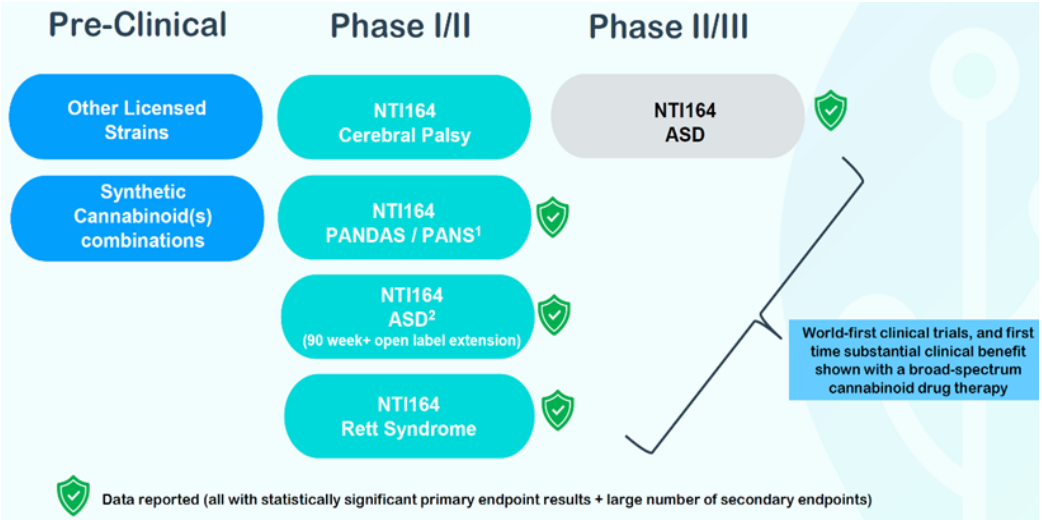
Growing medicinal cannabis regulation - There is a global trend toward legalisation of cannabis, including for medicinal use. This has led to a call for clarity and regulation to allow clinicians and patients to understand and differentiate cannabinoid formulations with proven clinical outcomes. NTI164 is a cannabinoid extract seeking to distinguish itself as a fully approved medicinal cannabis-derived therapy.

Targeting untreated neurological diseases with a large addressable market - NTI is targeting four neurological indications for which limited therapeutic options exist.

1. Autism Spectrum Disorder (ASD)
2. Rett Syndrome (RS)
3. Cerebral Palsy (CP)
4. Paediatric Acute-onset Neuropsychiatric Disorders (PANS) / Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS)

There is urgency in the market for regulation of medicinal cannabis.

Figure 2: NTI164 clinical pipeline



Source: MSTe, NTI

NTI will seek to establish if NTI164 lowers neuroinflammation and therefore treats the underlying pathology and symptoms of these neurological diseases.

Precedent is relevant - MST's investment thesis compares and tracks NTI with GW Pharmaceuticals' Epidiolex. The latter remains the first and only US FDA approved cannabis-derived drug. GW Pharma was acquired by Jazz Pharma for US$7.2b (13.7x revenue multiple). At the time of acquisition, Epidiolex generated revenue of $510.5m (~97% of the firm's revenue) and had received approval in 3 different seizure indications. Epidiolex is still generating exceptional revenue and Jazz Pharma believes Epidiolex will generate >US$1b in revenue in CY25.

MST notes five key aspects underpinning Epidiolex's success prior to its acquisition:

1. **Clinical trials -** >700 patients studied across four Ph3 randomised, double-blind, placebo-controlled clinical trials including one published in the esteemed Lancet journal
2. **Efficacy -** 44% & 41% reduction in drop seizures and total seizures (vs 22% and 14% in placebo)
3. **Safety -** No significant increase in adverse events vs placebo
4. **Indications -** Received US FDA approval in 3 different forms of seizures and EMA in two forms.
5. **Commercialisation -** Successful commercial launch with revenue hitting US$510.5m within ~5yrs on market.

NTI has a two-stage launch strategy for Australia & ROW, using a '**Cash flow light'** approach:

1. **FY27 target for Australian launch**: Clinical trials are being conducted solely in Australia and are low-cost NTI-sponsored "proof of concept" trials conducted by three paediatric neurologists, with launch support also in place. Australian market launch in FY27 will be a precedent for commercial launch globally.
2. **US & Global to Follow by late FY29**: Successful Aust launch likely sets up opportunities for US royalty deal (similar to Aust pharmaceutical company NEU and Acadia for Daybue); with partners to fund trials and commercialisation. NTI has recently signed with contract research organisation (CRO) 'Fenix' to work on increasing manufacturing capabilities to satisfy future demand.

Medicinal Cannabis vs NTI164

The US FDA has not approved medicinal cannabis for the treatment of any disease or condition. However, certain cannabinoids are approved for therapeutic use. Cannabinoids are naturally occurring chemicals found in the cannabis plant. The US FDA says there are >80 naturally occurring found in cannabis. Cannabinoids are also found naturally in the human body as part of the endocannabinoid system, where they act as messengers sending signals to the brain, gut, or other parts of the nervous system to help regulate basic bodily functions. NTI164 differentiates itself from medical cannabinoids with CBDA as the major constituent cannabinoid and is seeking to validate its legitimacy vs nutraceutical cannabis claims by conducting clinical trials.

How does it work?

NTI164 is a unique combination of cannabinoids that provides anti-inflammatory effects with several modes of action: (1) Neuro-protection (2) Neuro-modulation and (3) Neuro-regulation.

Current data to date has reportedly shown children dosed with NTI164 daily experienced marked improvement with socialisation, attendance at school, and classroom behaviour. These children also experienced improvement to their levels of anxiety, irritability and hyperactivity. NTI164 also demonstrated excellent safety and efficacy results and was shown to be well-tolerated, with only 1 serious adverse event over 2 years across 94 patient and all doses.

Dosing – small quantities offer a therapeutic outcome

Current clinical trials to date have with dose escalation of 5, 10, 15 and 20 mg/kg over 52 weeks, to establish tolerance which averaged ~13-15mg/kg. Assuming an average child weight of ~50kg, the clinically administered daily doses are equivalent to ~250mg, ~500mg, ~750mg and 1g/day,

Sensible launch phasing. Big growth opportunity, back-end loaded – Management describes themselves as "balance sheet aware" and are aiming to both prove the model and be cash flow positive in the Australian market first. Commercialisation in Australia will help fund the clinical trials necessary to enter the US market. MST expects commercialisation in the US in late FY29. NTI's 'peak earnings' opportunity will come from the US market which has a larger and more lucrative patient pool (US attainable TAM of >US$4b).

TAM / Business case: MSTe global attainable TAM is >A$12b for all four indications

NTI's target syndromes represent a large total addressable market (TAM) with few therapeutic options.

Figure 3: MSTe - NTI Total Addressable Market is >A$12b

Condition	#MSTe TAM (A$)	Global Prevalence (Patients)	Competitive landscape
Autism Spectrum Disorder (ASD)	Globally: $7.2b	Global: 27m	Two US FDA approved drugs: (1) Risperdal (2) Abilify. used to manage symptoms of aggression & irritability. All therapies (including NTI164) only address symptoms.
Rett Syndrome (RS)	Globally: $136m	Global: 40-55k	One US FDA approved drug: Daybue. >30% of US Rett Syndrome patients have tried Daybue.
Cerebral Palsy (CP)	Globally: $5.1b	Global: 17.3m	Two US FDA approved drugs for Spastic Cerebral Palsy: (1) Baclofen (2) Botox.
Paediatric Acute-onset Neuropsychiatric Disorders Associated with Streptococcus (PANS) / Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS)	Globally: $149m	Global: 182k	No US FDA OR EU EMA approved products. Intravenous immunoglobins (IVIG) is used off label in some cases.
Total	**Globally: $12.6b**	**Global: 46.4m**	

*Source: MSTe, NTI, NEU. Note: *TAM = Total Addressable Market. #MSTe TAM is estimate of attainable market penetration, a sub-segment of materially higher TAM.*

Big growth opportunity that is back-end loaded – NTI is targeting a large unaddressed global total addressable market of >A$12b (MSTe attainable) across four neurological indications. NTI is still undergoing clinical trials and MST expects commercialisation to begin in Australia in FY27. Commercialisation in Australia will help fund and refine the clinical trials necessary to enter the US market. MST expects NTI will begin commercialising its first indication in the US in late FY29. Most of NTI's earnings opportunity will come from the US markets which has a larger patient pool.

Expect value to be realised in stages – Australian market launch in FY27 will be a precedent for commercial launch elsewhere globally.

Trial process / endpoints

Australian clinical trials and results to date are shown in the figure below.

Figure 4: NTI164 clinical trial pipeline

Condition	Stage of clinical trial	Results to date
ASD	Ph1/2 (complete) & Ph2/3	Ph 2/3 showed a 56% improvement from baseline (Day 0) to week 12 for NTI164 vs placebo, noting results showed 36% improvement from week 8 to week 12.
Rett Syndrome	Ph1/2	Ph1/2 showed 93% of patients improved with 36% "very much/much improved" at 12wks
CP	Ph1/2	Schedule to begin in late CY24.
PANS/PANDAS	Ph1/2	Ph1/2 showed 32-45% improvement vs baseline at 52 wks

*Source: MSTe, NTI, NEU. Note: *TAM = Total Addressable Market*

Key Pivotal events / dates / catalysts

- **Ongoing** - Journal publication of ASD Ph1/2 + pre-clinical trial
- **Ongoing** - Release of open-label extension data for ASD, PANS/PANDAS, Rett Syndrome
- **2QCY24** - Aust Therapeutic Goods Administration (TGA) Regulatory Advice re PANDAS/PANS
- **3QCY24** - Update on clinical, regulatory and strategy development
- **2HCY24 -** Commence Phase I/II Cerebral Palsy Clinical Trial
- **2HCY24 -** Orphan drug designation in numerous markets

Valuation & Risks

MST values NTI at A$0.60ps using an NPV on future earnings (current share price of A$0.08ps). Further details on valuation methodology and assumptions at page 54.

Key assumptions

Current cash burn & FCF outlook

- FCF generating by FY29 2yrs post Australian launch; using market penetration at a subset of TAM
- proforma cash balance of A$13.6m, qrtrly cash burn ~$1.7m, implies a runway of ~8 qtrs of cash.
- MST assumes NTI will raise capital in the future

Key Risks

- Investment case for NTI hinges on successful clinical trials for NTI164, reimbursement & adoption.
- Medicinal cannabis carries risk of positive & negative regulatory change, often moving at slow pace.
- Further detail on risks can be found in competition and risks in the Risk section of this report.

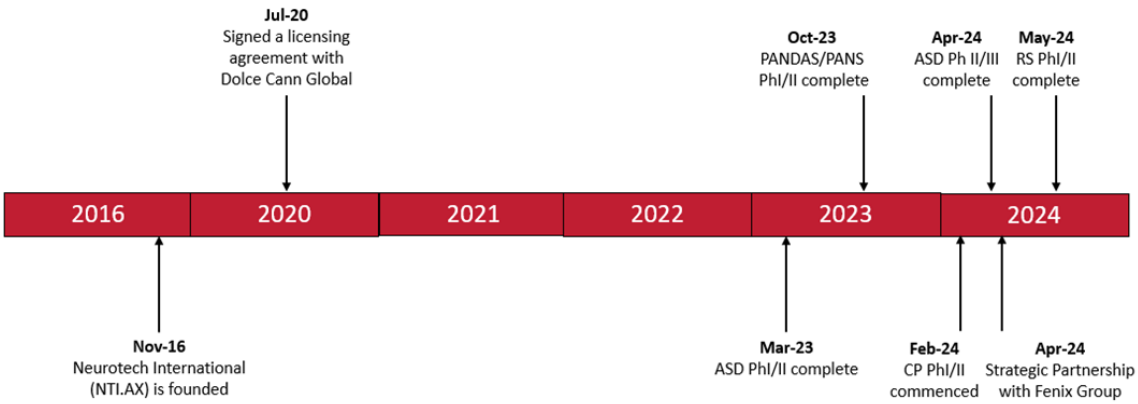
Introduction: Neurotech

Neurotech International (ASX: NTI) is an Australian-listed biopharmaceutical company focused on treating rare paediatric neurological disorders. Its primary drug 'NTI164' is a cannabis-derived therapy targeting four neurological indications with clinical trials.

Background - Old technology gone & New focus in place

NTI initially listed in 2016 as a medical device company focused on commercialising its Mente Autism device, which was a portable electroencephalographic (EEG) medical device intended to treat Autism Spectrum Disorder (ASD). In Jul-20, NTI reorientated its focus and signed a global licensing deal for Dolce Cann's proprietary cannabis strains and shifted focus to its current therapeutic candidate NTI164.

Figure 5: Historical timeline of NTI164



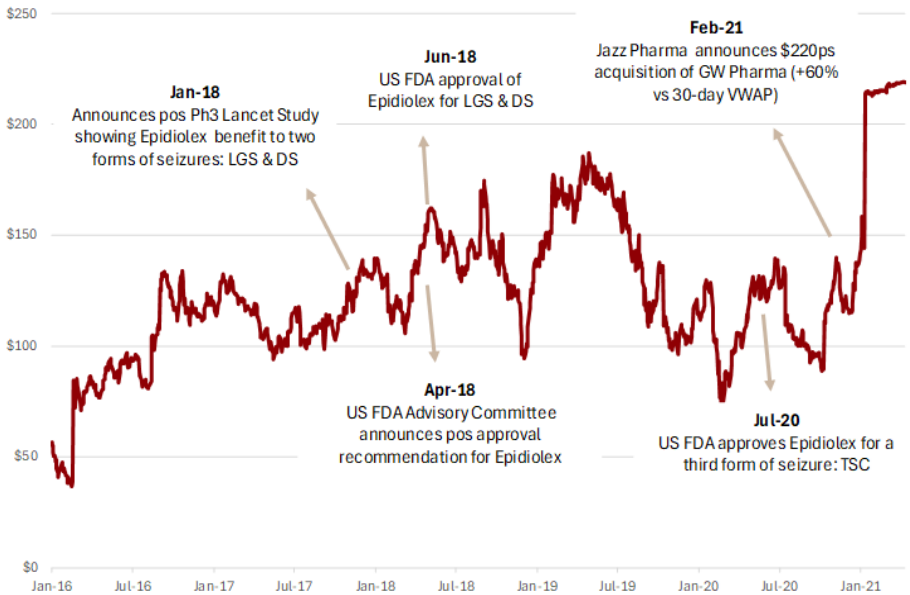
Source: MSTe, NTI, NEU

Epidiolex pathway - Template for Success

We profiled Epidiolex as the only US FDA approved cannabis-derived drug. NTI could parallel Epidiolex's pathway to success

MST's investment thesis references GW Pharmaceuticals' Epidiolex which became the first and remains the only US FDA approved cannabis-derived drug. GW Pharma was acquired by Jazz Pharma for US$7.2b (13.7x revenue multiple). At the time of acquisition, Epidiolex generated +70% vs pcp revenue of $510.5m (~97% of the firm's revenue) and had received approval in 3 different seizure indications. Epidiolex was only in the US market for ~2.5yrs and began multiple ex-US launches.

Figure 6: GW Pharma Share Price – Acquired by Jazz Pharma for US$7.2b (13.7x revenue)



Source: Source: MST, GW Pharma. Note: US FDA approvals: Lennox-Gastaut Syndrome (LGS), Dravet Syndrome (DS) & Tuberous Sclerosis Complex (TSC)

In order to receive US FDA approval, GW Pharma studied Epidiolex in >700 patients across four randomised, double-blind, placebo-controlled clinical trials. Epidiolex was shown in conjunction with other anti-epilepsy drugs (AEDs) to significantly reduce the number of seizures patients experienced compared to placebo even in those patients who were resistant to standard-of-care AEDs.

An understanding of the regulatory benchmarks set and licensing revenue generated by Epidiolex provides some indication of the requirements and market potential for NTI164. NTI's management aspires to model the pathway that Epidiolex took to market as a blueprint for NTI164 success. GW Pharma expects to generate >US$1b in annualised revenue in CY25. MST views Epidiolex's success as a benchmark for NTI164 and demonstrates "it can be done" even in neurological conditions such as seizures.

What is NTI164?

NTI164 is an Australian-grown medicinal cannabis (Sativa L)-derived biopharmaceutical that offers the benefits of medicinal cannabis without the psychoactive effects of Tetrahydrocannabinol (THC). The drug uses a unique combination of cannabinoids with high levels of cannabidiolic acid (CBDA) and minor cannabinoids including cannabidiol (CBD), cannabigerol (CBG), cannabidiophenol (CBDP) and cannabinol (CBN). THC levels are below 0.1%, making NTI164 suitable for children.

The unique combination of cannabinoids reportedly provides anti-inflammatory effects through several modes of action: (1) Neuro-protection (2) Neuro-modulation and (3) Neuro-regulation.

In-vitro evidence suggests that the anti-inflammatory effect of NTI-164 may be due to the synergistic interaction of the compounds in the cannabis extract having an "entourage effect" with positive outcomes for microglial cells and the proliferation of neural progenitors, promoting the survival of neurons under a cytotoxic state. In contrast, pure cannabidiol (CBD, a major cannabinoid) used as a control had shown a limited effect. The translational relevance of these findings needs to be further explored using appropriate in-vivo models.

How is NTI164 manufactured?

NTI164 is a cannabinoid oil extract derived from the cannabis plant and is manufactured across multiple licensed sites in Australia. The solvent used to extract NTI164 is Cobram olive oil (high in fatty acids).

The manufacturing cycle from cannabis seed to the final product takes a total of 14wks and can occur across all seasons. Once the cannabis extract reaches the manufacturing site, it is a 7-step process that takes 2-5hrs to form NTI164.

NTI has signed an agreement with Fenix International Group (a Melbourne-based Contract research organisation [CRO]), a Good Agricultural and Collection Practices (GACP) certified company, to capable of manufacturing the 120 litres of NTI164 required by ongoing clinical trials. Fenix can upscale for commercial production. To put manufacturing in perspective, the daily dose for a 50kg child is ~1g/day.

Dolce Cann has developed proprietary cannabis genetics from 13 rare chemovars. These strains have been selectively developed over 20 years to enhance their phytochemical content, including cannabinoids like CBG, CBC, CBN, and CBDV, which have potential therapeutic benefits for neurological disorders. A notable feature of Dolce Cann's strains is their low THC content (less than 0.3%), minimizing psychoactive effects and making them suitable for use in children.

NTI164 offers a unique combination of cannabinoids

Unlike other cannabinoids, there are several reasons NTI164 stands out:

- **Composition** - The importance of the NTI164 composition is that it contains a combination of 7 cannabinoids (Major constituent: CBDA. Minor Constituents: CBC, CBDP, CBDB, CBN) and <0.1% of THC extracted from a single cannabis chemovar.
- **Entourage effect** - NTI claim that each cannabinoid in NTI164 impacts a unique endocannabinoid pathway with an "entourage effect of anti-inflammation".
- **CBDA potency** - The primary cannabinoid present in NTI164 is CBDA which is the precursor to CBD. It is theorised that the presence of CBDA may lead to higher potency of CBD. The ratio of how much CBDA is metabolized into CBD has not been determined.
- **Genetic expression** - NTI is currently identifying biomarkers that show NTI164 impacts gene expression and reduces inflammation. They want to be the first broad-spectrum cannabis pharmaceutical company to identify a relevant biomarker.

Figure 7: Difference between NTI194 and pure CBD/THC.

NTI164	Pure CBD/THC
High Cannabidiolic acid (CBDA)	No CBDA
Rarer cannabinoids: CBD, CBDP, CBDB, CBN, CBG	No rare cannabinoids
Naturally <0.3% THC	Not a full plant extract
Patent applications submitted	No patent protection

Source: NTI. Notes: Rare cannabinoids are cannabinoids found in smaller quantities in the cannabis plant compared to the more well-known cannabinoids like THC and CBD. These rare cannabinoids are gaining attention for their unique properties and potential health benefits.

Broad-spectrum vs Full-spectrum

NTI164 is a "broad-spectrum" cannabinoid product. Broad-spectrum cannabis products contain cannabidiol and other compounds within the plant. Broad-spectrum products are a potential option for patients who cannot have any traces of THC in their system. This is in contrast to a "full-spectrum" cannabis extract which contains all phytochemicals naturally found in the plant. Broad and full spectrum products may contain active compounds that can work together to enhance or amplify the benefits of individual cannabinoids.

Route of administration

NTI164 is administered orally as an oil formulation. Oil has become a popular route of administration for many medical users, especially among paediatric patients. This is because oil extracts allow the intake of a large dose of cannabinoids in an easily ingestible form.

Currently, the market is developing more sophisticated products, including oral gel caps, sublingual sprays, skin creams, and bottled CBD chewing gums containing CBD.

Target disorder/syndrome targets

NTI's pipeline features the use of NTI164 for four neurological diseases. NTI is also working on preclinical development for other licensed strains as well as the possibility of using NTI164 in combination with corticosteroids to lower inflammation in the nervous system.

The four indications in the pipeline for NTI164 are:

1. **Autism Spectrum Disorder (ASD)** - Neurological and developmental disorder that impacts a person's ability to socially interact, communicate, learn, and behave. NTI164 has completed a Ph2/3 and an ongoing Ph1/2 open-label trial in ASD (now exceeds 2yrs).
2. **Rett Syndrome** - A progressive X-linked chromosomal disorder that is associated with severe neurological disability. NTI164 has completed a Ph1/2 trial in Rett Syndrome.
3. **Cerebral Palsy** - Neurological disorder that impacts movement and posture. NTI164 has approval to commence a Ph1/2 trial in Cerebral Palsy, which is planned for 2HCY24.
4. **Paediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS)/ Pediatric Acute-onset Neuropsychiatric Disorders Associated with Streptococcus (PANS)** - A condition in which a streptococcus infection causes a sudden-onset of obsessive-compulsive disorder (OCD) and/or tic disorders in children. NTI164 has completed a Ph1/2 trial in PANDAS/PANS.

NTI's target syndromes represent a large total addressable market (TAM) with few therapeutic options.

Figure 8: NTI Total Addressable Market is >A$12b

Condition	#MSTe TAM (A$)	Prevalence (Patients)	Competitive landscape
Autism Spectrum Disorder (ASD)	Globally: $7.2b US: $3b EU: $816m ROW: $2.9b Aust: $427m	Global: 27m US: 2m EU: 680k ROW: 24m Aust: 178k	Two US FDA approved drugs: (1) Risperdal (2) Abilify. used to manage symptoms of aggression and irritability. All therapies (including NTI164) only address symptoms.
Rett Syndrome (RS)	Globally: $136m US: $58.8m EU: $55.2m ROW: 5.7m Aust: $2m	Global: 40-55k US: 6-9k patients EU: 9-14k ROW: 47.5k Aust: ~380	One US FDA approved drug: Daybue. >30% of US Rett Syndrome patients have tried Daybue.
Cerebral Palsy (CP)	Globally: $5.1b US: $1.2b EU: $1.8b ROW: $2.1b Aust: $44m	Global: 17.3m US: 500k EU: 1.5m ROW: 17.3m Aust: 37k	Two US FDA approved drugs for Spastic Cerebral Palsy: (1) Baclofen (2) Botox.
Paediatric Acute-onset Neuropsychiatric Disorders Associated with Streptococcus (PANS) / Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS)	Globally: $149m US: $65m EU: $61m ROW: $19m Aust: $3.5m	Global: 182k US: 7k patients EU: 12.8K ROW: 162k Aust: 725	No US FDA OR EU EMA approved products. Intravenous immunoglobins (IVIG) is used off label in some cases.
Total	**Globally: $12.6b US: $4.4b EU: $2.7b ROW: $5b Aust: $475m**	**Global: 46.4m US: 2.5n EU: 2.1m ROW: 41.5m Aust: 216k**	

*Source: MSTe, NTI, NEU. Note: *TAM = Total Addressable Market. #MSTe TAM is estimate of attainable market penetration, a sub-segment of materially higher TAM*

For the purpose of estimates, MST considers realistic penetration is lower subset & longer term.

Figure 9: NTI Total Addressable Market - realistic penetration uses lower subset & longer term

Condition	Stage of clinical trial	#Realistic Penetration of Market Used
ASD	Ph2/3 & Ph1/2	US: 5% EU: 5% ROW: 1% Aust: 10%
Rett Syndrome	Ph1/2	US: 20% EU: 20% ROW: 1% Aust: 20%
Cerebral Palsy	Ph1/2	US: 5% EU: 5% ROW: 1% Aust: 5%
PANDAS	Ph1/2	US: 20% EU: 20% ROW: 1% Aust: 20%

*Source: MSTe, NTI, NEU. Note: *TAM = Total Addressable Market. #estimate of attainable market penetration*

NTI is currently conducting four clinical trials with details set out in the table below.

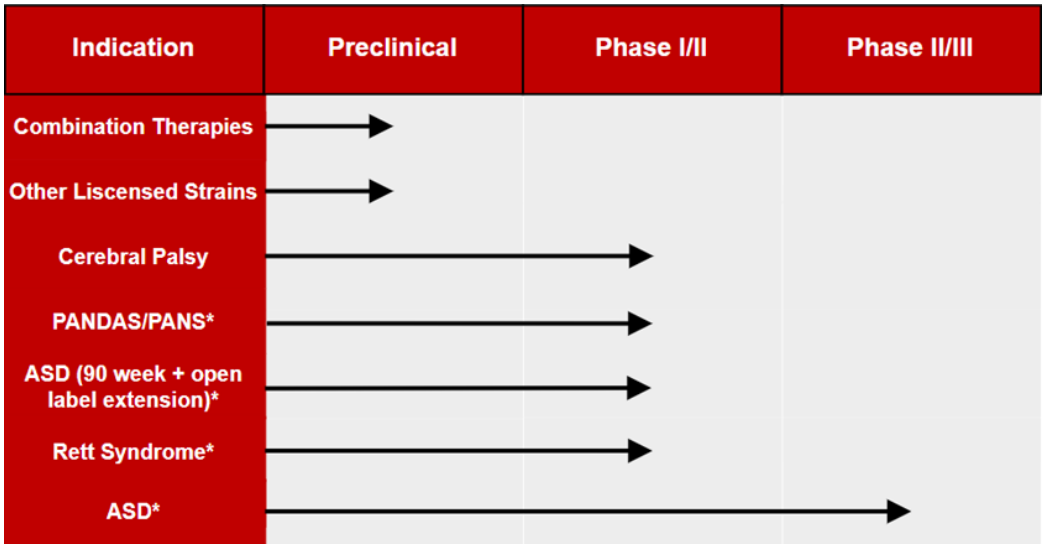
NTI is also working on preclinical trials for other licensed strains as well as the possibility of using NTI164 in combination with corticosteroids to lower inflammation in the nervous system.

