Stock Data

Share Price:	0.33p
Market Cap.:	£7.03m*
Shares in issue:	2,129.62m*
52 week high/low:	1.39p/0.25p

**Post-Placing numbers*

Company Profile

Sector:	Health Care
Ticker:	TCF
Exchange:	AIM

Activities

TheraCryf plc ('TCF', 'TheraCryf' 'the Group') is a clinical stage therapeutics company developing a new generation of innovative therapeutics in oncology and behavioural brain disorders.

5-year share price performance

Source: *LSE*

Past performance is not an indication of future performance.

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TPI will act as joint broker to TheraCryf plc from First Admission.

Attention is drawn to the disclaimers and risk warnings at the end of this document.

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TheraCryf plc

TheraCryf has raised £4.25m (gross) new funding through a conditional equity placing and subscription ('the Placing') priced at 0.25p/share (representing a 75% discount to yesterday's close). The issue is being split into a firm placing using existing authorisation and a conditional placing, which remains subject to a General Meeting ('GM') that is expected to be held on 7 March 2025. Together with the Group's present c.£1.0m cash/near-cash plus anticipated receivables, the Board considers it now has runway through to end-2026. During this time, it expects to pass through a number of value inflection points. While certain Group projects remain supported by non-dilutive grants, today's funding will be used primarily for the advancement of Ox-1, a blocker (antagonist) of the brain orexin-1 receptor with several applications in neuropsychiatry, developed to late preclinical stage for indications such as addiction and anxiety, by recently acquired Chronos Therapeutics ('Chronos'). The raise is expected to enable completion of remaining development steps, up to and including securing approval/clearance to progress to clinical trials in man. It will also continue supporting SFX-01's glioblastoma ('GBM') clinical program while satisfying anticipated working capital needs. In support of this, TheraCryf has announced its immediate appointment of Dr Alastair Smith as Non-Executive Chairperson, following Dr Sue Foden's passing last November. Being the founder and former Chief Executive Officer of Avacta Group plc (AIM: AVCT, 'Avacta'), Alastair focussed his clinical-stage, oncology biotech's development on its pre|CISION™ tumour targeting platform and related therapeutic developments. Obvious parallels between the two businesses, including the building of pipelines that are strongly differentiated by proprietary technologies with opportunity for early commercialisation through licensing, suggest his extensive scientific experience, widespread contacts and reputation in industry/financial markets will provide valuable support in progressing the Group's ambitions. Turner Pope will be appointed as TheraCryf's joint broker from Admission.

Use of funds raised

TheraCryf now has potential to reach a number of different value inflection points before end-2026. Together with its existing cash resources, the Placing's net proceeds will be directed toward completing Ox-1's preclinical development for addiction/anxiety to the point of Phase 1 readiness, while producing SFX-01 tablets for use in Erasmus Medical Centre's ('Erasmus') Glioblastoma ('GBM') clinical study. Funds will also be used for maintenance of the enlarged Group's patent portfolio and to satisfy working capital needs.

Allocation of Funds (incl. Working Capital Requirements)	Amount*
Preclinical development of Ox-1 (addiction/anxiety) to clinical, Phase 1 readiness, plus supply of SFX-01 tablets for Erasmus GBM clinical study	£2.80 million
Development staff, consultants etc.	£0.60 million
Intellectual Property, investor relations, legal, listing and financing costs plus associated advisors	£0.85 million
Total	**£4.25 million**

**Approx., qualifying for up to £4.3m VCT/EIS relief Source: TheraCryf, RNS of 19 Feb. 2025, TPI*

Cash on hand as of 30 September 2024 was £1.2m. The remaining balance will help offset total 2025-26 expenditure, during which time the Group also expects

to collect total R&D tax credits of c.£1.2m. Over this period, non-Dilutive funding will also be sought in support of its inhibitor of brain dopamine reuptake ('DAT') programme (fatigue, Long COVID and narcolepsy).

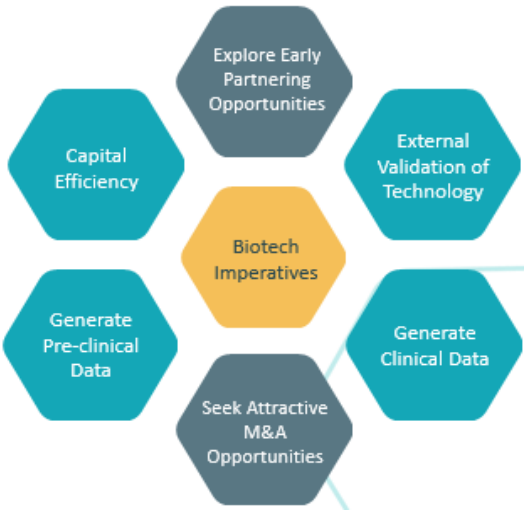
Dr Alastair Smith – Experienced early-stage biotech CEO joins as Non-exec. Chairperson

Founded and incorporated back in 2005, Dr Smith advanced Avacta's development of AVA6000, a peptide drug conjugate form of doxorubicin (for which it acquired rights in 2018), through Phase 1a clinical trials for local treatment of advanced or metastatic solid tumours ('MST'). Utilising its proprietary pre|CISION™ platform technology, the molecule demonstrated capability to significantly reduce the toxic side effects of doxorubicin chemotherapy, therein opening opportunity for development of a range of safer and better tolerated cancer therapies. Alastair stepped down from Avacta in 2024. Avacta's valuation peaked in 2020 when its intraday market capitalisation approached US$1billion. More recently, benefitting from his extensive R&D leadership experience, Alastair has assumed the role of Non-executive Director of N4 Pharma plc (AIM: N4P) and is also the Chairperson of SPARTA Biodiscovery Limited.