Clinical trials

Clinical trials are being conducted solely in Australia, where NTI can take advantage of lower cost setting, with the support of KOL paediatric neurologists, thus building a foundation and de-risking future US FDA registered trials. In FY23, clinical trial expenditure was ~$6m which in MST's view is in line with the cost for sponsored-initiated trials.

NTI has formed a strategic collaboration with contract research organisation (CRO) Fenix Innovation Group to assist with the clinical trials as well as manufacturing the drug. In turn, Fenix will receive ~60m performance rights (shares) depending on certain milestones.

Figure 10: NTI164 clinical & preclinical drug pipeline – All trials are registered in Australia only



*Source: NTI *Data reported with statistically significant primary endpoint results*

Initial Results - NTI164 shows marked improvement in children

Current data to date has reportedly shown children taking NTI164 daily have experienced marked improvement in socialisation, attendance at school, and classroom behaviour. These children also experienced improvement to their levels of anxiety, irritability, and hyperactivity. NTI164 also demonstrated excellent safety results and was shown to be well-tolerated, with no reports of serious adverse events across all doses.

Figure 11: NTI164 Clinical Trials

Condition	Stage of clinical trial	Primary endpoint (Scale used)	Secondary endpoints (Scale used)	Results to date
ASD	Ph2/3	▪ Clinical Global Impression – Severity of illness (CGI-S).	▪ Behaviour (Vineland-3) ▪ Sociability (SRS-2) ▪ Anxiety (ADAMS) ▪ Clinicians' evaluation (CGI-I)	▪ At 8 wks (Primary Endpoint) : 28% improvement in CGI-S for NTI164 vs placebo & 32% vs baseline ▪ At 12 wks: 56% improvement from baseline (Day 0) to week 12 ▪ At 8 wks: Secondary endpoint – ADAMS score in treatment arm saw 39% improvement
RS	Ph1/2	▪ Clinical Global Impression Scale-Improvement (CGI-I).	▪ Behaviour (RSBQ) ▪ Clinicians' evaluation (CGI-I)	▪ At 12 wks: 93% of CGI-I patients improved with 36% "very much/much improved" ▪ At 20 wks: 100% of CGI-I patients improved with 57% "very much/much improved" ▪ At 4 wks: RSBQ Behaviour improved with a mean difference of -4.4 vs baseline ▪ At 12 wks: RSBQ improved with a mean difference of -13.4 vs baseline and a +205% mprovement from wk 4 ▪ At 20 wks: RSBQ improved with a mean difference of -10.5 vs baseline and a +205% improvement from wk 4
CP	Ph1/2	▪ Caregiver Priorities and Child Health Index of Life with Disabilities (CPCHILD) ▪ Questionnaire evaluating caregivers' perceptions of health-related quality of life (HRQOL) ▪ The impact on caregivers of children with CP.	▪ Safety ▪ Pain ▪ Sleep ▪ Seizure frequency ▪ Dystonia ▪ Spasticity.	Scheduled to begin in late 2024
PANS/PANDAS	Ph1/2	▪ Revised Children's Anxiety and Depression Scale-Parent-rated score (RCADS-P) ▪ CGI-S ▪ CGI-I ▪ Clinical Global Impression – Therapeutic Effect (CGI-TE)	▪ Tics (YGTSS) ▪ OCD (CY-BOCS) ▪ Conners Scale (ADHD) ▪ Unique blood transcriptomic and/or epigenetic signature	▪ 45% improvement in anxiety & depression vs baseline (RCADS-P) at 52 wks ▪ CGI improvement of 32% vs baseline at 52wks

Source: NTI

Key people

Experienced board including:

- **Dr Thomas Duthy (Exec Director) -** >20yrs experience in financial markets and executive-level/board experience with ASX listed companies.
- **Mark Davies (Chairman) -** >20yrs experience in trading, investment banking and corporate advisory; including Founder and Managing Director at 1861 Capital.
- **Robert Maxwell Johnston (Non-Exec Director) -** Prev president & CEO of J&J pacific division for >11yrs.
- **Gerald Quigley (Non-Exec Director) -** Pharmacist and consumer health commentator with expertise in regulatory landscape.

Senior management:

- **Dr Alexandra Andrews (Chief Operating Officer) -** PhD in neuroscience and has expertise in corporate development, investor engagement, product development and commercialisation, clinical trials, and regulatory environments.
- **A/Prof Carolyn Ellaway (Chief Medical Officer) -** Internationally recognised clinical geneticist and key opinion leader

Key challenge - NTI must differentiate itself from illegitimate cannabinoid players

Legitimate CBD products vs Illegitimate nutraceutical blends

Currently in the nutraceutical market, there are a plethora of companies that claim their nutraceutical blend of cannabinoids can be used to treat various conditions without evidence from clinical trials. It is MST's view that NTI's key challenge is to legitimise and differentiate its key compound 'NTI164' from other illegitimate nutraceutical blends through successful clinical trials.

Cannabinoid research is booming … but few are focused?

Despite there only being one US FDA approved cannabis-derived drug, there are ~661 ongoing trials with cannabinoids with ~50 studies in Ph2 & 3 currently active. Further, there are >700 cannabis-centric patent applications. Most are low dose CBD oil to be sold over-the-counter.

Business Case

Growing medicinal cannabis regulation - There is a global trend in markets moving toward legalising medicinal cannabis. This has led to greater regulation with clinicians and patients calling for proven cannabinoid formulations with meaningful clinical outcomes for patients. NTI164 is a cannabinoid extract seeking to distinguish itself among other medicinal cannabis-derived therapies.

Targeting untreated neurological diseases with a large addressable market - NTI is targeting four neurological indications for which limited therapeutic options exist. NTI claims that NTI164 lowers neuroinflammation and therefore treats the underlying pathology of various neurological diseases.

Cash flow light model - NTI has decided to take on the unconventional pathway of targeting the Australia market first. Management describes themselves as "balance sheet aware" and are aiming to be cash flow positive from penetrating the Australian market before extending themselves to more lucrative but costly markets such as the US. This staged and less costly strategy to pathway materially de-risks NTI.

Precedent is relevant - MST's investment thesis compares and tracks NTI with GW Pharmaceuticals' Epidiolex. MST's investment thesis compares and tracks NTI with GW Pharmaceuticals' Epidiolex. The latter became the first and remains the only US FDA approved cannabis-derived cannabinoid. GW Pharma was acquired by Jazz Pharma for US$7.2b (13.7x revenue multiple).

MST notes five key milestones that delivered Epidiolex success prior to its acquisition:

1. **Clinical trials -** >700 patients studied across 4 Ph3 randomised, double-blind, placebo-controlled clinical trials including one published in the Lancet journal
2. **Efficacy -** 44% & 41% reduction in drop seizures and total seizures (vs 22% and 14% in placebo)
3. **Safety -** No significant increase adverse events vs placebo
4. **Indications -** Received US FDA approval in 3 different forms of seizures and EMA in two forms.
5. **Commercialisation -** Successfully commercialised Epidiolex, where revenue grew >70% on pcp to US$510.5m within ~5yrs on market.

Competitor Drugs - provide symptom relief but do not treat the underlying cause

NTI's target markets are largely untreated as the current drugs on the market only treat the symptoms rather than the underlying cause of the neurological diseases. On the other hand, NTI claims that NTI164 lowers neuroinflammation and therefore treats the underlying pathology of various neurological diseases.

In all but Rett Syndrome, most of NTI's target syndromes, current patient care is generally based on treatment of symptoms, such as anticonvulsants for seizures, physiotherapy for movement impairment and speech therapy for language delay. However, MST notes that there are numerous clinical trials in development for the neurological conditions that NTI164 is targeting – as set out in the figure below.

Figure 12: Competitive landscape - Numeours clinical trails in development with current drugs on market being inadequte

Condition	Number of active clinical trials (Currently in Ph3)	Competitive landscape
ASD	128 (8)	Two US FDA approved drugs: (1) Risperdal (2) Abilify. Neither drugs treat the underlying cause of autism but are used to manage symptoms of aggression and irritability.
RS	56 (2)	One US FDA approved drug: Daybue. >30% of US Rett Syndrome patients have tried Daybue.
CP	18 (2)	Two US FDA approved drugs for Spastic Cerebral Palsy: (1) Baclofen (2) Botox.
PANS/PANDAS	49 (37)	No US FDA OR EU EMA approved products. IVIG used off label.
Total	**251 (49)**	

Source: MST, Global Data, US FDA

MST also notes neurodevelopmental disorders are often caused by gene mutations, which suggests that gene therapy could be a possible treatment. While there is exploration of its use, research remains at an early stage.

Pathway to market - NTI has is seeking to bring certainty & de-risk the pathway

NTI will need to conduct Ph3 randomised, double-blind, placebo-controlled clinical trials in order to receive regulatory approval in Australia, US or EU. The cost of these trials varies enormously depending on where they are conducted.

Approval process - NTI met with the US FDA and now have clearer understanding

In order to conduct a clinical trial in the US & EU, NTI must submit an Investigative New Drug (IND) application. NTI aims to secure an IND approval in the US & EU, but to date have not disclosed a preferred indication. NTI aims to secure an IND in parallel with the Australian go-to-market strategy and has held a pre-IND meeting with the US FDA Management to understand the necessary pre-clinical toxicology and human pharmacokinetic clinical trials required to support a future IND.

In parallel, NTI is positioning itself with the Australian TGA to examine the requirements for approval in Australia, noting potential access to a provisional registration pathway with the TGA for NTI164. NTI expects to meet with the TGA in 2QCY25 to discuss the provisional determination application and subsequent submission is expected in 2H25. The TGA approval process for provisional registrations takes about 220 working days and hence approval is expected in FY27 (In-line with MSTe)

Pre-clinical toxicology & human pharmacokinetic (PK) study underway

Following the US FDA meeting, NTI understands the necessary in vitro & in vivo assessments on NTI164 required to allow for a successful IND submission. Using available cash reserves, NTI intends to complete the necessary pre-clinical toxicology and human pharmacokinetic (PK) trials in line with US FDA, Aust TGA and EU EMA before the end of 1QCY25 with aspirations to receive approval in at least one paediatric indication in 1HCY25.

Go to market strategy NTI is targeting a cash flow light strategy

Stage 1 – Australian Market

NTI will take a staged approach to market entry, targeting the Australian market first. Management describes themselves as "balance sheet aware" and are aiming to be cash flow positivity from penetrating the Australian market before extending themselves to more lucrative but costly markets such as the US. This pathway materially de-risks NTI who have opted in for a safer and less costly strategy. Unlike other market strategies, NTI intends to maintain 100% commercial ownership of NTI164 in the Aust market.

Stage 2 – US & Global Markets

Licensing deal in the US is the likely option

Management are focussed on global commercialisation, particularly US & EU markets. MST assumes that entry into the US & Global markets will require a licensing partner. We assume NTI will enter into a licensing agreement similar to the agreement between Neuren Pharmaceuticals & Acadia Pharmaceuticals (ACAD) which will incorporate both sales milestones and tiered royalties.

Orphan drug designation offers expedited approval as well as other incentives including a period of market exclusivity. Management aims to receive US/EU orphan drug designation for all their indications except for Autism which is not eligible (the patient pool is too large to be considered a rare disorder). NTI has applied to the US FDA for PANDAS and PANS. NTI also plans to secure an ODD for Rett Syndrome in the US and Europe in 2HCY24.

Asian markets could provide even further upside

MST believe the Asian market for NTI could be 2x the size of the US market, and an Australian approval would bode favourably for an Asian approval. However, MST notes Cannabis, including medicinal cannabis, is restricted in some parts of Asia including China. However, more recently pharmaceutically derived medical cannabinoid medicines (including Epidiolex) have been approved in Korea and Japan. We would expect this trend to continue across the region.

The licensing deal with Dolce Cann Global

In Jul-20, NTI signed exclusive, global licensing agreement for use of NTI164 in neurodevelopmental disorders from Dolce Cann Global. As part of the deal, NTI agreed to issue Dolce shares upfront with the only forward commitment being Dolce will receive <5% royalties on sales.

Pricing of NTI164 expected to be similar to Epidiolex

MSTe the 'per gram' pricing of NTI164 could be similar to that of Epidiolex. The latter is priced at an average of A$24k in Australia and US$33k in the US (uses average of adult vs child dosing).

Basics - Cannabinoids for therapeutic use

Hemp vs Marijuana

Hemp and Marijuana both stem from the cannabis plant, but are cultivated for different uses, being:

- **Hemp refers to varieties of the Cannabis sativa plant species** cultivated specifically for industrial use (including fibre for textiles). Hemp typically has higher levels of CBD (cannabidiol). CBD is non-intoxicating and known for its potential therapeutic effects. Hemp typically contains very low levels of THC (tetrahydrocannabinol), the psychoactive compound in cannabis (<0.3% THC by dry weight). Hemp is generally legal in most jurisdictions.
- **Marijuana is generally cultivated for its higher THC levels** (THC stands for delta-9-tetrahydrocannabinol) which produces psychoactive effects when consumed. Marijuana is generally illegal in most jurisdictions.

Medicinal Cannabis

The US FDA has not approved medicinal cannabis for the treatment of any disease or condition. However, certain cannabinoids are approved for therapeutic use. Cannabinoids are naturally occurring chemicals found in the cannabis plant. The US FDA says there are >80 naturally occurring cannabinoids found in cannabis. Cannabinoids are also found naturally in the human body as part of the endocannabinoid system, where they act as messengers sending signals to the brain, gut or other parts of the nervous system to help regulate basic bodily functions.

There are two categories of cannabis therapeutics (Figure Figure 13):

2. **Cannabis-derived compounds -** Compounds that are naturally extracted from the cannabis plant. There is only one US FDA approved cannabis-derived compound – Epidiolex.
3. **Synthetic cannabis-related compounds -** Compounds that are created in the lab. These compounds may or may not occur naturally in the cannabis plant**.** There are 3 US FDA approved synthetic cannabis-related compounds.

Figure 13: Two categories of therapeutic compounds: Cannabis-derived & Cannabis-related

Source: US FDA

The U.S. Food and Drug Administration (FDA) has disclosed that more than 400 Investigational New Drug (IND) applications for cannabis-derived products have been submitted to them over the last 10 years. Over half (53%) of all applications were for research in the field of addiction and pain medicine, followed by neurological conditions (19%), immunology and inflammation (14%) and psychiatry (9%). According to the cannabis advocacy group NORML, over 32,000 peer-reviewed papers specific to cannabis have been published with the annual number increasing each year since 2010.

Figure 14: Overview of each of the cannabinoids in NTI164

Cannabinoids (% of NTI164)	Brief Description	Apparent Therapeutic Effect	Detailed Description including Previous Research
Cannabidiolic Acid (CBDA) (40 - 60%)	Acidic precursor to cannabidiol (CBD)	Anti-inflammatory, anti-nausea, anti-cancer.	CBDA has shown potential in preclinical studies for its anti-inflammatory, anti-nausea, and anti-cancer properties. It interacts with the endocannabinoid system differently than CBD and may have unique therapeutic benefits
Cannabigerol (CBG) (1 - 10%)	Precursor to other cannabinoids.	Anti-inflammatory, antibacterial, neuroprotective. CBG is non-psychoactive	CBG is one of the many cannabinoids found in the cannabis plant. It is considered the precursor or "mother" cannabinoid from which other cannabinoids are synthesized.
Cannabidibutol (CBDB) (1 - 10%)	Similar to CBD	Limited research, potential anti-inflammatory and analgesic. Similar to CBD but with a different side chain structure.	Limited research on CBDB, but it is believed to have similar properties to CBD, including potential anti-inflammatory and analgesic effects. More research is needed.
Cannabigerolic acid CBGA (1 - 10%)	Precursor to major cannabinoids such as CBD & THC	Anti-inflammatory, antimicrobial and antioxidant properties.	CBGA is known for being the precursor to several major cannabinoids and plays a crucial role in the plant's biochemistry.
Cannabidiol CBD (1 - 5%)	Proven therapeutic benefit. Approved an anti-epileptic treatment.	Anti-inflammatory, anti-nausea, anti-cancer, anti anxiety, pain relief and anti-epileptic	CBD is the most prominently researched cannabinoid and has been approved as an anti-epileptic treatment called Epidiolex.
Cannabidiphorol (CBDP) (1 - 5%)	Similar to CBD with a longer side chain	Potentially stronger binding to receptors, early research stage	CBDP may have stronger binding affinity to cannabinoid receptors compared to CBD, potentially making it more effective in certain therapeutic applications.
Cannabinol (CBN) (1 - 3%)	Psychoactive, produced as THC ages	Sedative, anti-inflammatory, antibacterial	CBN is known for its sedative effects and is often used as a sleep aid. It also has potential anti-inflammatory, antibacterial, and appetite-stimulating properties.
Tetrahydrocannabinol (THC) (<1%)	Primary psychoactive component of cannabis.	Euphoria, pain relief, anti-nausea, muscle spasm reduction	THC has a wide range of effects, including euphoria, relaxation, altered perception of time, and increased appetite. Therapeutic uses include: pain relief, anti-nausea, and muscle spasm reduction. However, it can also cause anxiety and paranoia in some users

Source: WebMD, NCBI, Forbes, Science Direct,

US regulatory setting in brief

The regulation of cannabinoid products in the USA occurs at both a Federal and State level, with broad responsibilities as follows:

US Federal Government regulation

The US Government regulates controlled substances (Schedule 1 drugs such as LSD & heroin); & the US Food and Drug Administration (FDA) regulates medicinal approval, plus any health & dietary claims. Schedule 1 drugs are subject to a prohibition of legal commerce, which blocks access to legal and financial system services.

US Federal law has evolved to facilitate approval of cannabinoid products for medicinal use as follows:

- **Farm Bill & de-scheduling of hemp-derived CBD products** - The US Federal Agricultural Improvement Act of 2018, commonly known as the Farm Bill, de-scheduled industrial and commercial hemp (and hemp-derived CBD products) from the Federal list of controlled substances.
- The 'Farm Bill' defines hemp as any part of the Cannabis sativa L species which contains <0.3% THC. The 'Farm Bill' also allows interstate commerce.
- The Farm Bill explicitly preserved the FDA's authority to regulate products containing cannabis or cannabis-derived compounds. This means that any hemp-derived products, including those containing CBD, must comply with FDA regulations

State Government regulation

States determine laws regarding the cultivation, sale, possession, and use of cannabinoids. Regulation of use may extend to medicinal, recreational commercial and extraction.

- States have adopted varying regulatory approaches - as of 2024, 38 U.S. states have legalised medicinal cannabis, and 24 states have legalised, including some allowing marijuana-derived CBD with higher THC content.
- 10 other states continue to ban hemp products with any amount of THC.

Conclusions

While there are some emerging exceptions, the 2018 Farm Bill does not permit US pharmacists to fill prescriptions for cannabis. Sale of hemp-derived medicinal products must still comply with FDA regulations. Cannabis products with higher THC levels remain illegal.

Epidiolex is the only cannabis hemp-derived prescription medication approved by the US Food and Drug Administration (FDA). Epidiolex is also 'legal' under the Farm Bill as it is cultivated from the hemp plant Sativa L cannabis plant (as is NTI164) as the THC concentration is <0.3%.

Recent US regulatory developments: Funding of NTI164 trials less restrictive

The US Attorney General has formally proposed moving marijuana from "Schedule I" drug to a "Schedule III" drug under the **Controlled Substances Act. The Drug Enforcement Administration (DEA)** took submissions from industry experts (in May-24, the DEA published a Notice of Proposed Rulemaking, initiating a 62-day public comment period).

The DEA is currently in the process of reviewing public comments. The timeline for finalising the rule is not specified (some suggest Q4CY24), and the DEA's decision will depend on the review of comments, budget and potential hearings.

The rescheduling of cannabis to Schedule III will not have a direct regulatory impact on the approval of NTI164 since:

- it has an extraordinarily low THC content, and
- it is hemp-derived and is already covered under the Farm Bill.

However, a Schedule III will make legal interpretations clear, open access to financial services including Federal tax deductions and remove certain barriers to cannabis research. **This means that the clarity for funding of clinical trials for NTI164 will be less restrictive.**

Farm Bill 2024 amendment could make medicinal THC regs clearer but complicated

'Recreational' Hemp companies have found a way to produce a hemp derived Delta-8 & stronger Delta-9 THC beverages and edibles which are intoxicating for most people; without breaking the THC <0.3 guidelines of the Farm Bill.

We flag that, the Farm Bill 2024 (formally known as the Farm, Food, and National Security Act of 2024), was introduced to the U.S. Congress in May-24, and is currently with the House Committee on Agriculture for further review. Proposed amendments and ongoing discussions are considering:

- A ban on all ingestible hemp products with any level of THC, to close the loophole.
- Change the definition of hemp to only include the cannabis sativa L. plant and its derivatives with less than 0.3% THC. This would exclude synthetic cannabinoids.
- Regulating psychoactive THC hemp products similarly to marijuana and alcohol, including enforcing age restrictions.

Australian market

Cannabinoids in general are not medically available in Australia. However, specific cannabinoids such as CBD (Schedule 4 - Prescription Only) & THC (Schedule 8 - Controlled Drug) are medically available. As NTI164's composition is similar to CBD, MST expects on approval it would be classified as a Schedule 4 - Prescription Drug.

Other markets have reclassified cannabinoids

The United Nations, United Kingdom and the European Commission have all reclassified cannabinoids as non-narcotics but instead as "novel foods".

Novel food classification poses several benefits

The reclassification of cannabinoids as a novel food has the following implications for NTI164:

1. **Consumer safety -** Being a novel food requires cannabinoids to adhere to food safety and quality standards set by the European Food Safety Authority (EFSA) and the UK's Food Standards Agency (FSA).
2. **Market regulation and standardisation -** Clear guidelines on how cannabinoids are manufactured, distributed and sold.
3. **Research & Development -** Allows companies to conduct R&D activities that can receive Govt grants & tax incentives.

Pathway to market – Case Studies

Case Study 1 – Epidiolex template for cannabinoid success

MST's investment thesis compares and tracks NTI with GW Pharmaceuticals' Epidiolex. The latter became the first and remains the only US FDA approved cannabis-derived cannabinoid.

In March 2016, GW Pharmaceuticals presented successful Phase 2 results for Epidiolex in epilepsy. The clinical trial showed that Epidiolex significantly reduced seizures in patients with Dravet syndrome, a rare form of epilepsy, compared to a placebo. Specifically, patients taking Epidiolex experienced a 39% reduction in monthly convulsive seizures, compared to 13% for the placebo group. The market capitalisation of GW Pharmaceuticals gained 125% to ~US$1.6b.

GW Pharma was acquired by Jazz Pharma for US$7.2b (13.7x revenue multiple).

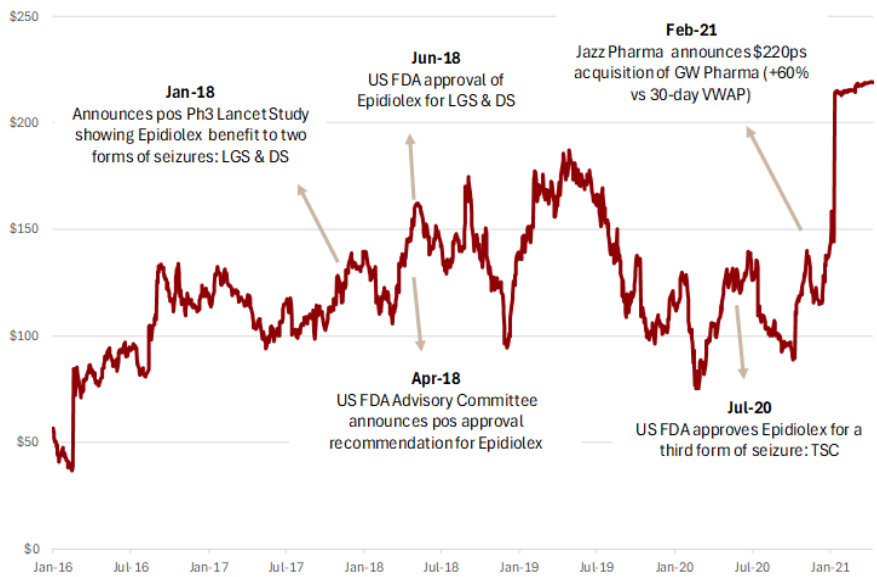
An understanding of the regulatory benchmarks set and licensing revenue generated by Epidiolex provides some indication of the requirements and market potential for NTI

An understanding of the regulatory benchmarks set and licensing revenue generated by Epidiolex provides some indication of the requirements and market potential for NTI164. NTI's management aspires to model the pathway that Epidiolex took to market as a blueprint for NTI164 success. MST views Epidiolex's success derisks and validates NTI164 as it demonstrates "it can be done" even in neurological conditions such as seizures.

MST notes five key milestones that delivered Epidiolex success prior to its acquisition:

1. **Clinical trials -** >700 patients studied across 4 Ph3 randomised, double-blind, placebo-controlled clinical trials including one published in the esteemed Lancet journal
2. **Efficacy -** 44% & 41% reduction in drop seizures and total seizures (vs 22% and 14% in placebo)
3. **Safety -** No significant increase adverse events vs placebo
4. **Indications -** Received US FDA approval in 3 different forms of seizures and EMA in two forms.
5. **Commercialisation -** Successfully commercialised Epidiolex, where revenue grew >70% on pcp to US$510.5m within ~5yrs on market.