TheraCryf – Now funded to the point of reaching important value inflection points

TheraCryf has a broad clinical and preclinical pipeline in oncology and behavioural brain disorders. It is presently focused on profitable segments/under-developed indications including glioblastoma, addiction and fatigue. Its executive management comes with an extensive track record, including over 120 years of combined drug development and commercialisation experience, more than 50 drug development programmes and in excess of 30 in-and-out licensing agreements plus M&A deals, totalling multiple US$m biotech transactions. The Group's business strategy is to deliver value to shareholders based on generation of compelling preclinical/clinical data sets considered sufficiently attractive to be monetised through the partnering and/or licensing of its programmes with mid-size to large pharmaceutical companies.

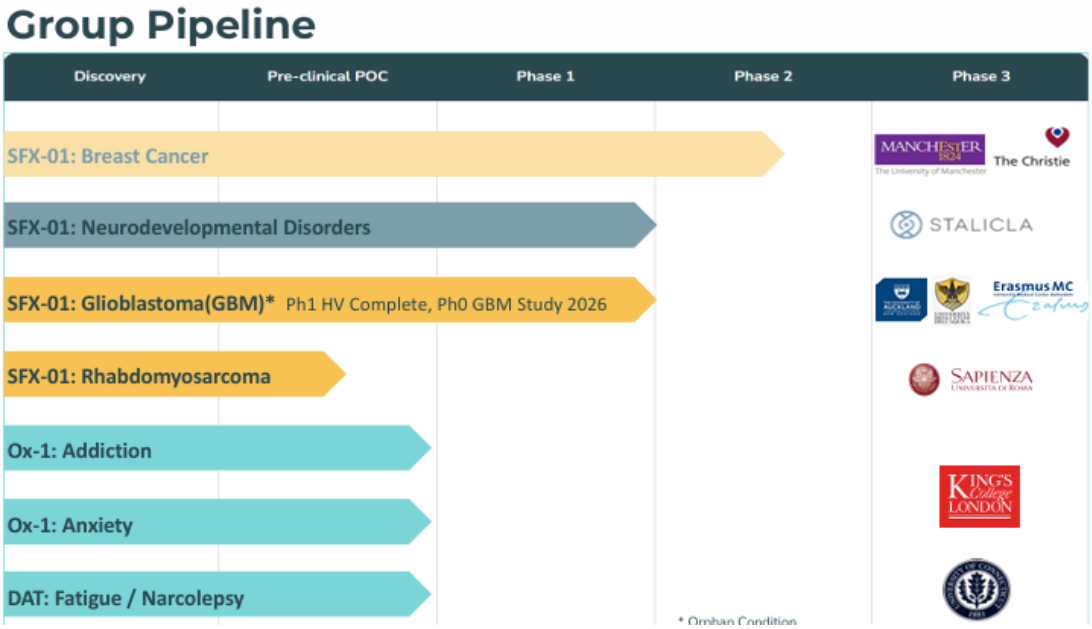
TheraCryf – Business Model



Source: TheraCryf, Investor Presentation, January 2025

The Board believes that today's funding, together with its present c.£1.0m cash-in-hand plus anticipated receipt of a further £1.2m in the form of R&D tax credits plus other receivables, will be sufficient to support operations to the point of reaching several different value-inflection points before end-2026. Note that this projection includes no contribution from the ongoing dispute with TheraCryf's SFX-01 neurodevelopment partner, STALICLA SA ('STALICLA'), in which amicable discussions are continuing regarding the Group's claimed US$0.5m milestone payment (associated with completion of SFX-01/STP2's Phase 1/1b study in healthy volunteers); it is understood that as of 5 January 2025, STALICLA had raised total new funding of US$21.6m over 4 rounds from 8 investors. Any settlement leading to full/partial payment of the outstanding could provide additional flexibility/options for TheraCryf's ongoing development programmes.

TheraCryf – Group Pipeline Detailing Status and Investigator Collaboration(s)



Source: TheraCryf, Investor Presentation, January 2025

Generation of compelling data across a range of indications for both its lead asset ('SFX-01') and its acquired neuropsychiatry pipeline ('Ox-1', 'DAT') will continue to de-risk TheraCryf's long-term investment thesis. Ongoing investigator collaborations build on the credibility of the Group's clinical and preclinical programmes, while providing non-dilutive development funding combined with technical/laboratory support. Allocating the new funds raised principally to two priority pipeline opportunities, the Board has outlined a busy schedule of announceable milestones/value inflection points that it considers to be achievable before end-2026.

TheraCryf Newsflow* – Funding Extends Runway to Reach Major Milestones before end-2026**

Q1 2025	• Neuropsychiatry programme restarts • Ox-1 manufacturing optimisation commences • New board appointment/s
Q2 2025	• Further SFX-01 in vivo data from Erasmus GBM collaboration expected • Ox-1 bulk manufacturing commences
Q3 2025	• Ox-1 bulk manufacturing complete • Ox-1 formulation for toxicology studies complete
Q4 2025	• Ox-1 chronic toxicology studies commence • SFX-01 GBM clinical trial preparations commence
H1 2026	• SFX-01 1st GBM patients dosed in Ph0 study • Ox-1 enabling studies, for first in man clinical trials, complete • **Ox-1 regulatory submission (IND/CTA) outcome of regulatory interactions (MHRA/FDA etc)**
H2 2026	• SFX-01 GBM clinical data flow • **Ox- 1 MHRA/FDA approval for Phase 1 study** • [Ox-1 Phase 1 study start]* • [Ox-1 Phase 1 study complete]*

**Subject to further funding* ***Forecast, subject to technical success*

Source: TheraCryf, Investor Presentation, January 2025

TheraCryf's priority development programmes

1. Ox-1 (known as 'CT-010018'): Late preclinical stage, class-leading Orexin 1 Competitive Antagonist with potential for utility in addiction and anxiety, targeting the securing of regulatory approval/clearance to progress to clinical trials in 2026.
2. SFX-01: Biologically active stabilised composition of 'sulforaphane' presently at clinical stage and funded by a grant from the KWF Dutch Cancer Society to provide first clinical data in GBM in 2026.

43% of the global population affected by disorders of the central nervous system ('CNS')

According to recent studies by the Lancet Neurological Journal, c.3.4 billion people worldwide are living with a CNS disease (from a list of 37 conditions, including Alzheimer's, Parkinson's, brain or spinal cord injury/ tumour, Meningitis, depression, Amyotrophic Lateral Sclerosis ('ALS'), addiction, anxiety, epilepsy, etc.) This represents roughly 43% of the global population, making neurological conditions the leading cause of illness and disability globally. It is not surprising that this development opportunity continues to attract significant attention from both Big Pharma and mid-size biotechs seeking to improve patient outcomes.

In contrast to the success of novel blockbuster technologies in areas such as oncology, the past couple of decades saw research into CNS indications (particularly in the area of neuropsychiatric diseases) take few important steps forward. Existing therapies continue to be criticised for providing inadequate responses and/or significant side-effects/safety issues. A resurgence of interest in this field has nevertheless been seen more recently, spurred by new technologies/therapeutic approaches and other initiatives. These in turn have delivered a relative rush of new approvals, generating renewed investment interest from Big Pharma in the form of collaborations, acquisitions (including Abbvie Inc. (NYSE: ABBV) which completed its US$8.7bn take-over of Cerevel Therapeutics Holdings Inc. in August 2024 and Bristol Myers Squibb Co. that purchased Karuna Therapeutics for a total value of US$14bn in December 2023) and numerous licensing deals.

Substance Use Disorder ('SUD') – A CNS condition with few available treatment strategies

Addiction can be conceptualised as a disease related to the brain's reward system. SUD is a negative chronic relapsing disorder characterised by repetitive substance use and seeking behaviours. It is a multifactorial disease with psychological, neurobiological and sociological aspects, suggesting individualisation of appropriate psychotherapy and pharmacological treatments with different neural targets could together provide the most effective treatment.

There are presently only a small number of pharmacological treatment strategies available for the condition and although these have been shown to reduce substance-related mortality, existing therapies are approved only for a limited number of substances, only found to be effective for a subset of the patient population and, even then, only in a limited, often short-term, sense. As knowledge of the neurobiological, genetic, epigenetic, and environmental mechanisms involved in the addiction process improves, new targets for prevention and treatment interventions are being identified. Emerging technologies such as neuroimaging and brain stimulation or mobile health interventions offer additional, possibly personalised approaches. Complexities in the development of novel SUD medications have included legal issues including scheduled/controlled drug status of several effective medicines, high psychiatric comorbidity, stigma, relapse rates and elevated treatment goals, although these are now being challenged by new approaches to the neurobiological mechanisms responsible.

TheraCryf – Positioned to capitalise on recently renewed interest in neuroscience

The entire share capital of Chronos Therapeutics Limited ('Chronos'), a private biotechnology company specialising in central nervous system ('CNS') disorders, was acquired in March 2024 for £0.9m up front plus up to c.£2.5m in milestone payments, all in TheraCryf shares. Chronos shareholders (which included Vulpes, Odey, Oxford University, WA Capital and Takeda) were locked in for 18 months.

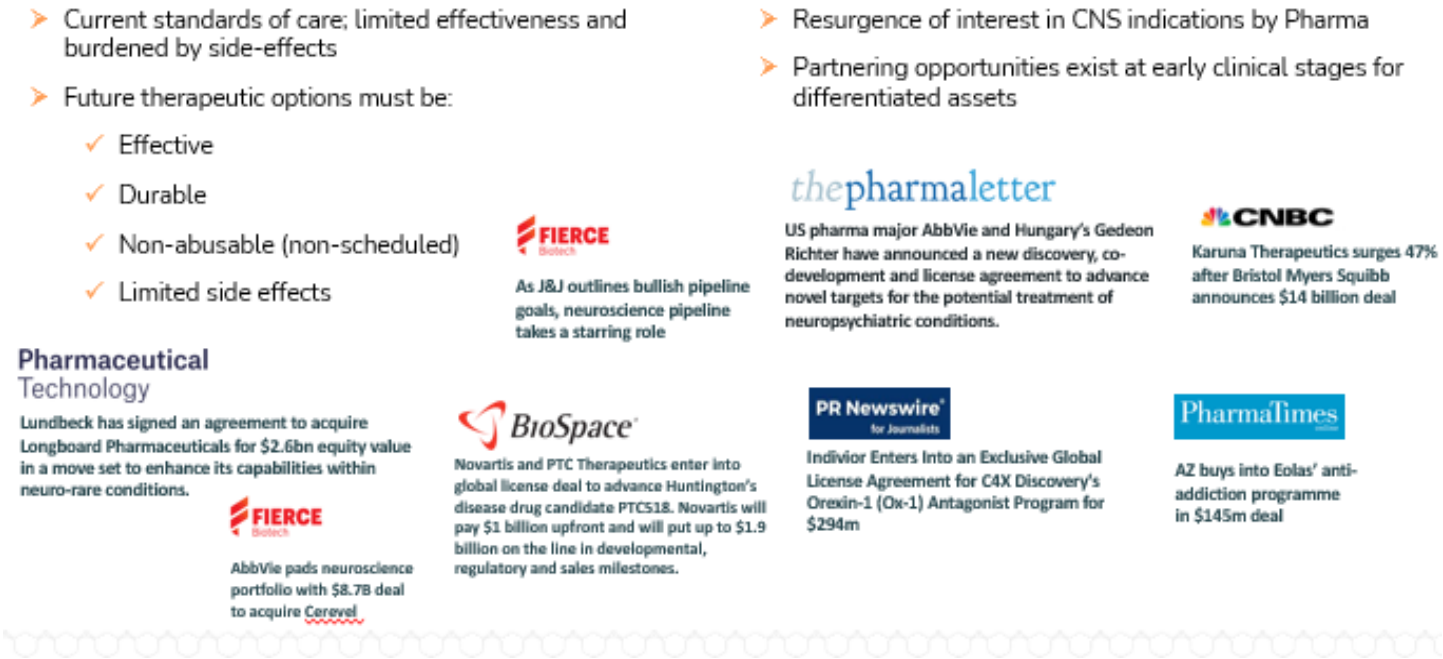
Chronos' neuropsychiatry assets were considered complementary to TheraCryf's existing neurodevelopmental disorders and brain cancer developments presently being undertaken by STALICLA, while introducing a considerably enlarged pipeline with novel IP plus potential to reach significant, relatively short-term value inflection points. While lowering the Group's overall risk profile, the Board also sees potential to substantially increase the value of the acquired assets. Although the door always remains open, at this time TheraCryf is not targeting any further bolt-on assets or other businesses additions.