Figure 15: GW Pharma Share Price – Acquisition by Jazz Pharma at +60% premium



Source: MST, GW Pharma. Note: US FDA approvals: Lennox-Gastaut Syndrome (LGS), Dravet Syndrome (DS) & Tuberous Sclerosis Complex (TSC)

Epidiolex clinical trials - demonstrated efficacy & a tolerable safety profile vs placebo

In order to receive US FDA approval, GW Pharma studied Epidiolex in >700 patients across four randomised, double-blind, placebo-controlled clinical trials. Epidiolex was shown in conjunction with other anti-epilepsy drugs (AEDs) to significantly reduce the number of seizures patients experienced compared to placebo even in those patients who were resistant to standard-of-care AEDs. Further details on Epidiolex clinical research is illustrated in Appendix C.

Figure 16: US FDA approved indications for Epidiolex

Indication	Onset	AED* Resistance	Approval	Efficacy	Side effects
Lennox-Gastaut Syndrome (LGS) - a severe form of epilepsy.	3-5 yrs old	Likely	**US:** Jun-18 **EU:** Sep-19	44% & 41% reduction in drop seizures and total seizures (vs 22% and 14% in placebo)	86% of patients experienced adverse events (vs 69% in placebo) By the end of the trial, 61% patients' adverse events were resolved (vs 64% in placebo) Serious adverse events impacted 20 patients (vs 4 patients in placebo) 12 patients to discontinued treatment (vs 1 patient in placebo)
Dravet Syndrome (DS) - a rare, severe form of epilepsy	1st year of life	Highly likely	**US:** Jun-18 **EU:** Sep-19		
Tuberous Sclerosis Complex (TSC) – leads to benign tumours and seizures.	1st year of life	Highly likely (>60%)	**US:** Jul-20 **EU:** Apr-21	48% reduction in total seizures (vs 24% in placebo)	88-97% of patients experienced adverse events (vs 89% in placebo) Serious adverse events were experienced in 13-21% of patients (vs 2% in placebo)

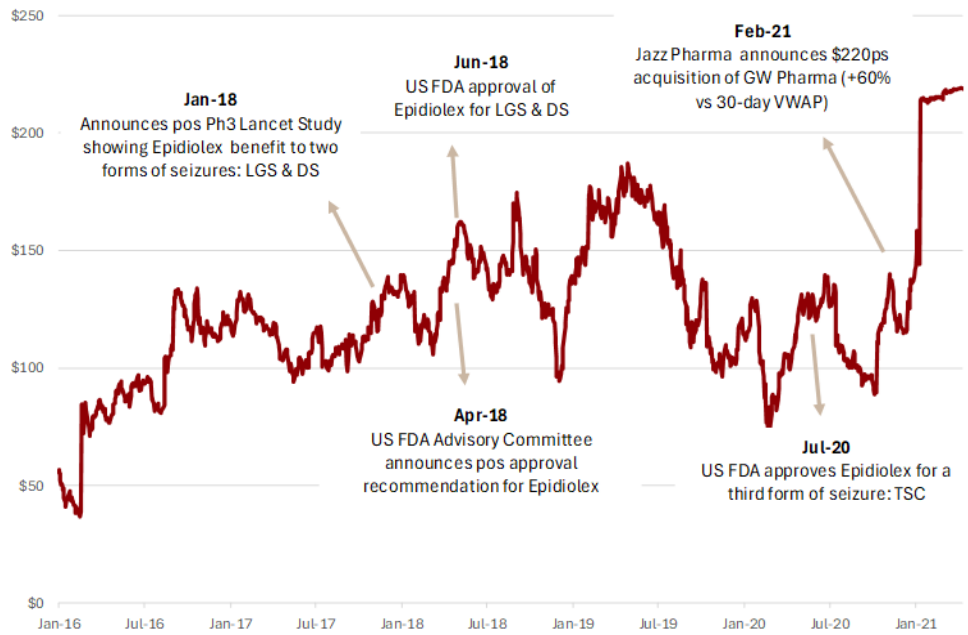
Source: MST, US FDA, EU EMA, Jazz Pharmaceuticals. AED = Anti-epileptic drugs

In MST's view, the clinical research required to bring Epidiolex to market was extensive as it was the first cannabinoid to market. Future cannabinoids may not require as extensive research.

Commercialisation of Epidiolex was a success

GW Pharma began commercialising Epidiolex in Jul-18 and within ~2.5yrs, the drug was able to generate >70% in revenue to US$510m before being acquired by Jazz Pharma. The majority of the revenue was generated in the US (US$467.6m), however, Epidiolex had been launched across several EU countries and was seeking approval in numerous other countries.

Figure 17: GW Pharma Share Price – Acquisition by Jazz Pharma at +60% premium



Source: MST, GW Pharma. Note: US FDA approvals: Lennox-Gastaut Syndrome (LGS), Dravet Syndrome (DS) and Tuberous Sclerosis Complex (TSC)

Jazz Pharma maintains ambitious growth targets for Epidiolex

In 1QCY24, Jazz Pharmaceuticals (JAZZ NASDAQ), revenue for Epidiolex grew +5% vs pcp to US$199m. JAZZ will target >US$1b in annualised revenue in CY25.

Epidiolex has generated >US$2.2b in revenue since being acquired in May-21. Jazz Pharma expects Epidiolex to have additional ex-US launches and indication expansion throughout CY24.

Reimbursement - Payor coverage supported Epidiolex launch in the US

At the time of acquisition, Epidiolex had received a +70% increase in payor covered across >110m lives with no broad prior authorisation. Epidiolex has orphan drug exclusivity in both the US & EU with 14 patents (13 expiring in CY35).

Case Study 2 - Neuren's Daybue – template for syndrome success

In Mar-23, Neuren Pharmaceuticals' (NEU.AX) Daybue (Trofenitide) became the first Rett Syndrome (RS) treatment to receive US FDA approval.

NTI164's pathway to approval may similarly be determined based on subjective benefits.

Daybue's US approval was based on subjective behavioural primary endpoints rather than physical biomarkers. NTI164's pathway to approval may similarly be determined based on subjective benefits.

As of Mar-24, >1.3k US RS patients have started treatment with Daybue which is ~1 in 4 diagnosed RS patients. MSTe the price of Daybue to be ~US$380k annually.

Trial size not 'huge'; US FDA approval based on Ph3 'Lavender' trial of 187 patients

NEU's Phase 3 'Lavender' trial resulted in US FDA approval in Mar-23. The trial was a 12wk randomised, double-blinded, placebo-controlled trial of 187 girls and young women aged 5-20yrs with Rett Syndrome (RS). The primary and secondary endpoints were based on subjective measures rather than demonstrable biomarker improvements.

Demonstrating behavioural improvement is sufficient

Lavender Trial Key Takeaways

- **P-value:** Lavender trail showed Daybue met its primary end points of "Rett Syndrome Behaviour Questionnaire" (RSBQ) & "Clinical Global Impression – Improvement" (CGI-I) with very low p values (see Figure below) and offering a clear positive signal on Daybue's efficacy.
- **Consistency of data** - The Ph3 results followed the trend seen in the Ph2 trial and are in keeping with data emerging from Acadia Pharmaceuticals Inc, (NASDAQ: ACAD), Lilac extension trial. There was also consistency across the different age groups, severity of disease and sub scores of the Rett Syndrome Behavioural Questionnaire (RSSBQ).
- **Open-label extension trial -** >95% of the participants continued to the Lilac extension trial which strongly signals patient/carer support.
- **Safety -** Adverse effects were generally not significant. Diarrhoea was the main cause of patients who withdrew from the trial. The diarrhoea was attributed to an interaction of Daybue with laxative medications.

Figure 18: Lavender Trial Key Takeaways

ENDPOINT		TYPE	ASSESSMENT	p VALUE	EFFECT SIZE
Rett Syndrome Behaviour Questionnaire	RSBQ	Primary	Caregiver	**0.0175**	0.37
Clinical Global Impression – Improvement	CGI-I	Primary	Physician	**0.003**	0.47
CSBS-DP-IT Social Composition Score	CSBS-DP-IT	Secondary	Caregiver	**0.0064**	0.43

Source: MST, NEU. Note: p values of ≤0.05 are regarded as 'significant' or positive

NTI is targeting similar clinical trial endpoints

The data shown in the Lavender trial was supportive from both a regulatory and commercial perspective. NTI intends to demonstrate similar subjective endpoints for its four neurological conditions. Further detail on the endpoints is discussed in the target disorders section of the report.

NEU's initial commercialisation agreement with ACAD in North America

In Aug-18, Acadia Pharmaceuticals Inc, a US based biopharmaceutical company (NASDAQ: ACAD), acquired the North American rights to Trofinetide for all indications, including Rett and Fragile X

syndromes. Acadia specialises in the development and commercialization of innovative medicines used to treat central nervous system disorders.

Key elements of the licensing agreement between ACAD and NEU is as follows:

- **Milestones:** Received two milestone payments to date of US$10m (FY22) for NDA & US$40m (1H23) through first US commercial sale. The potential sales milestones yet to be received in the US are US$350m.
- **Royalties:** Tiered royalty ranging from 10% to 15% of net sales
- **Rare Paediatric Disease Priority Review Voucher & potential sale:** 1/3 ownership (estimated to be worth ~US$100m), implying ~US$33m to NEU on sale.
- **Clinical trial development:** ACAD will fund and execute the remaining clinical trial developments in Rett Syndrome (at the time of the licensing agreement Daybue was in Ph3)

Figure 19: Tiered Royalty Rates & Potential Sales Milestones

Tiered Royalty Rates (Annual Net Sales)	
≤250M	10%
>250M but ≤500M	12%
>500M but ≤750M	14%
>750M	15%
Potential Sales Milestones	
Net Sales >250M in one calendar year	$50M
Net Sales >500M in one calendar year	$50M
Net Sales >750M in one calendar year	$100M
Net Sales >1B in one calendar year	$150M

Source: NEU

The agreement also provides for NEU to receive one third of the market value of a Rare Paediatric Disease Priority Review Voucher, if awarded by the FDA upon market approval of Trofinetide in the treatment of Rett Syndrome. Under this program, once a drug is approved for a 'rare paediatric disease' the sponsor qualifies for a voucher that can be redeemed to receive a priority review of a subsequent marketing application for a different product. The vouchers can be sold. Review of recent sales shows an average voucher price of around US$100m.

Expansion of NEU commercialisation agreement to the ROW

After receiving US FDA approval in Mar-23 and beginning commercialisation in Apr-23, NEU signed the rest of the world licensing agreement with ACAD at much more favourable terms (Figure 19)

- **Milestones:** US$100m upfront milestone payment (received Jul-23). First commercial sale milestone payment of up to ~US$35m; with other first sales milestones adding a further US$29m).
- Potential sales-based milestone payments (excl first sale milestone payment) of US$363m.
- **Royalties:** Tiered royalties ranging from mid-teens to low 20% of Acadia's net sales.

Figure 20: Tiered Royalty Rates & Potential Sales Milestones for ROW operations

Trofenitide	Payment
Upfront Payment (received on 27 July)	US$100m
Upon 1st commercial sale for Rett in EU	US$35m
Upon 1st commercial sale for Rett in Japan	US$15m
Upon 1st commercial sale for second indication in EU	US$10m
Upon 1st commercial sale for second indication in Japan	US$4m
Total development milestones	**US$64m**
EU	Up to US$170m
Japan	Up to US$110m
ROW	Up to US$83m
Total sales milestones on achievement of escalating annual net sales thresholds	**Up to US$363m**
Tiered royalties on net sales	**Mid-teen to low twenties per cent**

Source: NEU

Background

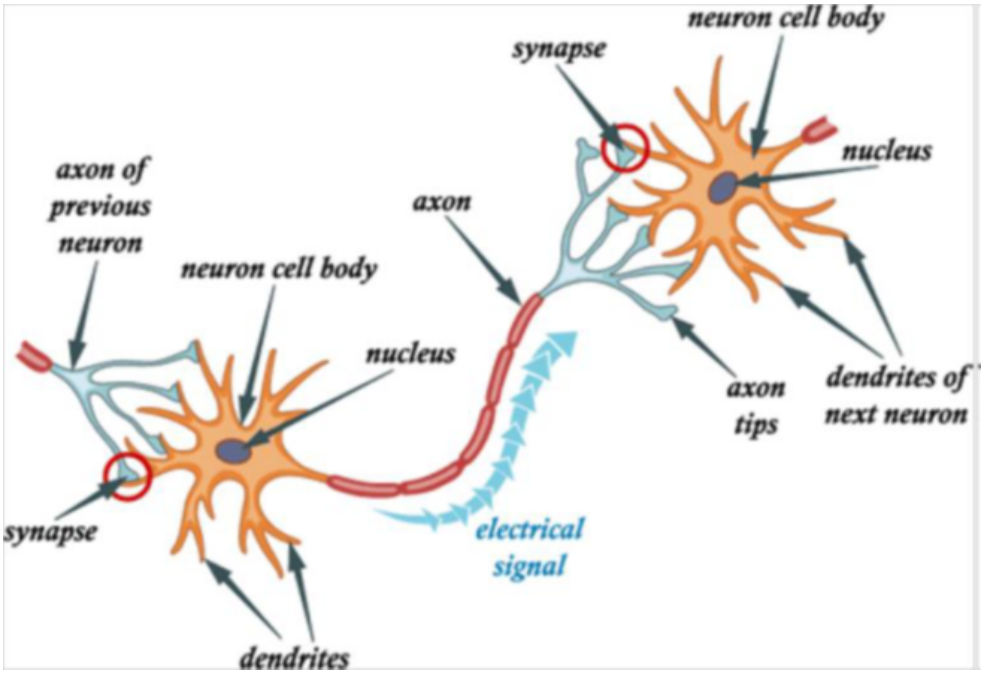
Neurological Disorders

Neurotech's drug candidate NTI164 is targeting neural disorders. The human nervous system is the body's wiring system acting via a relay of electric impulses that assist in controlling the body's different systems. Its role includes:

- Cognition, learning and memory
- Movement – including both voluntary such as speech and walking and involuntary movements such as breathing and blinking
- Autonomic functions - heart function, blood pressure, digestion, sweating and shivering.
- Senses - sight, hearing, taste, touch and smell are all controlled by the nervous system.

Loss of function or efficiency in any component of the nervous system can have a profound effect on the body. The nervous system is complex and highly integrated with the other body systems, which poses challenges to treating any impairment or dysfunction. However, the commonality of how the nervous system functions and its widespread effect in the body's other systems opens the opportunity for therapeutics to have benefits across many neural syndromes.

Figure 21: Diagram of a nerve cell pathway



Source: Pulpbits.

The nervous system comprises neurons or nerve cells imbedded in different support cells. The neuron is a specialised cell with dendrites that receive stimuli from surrounding cells. The neuron's elongated tail, the axon, passes an electrical signal to the neighbouring cells. The electrical signal passes the gaps or synapses between the neurons via neurotransmitter fluids. A neuron may receive signals from many cells and then may pass it on to multiple cells. The signal continues until it reaches the target cell where it can induce the desired action – for example a muscle contraction to move or take a breath, establish a memory. A complex system of support cells and regulatory proteins coordinate with one another to control the nervous system. Disruption of any part of the nervous system can have widespread effect leading to profound symptoms affecting all the body's systems.

Shared pathological features offers wide ranging treatment

Studies have shown that different neural diseases and brain trauma often trigger the same pathological effects at the cellular and molecular level. The common pathological features include the following:

- **Inflammation -** The release of cytokines in inflammation can result in a disruption of signal delivery, often leading to cell death and seizures in patients.
- **Dendrites changes -** Alterations in the number, density, size, and shape of dendritic spines have been correlated with neuronal dysfunction in several disorders associated with intellectual disability, including Rett syndrome.
- **Impairment of support cells** - Microglia, one type of neural support cells, have a central role in maintaining the dendrites. They are commonly affected in neurological disease, impairing the transmission of the electric signals. They also respond to disease by producing inflammatory cytokines which can further compound the damage to neuron signalling.
- **Reduced IGF-1 levels -** Studies have shown depressed levels of IGF-1 in a wide range of neurological disorders.

The combined effects of these pathological features result in impairment of the neural signalling and can thereby negatively impact all brain activity with flow-on effects across all the body's systems. Cognition, memory, vascular regulation, voluntary and involuntary movement, growth and physical features can all be affected by impairment of neural signalling. In a research model of Rett syndrome, it has been shown that increasing the levels of IGF-1 corrects deficits in dendritic spines.

Studies in isolated cells from human Rett syndrome patients, have shown that both IGF-1 and GPE were able to partially reverse the deficits in cellular function and neurological disorders in general. However, neurological diseases are usually difficult to treat because of the protective function of the Blood Brain Barrier (BBB) which prevents or limits a drug's passage to the targeted brain cells. We note cannabinoids readily cross the BBB.

NTI - Target Disorders

Success begets success – Approval in one indication will create confidence

The common pathological process with each of NTI's target syndromes is neuroinflammation. If NTI164 can demonstrate efficacy and safety in one indication to the degree that it receives approval in a key market such as Australia, then this will build confidence that it can be approved in other indications and markets.

Autism Spectrum Disorder (ASD)

Autism spectrum disorder (ASD) is a lifelong neurological condition that affects how an individual behaves, particularly in relation to interpersonal communication, learning and interactions with the surrounding environment.

Although ASD is diverse, some common symptoms incl:

- Behavioural issues
- Irritability
- Repetitive movements
- Difficulty focusing on specific tasks
- Compulsive behaviour

Causes - ASD is a multifactorial disease

Besides PANS/PANDAS, the actual underlying cause of the indications NTI is targeting isn't known (more info can be found in Appendix H). There is no single known cause of ASD. Instead, an interaction between genetic and environmental factors is thought to affect a child's development in a way that results in ASD.

Certain genetic conditions can predispose an individual toward developing ASD incl:

- Rett syndrome
- Fragile X Syndrome
- Down Syndrome
- Siblings with ASD

Other risk factors incl:

- Older parents during maternity
- Low birth weight
- Viral infections
- Air pollutants
- Certain medications (e.g., frequent use of acetaminophen by the mother during pregnancy)
- Complications during pregnancy (e.g., bleeding, pre-pregnancy obesity and low-weight mothers)

Prevalence

Recent studies show that ASD prevalence has increased over time and varies greatly within and across sociodemographic groups. Changes in the definition of ASD as well as differences in clinical research methodology have been reported as reasons for the increase in ASD prevalence. Prevalence data for many low- and middle-income countries remains unreported.

Key Prevalence Rates (including MSTe)

- **Global:** 1 in 100 children. Median male-to-female ratio at diagnosis is 4.2. MSTe there are 27m patients globally.
- **US:** 1 in 36 children. An increase from 1 in 54 in 2020 and >317% increase since 2000. NTI & MST believe there are ~2m ASD patients aged <18yrs in the US.
- **EU:** 1 in 100 children. MSTe there are 680k patients in the EU.
- **ROW:** 1 in 100 children MSTe there are 24m patients in ROW.
- **Australian:** 1 in 20 to 1 in 40.ASD prevalence rates in Australia are among the highest in the world (Figure 21) making it an attractive market for NTI to target. Australian ASD patients are estimated to number ~232k of which ~178k are children.

Total Addressable Market (TAM)

NTI estimates the total global ASD market at US$7.9b & the US market at US$2b.

MSTe the Australian market at A$427m (Figure 22 shows MSTe).

Figure 22: NTI164 Total Addressable Market in ASD (A$)

#MSTe TAM	Prevalence (Patients)	Competitive landscape
Globally: $7.2b US: $3b EU: $816m ROW: $2.9b Aust: $427m	Global: 27m US: 2m EU: 680k ROW: 24m Aust: 178k	Two US FDA approved drugs: (1) Risperdal (2) Abilify. Neither drugs treat the underlying cause of Autism but are used in managing symptoms of aggression and irritability.

*Source: MSTe, NTI, NEU. Note: *TAM = Total Addressable Market. #MSTe TAM is estimate of attainable market penetration, a sub-segment of materially higher TAM.*

Need vs current treatment - ASD has a significant unmet need

Although evidence suggests that there are many factors that make a child more likely to develop autism there are still no medications available that can cure ASD or the entirety of its symptoms.

Treating the underlying cause of disease vs symptom control

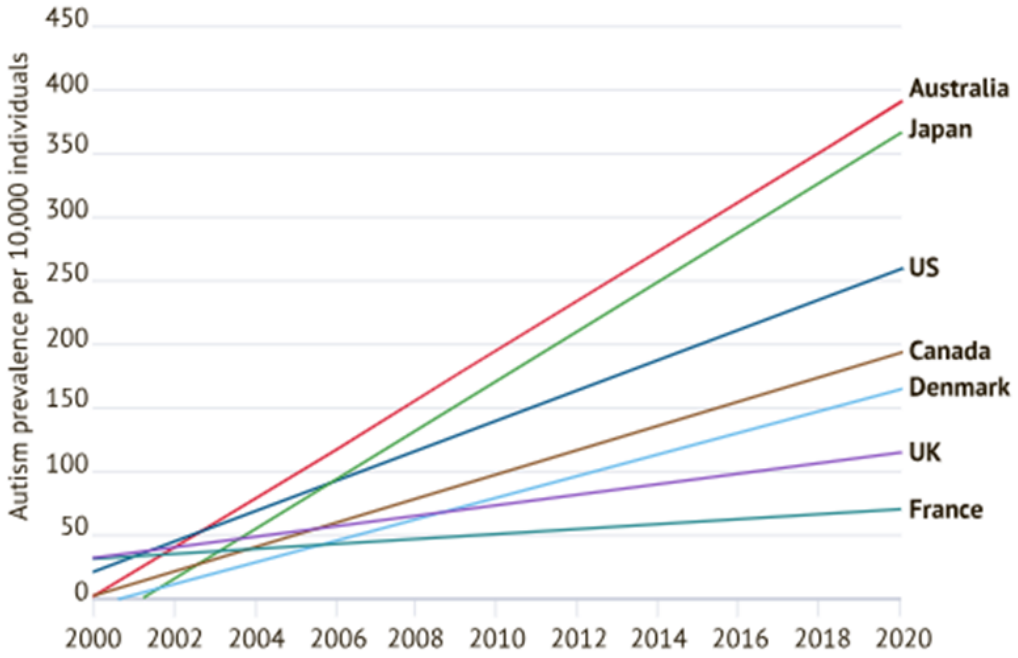
As there are no existing treatments that treat the underlying neuroinflammatory damage associated with ASD, a critical need exists for effective and tolerable treatment options. Currently, the only ASD treatments approved by the US FDA are drugs that ameliorate the symptoms of aggression and irritability. No approved therapies exist for other core symptoms of ASD.

Two drugs have been approved by the US FDA to treat irritability and aggression in ASD:

1. **Risperdal (Risperidone)** - Atypical antipsychotic approved for ASD children aged 5-16 yrs
2. **Abilify (Aripiprazole) -** Atypical antipsychotic approved for ASD children aged 6-17 yrs

While there is currently no published evidence that NTI164 treats the underlying pathology of ASD, the treatment goal is to help children with ASD develop greater functional skills and independence by improving their social capabilities whilst minimising the impact of restrictive behaviour.

Figure 23: Autism prevalence in studies of children by country



Source: Understanding Autism Prevalence' by Maathu Ranjan, Australian National University

Drugs under development

There are at least 128 active clinical trials for the treatment of ASD (Figure 23) with 8 trials in phase 3.

Figure 24: Number of ASD drugs in development by stage

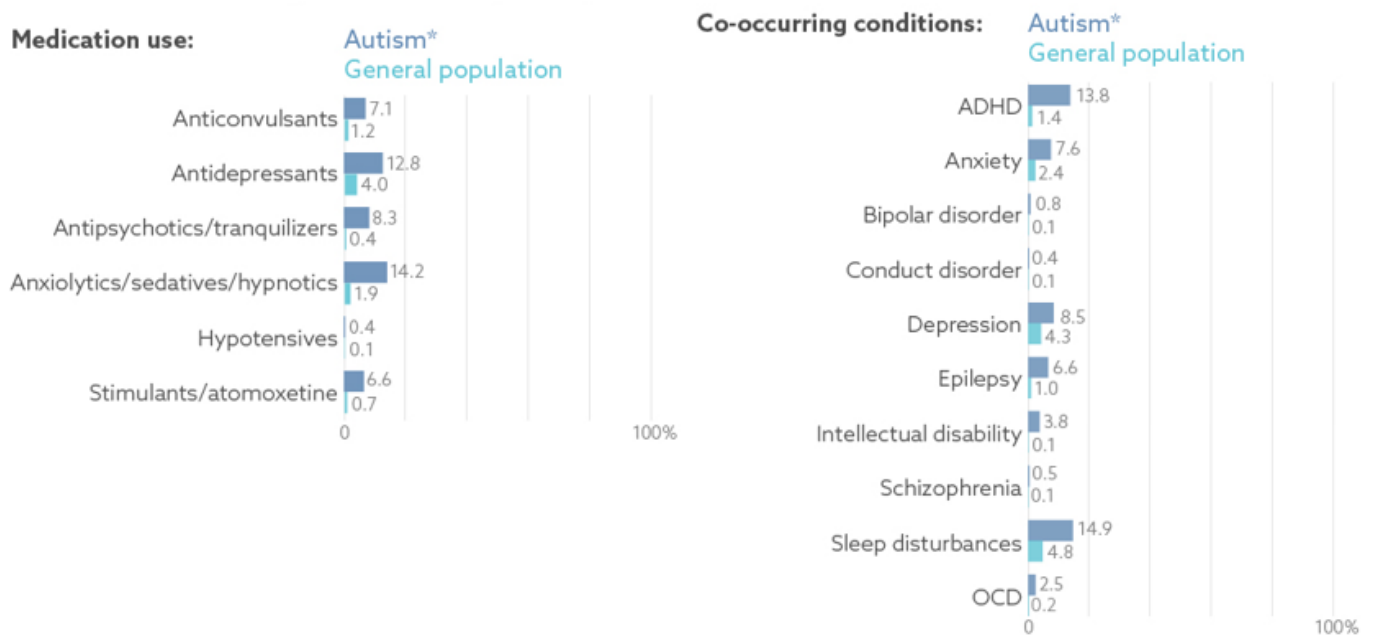
	Development stage								Total Active
	Discontinued	Inactive	Discovery	Preclinical	IND/CTA Filed	Phase I	Phase II	Phase III	
Number of drugs	6	107	20	64	1	14	21	8	128

Source: GlobalData 2024

Drugs in the market used for off-label treatment of ASD

Several classes of medication are prescribed off-label to manage the symptoms of autism and co-occurring conditions, and their usage is significantly higher than in the general population.