Selection of Neuroscience Drugs Recently Approved by the FDA

Alzheimer's disease
• Kisunla (donanemab-azbt) – Approved in July 2024 for adults with mild cognitive impairment/dementia
• Donanemab – Approved July 2024 for adults with early symptomatic conditions, mild cognitive impairment/dementia
• Lecanemab-irmb – Approved July 2023 to clear amyloid beta plaques from the brain, despite safety concerns
• Aducanumab – Granted accelerated approval in 2021 for ability to clear amyloid plaques in brain
Migraine
• Zavzpret (zavegepant) – Approved March 2023, nasal Spray for the treatment with or without aura.
• Atogepant (Qulipta) – Approved September 2021 for preventative treatment of episodic condition in adults
Schizophrenia
• COBENFY (xanomeline and trospium chloride) – Approved September 2024 for the psychiatric disorder
Glioma
• Vorasidenib – Approved August 2024 for patients with Grade 2 gliomas with IDH1 or IDH2 mutations

Source: Company websites, FDA TPI research,

CNS Therapeutic Sector – Recent Transactions Highlight Renewed Level of Investment Interest



Source: TheraCryf, Investor Presentation, January 2025

Ox-1, an OX1 antagonist (previously coded 'CT-010018')– Targeting regulatory submission

Following Chronos's assimilation into the enlarged Group and receipt of new funding, TheraCryf plans to restart Ox-1's research programme. Ox-1, a competitive antagonist of the orexin-1 receptor, is designed to inhibit specific biological responses associated with CNS conditions such as addiction and anxiety. The program's goal is to complete all necessary preparations for regulatory submission, including readiness for Investigational New Drug Application ('IND')/Clinical Trial Application ('CTA') by mid-2026. This milestone will mark a significant value inflection point and position TheraCryf for first-in-human clinical trials with this asset.

Orexins are neuropeptides found in the brain and its periphery that help regulate sleep, wakefulness, energy balance and thermogenesis. An imbalance in orexin production and stimulation has been linked to anxiety, addiction and other neuropsychiatric disorders/mental health conditions. Also known as hypocretins, they operate by binding to and activating either orexin type 1 or 2 G protein-coupled receptors ('Ox1R' or' Ox2R') to stimulate a neurological response. It is generally accepted that Ox1R is mainly involved in motivation and reward and Ox2R in the modulation of sleep/wake cycle and energy homeostasis. Both have been clinically validated through approvals of dual orexin receptor antagonists ('DORAs'), which are a drug class that block the action of orexin receptors that stimulate wakefulness. Examples of DORAs include Suvorexant (Merck & Co.), QUVIVIQ (Idorsia Pharmaceuticals), Lemborexant (Eisai Inc.) etc.

Given that there are presently some 200 on and off-label drugs (including generics) that are commonly prescribed for neurological conditions (including Alzheimer's, ALS anxiety, depression, etc.), the market already appears to be competitive. The standard of care, however, is dominated by dopamine and serotonin receptors (DRD_2 and 5-HTR, resp.) targeting antagonists which are burdened with safety, side effect and efficacy issues. With the search on for novel mechanism of action ('MOA') in CNS disease areas, Ox1R and Ox2R make compelling drug targets and continue to attract attention from Big Pharma whose own existing pipelines presently comprise inferior development candidates. Rationale for the receptor's potential effectiveness comes from early clinical efficacy in anxiety by a Johnson & Johnson (NYSE: JNJ) tool molecule in 2020. Moreover, TheraCryf's Ox-1 development aligns growing pharmaceutical interest in orexin-1 pathways, as was highlighted by Indivior's originally priced US$294m global licensing agreement with C4X Discovery for addictive disorders back in March 2018. Other early-stage clinical investigations by majors such as AstraZeneca and Cerevance further validate the drug target's potential in treating CNS conditions, including addiction and anxiety.

Pharmacologic treatment approaches for SUD are generally based on three strategies: 1) Blocking the target of the substance; 2) Mimicking the effects of the substance; and 3) Intervening in the process of addiction formation. Ox-1's MOA, however, differentiates itself by selectively inhibiting Ox1Rs, with therapeutic focus on the twin related disorders of addiction and anxiety. These are areas that scientists broadly recognise as falling within a specific personality type and where evidence-based assessment is relatively obvious along with a reasonably transparent development pathway. This contrasts strongly with the more opaque (even 'muddy') circumstances presented by most other CNS-related conditions. To date there have been no drug approvals for neuropsychiatric indications with a MOA that specifically targets Ox1R. ClinicalTrials.gov, identifies just two ongoing clinical studies (sponsored by Cerevance and Indivior) in this field, suggesting there is presently a relatively low level of investigative activity on such inhibitors. Recognising that Ox-1 could possess more general clinical utility across neuropsychiatric indications, the tabulation below details stages, status and transaction value (where available) of recently completed clinical deals to provide an indication of the developing competitive environment.

Ox-1 Competitive Environment, Anxiety, Addiction

Company	Stage	Status	Deal Size	Indication
Indivior (C4X)	Ph2	First patient dosed in Ph2 opioid use disorder trial in June 2024, trial ongoing	$294m deal 2018 incl. $10m upfront. £15.95m Aug 2023 (bought from C4X)	Opioid use disorder
Cerevance (Takeda)	End Ph1	Completed Ph1, planning to initiate Ph2 in Schiz and BED patients, current timings not disclosed	N/A	Schizophrenia, BED
AZ (Eolas)	Ph1/2	Discontinued after dosing in opioid users taking additional medications highlighted a DDI (announced Nov 2024)	>$145m plus royalties (licensed from Eolas)	Smoking cessation, opioid use disorder
JnJ	Ph1/2	Unknown, not currently reported in pipeline, possibly shelved **due to somnolence observed in clinic due to inadequate selectivity for Ox-1 over Ox-2**	N/A	Panic/anxiety, depression
Idorsia (Actelion)	Ph2	2022 missed Ph2a endpoint in BED (query receptor occupancy), shelved	N/A	BED, anxiety

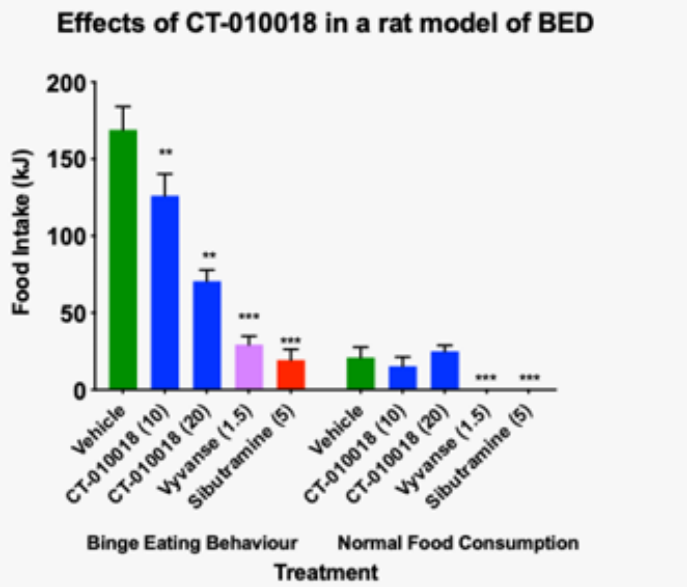
Source: TheraCryf, Investor Presentation, January 2025

TheraCryf has secured patents, for Ox-1, in the principal global territories, including the USA, Asia and Europe. As recently as 18 December 2024, the European Patent Office granted a Composition of Matter patent (which is generally recognised as offering the strongest available IP protection), covering the candidate compound and associated structures.

TheraCryf's OX1 Antagonist - Structurally distinct from competitor molecules

Ox-1 displays improved properties compared with first generation OX1 antagonists and differentiates itself in the competitive environment. The mechanistic evidence suggests that OX1 antagonists would not themselves be liable to abuse (the principal issue associated with psychoactive drugs). Preclinical studies demonstrated that TheraCryf's compound is effective, offers class leading pharmacological selectivity, good brain penetration and physicochemical properties. With Ox-1's initial scale-up and preliminary formulation complete, Chronos successfully conducted 7-day (non-GLP) *in vivo* toxicology, pharmacokinetic modelling, receptor occupancy and *in vivo* efficacy studies, confirming successful target engagement, efficacy and unremarkable preclinical safety. The comprehensive preclinical data package assembled by Chronos accounts for c.80% of the data required to complete the preclinical regulatory package necessary to gain authorisation to begin a human study.

In Vivo Pharmacology BED – Efficacy Comparison



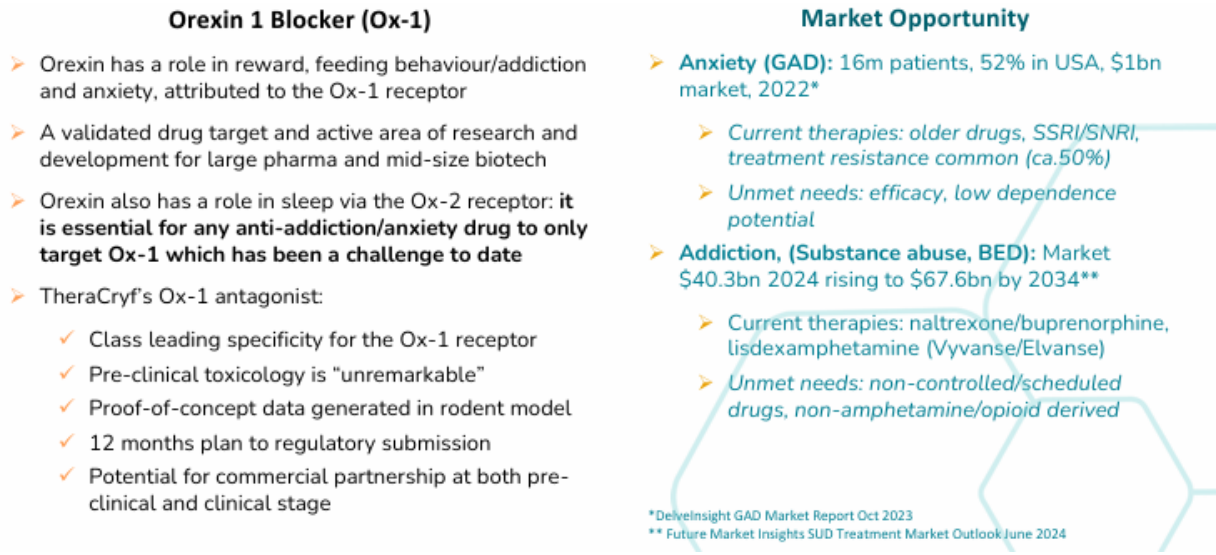
Source: TheraCryf, R&D Day Presentation, June 2024

BED is a psychiatric condition validated by American Psychiatric Association handbook DSM 5, that is said to be more common than anorexia and bulimia combined. It is not treatable with anti-obesity drugs and the only approved medication is the class II scheduled drug, Vyvanse, an amphetamine prodrug. Orexin 1 antagonism is viewed as one of the most attractive targets in binge-eating disorder ('BED'), introducing no abuse liability or anhedonia, with ability to target both aberrant reward and anxiety driven aspects of the disease. Proof-of-concept ('POC') has been demonstrated *in vivo* through a rodent model administered with Ox-1; this demonstrated good efficacy relative to the standard of care in controlling the urge to binge-eat chocolate, without negatively affecting the animal's regular eating patterns. The follow-on standard development study, chronic toxicology, has already been planned, this time utilising two different laboratory species over an extended 28-day dosing period. Other steps required to enable first-in-human trials include manufacturing scale-up and finalisation of formulation. All associated costs are expected to be covered through todays fundraise.