Figure 25: Psychotropic medications used for autism symptom management and co-occurring conditions



Source: Houghton et al. 2018

Selective serotonin re-uptake inhibitors (SSRIs)

A group of antidepressants that can reduce the frequency and intensity of repetitive behaviours, while decreasing anxiety, irritability, tantrums, and aggressive behaviour. Examples include fluoxetine (Prozac), fluvoxamine (Faverin), and citalopram (Celapram).

In general, SSRIs are not well tolerated in young people and adverse effects can include increased energy, impulsivity, reduced concentration, diarrhea, and insomnia.

Tricyclic antidepressants

Another type of antidepressant (e.g., Clomipramine, sold under the brand name Anafranil) is used to treat depression and obsessive-compulsive behaviours. It has been reported to cause fewer and more minor side effects when compared to SSRIs.

Psychostimulants

Psychostimulants such as methylphenidate, amphetamine and dextroamphetamine act primarily on the dopamine system and are used to reduce hyperactivity in people with ASD. Methylphenidate (Ritalin) has been found to decrease hyperactivity and non-compliant behaviours.

Adverse effects associated with its use include irritability, appetite and sleep changes, emotional volatility, lethargy, anxiety, depression, social withdrawal, headaches and diarrhoea.

NTI164 Phase I/II ASD trial

NTI's trial is conducted under an Australian compassionate use under a special access scheme category B, with supportive clinicians.

NTIASD1 was a single-arm, open-label, Ph1/2 clinical trial that recruited 14 children between 8 and 17 years of age with a medical diagnosis of Level 2 or 3 ASD (more severe cases). The primary endpoints of the trial were safety and tolerability and secondary endpoints included Clinical Global Impression (CGI) of severity (CGI-S) and improvement (CGI-I).

In May-24 the company advised that 11 patients were now at >2yrs of daily administration with no serious adverse events, nor any diminution in clinical improvements that would warrant withdrawal from treatment.

NTI has a focus on Partnering with Key Opinion Leaders / Clinicians

Results

- At four weeks, 93% of patients showed symptom improvement relating to the severity of illness after daily treatment with NTI164.
- Significant improvement across several clinical assessments versus baseline (Day 0) and additional improvement from 20-week analysis reported in Oct-22.
- After 52 weeks of treatment, ASD measures vs baseline showed clinical meaningful improvements in severity of illness (p=0.032), social responsiveness (p=0.049) and adaptive behaviour (p=0.028).
- Significant effects on severity of illness, with children re-classified from moderately ill (CGI-S: 4.3) at baseline to borderline/mildly ill (CGI-S: 3.0) at 52 weeks, representing a 30% improvement (p=0.03).
- 11 patients now at >2yrs of daily administration

Safety & adverse events

- Safety and efficacy effects of daily oral treatment with NTI164 maintained at 52 weeks.
- No serious adverse events were recorded and no changes to blood analysis or liver function tests over the full 52-week period across all doses (5, 10, 15 and 20 mg/kg).
- No serious adverse events were recorded from 52wks to 2yrs.

NTI164 Phase II/III ASD trial

NTI has entered a Ph2/3 trial of NTI164 in 54 children with ASD. NTIASD2 is a Ph2/3 Double-Blind, Randomised and Controlled-to-Open-Label Study to assess the efficacy of NTI164 up to 20mg/kg/day on the severity of ASD in up to 54 patients aged 2-17 years (inclusive) (See Appendix F for full detail of clinical trial methodology).

Results

Primary & Secondary endpoints were measured at week 8 as follows:

- 32% improvement in CGI-S from baseline (Day 0) to week 8
- Secondary endpoint at 8 wks: – ADAMS score in treatment arm saw 39% improvement
- Statistical significant improvement in Vineland-3 adaptive behaviour score (clinical treatment effect of 3.23)

The current results to date at 12 weeks are as follows:

- 56% improvement from baseline (Day 0) to week 12
- 36% improvement from week 8 to week 12
- Secondary endpoint at 8 wks: – ADAMS score in treatment arm saw 39% improvement
- Patients who initially received placebo (n=28) then received NTI164 after week 8 onwards showed immediate positive clinical benefits (21% improvement) after just 4 weeks of treatment

Safety & adverse events

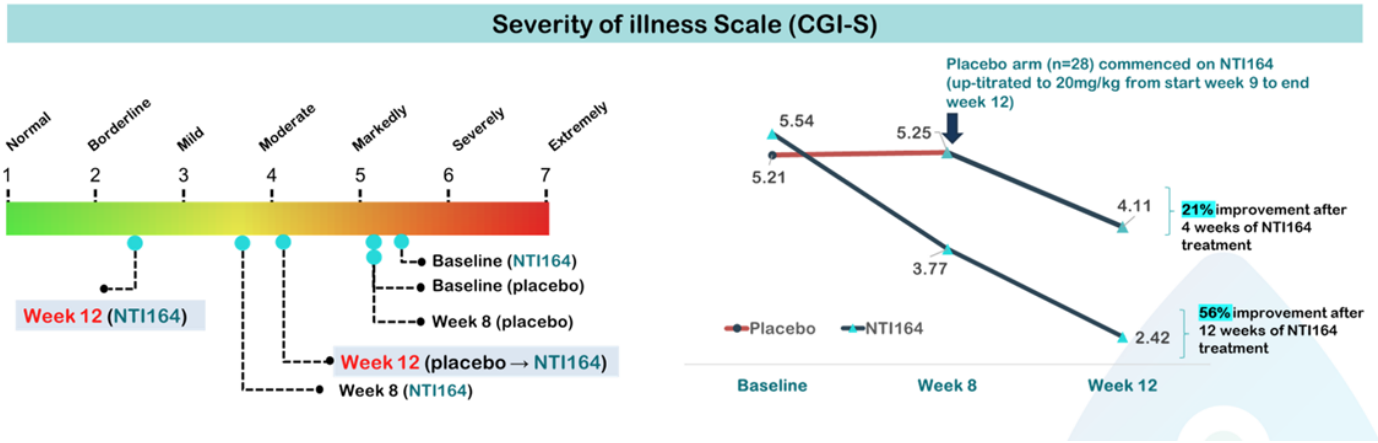
No serious adverse events were reported for NTI164 and placebo across the initial period of 8 weeks.

Adverse events were tolerated and manageable (total of 11 Aes across 7 patients for both arms).

Between week 8 and week 12, there were no serious adverse events related to NTI164. However, 5 patients experienced common mild adverse events such as a headache, viral infections and a single urinary tract infection (not deemed NTI164 related).

Evaluation / Commentary

Figure 26: ASD patients treated with NTI164 showed significant improvement at 12 weeks



Source: NTI

When assessing the impact of clinical trial results, there can be a distinction between treatment effects that are statistically significant, and treatment effects that are clinically relevant for regulatory approval. Clinical relevance is an important conclusion that may be gauged through the peer review process, and considerations include the suitability of endpoints measured, the magnitude of a treatment effect within a population size, and the rigour of the controls used.

MST notes that NTI has signalled its intention to subject its data to peer review at a later time, which will enable a more consensus-guided analysis of its findings. The publication of trial results indicating significant patient benefit would likely generate further investment interest.

The primary endpoint in NTIASD2 is Clinical Global Impression Scale-Severity (CGI-S). Although widely used as a secondary endpoint in psychiatric trials, CGI has been criticised for its reliance on the subjective opinions of clinicians and not fully representing the view of the patient on the severity of their impairment.

The most common primary endpoint used in late-stage ASD trials has been ABC-I (Adaptive Behaviour Composite-Iceberg; Aspy & Grossman, 2011), which examines the antecedents, behaviours, and consequences observed and considers the characteristics of autism as they relate to the observed behaviour (see Table below). The ABC has questions grouped into five subscales: Sensory, Relating, Body and Object Use, Language, and Social and Self-Help skills.

Clinical trials assessing behavioural improvement are often susceptible to subjective bias, particularly when supportive biomarkers are absent. Despite efforts to maintain a study's double-blindedness, for some botanical drugs, it may be difficult to create a placebo with the identical taste, odour, and appearance of the active drug.

Figure 27: Comparison of NTI164 Ph2/3 ASD trial design with other ASD drugs approved and in late-stage development

Active Ingredient (Brand name) / Company	NTI164 (Cannabis) / Neurotech	Risperidone (Risperdal) / Janssen	Aripiprazole (Abilify) / Otsuka	Pimavanserin (Nuplazid) / Acadia	CM-AT / Curemark	GWP42003-P (Cannabidiol) / Jazz (GW)
Highest Stage	Phase 2/3	Approval	Approval	Phase 2/3	Phase 3	Phase 2
Approval Date	N/A	2006-10	2009-11	N/A	N/A	N/A
Study Completion	2024-04-10			2024-09	2017-12-22	2023-12-21
Indication	Autism Spectrum Disorder	Irritability associated with Autistic disorder	Irritability associated with Autistic Disorder	Irritability associated with ASD	Autism with all levels of fecal chymotrypsin	Autism
Target Population	8-17 years	5-17 years	6-17 years	5-17 years	3-8 years	6-17 years
No. of Enrolled	54	101	98 / 218	228	190	108
Comparator	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo
Primary Endpoint	CGI-S	ABC-I CGI-I	ABC-I / ABC-I	ABC-I	ABC-I	ABC VABS-3 CGI-I CGI-S
Timeframe	Week 8	Week 8	Week 8	Week 6	Week 12 / Termination visit	Day 85
Secondary Endpoint	VABS * SRS-2 * CGI-I ** ADAMS * SDSC ** Anxiety ** CGI-CA ** CGI-C TB **	ABC subscale CGI-G Children's Yale-Brown Obsessive Compulsive Scale	CGI-I / CGI-I	ABC subscale CGI-S CGI-I RBS-R VABS CGSQ	ABC-Community for lethargy/social withdrawal	Severe TEAE Clinically Significant (Laboratory, V/S, PE, 12-lead ECG) C-SSRS
Timeframe	* Week 16, 28, 40, 52 ** Week 4, 8, 12, 16, 28, 40, 52		Week 8	Week 6	Week 12 / Termination visit	Up to Day 106/92/85
Geography	Australia	US	US	US, Australia, France, Hungary, Italy, Poland, Serbia, Spain	US	US, Australia Canada, Germany Spain, UK

Source: MST, GlobalData 2024

Notes: Clinical Global Impression-Severity, VABS: Vineland Adaptive Behaviour Scales, SRS-2: Social Responsiveness Scale, CGI-I: Clinical Global Impression-Improvement (CGI-I), ADAMS: Anxiety, Depression and Mood Scale, SDSC: Sleep Disturbance Scale for Children, CGI-CA: Caregiver Global Impression of Change in Attention, CGI-C: Caregiver Global Impression of Change in Target Behaviour, ABC-I: aberrant behavior checklist irritability subscale score, RBS-R: Repetitive behavior scale-revised, CGSQ: Caregiver Strain Questionnaire, C-SSRS: Columbia-Suicide Severity Rating Scale, PRAS-ASD: Parent-rated anxiety scale for Youth with ASD, CGSQ SF-7: Caregiver Strain Questionnaire Short Form 7-Item.

Approval Process and Go-To-Market Strategy

MST see NTI's Go-To-Market Strategy in two key stages, which MST describe as a **Cash flow light approach:**

Stage 1 - The Australian market will be the precedent for a global launch

NTI will initially target the Australian market as the company is cognisant of balance sheet constraints. The intention is for initial sales in the Australian market to create positive cash flow, which will then be used to enter other markets such as the US, EU & ROW/Asian market (South Korea, Taiwan, etc). NTI has indicated commercialisation in global markets for NTI164 will likely follow from a successful Australian launch, however MST notes partnership in global markets is not reliant on an Australia launch.

MST expects NTI to begin generating receipts from customers in Australia in FY27. The cash generated in Australia is assumed to ramp up over several years. The cashflow generated in Australia will fund the business without the need for further capital raisings.

Stage 2 – US & Global market strategy

We expect NTI will examine the opportunity for a US, EU & ROW milestone and royalty deal (similar to that of NEU and Acadia for Daybue) with a partner to fund trials and commercialisation. NTI's negotiating position is strengthened by progess to date – on trials, launch outlook, coupled with the IND-enabling work and the prospect of multiple ODDs.

MSTe in FY29, US commercialisation will begin, which will drive free cash flow positivity in FY30. From FY30 onwards, commercialisation in multiple indications and geographies is expected to begin and generate significant receipts. MST assumes that NTI will partner with a larger company to assist in US & EU clinical trials and commercialisation.

NTI is currently in Phase 2/3 for ASD in Australia. MST views commercialisation several years ahead and estimates the following timeline for commercialisation: Aust (FY27); US (FY29); EU (FY30); ROW (FY31). We assume a modest max penetration rate of the following: Aust (10%); US (5%); EU (5%); ROW (1%)

Manufacturing

MST notes that manufacturing at scale may be an issue. NTI has signed an agreement with Fenix Innovation Group (a Melbourne-based Contract Research Organisation [CRO]) to manufacture 120 litres of NTI164 per year and is working on further scaling up manufacturing capabilities. To put this in perspective of dosing, the daily dose for a 50kg child is ~1g/day.

Typical pricing/Royalty deals

Few Australian companies (CSL being an exception) have the manufacturing or distribution footprint required to successfully launch an innovative pharmaceutical in the US, EU and Asian markets. To realise the full potential of a new drug, it is therefore necessary for Australian companies with clinical-stage assets to partner with larger international counterparts. Some examples of recent partnering deals for ASD are listed below.

Figure 28: Examples of recent ASD deals

Date	Acquirer	Target	Deal in Brief	Deal Value
Apr-17	Q BioMed	Asdera	Worldwide licensing agreement for QBM-001 (ASD-002) an ester-prodrug of mefenamic acid	US$0.05 million upfront 125k shares
Oct-22	Stalicla	Evgen Pharma	Global rights for lead asset SFX-01, a patented composition of synthetic sulforaphane and alpha-cyclodextrin in Phase II	US$0.5m upfront. Total Milestone payments >US$190m. Royalties payable to Evgen on sales are in the low to medium double-digit range in all scenarios.
Jun-23	Beyond Air	Yissum R&D Company of the Hebrew Uni of Jerusalem	Commercial rights for multiple, preclinical stage, neuronal nitric oxide synthase (nNOS) inhibitor candidates.	Undisclosed fees associated with certain pre-clinical, clinical, regulatory and sales milestones. Low single digit royalty on net sales.

Source: GlobalData 2024, MST

Estimates

The market estimates several new drugs for ASD will eventually progress to commercialisation by 2030 (Figure 28).

Figure 29: Projected global sales of ASD therapeutics to 2030 (All US$m)

Developer	Product	Global sales 2023	Global sales 2024F	Global sales 2025F	Global sales 2026F	Global sales 2030F	Peak sales	Peak sales year to 2030
BrainStorm Cell Therapeutics	NurOwn	-	-	-	-	3,350	3,350	2030
Compass Pathways	Psilocybin	-	-	-	24	1,087	1,087	2030
Oryzon Genomics	Vafidemstat	-	-	-	-	610	610	2030
Otsuka Holdings	Abilify	246	206	171	145	77	246	2023
Various (generic)*	Risperidone	The risperidone market was valued at **US$544m in 2022** & is expected to grow at a CAGR of 5% from 2023-2030						

Source: *GlobalData 2024*

**Risperidone's patent expired in 2008 and there are now at least 330 generic formulations manufactured globally (UnivDatos). Typical dosing of risperidone costs approximately $125 (0.25-mg tablets) to $137 (for 0.5-mg tablets) per month. Haloperidol, which is also used to control behaviour, costs approximately $44 to $51 per month for the maximal dosage of 6 mg per day in children.*

The commercial potential of NTI164 will be dependent on the specific type of ASD indication for which it is approved. Peak global sales may reach hundreds of millions, although initial sales will be limited to the Australian market under NTI's current go-to-market strategy. Partnering outcomes may create earlier cash flow opportunities, although MST notes that licensing agreements in the ASD market have been modest to date (Figure 28).

Rett Syndrome (RS)

Rett syndrome (RS) is a progressive X-linked chromosomal disorder that is associated with severe disability.

Symptoms present from 6-12mths of age with developmental regression resulting in the onset of a variety of manifestations incl:

- Loss of acquired language
- Intellectual disability
- Seizures
- Anxiety
- Autonomic dysfunction causing breathing, cardiovascular and gastrointestinal difficulties.

Cause - Rett is a genetic disorder

The majority of Rett-affected patients carry mutations in the methyl CpG-binding protein 2 (MECP2) gene. Approximately 900 different mutations have been reported in MECP2 genes, most of which arise naturally. Through a process known as alternative splicing, MECP2 is believed to play an essential role in the modification of other proteins that are critical for brain cell function and normal communication between neurons.

In RS, microglia and astrocytes (key neuronal support cells) are overactivated with exaggerated maintenance of existing synapses leading to underdeveloped and insufficient synapse formation.

Prevalence

The disease primarily affects girls with prevalence in males being significantly rarer.

Prevalence rates:

- **Global:** Between 1:10,000 - 15,000 births, 40-55k patients globally.
- **US:** 6-9k addressable patients with prevalence up to ~15k patients
- **EU:** 9-14k
- **ROW:** 5k
- **AU:** ~380 patients

Total Addressable Market (TAM)

NTI estimates the global Rett market at US$2.0b. As there are likely 380 patients in Australia, MSTe the Australian market at ~$2m (penetration of 20% market). However, MST acknowledges if NTI is able to achieve a penetration rate of >50%, the TAM can be 2.5x higher (Figure 29 shows MSTe).

Figure 30: NTI164 Total Addressable Market in Rett Syndrome (A$)

#MSTe TAM	Prevalence (Patients)	Competitive landscape
Globally: $136m US: $58.8m EU: $55.2m ROW: $5.7m Aust: $2m	Global: 40-55k US: 6-9k patients EU: 9-14k ROW: 47.5k Aust: ~380	One US FDA approved drug: Daybue. >30% of US Rett Syndrome patients have tried Daybue.

*Source: MSTe, NTI, NEU. Note: *TAM = Total Addressable Market. #MSTe TAM is estimate of attainable market penetration, a sub-segment of materially higher TAM.*

Need vs current treatment – there is only one approved drug for RS

Neuren Pharmaceutical's Daybue - the first US FDA approved drug to treat Rett Syndrome

No treatment existed for RS until Mar-23 when FDA approved Neuren Pharmaceuticals' Daybue (Trofinetide) oral solution as the first treatment for Rett syndrome, in adults and children 2 years of age and older.

Composition

Daybue is a water-soluble analogue of glycine-proline-glutamate (GPE). GPE is an N-terminal tripeptide product of the cleavage of insulin-like growth factor 1 (IGF-1) found in the brain and is neuroprotective at minimal doses.

Mechanism of Action

The mechanism of action of Trofinetide for treating RS is not entirely understood but is thought to work on the same principle as GPE with a longer half-life. Daybue exerts its effect by enhancing synaptic activities, restoring synaptic structure, suppressing the effects of inflammatory compounds in the brain, increasing antioxidative reactions, decreasing injury-triggered cell death, and increasing the presence of IGF-1 in the central nervous system.

Side effects

Daybue is associated with some unwanted side effects, especially diarrhoea. In a 12-week study and in long-term studies, an aggregate of 85% of patients treated with Daybue (Trofinetide) experienced diarrhoea. Of those, 49% either had persistent symptoms or recurrence after resolution despite dose interruptions, reductions, or concomitant antidiarrheal therapy. Diarrhoea severity was of mild or moderate severity in 96% of cases. The carcinogenicity of Trofinetide is yet to be established, making it an important consideration given the need for long-term administration of the drug.

Dosage

The recommended dose of Daybue is based on patient weight and taken twice daily, morning and evening, with or without food, either orally or via a gastrostomy tube. There are still no RS treatments approved in Europe, Japan or Australia.

Drugs used for symptom management

The exact mutations responsible for Rett syndrome are still unknown, so treatment options focus on symptom management.

Current symptom treatments are generally based on a combination of supportive therapy:

- Physiotherapy
- Speech and language therapy
- Occupational therapy
- Scoliosis surgery
- Ankle-foot orthosis
- Ketogenic diet

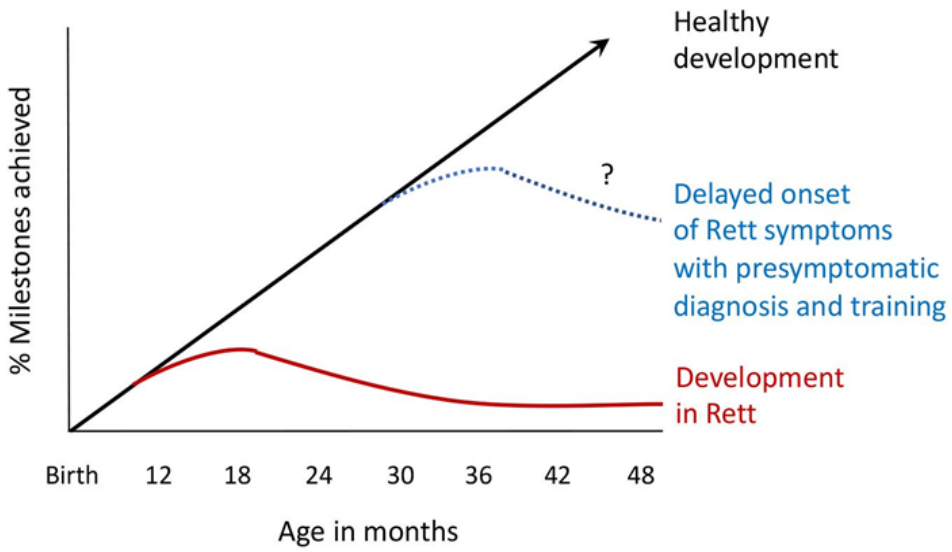
Other symptom management including therapeutics such as:

- Antiepileptic drugs
- Sedative/hypnotics
- Prokinetic agents
- Antiarrhythmic drugs
- Nutritional supplements

Treatment goal

The goal of NTI164 therapy is to help young patients develop greater functional skills and independence by improving their mobility. Evidence suggests that early behavioural and motor interventions may lead to developmental benefits.

Figure 31: RS is an extremely debilitating disease with onset beginning as early as 6mths



Source: *Huda Zoghbi.*

Notes: At first, infants with RS (red line) develop like healthy infants (black line), reaching typical developmental milestones such as rolling over, sitting up, and crawling. But after about a year, the babies begin to lose the skills they've learned. Behavioural training before RS symptoms develop (blue dotted line) could potentially delay the disease's onset.

Drugs under development

There are currently 59 active clinical trials for the treatment of RS with two trials in Ph3 (Figure 30).

Figure 32: Number of Rett syndrome therapeutics drugs in development by stage

	Development stage								Total Active
	Discontinued	Inactive	Discovery	Preclinical	IND/CTA Filed	Phase I	Phase II	Phase III	
No. of drugs	2	34	15	26	2	4	7	2	59

Source: GlobalData 2024

Drugs in the market used for off-label treatment of Rett syndrome

RS patients can experience seizures. Valproate, lamotrigine, and carbamazepine, in addition to oxcarbamazepine, are anti-epileptic drugs that have been shown to be effective in seizure management. The use of levetiracetam was shown to be effective in reducing seizure frequency in patients suffering from drug-resistant seizures.

NTI164 Early Clinical data (to date)

The NTIRTT1 Ph1/2 clinical trial examined the effects of daily oral treatment of NTI164 in 14 RS patients. The trial was an open-label, exploratory study, over 16 weeks of treatment with NTI164 at the maximum tolerated dose of 20 mg/kg/day.

Primary endpoint

The primary endpoint at 12 weeks of treatment is the change in Clinical Global Impression Scale-Improvement (CGI-I).

Secondary endpoints

The secondary endpoint at week 12 was the Rett Syndrome Behavioural Questionnaire (RSBQ). Other secondary endpoints measured are unknown.

Week 12

The primary endpoint, CGI-I at 12 weeks versus baseline on four core Rett-anchors highlighted 93% of patients improved with 36% “very much/much improved” (p=0.001).

The secondary endpoint, the RSBQ showed a mean difference of -13.4 versus baseline (p<0.001) and a 205% improvement from week 4 to week 12. Improvement in various other secondary endpoints was noted.

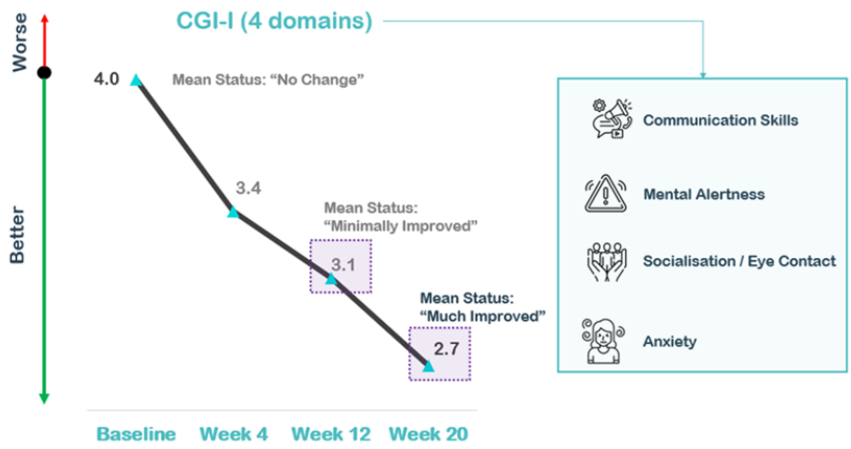
Week 20

CGI score of 2.7 (vs 3.1 at Week 12 & 3.4 at Week 4).

All NTI164 patients showed an improvement in CGI (vs 93% in week 12) with 57% showing “very much or much improved” (vs 36% at week 12).

RSBQ score of -10.5 demonstrating a 24% improvement (vs 30% and 10% improvements in Week 12 and Week 4 respectively)

Figure 33: CGI improvement in RS Ph1/2 clinical trial



Source: NEU

Safety & adverse events

Week 12

A single serious adverse event was recorded over 12 weeks of treatment (i.e., urticaria), while treatment-related adverse events (Aes) were minimal (i.e., 11 Aes, 4 patients) and manageable.

Week 20

No serious adverse events

Adverse events occurred in 14% of patients (nausea/vomiting) at week 12. Between Week 12 & Week 20, no additional adverse events have occurred.

No weight loss demonstratable from Week 12 to Week 20

All patients have remained on treatment at Week 20

Comparison of NTI164 trial design to Daybue trial

The only US FDA approved drug for Rett Syndrome is NEU's Daybue. A comparison between clinical trials result is illustrated in Figure 34 .

Figure 34: Difference between NTI164 & Daybue in Rett Syndrome patients

Clinical data point	NTI164 (at week 20)	Daybue (at week 40)
CGI	2.7	3.1
RSBQ	-10.5	-7.3
Adverse Events (% of patients)	Vomiting/Nausea (14%)	Diarrhoea (75%) & Vomiting/Nausea (29%)

Source: NTI, NEU

Although at differing clinical stages of development, the details for trofinetide's trial design below provide some indication of regulatory expectations in relation to endpoints and the number of patients enrolled.

Figure 35: Clinical trials – NTI's NTI164 vs NEU's Trofinetide (Daybue)

Active Ingredient (Brand name) / Company	NTI164 (Cannabinoids)/ Neurotech	Trofinetide (Daybue) / Neuren			
Highest Stage	Phase 1/2	Approval (Phase 3)	Approval (Phase 3) (Extension)	Approval (Phase 3) (Extension)	Approval (Phase 2/3)
Approval Date		2023-3-10	2023-3-10		
Study Completion				2023-06-30	2023-05-31
Regulatory		Fast Track (US) Orphan Drug Designation (US, EU) Rare Pediatric Disease Designation (US)	Fast Track (US) Orphan Drug Designation (US, EU) Rare Pediatric Disease Designation (US)	Fast Track (US) Orphan Drug Designation (US, EU) Rare Pediatric Disease Designation (US)	Fast Track (US) Orphan Drug Designation (US, EU) Rare Pediatric Disease Designation (US)
Indication	Rett Syndrome	Rett Syndrome	Rett Syndrome	Rett Syndrome	Rett Syndrome
Target Population	5-16 years	Adults / 2 years and older	5-21 years	5-22 years	2-5 years
NCT no / Study name	ACTRN12623000563662 (ANZCTR number)	NCT04181723 (LAVENDER)	NCT04279314 (LILAC-1)	NCT04776746 (LILAC-2)	NCT04988867 (DAFFODIL)
No. of Enrolled	14	187	154	78	15
Comparator	N/A	Placebo	N/A	N/A	N/A
Primary Endpoint	CGI-I	RSBQ CGI-I	TEAE SAE ECG, V/S, B.wt	TEAE SAE ECG, V/S, B.wt, Laboratory Parameter	*Safety and tolerability of treatment **AUC, Cmax, t1/2
Timeframe	Week 4, 12, 16	Week 12	40 weeks	32 months	*24 months **pre-dose, week 2, 4, 8, 12
Secondary Endpoint	RTT-SIS RSBQ RTT-DSC-VAS CSBS-DO-IT Social ICND RTT-CBI ICND-QoL Lab (liver, kidney)	CSBS-DP-IT Social ICND total score RTT-HF RTT-AMB RTT-COMC RTT-VCOM CGI-S RTT-CBI ICND	RSBQ CGI-I CSBS-DP-IT ICND RTT-HF RTT-AMB RTT-COMC RTT-VCOM CGI-S RTT-CBI ICND	N/A	N/A
Timeframe	Week 4, 12, 16	Week 12	40 weeks	N/A	N/A
Geography	Australia	US	US	US	US

Source: GlobalData 2024

Notes: RSBQ: Rett Syndrome Behaviour Questionnaire, CGI-I: Clinical Global Impression-Improvement Score, CSBS-DP-IT Social: Communication and Symbolic Behavior Scales Developmental Profile Infant-Toddler Checklist-Social Composite Score, ICND: Impact of Childhood Neurologic Disability Scale, RTT-HF: Rett Syndrome Clinician Rating of Hand Function, RTT-AMB: Rett Syndrome Clinician Rating of Ambulation and Gross Motor Skills, RTT-COMC: Rett Syndrome Clinician Rating of Ability to Communicate Choices, RTT-VCOM: Rett Syndrome Clinician Rating of Verbal Communication, CGI-S: Clinical Global Impression-Severity, RTT-CBI: Rett Syndrome Caregiver Burden Inventory.

Evaluation / Commentary

The rarity of RS poses benefits and challenges for drug developers. NTI164 may be eligible for Orphan Drug Designation, which would enable tax credits, fee waivers and a period of market exclusivity (see Appendix E for further details on orphan drug designations). MST notes NTI is seeking Orphan Drug Designation in the US & EU.

The limited clinical data available for NTI164 in RS appears promising, but regulatory approval for this indication in Australia or major international markets will not be possible without a pivotal trial enrolling a sufficient number of patients. The LILAC-1 and LAVENDER trials for Trofinetide enrolled >300 patients combined, and a similar number will likely be required for NTI164 approval, nothing this may vary depending on the response rate. Due to the fact that there are only ~380 Rett syndrome patients in Australia (not all of which will be eligible), it will not be possible to conduct such a study without opening overseas sites. This will likely require an IND application.

Approval Process and Go-To-Market Strategy

A significant opportunity exists in the global market but success will be shown in Australia first

Similar to other neurological indications NTI is targeting, the first Go-To-Market will be Australia followed by the US, EU and ROW. However, MST notes that this strategy may not be lucrative as other neurological indications NTI is targeting. This is because the RS population in Australia is ~380 patients. However, demonstrated real-world efficacy and safety will be useful once they apply for approval in larger markets globally.

A significant opportunity exists as there are no approved Rett syndrome drugs in Europe, Japan or Australia. In the US, NEU's Daybue is the only approved product. NTI describes concentrated market dynamics with 18 Rett syndrome Centres of Excellence in the US and 3 in Australia. NTI notes that clinical, regulatory, and commercial strategies are in development and anticipate finalisation by Q3 CY2024.

NTI is currently in Phase 1/2 for RS in Australia. MST views commercialisation several years ahead and estimates the following timeline for commercialisation: Aust (FY30); US (FY31); EU (FY32); ROW (FY33). Since RS is a rare disease with no competition besides NEU's Daybue in the US, MSTe a high penetration rate as follows: Aust (20%); US (20%); EU (20%); ROW (1%).

Typical pricing/Royalty deals

The acquisition of Daybue by Acadia (ACAD) from Australia's Neuren Pharmaceuticals (NEU) represents a significant achievement for Australian innovation and a benchmark for deal potential in the Rett syndrome disease area.

Figure 36: Financial details of the Daybue (Trofinetide) acquisition deal (NEU & ACAD)

Date	Acquirer	Target	Deal in Brief	Deal Value
Aug-18 (US) Jul-23 (ROW)	ACAD	NEU	Exclusive license agreement for the commercialisation of Daybue in Rett Syndrome.	**US Operations** ▪ **Approval/launch:** Daybue (Trofinetide) was approved in the US in Mar-23 and launched in Apr-23 ▪ **Milestones:** Received two milestone payments to date of US$10m (FY22) for NDA & US$40m (1H23) through first US commercial sale. The potential sales milestones yet to be received in the US are US$350m. ▪ **Royalties:** Tiered royalty ranging from 10% to 15% of net sales (See figure 3) ▪ **Rare Paediatric Disease Priority Review Voucher & potential sale:** 1/3 ownership (estimated to be worth ~US$100m), implying ~US$33m to NEU on sale. **ROW Operations** ▪ **Milestones:** US$100m upfront milestone payment (received Jul-23). First commercial sale milestone payment of up to ~US$35m; with other first sales milestones adding a further US$29m). ▪ **Potential sales-based milestone payments** (excl first sale milestone payment) of US$363m. ▪ **Royalties:** Tiered royalties ranging from mid-teens to low 20% of Acadia's net sales.

Source: GlobalData 2024, MST

MST notes NEU's second licensing agreement for the ROW market offered much greater upside to NEU. This is because NEU signed the ROW licensing deal post Ph3 clinical trial results. The decision on whether to take NTI164 through to Ph3 completion before signing a licensing agreement will be up to NTI management and whether they can fund the drug through Ph3.

Estimates

A comparable deal size to Daybue may be possible for NTI164 if clinical development reaches a similar level of maturity. This will require significant funding to recruit a sufficient number of patients internationally.

However, it remains to be seen whether Daybue is approved for the Australian market. If this occurs, it may negatively impact an ODD application for NTI164 as Australian eligibility requirements stipulate that no other therapeutic goods intended to treat, prevent or diagnose the condition are included in the TGA register (or if any such product exists, the medicine provides a significant benefit in relation to efficacy, safety or a major contribution to patient care).

Figure 37: Projected global sales of RS therapeutics to 2030 (All US$m)

Developer (all US$m)	Product	Global sales 2023	Global sales 2024F	Global sales 2025F	Global sales 2026F	Global sales 2030F	Peak sales	Peak sales year to 2030
Acadia Pharmaceuticals	Daybue	177	407	499	631	1,017	1,017	2030
Taysha Gene Therapies	TSHA-102	-	-	-	-	894	894	2030

Source: GlobalData 2024

Cerebral Palsy (CP)

Cerebral Palsy (CP) is a neurological disorder that impacts movement and posture.

There are four types of CP:

- **Spastic CP:** This is the most common type (accounting for ~70-80% of diagnoses), characterised by stiff muscles and exaggerated reflexes. It can be further divided into:
  - Spastic Hemiplegia: Affects one side of the body.
  - Spastic Diplegia: Primarily affects the legs.
  - Spastic Quadriplegia: Affects all four limbs, the trunk, and the face.
- **Dyskinetic CP (also includes athetoid, choreoathetoid, and dystonic CP):** Involves uncontrolled, slow, writhing movements or rapid, jerky movements, often affecting the hands, arms, feet, and legs. This type includes athetoid, choreoathetoid, and dystonic cerebral palsies.
- **Ataxic CP:** Characterized by problems with balance, depth perception and coordination, leading to unsteady movements and difficulties with precise actions, such as writing or buttoning a shirt.
- **Mixed CP:** When symptoms of more than one type of CP are present, such as a combination of spastic and dyskinetic movements.

The long-term prognosis for cerebral palsy can vary widely depending on its severity. When CP is more severe, the outlook is less positive and is associated with reduced life expectancy.

Causes - CP is caused by nervous system abnormalities

CP is caused by the abnormal development of part of the brain (cerebral dysgenesis) or by damage to parts of the brain that control movement. This damage can occur before, during, or shortly after birth. The prime risk factors for CP are delivery before 37 weeks and birth weight of less than 2.5 kg as well as the health condition of the mother before conception.

Symptoms of CP

Cerebral palsy often manifests simultaneously with other conditions that affect brain function. These other conditions may arise from the same damage that caused CP and include:

- Epilepsy
- Intellectual disability
- Vision and hearing problems
- Communication difficulties
- Bone (osteopenia)

- Muscle conditions
- Pain
- Feeding issues
- Behavioural problems.

Most children with cerebral palsy are diagnosed during the first two years of life, but if a child's symptoms are mild, it can be difficult for a doctor to make a reliable diagnosis before the age of 4 or 5.

Genetic risk factors are the main cause of CP

The majority of patients have congenital CP (~80%), although it may not be detected until months or years later. Possible causes of congenital CP include genetic abnormalities, congenital brain malformations, maternal infections or fevers, and foetal injury.

A small number of individuals (~10%) have acquired cerebral palsy, resulting from brain damage early in life, brain infections, problems with blood flow to the brain, asphyxiation, intracranial haemorrhage or head injury. In many cases, the cause of cerebral palsy is unknown.

Prevalence

The incidence of CP has been reported as stable in worldwide epidemiological studies, but the unsatisfactory management of premature birth complications is still a contributing factor to the incidence rate.

- **Global Prevalence:** 2-3 in every 1,000 live births. MSTe 20m globally.
- **US Prevalence:** 1 in every 345 children. MSTe 500k.
- **EU Prevalence:** 2-3 in every 1,000 live births. MSTe 5m
- **Australian Prevalence:** ~34-40k

Total Addressable Market (TAM)

Estimating the total addressable drug market for CP is complex, as patients also require physical care and mobility support. Parallels can be made by assessing the two US FDA-approved drugs for Spastic Cerebral Palsy: Baclofen and Botox (Figure 37 shows MSTe).

Figure 38: NTI164 Total Addressable Market (A$)

#MSTe TAM	Prevalence (Patients)	Competitive landscape
Globally: $5.1b US: $1.2b EU: $1.8b ROW: $2.1b Aust: $44m	Global: 17.3m US: 500k EU: 1.5m ROW: 17.3m Aust: 34-40k	Two US FDA approved drugs for Spastic Cerebral Palsy: (1) Baclofen (2) Botox.

*Source: MSTe, NTI, NEU. Note: *TAM = Total Addressable Market. #MSTe TAM is estimate of attainable market penetration, a sub-segment of materially higher TAM.*

Need vs current treatment - No cure for CP

Although cerebral palsy isn't curable, the symptoms are treatable and dependent on the disease severity and symptoms and how they affect the individual. Due to the heterogeneity of symptoms and the individual differences in the way they manifest in the patient population, there is no standard therapy.

Current treatment protocols focus on symptom control and are based on a combination of support and therapeutics incl:

- **Supportive therapy** - physiotherapy, speech and language therapy and occupational therapy
- **Therapeutics -** Diazepam, baclofen, clonazepam, dantrolene sodium, tizanidine, Botulinum toxin and intrathecal baclofen.

Oral medications such as diazepam, baclofen, clonazepam, dantrolene sodium, and tizanidine are generally used as first-line treatments to relax stiff, contracted, or overactive muscles.

Side effects of current treatments

- Drowsiness
- Changes in blood pressure
- Risk of liver damage that requires continuous monitoring.

Oral medications are most appropriate for children who need only mild reductions in muscle tone or who have widespread spasticity.

There are only two drugs that have been approved for Spastic CP: Baclofen and Botox.

- **Botulinum toxin (BT-A)** is injected locally into muscles (first given between 18 and 24 months of age) and has become the standard treatment for overactive muscles in children with spastic CP, offering three months of respite. BT-A injections work best for children who have some control over their motor movements and have a limited number of muscles to treat.
- **Intrathecal baclofen** therapy uses an implantable pump to deliver baclofen, a muscle relaxant, into the fluid surrounding the spinal cord. It is reserved for extreme spasticity cases and is expensive, while relief is of short duration.

Drugs under development

There are currently 18 active clinical trials for the treatment of CP with 2 trials in ph3. MST views the CP market as heavily under-researched and untreated.

Figure 39: Number of cerebral palsy therapeutics drugs in development by stage

	Development stage								Total Active
	Discontinued	Inactive	Discovery	Preclinical	IND/CTA Filed	Ph1	Ph2	Ph3	
No. of drugs	-	10	1	9	2	1	3	2	18

Source: GlobalData 202

NTI164 Phase 1/2 trial

NTI plans to initiate a first-in-human trial in 2HCY24. A comparison of known information regarding CP trials is listed below.

Figure 40: Comparison of CP trials – NTI's NTI164 vs Ipsen's Abobotulinumtoxin A

Active Ingredient (Brand name) / Company	NTI164 (Cannabis)/ Neurotech	Abobotulinumtoxin A (Dysport) / Ipsen	Abobotulinumtoxin A (Dysport) / Ipsen
Highest Stage	Ph1/2 (planned)	Approved (Ph3)	Approved
Approval Date	N/A	2016-7-29	2020-07-08
Study Completion		2014-02	2018-09-04
Regulatory		Orphan Drug Designation (1999)	Orphan Drug Designation (1999)
Indication		Lower limb muscle spasticity d/t Cerebral Palsy	Upper limb muscle spasticity d/t Cerebral Palsy
Target Population		2-17 years	2-17 years
NCT no / Study name		NCT01249417	NCT02106351
No. of Enrolled		235	212
Dose		10U/kg/leg, 15U/kg/leg	2U/kg, 8U/kg, 16U/kg
Comparator		Placebo	
Primary Endpoint	CPCHILD HRQOL	MAS score in the GSC at the Ankle Joint of the (Most) Affected Lower Limb	MAS score in the PTMG
Timeframe		Week 4	Week 6
Secondary Endpoint	Pain, sleep seizure frequency, dystonia, spasticity	PGA GAS	PGA GAS
Timeframe		Week 4	Week 6
Other Endpoint			
Timeframe		Week 12	Week 16
Geography		US, Mexico, Poland, Turkey, France	US, Belgium, Czechia, Israel, Mexico, Poland, Spain, Turkey

Source: Global Data 2024

Notes: CPCHILD: caregiver priorities and child health index of life with disabilities, HRQOL: Health-related quality of life, MAS: Modified Ashworth Scale, GSC: Gastrocnemius-soleus Complex, PGA: Physician's Global Assessment, GAS: Goal Attainment Scale, PTMG: Primary targeted muscle group

Approval Process and Go-To-Market Strategy

Similar to other neurological indications NTI is targeting, the first Go-To-Market will be Aust followed by the US, EU and ROW.

NTI is currently in Phase 1/2 for CP in Australia. MST views commercialisation several years ahead and estimates the following timeline for commercialisation: Aust (FY30); US (FY31); EU (FY32); ROW (FY33).

MSTe the following max market penetrations: Aust (5%); US (5%); EU (5%); ROW (1%). As CP is a much larger patient pool than other neurological indications (especially in the ROW), MSTe a lower max penetration vs other indications.

Typical pricing/Royalty deals

Licensing agreements in the CP space have been rare. MST views the disease as largely unaddressed.

Figure 41: Examples of CP recent deals

Date	Acquirer	Target	Deal in Brief	Deal Value
Oct-18	Neos Therapeutics	NeuRx Pharma	Licensing agreement to develop, manufacture, and commercialise NRX 101, a candidate for the treatment of sialorrhea (excessive salivation or drooling) in adult and paediatric patients with neurological conditions including CP, Parkinson's disease, mental retardation, and amyotrophic lateral sclerosis	▪ **Upfront:** US$0.17m ▪ **Milestones:** US$5.45m ▪ **Royalties:** Multi-tier rate, ranging from high single digits to low double digits of annual net sales
Jan-14	Allergan	Medytox	Exclusive rights, worldwide outside of Korea, to develop and if approved, commercialise certain neurotoxin product candidates currently in development, including a potential liquid-injectable product	▪ **Upfront:** US$65m ▪ **Milestones:** US$297m upon achieving certain ▪ **Royalties:** Tiered royalties on sales.

Source: GlobalData 2024, MST

Estimates

MST only has projected sales estimates for Ipsen's botulinum toxin A (Dysport) as follows:

Figure 42: Projected global sales of Ipsen's Dysport® for lower limb spasticity to 2030 (All US$m)

Developer	Product	Global sales 2023	Global sales 2024F	Global sales 2025F	Global sales 2026F	Global sales 2030F	Peak sales	Peak year to 2030
Ipsen	abobotulinumtoxinA	702	781	840	891	1,122	1,122	2030

Source: GlobalData 2024

PANS/PANDAS

Paediatric Acute-onset Neuropsychiatric Syndrome (PANS)/ Paediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (PANDAS) is defined by the sudden onset of Obsessive-compulsive disorder (OCD) or eating restrictions and comorbid symptoms associated with at least two of the following:

- Anxiety (particularly separation anxiety)
- Emotional lability or depression
- Irritability, aggression, and/or severely oppositional behaviours
- Deterioration in school performance, sensory or motor abnormalities
- Somatic signs and symptoms, including sleep disturbances, enuresis, or urinary frequency

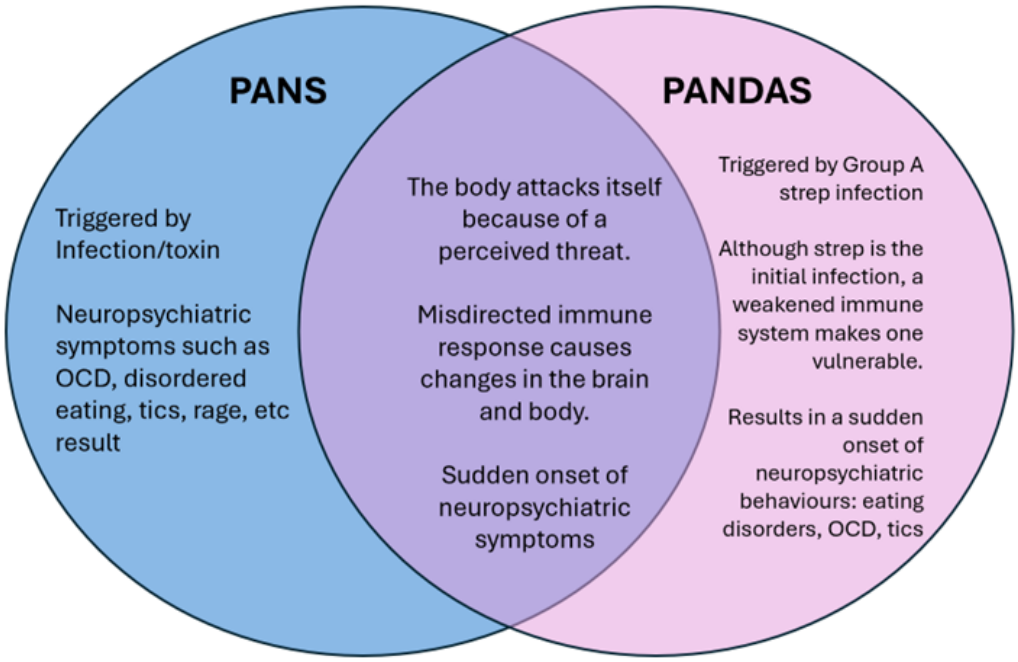
PANS/PANDAS is characterised by misdirected immune responses often with an encephalitic onset, that result in the acute onset of OCS, tics and/or restricted food intake, along with other neuropsychiatric and somatic symptoms.

PANDAS is a subcategory of PANS. It is a condition in which Group A Streptococcal (GAS) infection, is associated with the sudden development of OCD and/or tic disorders in children.

The sudden onset or worsening of symptoms is often followed by a slow, gradual improvement. When children with PANDAS encounter another strep infection, the symptoms often rapidly worsen again. This increase in symptom severity usually persists for at least several weeks but can last for several months or longer.

Symptoms can range from mild where children might function well enough to continue attending school, to severe cases where symptoms can become life-threatening due to extreme food restriction and/or suicidality.

Figure 43: PANDAS vs PANS – PANDAS is a subcategory of PANS



Source: Adapted from www.groundworkcounseling.com/pandas-pans-sudden-nset-ocd-in-children

Causes

PANS/PANDAS can be triggered by an infection, inflammation, or psychological/environmental factors and usually occurs in children aged 4 to 9 years. Brain inflammation occurs when the body's immune system mistakenly attacks healthy brain cells, leading to autoimmune processes that affect central nervous system function.

Prevalence

The estimated annual incidence of PANS/PANDAS in the US has been estimated as ~1 in 12k children between 3 and 12 years of age. However, the actual prevalence is largely unknown due to difficulties in diagnosis, with the PANS/PANDAS Research Consortium estimating that PANS/PANDAS affects as many as 1 in 200 children each year.

Using the data from a 2023 study on the incidence in 3 primary care populations in the US, NTI estimates that there are ~8k and ~6k PANS/PANDAS patients <18yrs old in EU/UK & US respectively.

Key Prevalence rates

- **Globally:** ~1 in 11k. MSTe 182k global patients under <18yrs.
- **EU:** ~8k <18 yrs old. MSTe 12.8k under <18yrs.
- **US:** ~1 in 12k children between 3-12 yrs of age (~7k patients)
- **ROW:** 162k patients
- **Aust:** 725 patients

Patient age at onset is 6.5 +/-2 years for tics and 7.4 +/- 2 years for OCD. The ratio for boys to girls is 2.6:1 with the ratio increasing to 4.7:1 for children below the age of 8 years.

Total Addressable Market (TAM)

NTI estimates the US PANS/PANDAS annual drug therapy market in the US at US$1.2b (Figure 43 shows MSTe).

Figure 44: NTI164 Total Addressable Market (A$)

#MSTe TAM	Prevalence (Patients) (All <18yrs old)	Competitive landscape
Globally: $149m **US: $65m** **EU: $61m** **ROW: $19m** **Aust: $3.5m**	Global: 182k US: 7k EU: 12.8K ROW: 162k Aust: 725	No US FDA OR EU EMA approved products. Intravenous immunoglobins (IVIG) is used off label in some cases.

*Source: MSTe, NTI, NEU. Note: *TAM = Total Addressable Market. #MSTe TAM is estimate of attainable market penetration, a sub-segment of materially higher TAM.*

Unmet need vs current treatment – there is no approved treatment for PANS/PANDAS

Since there are no approved treatments for PANS/PANDAS, the following information relates to the main associated manifestation, which is OCD.

OCD and tics are common hallmarks of PANS/PANDAS. Cognitive behavioural therapy (particularly Exposure Response Prevention) and minimising accommodation to OCD behaviours have been demonstrated as effective interventions for paediatric OCD. When it comes to medications, selective serotonin reuptake inhibitors (SSRIs) approved for use in paediatric OCD such as fluoxetine, sertraline, fluvoxamine, and clomipramine are the preferred choice. However, their use requires frequent monitoring of side effects and slow titration, as they can cause behavioural activation ranging from hyperactivity, mania, disinhibited behaviour, worsening OCD, aggression, irritability, agitation, to suicidality. Antipsychotic medications, such as risperidone (0.125–1 mg) and aripiprazole (0.5–2.0 mg), tend to be reserved for incapacitating OCD.

Irritability, aggression, and unprovoked violent behaviours are among the most troubling symptoms of PANS/PANDAS. In addition to early environmental interventions, benzodiazepines are often the first psychotropic used for the treatment of irritability related to anxiety. Antipsychotic medications or mood stabilisers have been shown to reduce the frequency and intensity of aggressive behaviours. Despite their associated adverse effects, they may be indicated for children whose aggressive behaviour poses a risk to themselves or others. FDA-approved medications for treating irritability in autistic children, such as risperidone and aripiprazole, tend to be the treatment of choice.