Based on TheraCryf's projected schedule, all enabling studies (including initial scale-up and formulation) for first-in-human clinical trials will be completed during H1 2026, with IND/CTA expected to rapidly follow outcome of routine interactions with the MRHA/FDA. Anticipating approvals for a Phase 1 study early in H2 2026, subject to further funding Ox-1's clinical study could potentially start and be completed within a further 6-month period. Early

clinical POC, possibly linking with first-in-human data and dose-ranging for subsequent Phase II studies, could possibly follow late-2027 or early-2028 subject to funding/commercial partnership/licensing agreement.

Oxexin-1 Blocker – Addiction and Anxiety Market Opportunity



Source: TheraCryf, Investor Presentation, January 2025

Ox-1 has possible utility in other addictive disorders, including impulse control disorders and panic disorder.

Market opportunity

According to Future Market Insights' published analysis of June 2024, the value of last year's global Addiction (SUD/BED) Treatment Market was US$40.3 billion. Over an assessment period from 2024 through to 2034, it forecasts growth at an overall 5.3% CAGR expanding this opportunity to US$67.6 billion.

Selected Medications Commonly Prescribed for Addiction Disorders

Lisdexamfetamine – Sold under band names Vyvanse, Elvanse amongst others: A stimulant medication that is used to treat attention deficit hyperactivity disorder in children and adults and for moderate-to-severe binge eating disorder in adults. Common side effects include loss of appetite, anxiety, diarrhoea, trouble sleeping, irritability, and nausea. A prodrug of dextroamphetamine that blocks the reuptake of norepinephrine and dopamine. Lisdexamfetamine is a scheduled/controlled drug.
Naltrexone – Sold under the brand name Vivitrol: A mu-opioid receptor antagonist/weaker antagonist of the kappa and delta-opioid receptors used to treat alcohol use disorder and opioid dependence. Binding to the receptors, blocks the euphoric effects linked with alcohol use or opioids.
Buprenorphine - Sold under the brand name Suboxone among others: A synthetic partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor used to treat opioid use disorder, acute pain, and chronic pain. Binding reduces opioid cravings, preventing withdrawal symptoms, and blocking the effects of other opioids.
Methadone - Sold under the brand names Dolophine and Methadone among others: A synthetic opioid analgesic with full agonist activity at the μ-opioid receptor. Used medically to treat chronic pain and opioid use disorder. Prescribed for daily use, the medicine relieves cravings and withdrawal symptoms.
Varenicline - Sold under the brand names Chantix and Champix among others: A nicotinic acetylcholine receptor partial agonist used for smoking cessation and for the treatment of dry eye syndrome. Partially activates nicotinic acetylcholine receptors while blocking nicotine from binding.
Bupropion - Sold under the brand name Wellbutrin: A norepinephrine/dopamine-reuptake inhibitor used most commonly for the management of Major Depressive Disorder (MDD), Seasonal Affective Disorder (SAD), and as an aid for smoking cessation. Reduces reuptake of dopamine and norepinephrine in the brain.

Source: Company Websites, FDA, TPI research

Although presently dominated by North America, the world's largest countries by population (India and China)

are forecast to exhibit CAGRs of 5.1% and 4.5% resp. during the same period based on increasing awareness and destigmatisation. Commonly prescribed therapies include Naltrexone, Buprenorphine and Lisdexamfetamine. Treatment resistance for this category, however, is put at c.50%, while also incurring significant safety concerns; Bupropion, for example, carries an FDA 'Black Box' warning and Lisdexamfetamine (sold under the brand names Vyvanse and Elvanse among others) is a scheduled drug. The latter nevertheless achieved US$2.14 billion in sales the first 9 months of 2023 for Takeda (of which c.15% is estimated to have been for BED), before going off-patent. This and the fact that a total of nine generics have launched since August 2024, provide an indication of the underlying strength of demand in this particular field.

Selected Medications Commonly Prescribed for Anxiety Disorders

Fluoxetine – Sold under the brand name Prozac: Selective serotonin reuptake inhibitors ('SSRI'), that increase serotonin levels in the brain to improve mood and reduce anxiety. Commonly used to treat obsessive-compulsive disorder, panic disorder, and social phobia.
Paroxetine – Sold under the brand names Paxil, Pexeva, Seroxat: An antidepressant medication of the SSRI class 7 used to treat major depressive disorder, obsessive-compulsive -disorder ('OCD') etc. Increases serotonin levels in the brain by blocking the serotonin reuptake transporter ('SERT').
Duloxetine, sold under the brand name Cymbalta among others: A serotonin and noradrenaline reuptake inhibitor ('SNRI') medication used to treat major depressive disorder, generalized anxiety disorder, obsessive-compulsive disorder etc. Increases the levels of serotonin and norepinephrine in the brain.
Carbamazepine, sold under the brand name Tegretol among others: An anticonvulsant medication used in the treatment of epilepsy, neuropathic pain and used as an adjunctive treatment in schizophrenia etc. Proposed MOAs include enhancement of sodium channel inactivation.

Source: Company Websites, FDA, TPI research

Although only Escitalopram (Lexapro) and Paroxetine (Paxil, Pexeva, Seroxat) are FDA-approved SSRIs for the treatment of Generalised Anxiety Disorder ('GAD'), off-label use across broader drug classes, including SNRIs and benzodiazepines, has become well established in recent decades.

Research examining the GAD Market that was conducted by DelveInsight in October 2023, for example, identified c.16m patients being prescribed both on and off label medication for the condition. Drug classes stretch across SSRIs, SNRIs, Benzodiazepines, Tricyclic Antidepressants/Azapirone (Buspirone) as well as antiepileptics and antipsychotics. It estimates this generated c.US$1.6 billion revenues in 2023, with the USA accounting for c.63% of the users. The research projected a global market CAGR of 7% out to 2034.

Dopamine transporter inhibitor ('DAT') Fatigue Associated with Multiple Sclerosis ('MS')

DAT (coded as 'CT-005404') is a dopamine transporter inhibitor with a non-stimulant profile that also originated from Chronos's pipeline. It shows pro-motivational effects in animals and reverses motivational deficits induced by tetrabenazine and interleukin-1β. Being highly differentiated from previous DAT inhibitors and clean in early 7-day toxicology studies, the molecule remains in preclinical development for treatment of fatigue associated with MS, Long COVID and Narcolepsy. TheraCryf sees potential for it to become the first approved drug with a label for MS Fatigue and, due to conservation of DAT's underlying neurotransmission mechanisms, believes this could allow expansion into other characterised conditions, such as, HIV and cancer chemotherapy. The notable absence of successful treatment across many such neurological disorders along with the recently heightened interest in drugs focussing on novel targets/MOAs, suggests this research offers significant potential. At this time, however, none of today's new funding has been specifically allocated to forward these projects, which instead await identification of a suitable Investigator Collaboration(s) or other external expressions of interest to provide new, non-dilutive support. DAT's Composition of Matter patent has been filed/granted in the US and EU.

Fatigue

The dopamine neuronal transporter targeted by DAT, is a brain protein that moves dopamine into and out of neurons; it is a key part of regulating dopamine neurotransmission, which in turn affect movement, motivation,

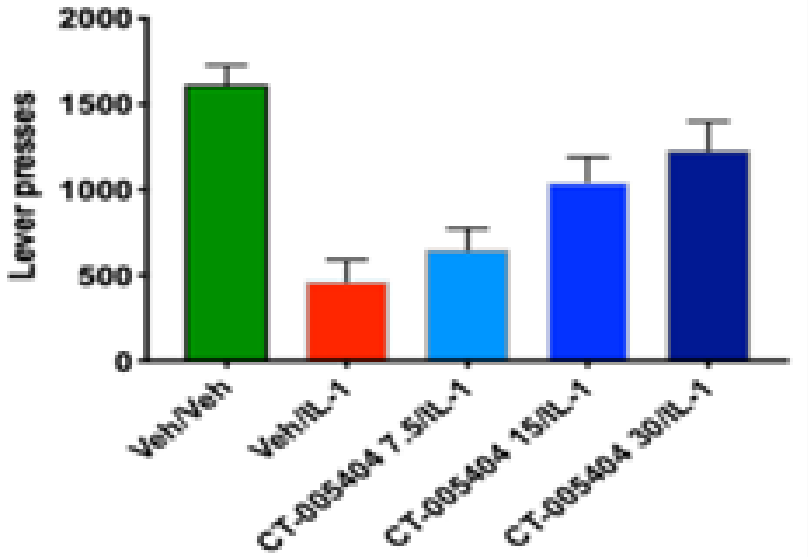
and learning. MS is a chronic, autoimmune disease that damages (attacks) healthy cells in the brain and spinal cord. Up to 80% of MS patients suffer from moderate to severe fatigue (depending on type of disease), roughly half of which depend on drugs to control (but not cure) the condition. There are currently no approved fatigue-based drug treatments with a label in MS.

Amantadine (an antiviral drug that is also used to treat Parkinson's disease), modafinil (a synthetic psychoactive compound that comes with an FDA Black Box warning) and methylphenidate (an amphetamine-like psychostimulant that can be addictive) are commonly prescribed off-label to treat fatigue MS, however, although their effectiveness remains a matter of dispute. Numerous other drugs, including Armodafinil, Pemoline and even Fluoxetine are also sometimes similarly prescribed.

Numerous past developments have failed/been abandoned primarily due to their inability to achieve pharmacological selectivity and/or a lack of therapeutic index vs hERG channel. DAT has demonstrated greater selectivity (>3,500x vs hERG and as much as 100x that of historic DAT inhibitors) compared with competitor molecules that use other types of neurotransmitter transporters, such as SERT (which transports serotonin) and NET (which transports norepinephrine). It does not have an amphetamine-like neurochemical profile, cause dopamine release from striatal synaptosomes or induce increased locomotor activity in rodents.

In vivo pharmacology POC studies carried out at the University of Connecticut established and validated a rodent model of CNS fatigue. Induced by chemical insult (tetrabenazine, fluoxetine, cytokine IL 1), fatigue results in reduced effort related choice (which is analogous to the human condition). DAT was seen to reverse CNS Fatigue (n=12, oral dosing with 4-hour pre-treatment).

in vivo Pharmacology PoC for DAT– CNS Fatigue



Source: TheraCryf, R&D Day Presentation, June 2024

Long Covid

There are presently no FDA-approved treatments for Long COVID. However, some treatments have been used off label to manage symptoms. These treatments include prescription and over the counter products such as antivirals, antihistamines, anticoagulants (blood thinners), analgesics (pain medicine), and corticosteroids, among others.

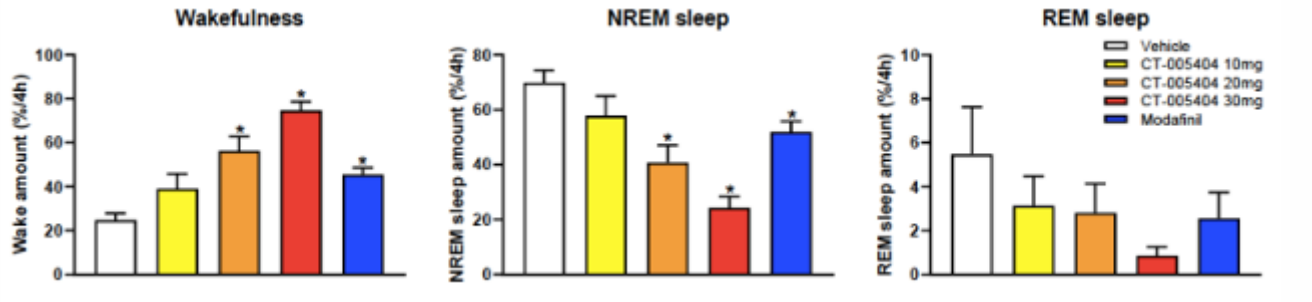
Narcolepsy

Narcolepsy, a relatively rare, chronic brain condition that makes it difficult to control sleep and wake cycles, has no known cure. But there are a good number of FDA-approved drug treatments for patients with extreme conditions: Xyrem (sodium oxybate), WAKIX (pitolisant), Provigil (modafinil), Nuvigil (armodafonil), Ritalin (methylphenidate)

and Adderall (amphetamine).