Current medication only minimises symptoms

Currently, there are no FDA/EMA/TGA approved drug therapies developed specifically for PANS/PANDAS. However, there are treatments that can minimise the severity of symptoms. The usual treatment for acute episodes is to treat the infection associated with the symptoms, with a single course of antibiotics (e.g., penicillin). However, the bacteria can be more difficult to eradicate in the sinuses and other sites, so the antibiotic treatment course may need to be longer than that normally used for streptococcus throat infections.

The PANS/PANDAS Research Consortium's treatment recommendations from 2017 incl:

For mild cases

- Antibiotics
- Nonsteroidal Anti-Inflammatory Drugs (NSAIDS)
- Steroids

For moderate cases

- Antibiotics (short/long term)
- Steroid burst or NSAIDS at immunomodulatory dose
- Intravenous Immunoglobulin (IVIG)
- Cognitive behavioural therapy (CBT) and/or psychiatric care

For severe cases

- Antibiotics (short/long term)
- Steroid burst or NSAIDS at immunomodulatory dose
- Intravenous Immunoglobulin (IVIG)

Drugs under development

There is limited active clinical trials for the treatment of PANS/PANDAS, however there are currently 49 active clinical trials for the treatment of OCD (Figure 44) with 37 trials in Ph3.

Figure 45: Number of OCD drugs in development by stage

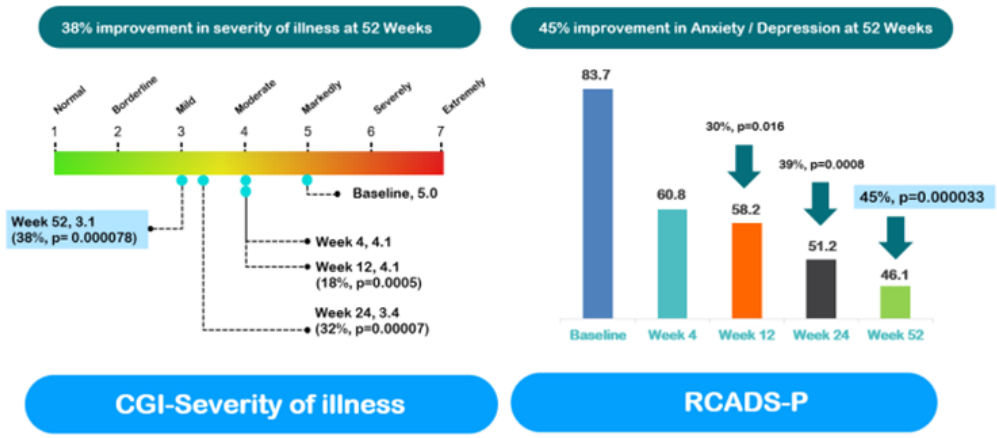
	Development stage								Total Active
	Discontinued	Inactive	Discovery	Preclinical	IND/CTA Filed	Phase I	Phase II	Phase III	
No. of drugs	5	20	2	4	3	2	1	37	49

Source: GlobalData 2024

NTI164 Early Clinical data (to date)

Ph1/2 trial results have been reported by NTI for 15 patients with moderate-severe PANS/PANDAS covering 12-week, (Oct-23), 24-week (Feb-24), and 52-week (Jun-24) time points. At 52 weeks, data collected for the Revised Child Anxiety and Depression Scale – Parent Version (RCADS-P), a 47-item parent-reported questionnaire of youth anxiety and depression, showed a 45% improvement in anxiety and depression for study participants compared to baseline (p=0.000033). Clinical Global Impression (CGI) is a physician/observer-rated scale synthesizing the clinician's impression of the global state of an individual, with NTI reporting a 32% improvement in disease severity among study participants at 52 weeks (p=0.00007).

Figure 46: NTI164 52 week PANDAS/PANS data



Source: NTI

A comparison of trial designs with Octapharma's Panzyga is shown below.

Trial design

Figure 47: Comparison of trial endpoints between NTI164 and Panzyga

Active Ingredient (Brand name) / Company	NTI164 (Cannabis) / Neurotech	Panzyga (IVG) / Octapharma
Highest Stage	Phase 1/2	Phase 3
Approval Date		
Study Completion	2023-10-06	2024-06-29
Regulatory		
Indication	PANS/PANDAS	PANS/PANDAS
Target Population	1-17 years	6-17 years
NCT no / Study name	ACTRN12622001419752	NCT04508530
No. of Enrolled	15	70
Comparator	NA	Placebo
Primary Endpoint	RCADS-P CGI-S	CY-BOCS
Timeframe	Week 4, 12, 16 Extension: Week 28, 40, 52	Week 9
Secondary Endpoint	Blood transcriptomic signature YGTSS scores CY-BOCS scores Conners Scale scores EQ-5D-Y	CGI Parent OC Impact scale Child OC impact scale SNAP-IV 26 PTQ
Timeframe	Week 4, 12, 16 Extension: Week 28, 40, 52	Week 18
Geography	Australia	US, Italy, Sweden

Source: Notes: RCADS-P: Revised Children's Anxiety & Depression Scale, CGI-S: Clinical Global Impression-Improvement, YGTSS: Yale Global Tic Severity Scale, CY-BOCS: Children's Yale-Brown Obsessive-Compulsive Scale, SNAP-IV: Swanson, Nolan, And Pelham Scale-Version IV, PTQ: Parent Tic Questionnaire

Approval Process and Go-To-Market Strategy

Australian market will be precedent for global launch

Similar to other neurological indications NTI is targeting, the first Go-To-Market will be Australia followed by the US, EU and ROW.

NTI is currently in Phase 1/2 for PANS/PANDAS in Australia. MST views commercialisation several years ahead and estimates the following timeline for commercialisation: Aust (FY32); US (FY33); EU (FY34); ROW (FY35).

MSTe the following max market penetrations: Aust (20%); US (20%); EU (20%); ROW (1%). As PANS/PANDAS is more likely to receive treatment in developed nations vs other nations, MSTe a higher penetration rate in developed nations vs ROW.

Typical pricing/Royalty deals

In Jan-23, Staticla SA (a Swiss-based pharmaceutical company) licensed STP7 from Novartis, a drug currently being developed for substance-abuse, which may have applications in wider neurological disorders including PANS/PANDAS.

Figure 48: Examples of recent OCD deals

Date	Acquirer	Target	Deal in Brief	Deal Value
Jan-23	Stalicla	Novartis	Exclusive in-licensing agreement to develop mavoglurant as a treatment for substance-use disorder and neurodevelopmental disorders.	Upfront fees and equity, and development and commercial milestones of up US$270m, plus royalties on sales.

Source: GlobalData 2024, MST

Estimates

The following estimates are for therapeutics intended to treat the symptoms of OCD.

Figure 49: Projected global sales of OCD therapeutics to 2030 (All US$m)

Developer	Product	Global sales 2023	Global sales 2024F	Global sales 2025F	Global sales 2026F	Global sales 2030F	Peak sales	Peak sales year to 2030
Compass Pathways	Psilocybin	-	-	-	24	1,087	1,087	2030
H. Lundbeck	Cipralex/Lexapro	310	274	254	238	184	310	2023
GSK	Seroxat/Paxil	-	133	127	119	92	133	2024
Eli Lilly	Prozac family	-	45	30	20	10	45	2024

Source: GlobalData 2024

Competition & Risk

Clinical trials – There is a risk that the clinical trials may not achieve their desired outcomes or may suffer delays. In order to receive Australian Therapeutics Goods Administration (TGA) approval, NTI is currently conducting four clinical trials in four different neurological indications. Three of these trials are in Ph1/2 and one is in Ph2/3. MST notes that NTI may need to conduct further clinical trials to receive approval in Australia. None of the current clinical trials are approved by the US FDA. NTI will need to conduct further clinical trials approved by the US FDA to enter the US market. Further, factors such as patient recruitment, regulatory approvals, and funding may result in delays or abandonment of the project(s).

Efficacy & Side effects – NTI164 efficacy is still being determined in current clinical trials. Data to date is promising but there is a risk that larger clinical trials or real-world data prove differently. Similar to any other medical therapy, drug tolerability is important and serious side effects could pose a risk to approval. MST notes medical cannabis has been shown to be safe and there is another cannabis-derived product already approved in the US market. MST also notes NTI is targeting niche neurological conditions and therefore the hurdle for approval is lower.

During the review of Epidiolex, the USA FDA found certain safety risks, and identified the potential for liver injury as a risk for THC.

Reimbursement – NTI is targeting niche neurological disorders with low incidence. There is a risk that some of these disorders may not be adequately reimbursed due to their complexity and scarcity. It could also be the case that reimbursement agencies do not reimburse cannabis-derived therapeutics.

Regulatory risk – NTI164 is a cannabis-derived product which is susceptible to regulation risk regarding cannabis and botanical therapeutics. It is possible that NTI's target markets place restrictions on or maintain medicinal cannabis's illegal status. To date, the US FDA has only approved one cannabis-derived drug and two synthetic analogs.

Intellectual property – NTI has three patent families (Composition, Combination and Methods). Two families have now entered the national phase and one family has entered the international (PCT) phase. If patents are successful approved, NTI164 will be patent protected until at least CY41. No patents as of yet have been granted and MST estimates it will take up to circa 18mths to 2yrs to be issued.There is a risk that the patents are not granted as botanical extracts can face challenges in proving novelty and inventiveness.

Sentiment risk – Medicinal cannabis has a long history of negative sentiment as it was once an illegal substance globally. However, there has been an increasing acceptance with >40 countries legalising its medicinal use including the key markets NTI is targeting of US, Aust and EU.

Funding risk – MSTe NTI will be free cashflow break even in FY30 and will need to raise capital to fund its clinical trials. MSTe NTI will raise $13.3m & $26.6m (net of fees) in 1HFY25 & 1HFY26 at 0.14cps & 0.28cps respectively (both 100m share issuances). Slower than forecast revenue growth or unexpected costs could force the company to seek additional funding.

Competition Risk – NTI is subject to the standard competition risks of any pharmaceutical or medical device company. The relatively small scale of the sellable products and the limited resources available to the executive team exacerbate this risk. A well-resourced and large-scale competitor could disrupt NTI's plans should they choose to directly compete. Mitigating this risk is the niche nature of NTI's target populations. MST has outlined in this report the number of active clinical trials for each indication NTI is treating.

Manufacturing/production risks – NTI is reliant on a single outsourced contract manufacturing organisation 'Fenix' for the production of their key drug NTI-164. We are not aware of the capabilities of this third party so we cannot determine the co-dependency between the two companies. The single-source nature of the manufacturing supply creates price risk and potential for production disruption. NTI claims adherence to Good Agricultural and Collection Practices (GACP) by Fenix International Group (a Melbourne-based Contract research organisation [CRO]) to manufacture 120 litres of NTI164 per year and is working on further scaling up manufacturing capabilities. To put this in perspective of dosing, the daily dose for a 50kg child is ~1g/day.

Purity – The cannabis plant contains >80 cannabinoids. The solvent used to extract NTI164 is Cobram olive oil (high in fatty acids). Two of the six cannabinoids found in NTI164 are considered functional impurities and therefore do not require extensive purity testing (as they are <20% of composite). The remaining cannabinoids need to be evaluated for purity. NTI claim they understand the potency of each cannabinoid and are able to manage the risk of impurities.

Third parties – NTI is reliant on Contract Research Organisation (CRO) Fenix Innovation Group (Fenix) to manage growers and extraction for NTI164 and assist with clinical trials. NTI also has a strategic collaboration that leverages Dolce Cann's unique cannabis strains and NTI's expertise in neurological research.

Third party relationships open up NTI to risk from:

- Outside financial, administrative and supply issues
- Regulatory approvals 'tether' NTI to certain manufacturers into the longer term
- Potential issues in evolving manufacturing capabilities necessary to scale
- 3rd party reputational risk; MST note a prior conviction relating to a Fenix director. In MST's view, this does not impact the provision of CRO services to NTI.

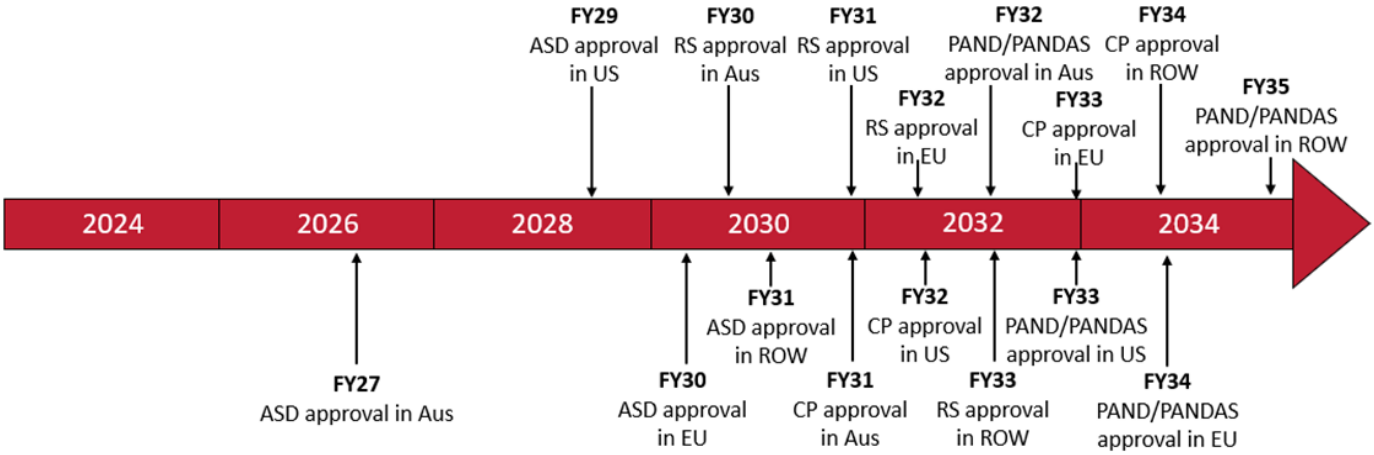
Financials

Profit & Loss

MST NTI model references Neuren Pharmaceuticals (NEU.AX) as a comparable company, which has comparables in terms of rare neurological disorders, royalty deal for US and EU launches and milestone payments. NEU is also a useful guide in terms of speed of adoption.

MSTe NTI164 is to be commercialised across different indications/geographies (Figure 50).

Figure 50: MSTe timeline of commercialisation of NTI164 across indications/geographies



Source: GlobalData 2024

Revenue

MST expects NTI will conduct a two-stage launch as follows:

- **Stage 1** – Australia from FY27 – with the initial launch in ASD. In FY30, MSTe revenue in Aust is expected to reach $44m. MST assumes NTI will be eligible to an R&D Tax Grant worth ~5% R&D spend until the company begins Australian commercialisation in FY27.
- **Stage 2** – US entry from late FY29 with the initial launch in ASD. In FY35, MSTe revenue in the US will reach $520m. MST assumes NTI will enter into a licensing agreement similar to the agreement NEU signed with Acadia Pharmaceuticals (NASDAQ: ACAD).
- NEU's licensing agreement including the royalty scheme and milestone payments established with ACAD were used to forecast NTI's revenue and journey to market. The implied royalty scheme is tiered royalties ranging from mid-teens to low 20%.

Other key assumptions:

Penetration

MST forecasts gradual market penetration in each market with max penetration as follows:

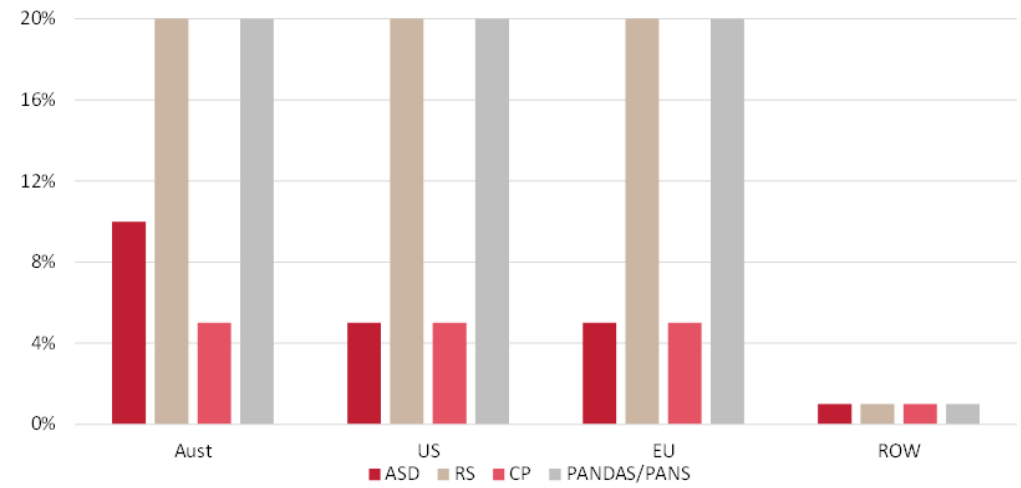
- **ASD** - Aust (10%); US (5%); EU (5%); ROW (1%)
- **RS** - Aust (20%); US (20%); EU (20%); ROW (1%)
- **CP** - Aust (5%); US (5%); EU (5%); ROW (1%)
- **PANS/PANDAS** - Aust (20%); US (20%); EU (20%); ROW (1%)

Pricing

MST forecasts expect pricing to be similar to that of Epidiolex:

- **Aust/EU:** A$24k
- **ROW:** A$12k
- **US:** A$49k

Figure 51: Market Penetration



Source: MSTe

Figure 52: Revenue vs EBITDA – MSTe significantly uplift in both from FY30 onwards

Source: MSTe, NTI

Base case MSTe at 9% and 1.5% penetration of the ASD market in Australia and in the US with $168m in sales and EBITDA of $145m (86% margin).

Costs

Royalty Expense

- In Jul-20, NTI signed a licensing agreement to acquire the developmental and commercialisation rights of NTI164 from Dolce Cann Global. As part of the deal, NTI agreed to issue Dolce shares upfront with the only forward commitment being the allocation of <5% royalties on sales. MSTe royalty to Dolce is 3% in perpetuity.

R&D

- NTI say they are operating a 'cash flow light' model targeting the Australian market first. Clinical trials in Australia are significantly cheaper to conduct than in the US. NTI is currently conducting 4 clinical trials in Australia with one trial in Ph2/3 (ASD) and the remainder in Ph1/2 (RS, CP and PANS/PANDAS).
- MST assumes NTI will eventually sign a licensing agreement with a much larger partner who will take on the majority of costs needed to complete late-stage Ph3 clinical trials in the US.
- The costs captured in the Aust clinical trial costs including: labour, materials, manufacturing, contract research organization, internal system and post clinical trial analysis. The only cost that isn't including in the forecast is the pre-commercial launch cost which will likely be deferred to the licensing partner.

- MST assumes 10% YoY R&D cost growth until FY27. From FY27 onwards, it is also assumed that R&D costs will rise by 20% YoY as NTI begins working with licensing partners on clinical trials in the US.

OPEX (ex R&D)

MST OPEX (ex R&D) to grow at 5% until FY27. From FY29 onwards, OPEX (ex R&D) ramps up significantly to 10% YoY growth as NTI begin to focus on commercialisation ex-Aust markets.

Figure 53: NTI P&L – MST expects a step up in revenue in FY30E

NTI P&L (A$m)	FY22	FY23	FY24E	FY25E	FY26E	FY27E	FY28E	FY29E	FY30E	FY31E
Royalty Income	0.0	0.0	0.0	0.0	0.0	0.0	1.8	7.4	25.8	91.8
Licensing/milestone revenue	0.0	0.0	0.0	0.0	0.0	0.2	12.9	12.1	142.4	219.8
Total sales revenue	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.2**	**14.7**	**19.5**	**168.3**	**311.6**
Other income/expense (incl R&D Grant & Royalty Exp)	0.6	1.2	3.2	2.3	2.5	2.8	-0.4	-0.6	-5.0	-9.3
Total group revenue	**0.6**	**1.3**	**3.2**	**2.3**	**2.5**	**3.0**	**14.2**	**18.9**	**163.2**	**302.2**
R&D costs	-2.6	-6.5	-5.4	-6.0	-6.6	-7.9	-9.4	-11.3	-13.6	-16.3
Corporate and administrative costs	-0.7	-1.0	-0.9	-0.9	-0.9	-1.0	-1.1	-1.2	-1.4	-1.5
Share based payment expense	-0.6	-1.6	-1.4	-1.4	-1.5	-1.6	-1.8	-2.0	-2.2	-2.4
Other expenses	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total operating expenses	-4.0	-9.0	-7.6	-8.3	-9.0	-10.6	-12.4	-14.6	-17.2	-20.3
EBITDA	**-3.4**	**-7.8**	**-4.4**	**-6.0**	**-6.5**	**-7.5**	**2.2**	**4.9**	**151.1**	**291.3**
D&A	0.0	0.0	0.0	0.0	0.0	0.0	-0.1	-0.2	-1.7	-3.1
EBIT	**-3.4**	**-7.8**	**-4.4**	**-6.0**	**-6.5**	**-7.5**	**2.1**	**4.7**	**149.4**	**288.2**
Net interest	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
PBT	**-3.4**	**-7.8**	**-4.4**	**-6.0**	**-6.5**	**-7.5**	**2.1**	**4.7**	**149.4**	**288.2**
Tax	0.0	0.0	0.0	0.0	0.0	0.0	-1.5	-2.7	-44.8	-86.5
NPAT	**-3.4**	**-7.8**	**-4.4**	**-6.0**	**-6.5**	**-7.5**	**0.6**	**2.0**	**104.6**	**201.7**
Revenue growth		1.1	1.6	-0.3	0.1	0.2	3.7	0.3	7.6	0.9
Opex growth		128%	-15%	9%	9%	17%	17%	18%	18%	18%
EBITDA growth		132%	43%	-35%	-8%	16%	-130%	118%	2989%	93%
R&D % of revenue	424%	515%	169%	259%	259%	260%	66%	60%	8%	5%
Corporate and administrative costs % of revenue	424%	515%	169%	259%	259%	260%	66%	60%	8%	5%
Share based payment expense % of revenue	119%	77%	27%	39%	37%	34%	8%	7%	1%	0%
Other expenses % of revenue	653%	721%	238%	360%	356%	349%	87%	77%	11%	7%
EBITDA margin	-553%	-621%	-138%	-260%	-256%	-249%	16%	26%	93%	96%
EBIT margin	-553%	-621%	-138%	-260%	-256%	-249%	15%	25%	92%	95%
NPAT margin	-553%	-621%	-138%	-260%	-256%	-249%	4%	10%	64%	67%

Source: NTI, MSTe

Balance Sheet

Capital management

- **Cash** - NTI has a proforma cash balance of A$11.6m as of 30 Jun-24. NTI raised $10m in Apr-24 ($9.4m after transaction costs)
- **Debt** - NTI has no debt. MSTe does not assume any debt raising.

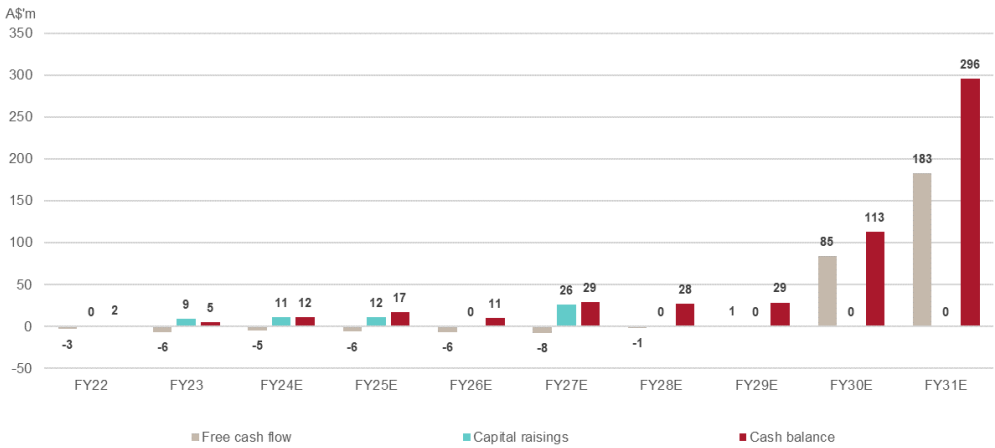
Figure 54: NTI Balance Sheet

NTI Balance Sheet (A$m)	FY22	FY23	FY24E	FY25E	FY26E	FY27E	FY28E	FY29E	FY30E	FY31E
Cash	1.9	5.0	11.6	17.1	10.6	28.9	27.7	28.8	113.3	296.1
Trade & other receivables	0.1	0.3	0.0	0.0	0.0	0.0	1.9	2.7	22.8	41.7
Inventories	0.0	0.0	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.2
Other	0.0	0.0	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
Total current assets	**2.0**	**5.3**	**12.1**	**17.6**	**11.1**	**29.5**	**30.1**	**32.1**	**136.6**	**338.4**
Property, plant & equipment	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-0.1	-0.5	-1.3
Intangible assets	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.5	1.3
Other	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total non-current assets	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**
Total assets	**2.0**	**5.3**	**12.1**	**17.6**	**11.1**	**29.5**	**30.1**	**32.1**	**136.6**	**338.4**
Trade & other payables	0.6	1.3	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Current tax liabilities	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Interest-bearing liabilities	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Other	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total current liabilities	**0.6**	**1.3**	**0.1**	**0.1**	**0.1**	**0.1**	**0.1**	**0.1**	**0.1**	**0.1**
Interest-bearing liabilities	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Other	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total non-current liabilities	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**
Total liabilities	**0.6**	**1.3**	**0.1**	**0.1**	**0.1**	**0.1**	**0.1**	**0.1**	**0.1**	**0.1**
Net assets	**1.4**	**4.0**	**12.0**	**17.5**	**11.0**	**29.4**	**30.0**	**31.9**	**136.5**	**338.2**
Contributed equity	25.8	34.4	46.7	58.2	58.2	84.1	84.1	84.1	84.1	84.1
Reserves	4.3	6.0	6.2	6.2	6.2	6.2	6.2	6.2	6.2	6.2
Retained earnings	-28.7	-36.4	-40.9	-46.9	-53.4	-60.9	-60.4	-58.4	46.2	247.9
Total equity	**1.4**	**4.0**	**12.0**	**17.5**	**11.0**	**29.4**	**30.0**	**31.9**	**136.5**	**338.2**

Source: NTI, MSTe

- **Share issuance –** MST assumes that NTI will raise capital in the future with an estimate of $11.5m & $25.9m (net of fees) in 1HFY25 & 1HFY27 at 0.12cps & 0.18cps, respectively (both 100m share issuances).
- **Exercise of Options:** There are ~111.7m company-issued options yet to be exercised with strike prices in the range of $0.0589ps to $0.15ps & expirary dates ranging from Sep-24 to Dec-27.

Figure 55: MST recognises NTI needs capital to fund Aust clinical trials



Source: MSTe, NTI

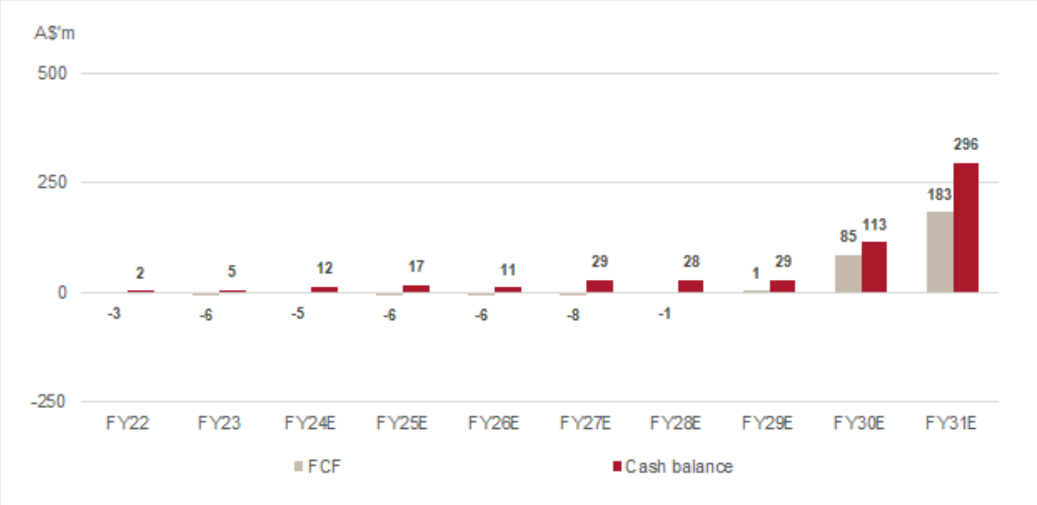
- **Performance rights & share issuance related to Fenix –** As part of the agreement between NTI and Fenix, NTI will issue a total of 60m shares. The details of these issuances and the dates for which they will be issued are outlined in Appendix C.

MST recognises that NTI will need to raise even further capital if the management decides to self-fund their Phase 3 clinical trials.

Cash Flow

- **Stage 1** - MST expects NTI to begin generating receipts from customers in Aust in FY27. The cash generated in Aust is assumed to ramp up over several years. The cashflow generated in Australia will fund the business without the need for further capital raisings.
- **Stage 2** - In FY29, US Commercialisation begins which will drive free cash flow positivity in FY30. From FY30 onwards, commercialisation in multiple indications and geographies is expected to begin and generate significant receipts.

Figure 56: FCF vs Cash reserves. Major cash uplift once NTI164 enters US market



Source: MSTe, NTI

- Other operating cash flows including R&D tax credit grant which will support funding for the current Aust clinical trials. MSTe the R&D tax credit grant will be available until Aust commercialisation in FY27.

Figure 57: NTI Cash Flow Statement – MST expects NTI to be FCF positive in FY29

NTI Cash Flow Statement (A$m)	FY22	FY23	FY24E	FY25E	FY26E	FY27E	FY28E	FY29E	FY30E	FY31E
Operating cash flows										
Receipts from customers / other	0.0	0.0	0.0	0.0	0.0	0.2	14.7	19.5	168.3	311.6
Payments to suppliers & employees	-3.6	-7.6	-7.8	-8.3	-9.0	-10.6	-12.0	-14.0	-12.1	-10.9
Income tax paid	0.0	0.0	0.0	0.0	0.0	0.0	-1.5	-2.7	-44.8	-86.5
Other operating cash flows	0.6	1.2	3.1	2.3	2.5	2.7	-2.3	-1.4	-25.1	-28.3
Net operating cash flows	**-3.0**	**-6.3**	**-4.7**	**-6.0**	**-6.5**	**-7.6**	**-1.1**	**1.3**	**86.2**	**185.9**
Investing cash flows										
Capex (R&D and PP&E)	0.0	0.0	0.0	0.0	0.0	0.0	-0.1	-0.2	-1.7	-3.1
Payment for investment in controlled entity	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Other investing cash flows	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Net investing cash flows	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**-0.1**	**-0.2**	**-1.7**	**-3.1**
Financing cash flows										
Proceeds from issues of shares	0.0	9.4	11.2	11.5	0.0	25.9	0.0	0.0	0.0	0.0
Proceeds from borrowings	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Payment of dividends	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Other financing cash flows	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Net financing cash flows	**0.0**	**9.4**	**11.2**	**11.5**	**0.0**	**25.9**	**0.0**	**0.0**	**0.0**	**0.0**
Net cash flow	**-2.9**	**3.1**	**6.6**	**5.5**	**-6.5**	**18.3**	**-1.3**	**1.1**	**84.5**	**182.8**
Closing cash balance	1.9	5.0	11.6	17.1	10.6	28.9	27.7	28.8	113.3	296.1
Free cash flow	**-3.0**	**-6.3**	**-4.7**	**-6.0**	**-6.5**	**-7.6**	**-1.3**	**1.1**	**84.5**	**182.8**

Source: NTI, MSTe

Comparable valuation – NTI is trading at a massive discount to MST'S valuation

MST's valuation of A$531m (A$0.60cps) for NTI at the current stage of development. This compares to ~US$1.45b for Epidiolex (GW Pharma), at time of launch of Ph2/3 trials for Epidiolex in the US. This is a massive discount to NTI's market cap of A$75m and MST's valuation of A$530m.

We view this as a like-for-like comparable to GW Pharma in regard to: (1) Pre-revenue; (2) Developing a cannabis-derived drug; and (3) Both companies had their cannabis-derived drug commencing Ph2/3 in an indication. MST acknowledges that a major difference between the two companies is that NTI's clinical trials are registered in Aust vs GW Pharma in the US.

Figure 58: GW Pharma Market Valuation was ~US$1.45b when it commenced Ph2/3

Source: MST, GW Pharma. Note: US FDA approvals: Lennox-Gastaut Syndrome (LGS), Dravet Syndrome (DS) & Tuberous Sclerosis Complex (TSC)

Valuation & Risks

MST values NTI at A$0.60ps using an NPV on future earnings (current share price of A$0.08ps).

The NPV calculations consider for:

- **Probability of approval** - MST risk adjusts the NPV calculation for the risk of approval. As trials progress with positive safety & efficacy data, MST will adjust upwards the probability of approval which will lead to an increase in valuation.
- **Discount rate** – A 15% discount rate to future earnings is used.

Figure 59: NAV Valuation – MST Values NTI at A$0.60cps

Neurodevelopmental Syndrome & Analogue	Current Phase (Aust registered only)	Incidence Rate	Addressable Market Aust	Addressable Market USA	Addressable Market EU	Addressable Market ROW	Commercial-isation Date (Aust 1st Market)	Probability	NPV A$m
ASD	Ph2/3	1/100	178k	2m	680k	24m	2027	70%	361
RS	Ph1/2	1/10k to 1/15k (mostly girls)	380	6-9k	9-14k	40-55k	2030	50%	114
CP	Ph1/2	2-3 in every 1k live births	34-40k	500k	1.5m	20m	2031	50%	55
PANS/PANDAS	Ph1/2	1/11k	725	6.6k	8k	182k	2032	50%	1
Discount Rate	0.15							NPV A$m	531
								Shares on Issue	893
								NPV per share	0.60

Source: NTI, MSTe

Board and Management

Execution credibility

In MST's view, NTI board and management is well rounded and capable of executing, particularly for the Australian launch phase. We would expect future key appointments to align with NTI's global aspirations.

Profile of Board – in brief

Mark Davies, Chairman

- **Tenure:** Appointed Apr-19
- **Previous Experience:** >20 years in investment banking, specialising in corporate advice & capital raising.
- **Current Positions:** Managing Director of 1861 Capital & co-founder of Cygnet Capital.

Dr Thomas Duthy, Executive Director

- **Tenure:** Appointed Sep-22.
- **Previous Experience:** >20 years of experience in financial markets including global head of IR & corporate development at Sirtex Medical.
- **Current Positions:** Chairman Arovella Therapeutics (ASX:ALA), Director of Invex Therapeutics (ASX:IXC).

Robert Maxwell Johnston, Non-Executive Director

- **Tenure:** Appointed Apr-24.
- **Previous Experience:** Held senior roles in several global companies including 11 years as President & CEO of Johnson & Johnson Pacific.
- **Current positions:** Non-Exec Director of Inoviq

Gerald Quigley, Non-Executive Director

- **Tenure:** Appointed Jul-22.
- **Previous Experience:** >50 years practicing as a community pharmacist
- **Current positions:** Media Health commentator

Profile of Senior Management

Dr Alexandra Andrews, Chief Operating Officer

- **Tenure:** Appointed CEO Mar-22, transitioned to COO Sep-22.
- **Previous Experience:** Director of Operations at NeuroScientific Biopharmaceuticals Ltd.

A/Prof Carolyn Ellaway, Chief Medical Officer

- **Tenure:** Appointed Jul-24
- **Previous Experience:** Internationally recognised clinical geneticist and key opinion leader

Substantial stockholders & option holders

Figure 60: Top 20 Stockholders

Substantial	Numbers	%
Quadrangle Capital Pty Ltd	44,000,000	5.03%
J & J Bandy Nominees Pty Ltd <Bandy P/F A/C>	41,796,178	4.78%
Jalaver Pty Ltd <Falcon Pension A/C>	40,268,347	4.61%
Gleneagle Securities Nominees Pty Limited	37,184,222	4.25%
Dutch Ink (2010) Pty Ltd	33,897,522	3.88%
Remaining Top 20 Shareholders	282,232,717	22.56%
Total of Top 20 Shareholders	**479,378,986**	**54.85%**

Source: NTI

Figure 61: Top 20 Option holders

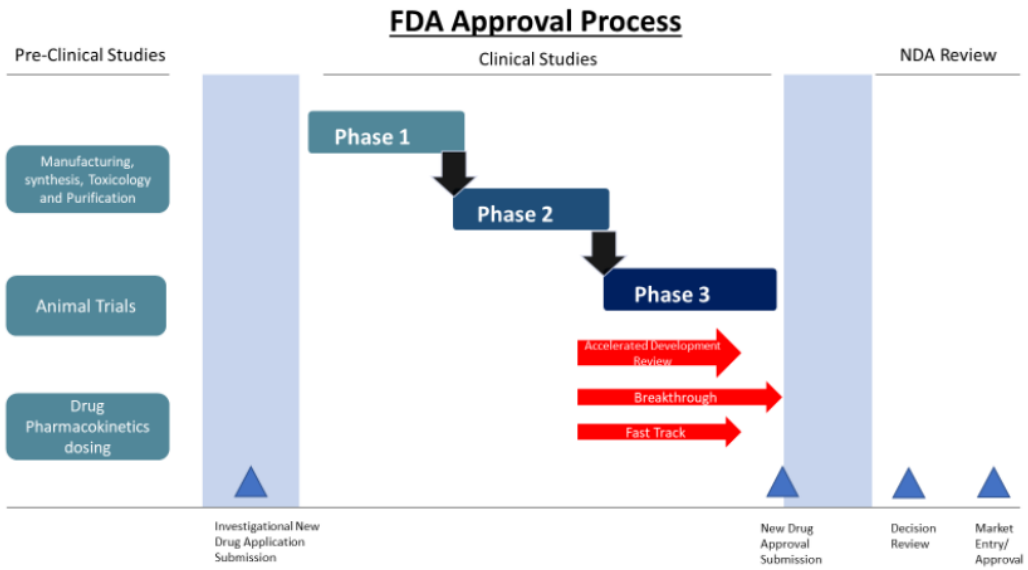
Substantial	Numbers	%
Stonehorse Nominees Pty Ltd	7,500,000	13.64%
The Trust Company (Australia) Limited <MBF A/C:	4,250,000	7.73%
Merrill Lynch (Australia) Nominees Pty Limited	3,750,000	6.82%
Citicorp Nominees Pty Limited	3,245,000	5.90%
Mr Shane Michael Gavegan	1,850,000	3.36%
Remaining Top 20 Shareholders	15,891,048	37.44%
Top 20 Option Holders	**36,486,048**	**66.33%**

Source: NTI

Appendix A - US FDA Clinical Trial program

The clinical trial program typically consists of three phases. The Phase I trial is the first-in-human trial, and is predominantly designed to confirm the safety of the drug. The participants in a Phase I trial usually comprise healthy volunteers. Phase II trials are designed to elicit first signs of efficacy. Efficacy is usually determined by the comparison of the trial drug to the current standard of care (SOC) for the target disorders. However, as there are no approved treatments for some conditions, efficacy can be based on improvement in other measures, such as neurobehavioural assessments by caregivers and health professionals.

Figure 62: FDA Approval Process



Source: FDA

As the US represents the largest pharmaceutical market, many drugs are tested under U.S. Food and Drug Administration (FDA) requirements during global development. Agreements between the different regulatory authorities allows registrational data from FDA-approved trials to support registration in markets such as the EU and Japan. There may be requirements to supply additional data. As an example, registration in Japan may require the clinical trial cohorts to include a defined percentage of Japanese patients or an additional trial that includes Japanese patients.

Over the last fifty years, the FDA has relied on p-values and significance testing to demonstrate the efficacy of new drugs in the premarket approval process. The statistical significance threshold of 0.05 has become the cornerstone of FDA decision-making.

Phase 3 Trial Endpoints

Generally, clinical trials are based on objective endpoints as they are regarded as being unbiased and more accurately measured and analysed. Common trial endpoints include physical changes – eg BP heart rate, tumour size, and oxygen saturation levels.

Clinical trials in neurodevelopmental and psychiatric disorders commonly rely on more subjective measurements. The RSBQ is a 45-item checklist developed to assess behavioural and emotional characteristics of Rett Syndrome patients. Items are rated 0 to 2, where 0 indicates that the behaviour is not true, 1 sometimes true and 2 often true. The questionnaire includes eight subscales: General Mood, Breathing Abnormalities, Hand Behaviours, Repetitive Face Movements, Body Rocking and Expressionless Face, Night-time Behaviour, Fear/Anxiety and Walking/Standing. Such studies can present challenges from a consistency/reproducibility perspective.

From a regulatory perspective, the review of psychiatric and other mental disorder clinical trials shows that there are a number of precedents of FDA approvals based on similar assessment formats.

From a regulatory perspective, review of psychiatric and other mental disorder clinical trials shows that there are a number of precedents of FDA approvals based on similar assessment formats

The Positive and Negative Syndrome Scale (PANSS) is commonly regarded as among the best-validated instruments for assessing schizophrenic patients. Several drugs have been approved using PANSS as the primary endpoint.

The scale is known as the "gold standard" for all assessments of psychotic behavioural disorders. It is a standardized, clinical 30-item interview that rates the presence and severity of positive and negative symptoms, as well as general psychopathology for people with schizophrenia. Symptom severity for each item is rated according to anchoring points on a 7-point scale.

The test parameters include:

- Positive scale including delusions, conceptual disorganization, hallucinations, excitement, grandiosity, suspiciousness/persecution, and hostility.
- Negative scale including blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity, flow of conversation and stereotyped thinking.
- A 16 item General Psychopathology scale assessing a wide range of attributes such as mannerisms and posturing, motor retardation, disturbance of volition, poor impulse, control depression, uncooperativeness, unusual thought content and disorientation.

The FDA recently approved viloxazine extended-release capsules for the treatment of attention-deficit hyperactivity disorder (ADHD). The Phase 3 study was a randomized, double-blind, placebo-controlled, two-arm trial. 374 eligible subjects were randomized 1:1 to viloxazine ER or matched placebo. The primary efficacy endpoint was the change from baseline at the end of study (week 6) in the **Adult ADHD Investigator Symptom Rating Scale (AISRS)** total score. The key secondary endpoint was the change from baseline at the end of study in the Clinical Global Impressions-Severity of Illness (CGI-S) score. A number of additional secondary outcome measures were also included.

Appendix B - Partnership with Fenix Innovation Group (CRO)

In Jun-24, NTI entered into a “Strategic Collaboration Agreement” with Fenix Innovation Group (Fenix), a contract research organisation (“CRO”) based in Melbourne, Australia. Fenix will work closely with NTI to assist in NTI164’s clinical trials and manufacturing.

In return for Fenix’s assistance, NTI will issue shares to Fenix as follows:

- 10m shares which will be subject to voluntary escrow for 12mths from the date of issue.

In addition to performance rights as follows:

- 5m shares upon NTI164 receiving a US Orphan Drug Designation for any paediatric neurological indication. MSTe shares will be issued in 1HFY25.
- 5m shares upon NTI164 receiving an Orphan Drug Designation in the EU for any paediatric neurological indication. MSTe shares will be issued in 1HFY25.
- 5m shares upon NTI164 receiving either a US FDA Investigational New Drug (IND) approval or an EU Competent Authority clearance for a human clinical trial in any paediatric neurological indication in respect of NTI164. MSTe shares will be issued in 1HFY26.
- 10m shares upon NTI signing a licencing deal with a 3rd party for any of the US, EU, Japanese, Canadian or Australian markets to gain registration and subsequent sales of NTI164. The issuance of these shares is contingent on NTI shares trading at a minimum volume-weighted average price (VWAP) A$0.25ps over 5 consecutive days. MSTe shares will be issued in 1HFY27.
- 20m shares upon NTI164 receiving a TGA approval (provisional or otherwise) allowing NTI to market and sell NTI164 in Australia for the treatment of any paediatric neurological disorder. The issuance of these shares is contingent on NTI shares trading at minimum VWAP A$0.30ps over 5 consecutive days. MSTe shares will be issued in 2HFY26.

The performance rights will expire 3 years from the date of issuance. Unconverted performance rights will immediately lapse upon termination of the agreement.

Appendix C - Epidiolex clinical trials in more detail

Case Study - Epidiolex (Cannabidiol/CBD) is a cannabis-derived drug

The US FDA has only approved one cannabis-derived product: 'Epidiolex' for the treatment of seizures in three indications in patients >2yrs old: (1) Lennox-Gastaut syndrome (LGS); (2) Dravet syndrome (DS); and (3) Tuberous Sclerosis Complex (TSC). The drug was developed by GW Pharmaceuticals which was later acquired in Feb-21 by Jazz Pharmaceuticals Plc (NASDAQ: JAZZ-US).

Epidiolex is a naturally occurring cannabis-derived cannabinoid known as cannabidiol (CBD). Unlike the common euphoria experienced when smoking cannabis, Epidiolex does not cause intoxication or euphoria. This is because the main psychoactive cannabidiol in cannabis is Delta-9-tetrahydrocannabinol (THC) and not CBD. While they are both naturally occurring cannabinoids found in the cannabis plant that impact the body by interacting with the endocannabinoid system, they each play different roles. THC is the psychoactive chemical responsible for causing a "high", while CBD is non-psychoactive and responsible for calmer, more relaxed feelings. CBD is a powerful antioxidant, and may support healthy immune function and positive, healthy moods. CBD is well tolerated, even in large doses, and is regarded by the WHO as generally safe.

Figure 63: US FDA approved indications for Epidiolex

Indication	Onset	AED* Resistance	Approval	Efficacy	Side effects
Lennox-Gastaut Syndrome (LGS) - a severe form of epilepsy.	3-5 yrs old	Likely	**US**: Jun-18 **EU**: Sep-19	44% & 41% reduction in drop seizures and total seizures (vs 22% and 14% in placebo)	86% of patients experienced adverse events (vs 69% in placebo) By the end of the trial, 61% patients' adverse events were resolved (vs 64% in placebo) Serious adverse events impacted 20 patients (vs 4 patients in placebo) 12 patients to discontinued treatment (vs 1 patient in placebo)
Dravet Syndrome (DS) - a rare, severe form of epilepsy	1st year of life	Highly likely	**US**: Jun-18 **EU**: Sep-19		
Tuberous Sclerosis Complex (TSC) – leads to benign tumours and seizures.	1st year of life	Highly likely (>60%)	**US**: Jul-20 **EU**: Apr-21	48% reduction in total seizures (vs 24% in placebo)	88-97% of patients experienced adverse events (vs 89% in placebo) Serious adverse events were experienced in 13-21% of patients (vs 2% in placebo)

Source: MST, US FDA, EU EMA, Jazz Pharmaceuticals. Anti-epilepsy drugs

Indications - Lennox-Gastaut Syndrome & Dravet Syndrome

Patients with Lennox-Gastaut Syndrome (LGS) often experience seizures with symptom onset beginning at the age of 3-5 yrs old. Common causes include brain malformations, severe head injuries, central nervous system infections and genetic neuro-degenerative or metabolic conditions. However, 30% of patients have no known cause. First-line treatment is usually anti-epileptic drugs (AED), although LGS patients often experience resistance to these drugs.

Patients with Dravet Syndrome (DS) often experience seizures in their first year of life and usually develop resistance to AED. The common cause of DS is a mutation in the SCN1A gene. First-line treatment is usually AED, but LGS patients often experience resistance to these drugs.

In Jun-18, the US FDA approved Epidiolex to treat LGS & DS in patients aged >2yrs. Epidolex became the first US FDA approved drug derived from the cannabis plant and the first treatment for DS patients. This was followed by EU approval for LGS and DS in Sep-19.

Indication - Tuberous Sclerosis Complex

Patients with Tuberous Sclerosis Complex (TSC) often experience seizures in their first year of life and are also extremely likely to develop resistance to AED (>60% vs 30-40% in the general epileptic population). TSC is a rare disease that causes benign tumours to grow in vital organs and is a leading cause of genetic epilepsy.

In Jul-20, the US FDA also approved Epidiolex (third indication) for the treatment of seizures associated with TSC in patients >1yrs old. This was followed by EU approval in TSC patients >2yrs in Aug-21.

Although TCS is a debilitating disease and patients tend to be heavily medicated, 88-97% of Epidiolex patients suffered non-adverse side effects vs 89% in placebo. Serious adverse events were experienced in 13-21% of the Epidiolex recipients vs 2% in the placebo group.

Clinical research required to bring Epidiolex to market

Across both indications, LGS & DS, the efficacy and safety of Epidiolex was studied in 516 patients across three randomised, double-blind, placebo-controlled clinical trials with one clinical trial being published in the esteemed Lancet journal. Epidiolex was shown in conjunction with other AEDs to reduce the number of seizures LGS/DS patients experienced compared to placebo even in patients who were resistant to AEDs.

To receive approval in TSC, GW Pharma conducted a Ph3 trial in 200 TSC patients over 16wks which showed a reduction in seizures compared to baseline (primary endpoint) of 48% reduction in the Epidiolex group vs 24% in the placebo group ($p<0.01$)

Lancet study - Landmark clinical trial for cannabinoids

The Lancet study was a pivotal clinical trial for cannabinoids which randomised 171 LGS patients across 24 US & EU centres between Epidiolex (86) and placebo (85) treatment. Patients were aged between 2-5 yrs old with the average age being 15 yrs old.

The treatment group arm was initially placed on a two-week dose escalation period and then placed on 20 mg/kg/day of Epidiolex over 12 wks (total 14 wks of treatment period). During the trial, patients were on three AEDs on average having previously tried and discontinued six AEDs on average prior to starting the trial.

The median baseline number of seizures each patient experienced prior to the study was 74 drop seizures per month (a more severe form of seizure). Over the 14 wk treatment period, patients experienced a 44% & 22% reduction in median monthly drop seizures (primary endpoint) in the Epidiolex and placebo group, respectively. The treatment impact of Epidiolex was experienced in the first month of treatment and was maintained throughout the 14 wk treatment period. MST notes that the study demonstrated a statistically significant p-value of 0.0135.

The clinical trial's secondary endpoints included the reduction in total seizure frequency and the number of patients experiencing a >50% reduction in drop seizures. The median percentage reduction of total seizures was 41% for Epidiolex patients vs 14% for the placebo ($p=0.0005$). Further, 44% of patients experienced a 50% reduction in drop seizures vs 24% in the placebo group ($p=0.0043$).

A subjective measure used in most neurological disorders is "Subject/Caregiver Global Impression of Change (S/CGIC) scale". CBD patients/caregivers were significantly more likely to report an improvement in their overall condition with Epidiolex (58%) than placebo (34%).

Side effects were predominantly modest with 86% & 69% of Epidiolex & placebo recipients experiencing an adverse event, respectively. By the end of the trial, 61% and 64% of Epidiolex and placebo patients, respectively, had their events resolved. Serious adverse events impacted 20 patients vs 4 patients in the placebo group. These serious adverse events caused 12 Epidiolex patients to discontinue treatment during the trial compared with 1 patient receiving placebo.

In MST's view, the clinical research required to bring Epidiolex to market was extensive as it was the first cannabinoid to market. Future cannabinoids may not require as extensive research.

Revenue to date

GW Pharmaceutical reported Epidiolex's revenue at +5% vs pcp to US$199m in 1QCY24 and aspires to generate >US$1b in annualised revenue in CY25.

Epidiolex generated >US$2.2b in revenue between May-21 to Mar-24. Jazz-US expects Epidiolex to have additional ex-US launches and indication expansion throughout CY24.

Australian market

Cannabinoids in general are not medically available in Australia. However, cannabinoids such as CBD (Schedule 4 - Prescription Only) & THC (Schedule 8 - Controlled Drug) are medically available. As NTI164's composition is similar to CBD, MST expects if NTI164 were to be approved it would be classified as a Schedule 4 - Prescription Drug.

Other markets have reclassified cannabinoids

The United Nations, United Kingdom and the European Commission have all reclassified cannabinoids as non-narcotics and instead as "novel foods".

Novel food classification poses several benefits

The reclassification of cannabinoids as a novel food has the following implications for NTI164:

1. **Consumer safety -** Being a novel food requires cannabinoids to adhere to food safety and quality standards set by the European Food Safety Authority (EFSA) and the UK's Food Standards Agency (FSA).
2. **Market regulation and standardisation -** Clear guidelines on how cannabinoids are manufactured, distributed and sold.
3. **Research & Development -** Allows companies to conduct R&D activities that can receive Govt grants & tax incentives.

Appendix D - US drug channels

Health coverage basics

NOTE: We will use the term 'manufacturer' to also apply where companies hold 'commercialisation rights or a licence' to market a drug.

US health insurance plans are provided by commercial and public agencies, split across broad provider categories as follows:

1. 65% Commercial insurance market provided via employer or direct purchase
2. 18% Medicare – Federally funded for over +65 yr olds; prescription coverage under Medicare Part D covered separately
3. 18% Medicaid – co-funded Federal/State-run covering the socially vulnerable.

Expect similar coverage to Epidiolex?

Epidiolex is covered for ~97% of applicable patients under commercial insurance plans, Medicare Part D, and some Medicaid programs (the latter varies by state). The list price is around $1,042 for a 60 mL bottle (100 mg/mL concentration).

Many commercial insurance plans cover Epidiolex with patients eligible for manufacturer co-pay savings programs to reduce out-of-pocket costs.

Drug Coverage

Coverage for outpatient drugs is generally included in commercial plans and is an additional purchase under an approved commercial US Medicare Part D plan (each 'element' of care is described and covered separately in Parts A to D. i.e. traditional or basic Medicare full funds Part A inpatient care and Part B outpatient services. However, Part C & D are voluntary and require an additional cost for coverage: Part C – Vision/Hearing/Dental and Part D – prescription drugs).

Some 50M of the ~63M US Medicare beneficiaries choose to enrol in either a: (1) stand-alone or supplement prescription drug plans under Part D; or (2) or switch to a Medicare Advantage (MA) plan that provides all Medicare-covered benefits in Part C & D, the latter covering prescription drugs.

More than 50% of Medicare beneficiaries have now switched to an MA plan. MA plans manage costs by limiting provider networks, requiring prior approval, or authorisation for coverage of some services.

How it works: What happens in the background when a pharmacist fills a prescription

When a covered beneficiary fills a prescription at a retail pharmacy, the pharmacy collects the beneficiary's copayment or coinsurance and dispenses the drug from inventory. The pharmacy passes the copayment to the PBM, and the PBM pays the pharmacy the negotiated reimbursement.

To re-stock inventory, the pharmacy purchases drugs from the wholesaler, who purchases them from the manufacturers. Periodically (e.g., quarterly), the PBM reconciles drug claims and the manufacturer pays the PBM any rebates, incentive payments or fees owed based on their negotiated contracts.

Appendix E – US vs Aust Orphan Drug Designation

Figure 64: Comparison of requirements and benefits for Orphan Drug Designation in the US and Australia.

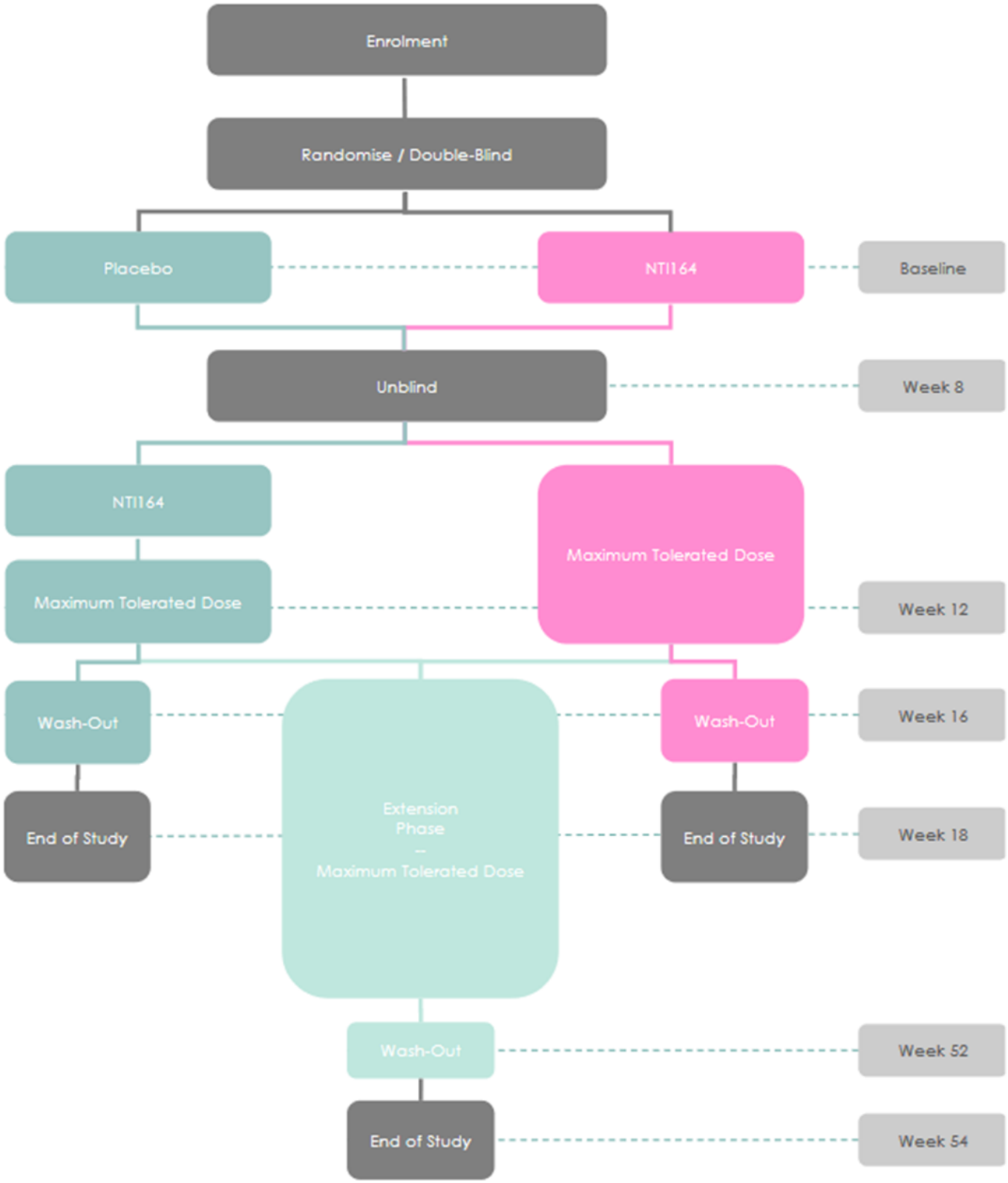
Aspect	US FDA	Australian TGA
Year of introduction	1983	1997
Financial incentives	Tax credits, fee waivers	Fee waivers
Market exclusivity	7 years	No
Scientific advice (protocol assistance)	Yes (free)	No
Aid for research	FDA Orphan Products Grant Program; NIH grants	No
Regulatory tools to accelerated approval	Fast-track approval Breakthrough designation Accelerated approval Priority review designation	
Prevalence condition	< 200,000 in US	< 5 in 10,000 in Australia
Medical need	Clinically superior: shown to provide a significant therapeutic advantage over and above that provided by an approved drug in one or more of the following ways: (i) Greater effectiveness; (ii) Greater safety in a substantial portion of the target populations; (iii) In unusual cases, where neither greater safety nor greater effectiveness has been shown, a demonstration that the drug otherwise makes a major contribution to patient care.	No other therapeutic goods intended to treat, prevent or diagnose the condition are included in the TGA register, OR if any such product exists, the medicine provides a significant benefit in relation to efficacy, safety or a major contribution to patient care.
Comparator	Only (FDA) approved medicinal products.	Any therapeutic goods included in the TGA register
Medical plausibility or scientific rationale	Usually in vivo data.	Usually in vivo data.
Alternative eligibility criteria	Not profitable within 7 years following FDA approval.	Not likely to be financially viable for the sponsor to market the medicine in Australia unless each fee referred to in paragraph 45(12)(c) of the Therapeutic Goods regulations were waived in relation to the medicine
Required Documentation	▪ FDA Form 4035 ▪ Data proving rare disease status ▪ Scientific rationale for the drug ▫ Drug description and MOA relevant to disease/condition ▫ Data: a) clinical studies relevant to drug and disease/condition b) in vivo: if no clinical data, animal studies conducted in a relevant animal model of disease may be considered in vitro: considered with supporting information if no relevant animal model exists for disease and when there is not clinical data ▪ Regulatory status and marketing history	▪ TGA application form ▪ Data proving rare disease status ▪ Attachments ▫ summaries of pivotal studies (e.g. study synopsis) ▫ supporting evidence based on clinical trial data ▫ summaries of any available other important safety data obtained in the preclinical and clinical setting ▫ published papers are highly relevant, the full text of such literature ▫ other forms of literature references or unpublished reports and expert statements ▫ applications for designation which are based on the financial viability of the medicine
Challenges	▪ Proving rare disease status ▪ Demonstrating clinical superiority	▪ Designation valid for only 6 months post-registration (one extension further six months) ▪ Demonstrating financial viability

Source: Global Data 2024, MST

The FDA extends generous financial and regulatory incentives through the ODD program, including tax credits for qualified clinical trials, waivers from user fees, seven years of market exclusivity post-approval, and FDA protocol assistance, expediting drug development.

Appendix F - NTI164 Ph2/3 ASD Clinical Trial

Figure 65: NTI164 Ph2/3 ASD Clinical Trial Methodology



Source: NTI

Appendix G - Disease-modifying vs symptom-control

Until the precise mechanisms underlying many neurological disorders including ASD, RS, and CP are known, it will remain challenging to create targeted drugs that can treat the underlying cause of these diseases. A slight distinction exists for PANS/PANDAS in that the cause of the disease is known to be streptococcus infection and therefore the prevention of such infection can eliminate disease onset. However, once developed, the mechanistic pathology of PANS/PANDAS shares similarities with other disorders in that there is a lack of validated targets for disease-modifying strategies.

Disease-modifying vs symptom-control strategies

There are advantages and disadvantages that apply to drugs with disease-modifying vs symptom-control strategies. Many drugs that solely treat the symptoms of a disease can be considered medical breakthroughs by any measure, with symptom control being a key endpoint that directly impacts quality of life. From a commercial and investment standpoint, symptom-controlling drugs can represent a larger market opportunity as patients will require ongoing treatment. However, a key risk is that upon first entry into the market of a disease-modifying drug, the superior long-term medical and economic benefits often lead to the gradual decline in the usage of drugs that solely treat symptoms.

Drugs derived from medical cannabis including CBD and THC extracts/derivatives have been broadly reported to influence the central nervous system, particularly dopaminergic and serotonergic processes. This provides logical explanation for limited reports of efficacy in childhood epilepsy.

It is reasonable to assume that the aberrant signalling pathways responsible for epileptic seizures could also be driving symptoms (e.g. irritability, involuntary muscle movement, hypersomnia) common to other neurological disorders. However, until peer-reviewed evidence emerges for cannabis-derived products impacting the underlying causes of neurological disease, it appears likely that drugs in this class will be limited to symptom control.

MST notes that the Therapeutic Goods Administration (TGA) has the following view on medicinal cannabis:

"Currently there is limited evidence about the effectiveness of medicinal cannabis for use in different medical conditions. There is also little known about the most suitable doses of individual cannabis products.

This is why, with the exception of one product (nabiximols), medicinal cannabis products are not registered on the Australian Register of Therapeutic Goods (ARTG) and, in like most other countries, are not available as registered prescription medicines.

For a particular product to be registered on the ARTG, a sponsor (usually a company) would need to submit a dossier of evidence on the clinical efficacy, safety and manufacturing quality of a particular medicinal cannabis product to the Therapeutic Goods Administration. At this time, the Australian Government does not subsidise the cost of medicinal cannabis products through the Pharmaceutical Benefits Scheme (PBS)."

Achieving regulatory approval in one indication creates greater confidence that a drug may have potential in other indications and markets.

Appendix H - Drugs in Clinical Trial Development

Figure 66: Number of ASD drugs in development by known molecule type

	Molecule type			Total
	Oligonucleotide	Biologic	Small molecule	
Number of drugs	3	61	148	212

Source: GlobalData 2024

Figure 67: Number of ASD drugs in development by known Mechanism of Action

	Mechanism of Action								Total
	Ion channel inhibitor + Transporter activator + toxin Inhibitor + receptor modulator + Protein & peptide activator	Enzyme activator	Ion channel blocker	Protein & peptide inhibitor	Transporter inhibitor	Enzyme inhibitor	Receptor antagonist	Receptor agonist	
Number of drugs	1 in each category	2	2	6	9	15	38	63	140

Source: GlobalData 2024

Figure 68: Examples of companies and institutions with competing assets

Company	Country	Asset	Therapeutic indication	Dev. stage
Acadia Pharmaceuticals	USA	pimavanserin tartrate	ASD	Phase 3
Astrogen	KOR	AST-001	ASD	Phase 3
Curemark	USA	CM-AT	ASD	Phase 3
Jazz Pharmaceuticals	IRL	cannabidiol	ASD	Phase 3
AbbVie	USA	cariprazine	ASD; Bipolar I disorder	Phase 3
Sumitomo Pharma	JPN	lurasidone hydrochloride	Bipolar Disorder); Schizophrenia; ASD	Phase 3
FamiCord Group	POL	Stem cell therapy	Cerebral palsy; ASD	Phase 3
Zynerba Pharmaceuticals	USA	cannabidiol	ASD	Phase 2
Paxmedica	USA	PAX-101	ASD	Phase 2
Johnson & Johnson	USA	JNJ-5279	Generalized Anxiety Disorder (GAD); ASD	Phase 2
Allos Pharma	USA	arbaclofen	ASD	Phase 2
Jazz Pharmaceuticals	IRL	cannabidivarin	ASD	Phase 2
Tonix Pharmaceuticals	USA	TNX-1900 oxytocin	Eating Disorder; (SAD/Social Phobia); ASD	Phase 2
Aardvark Therapeutics	USA	ARD-501	ASD	Phase 2
Axial Therapeutics	USA	AB-2004	ASD	Phase 2
Roche	SWI	alogabat	ASD	Phase 2
SciSparc	ISR	cannabidiol + palmidrol	ASD	Phase 2
Yamo Pharmaceuticals	USA	metyrosine	ASD	Phase 2
Cox Biosciences	USA	levoleucovorin calcium	ASD	Phase 2
Renascience	JPN	RS-8001	ASD	Phase 2
Nova Mentis BioTech Corp	CAN	psilocybin	ASD	Phase 2
Oryzon Genomics	ESP	vafidemstat	ADHD; ASD; Lewy Body Dementia	Phase 2
The Greater Cannabis Company	USA	CBD + two proprietary compounds	ASD	Phase 2
MapLight therapeutics Inc	USA	zolmitriptan	ASD	Phase 2
Bioprojet SCR	FRA	pitolisant hydrochloride	ASD	Phase 1
Merck	USA	Suvorexant	ASD	Phase 1
Stalicla	SWI	SFX-01	ASD	Phase 1
Enterin	USA	ENT-01	Parkinson's disease; ASD	Phase 1
Palisades Therapeutics	USA	Undisclosed	Dementia; ASD	Phase 1
EuMentis Therapeutics	USA	EM-113, memantine	ASD	Phase 1
Canopy Growth Corp	CAN	cannabidiol 2	ASD	Phase 1
Scioto Biosciences	USA	SB-121	ASD	Phase 1
Mind Medicine MindMed Inc	USA	MM-402	ASD	Phase 1
Stalicla	SWI	ibudilast + bumetanide	ASD	Phase 1
Gedeon Richter	HUN	RGH-338	ASD	Phase 1
IAMA Therapeutics	ITA	IAMA-6	Epilepsy; ASD	Phase 1
Jaguar Therapeutics	USA	JAG-201 gene therapy	SHANK3 Mut in ASD, Phel-McD Syndrome, etc.	Phase 1
BrainStorm Cell Therapeutics Inc	USA	debamestrocel	Parkinson's; HD; ASD; Peripheral Nerve Injury	Phase 1
Neuroventi	KOR	NV01-A02, E01, A03	ASD	Phase 1
Compass Pathways	UK	psilocybin	ASD	Preclinical
Intrinsic Medicine	USA	OM-001, OM-002	Anxiety Disorders; ASD	Preclinical
Connecta Therapeutics	ESP	CTH120 small molecule	ASD; Rett, Down's, DiGeorge syndromed	Preclinical
Q BioMed	USA	QBM-001	ASD	Preclinical
Epigen Biosciences	USA	EPGN-1370	ASD	Preclinical
EuMentis Therapeutics Inc	USA	EM-036	Alzheimer's; ASD; Rett syndrome	Preclinical
Nova Mentis BioTech Corp	CAN	NM-1014	ASD	Preclinical
Beijing Joekai Biotechnology	CHN	Agiforget	ASD	Preclinical
Psyneurgy Pharmaceuticals	USA	CDD-0102A	ASD	Preclinical
Neuroventi	KOR	NV01-062	ASD	Preclinical
MD Healthcare	KOR	MDH-014	ASD; Alzheimer's; Parkinson's; ALS	Preclinical
BMSystems	FRA	CADI-T2011	ASD	Preclinical
Boehringer Ingelheim	GER	KNX-200	(SAD/Social Phobia); ASD	Preclinical
Beyond Air	USA	Neuronal NOS Inhibitors	ASD; Unspecified Neurologic Disorders	Preclinical
Neurexstem	USA	T-NRX-06, 07	ASD	Preclinical
Intrinsic Medicine	USA	OM002, a 2'FL HiMO drug	ASD	Preclinical
Astrogen	KOR	AST-003	ASD	Preclinical
Paxmedica	USA	PAX-102	ASD	Preclinical
Axial Therapeutics	USA	AB-2004 PTR	ASD	Preclinical
Kingdom Therapeutics	IRL	KT 20610 cannabinoid	ASD	Preclinical

Source: GlobalData 2024

Figure 69: Number of Rett syndrome drugs in development by known Mechanism of Action

	Mechanism of Action								Total
	Ion channel inhibitor + Transporter activator + toxin Inhibitor + receptor modulator + Protein & peptide activator	Enzyme activator	Ion channel blocker	Protein & peptide inhibitor	Transporter inhibitor	Enzyme inhibitor	Receptor antagonist	Receptor agonist	
Number of drugs	1 in each category	3	3	5	10	13	18	58	3

Source: GlobalData 2024

Figure 70: Examples of companies and institutions with competing assets

Company	Country	Asset	Therapeutic indication	Development stage
Anavex Life Sciences	USA	blarcamesine hydrochloride	Rett syndrome	Phase 3
Biomed Industries	USA	NA-921	Rett syndrome	Phase 3
PharmaTer Holdings	CAN	racemic ketamine	Parkinson's; Drug-induced dyskinesia; Rett syndrome	Phase 2
AMO Pharma	UK	AMO-04, glutamate modulator	Rett syndrome	Phase 2
Taysha Gene Therapies	USA	TSHA-102	Rett syndrome	Phase 1/2
Neurogene	USA	NGN-401	Rett syndrome	Phase 1/2
Acadia Pharmaceuticals	USA	NNZ-2591, synthetic analogue of cyclo-glycyl-proline (cGP)	Rett syndrome; Fragile X syndrome	Phase 1
GEXVal	JAP	GXV-001	Rett syndrome; Fragile X syndrome; Angelman syndrome	Phase 1
Neurolixis	USA	NLX-101, activates serotonin 5-HT1A receptors	Rett syndrome; Fragile X syndrome	Phase 1
Unravel Biosciences	USA	RVL001, vorinostat formulation	Rett syndrome	Phase 1
Unravel Biosciences	USA	RVL002 mitochondrial metabolism	Rett syndrome; Fragile X syndrome; Leigh syndrome	Phase 1
DepYmed	USA	DPM-1003	Rett syndrome	Phase 1
Alcyone Therapeutics	USA	ACTX-101, AAV9-delivered miREX X-reactivation therapy	Rett syndrome	Preclinical
Prilenia Therapeutics Development	NED	pridopidine hydrochloride	Rett syndrome; Fragile X syndrome; Alzheimer's; Parkinson's	Preclinical
Connecta Therapeutics	ESP	CTH120 small molecule	ASD; Rett syndrome; Down's syndrome; DiGeorge syndrome	Preclinical
Connecta Therapeutics	ESP	CTH122 small molecule	Rett syndrome; Fragile X syndrome	Preclinical
Thiogenesis Therapeutics	CAN	TTI-0102	Rett syndrome	Preclinical
NeuroCores	JPN	KIT-13 s ynthetic derivitative of plasmalogen	Rett syndrome	Preclinical
Astrogen	KOR	AST-004	Rett syndrome	Preclinical
Aribio	KOR	AR1006 natural product	Rett syndrome	Preclinical
Herophilus	USA	HRP-12975	Rett syndrome	Preclinical
PharmatrophiX	USA	LM-22A4	Dravet syndrome; Rett syndrome	Preclinical
Epeius Pharma	ISR	CNS delivery platform to introduce MECP2 to MECP2 deficient neurons	Rett syndrome	Preclinical
Lucy Therapeutics	USA	mitochondrial-based small molecule therapies	Rett syndrome	Preclinical
Shape Therapeutics	USA	programmable RNA medicine	Rett syndrome	Preclinical
IAMA Therapeutics	ITA	IAMA-299	Rett syndrome	Preclinical
VICO Therapeutics	NED	RNA editing targeting Mecp2-R255X	Rett syndrome	Preclinical

Source: GlobalData 2024

Figure 71: Number of cerebral palsy drugs in development by known molecule type

	Molecule type		Total
	Biologic	Small molecule	
Number of drugs	21	7	28

Source: GlobalData 2024

Figure 72: Number of cerebral palsy drugs in development by known Mechanism of Action

	Mechanism of Action					Total
	Ion channel blocker	Receptor antagonist	Protein and peptide inhibitor	Enzyme inhibitor	Receptor agonist	
Number of drugs	1	1	2	2	3	58

Source: GlobalData 2024

Figure 73: Examples of companies and institutions with competing assets

Company	Country	Asset	Therapeutic indication	Development stage
Cell Tech Pharmed	IRN	Vartocell	Spastic CP	Phase 3
FamiCord Group	POL	Stem cell therapy	CP; ASD	Phase 3
ROHTO Pharmaceutical	JPN	UDI-001	Infantile CP	Phase 2
PT Prodia StemCell Indonesia	IDN	Umbilical cord mesenchymal stem cells	CP	Phase 2
Kashiv BioSciences	US	trihexyphenidyl hydrochloride ER	CP	Phase 2
Hope Biosciences	US	HB-adMSCs autologous	CP	Phase 1
S-Quatre Corporation	JPN	GCT-103 autologous SQ-SHED	CP	Phase 1
First Affiliated Hospital of Anhui Medical University	CHN	ANGE-S001 stem cells	CP	Phase 0
Hope Biosciences	US	HB-adMSC allogeneic	CP	IND/CTA filed
StemCyte	US	Regenecyte	CP	Preclinical
Baylx	US	BX-U007, hUC-MSC	CP	Preclinical
Meridigen Biotechnology	TWN	UMC-11910 stem cells	CP	Preclinical
Viatris	US	onabotulinumtoxinA biosimilar	CP; Migraine; Lower limb muscle spasticity; Spasmodic torticollis; Upper limb muscle spasticity	Preclinical
BrainRepair UG	GER	Stem cell therapy	CP	Preclinical

Source: GlobalData 2024

Figure 74: Number of cerebral palsy drugs in development by known Mechanism of Action

	Mechanism of Action						Total
	Transporter activator	Antigen inhibitor	Transporter inhibitor	Enzyme inhibitor	Receptor antagonist	Receptor agonist	
Number of drugs	1	1	3	3	14	14	36

Source: GlobalData 2024

Figure 75: Number of OCD drugs in development by known molecule type

	Molecule type		Total
	Biologic	Small molecule	
Number of drugs	2	33	35

Source: GlobalData 2024

Figure 76: Examples of companies and institutions with competing assets

Company	Country	Asset	Therapeutic indication	Development stage
Biohaven	US	BHV-4157 troriluzole	OCD	Phase 3
Biogen	US	rituximab	Schizophrenia; OCD	Phase 2
Ceruvia Lifesciences	US	psilocybin	OCD	Phase 2
Compass Pathways	UK	psilocybin	OCD	Phase 1
MycoMedica Life Sciences	US	psilocybin [INN]	OCD; Opioid addiction	Phase 1
Omeros Corp	US	OMS-527, PDE7 inhibitor	OCD; Alcohol dependence; Smoking cessation; Binge eating disorder; Movement disorders	Phase 1
Filament Health Corp	CAN	psilocybin [INN]	OCD; PTSD	Preclinical
Phytecs	US	PECS-101, CBD derivative	Anxiety disorders; Depression; OCD; Psychosis	Preclinical
Parow Entheobiosciences	US	P601, psychedelic	OCD	Preclinical

Source: GlobalData 2024

Personal disclosures

Andrew Goodsall and Roy Taouk received assistance from the subject company or companies in preparing this research report. The company provided them with communication with senior management and information on the company and industry. As part of due diligence, they have independently and critically reviewed the assistance and information provided by the company to form the opinions expressed in this report. They have taken care to maintain honest and fair objectivity in writing this report and making the recommendation. Where MST Financial Services or its affiliates has been commissioned to prepare content and receives fees for its preparation, please note that NO part of the fee, compensation or employee remuneration paid has, or will, directly or indirectly impact the content provided in this report.

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The companies and securities mentioned in this report, include:

Neurotech International Ltd (NTI.AX) | Price A$0.07 | Valuation A$0.60*;

Price and valuation as at 16 August 2024 (not covered)*

Additional disclosures

Within the past 12 months, MST and its associates have provided and received compensation for investment banking services, including acting as Joint Lead Manager for the Apr 2024 capital raising of approximately A$10 million for Neurotech International Ltd (NTI.AX).

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