In a rodent wakefulness study, DAT (10, 20 and 30 mg/kg, p.o.) increased the amount of wakefulness at the expense of NREM sleep in a dose-dependent manner.

In Vivo Wakefulness Study – DAT Displays Potential in Narcolepsy



Source: TheraCryf, R&D Day Presentation, June 2024

Neuropsychiatric indication – Potential value creation through early-stage licensing

A number of very early stage (preclinical, Phase 1) deals, licensing drugs across a range of neuropsychiatric indications, have been struck over the past several years with small and mid-size pharma/biotech. These typically include relatively modest upfront payments followed ultimately by quite substantial deal 'earn-in' values. A selection of these have been listed below. Interest in the field from Big Pharma has also been noted through AbbVie and Gedeon Richter announcing in October 2024 a collaboration to discover and develop novel targets for neuropsychiatric conditions under which the latter received and upfront payment of US$25m along with potential future development, regulatory, and commercialisation milestones; in January 2023, STALICLA entered an exclusive in-licensing agreement with Novartis, to develop mavoglurant as a treatment for substance-use disorder, neurodevelopmental disorders, and other indications in exchange for upfront fees and equity, and development and commercial milestones of up US$270 million, plus royalties on possible future sales.

Selected Early-Stage licensing Deals across Range of Neuropsychiatric Indications

Date	Licensor	Licensee	Status	Drug Code	Indications(s)	Upfront US$ Payment	Total US$ Deal Value
Nov. 2024	Enveric Biosciences	MycoMedica Sciences	Preclinical	EB-002.	Depression, anxiety, addiction disorders	n/a	US$62m
Feb. 2023	Goldfinch Bio	Karuna Therapeutics*	Phase 1	KAR-2618	Mood and anxiety disorders	US$15m	US$535m
May 2022	Sumitomo Pharma	Jazz Pharmaceuticals***	Phase 1	DSP-0187	Narcolepsy, idiopathic hypersomnia, sleep disorders	US$50m	US$1.14bn
Jan.2022**	KemPharm	Gurnet Point Capital	Preclinical	KP415	ADHD	US$10m	US$590m
Mar 2018	C4X Discovery	Indivior	Preclinical	C4X3256	Opioid and SUD	US$10m	US$294m

**Acquired by Bristol Myers Squibb in Dec. 2023 **Amended from original deal of Sept. 2019 ***Ex-Asia rights only*

Source: Company websites, Evaluate Pharma

Scale of global market opportunity be addressed across MS, Long COVID and Narcolepsy

The global therapeutic market for MS has been forecast by research institute Statista, to achieve revenue of US$21.74 billion in 2025, roughly half of which is expected to be generated in the USA. This projection indicates a steady annual growth rate of 0.96% between 2025 and 2029, leading to a market volume of US$22.59 billion by 2029. In 2022, it estimated that Roche (29%) and Biogen (24%) were the largest players, followed by Sanofi (1%) and Novartis (9%). Although there are no reliable estimates as the size and prospective growth of the Long COVID market, the US

National Library of Medicine estimated in August 2024 that the cumulative global incidence of Long COVID is around 400 million individuals, which is estimated to have an annual economic impact of approximately US$1 trillion-equivalent to about 1% of the global economy. On the other hand, a report by Coherent Market Insights in October 2024, estimated the 2024 value of the global Narcolepsy market to be US$2.53 billion in the year 2024, which it projected to reach US$4.68 Billion by 2031, based on a CAGR of 9.3% during forecast period.

TheraCryf – Enhancing the value of sulforaphane-based lead asset, SFX-01

TheraCryf continues to develop a new class of pharmaceuticals based on highly biologically active sulforaphane, an isothiocyanate derived from plant glucoraphanin through myrosinase activity, which has applications in multiple therapeutic areas based on a network of targets. Sulforaphane has been shown to inhibit breast cancer stem cells *in vitro* but its instability had hitherto rendered it impractical for drug development. TheraCryf's lead asset, SFX-01, is a proprietary synthetic pharmaceutical based upon a stabilised sulforaphane. The Group has extensive IP covering its platform stabilisation technology and SFX-01.

In preclinical models, *in vivo,* SFX-01 inhibited the activity of breast cancer stem cells and reversed resistance to the endocrine therapies, tamoxifen ('Tam') and fulvestrant ('Fulv'). This is relevant in relation to the development of disease resistance to certain CDK4/6 inhibitors, the current standard of care, for such conditions. Between January 2017 and July 2018, 46 patients were recruited in conjunction with the University of Manchester for an open label parallel arm exploratory Phase II trial, the STEM study, designed to investigate the potential of SFX-01 to reverse acquired resistance to Tam, Fulv and third generation aromatase inhibitor therapy. Final results released in October 2019 concluded SFX-01 300mg BD po was a generally well tolerated treatment with no significant safety concerns when combined with endocrine therapies ('ET'). It demonstrated objective responses and meaningful stabilisation of disease areas on which cancers were actively progressing and that further development of SFX-01 in metastatic breast cancer is warranted. Recognising, however, that mid-to-large pharma will likely demand greater mechanistic or biomarker rationale before becoming sufficiently incentivised to sponsor the expected US$50m+ cost to undertake a large controlled study, TheraCryf has for the time being chosen to instead focus efforts on development of a treatment for Glioblastoma ('GBM'), the most severe form (and most fatal) of the primary brain cancer glioma.

Lead development SFX-01: GBM program supported through non-dilutive funding

Non-dilutive funding for this lead program through to clinical evaluation has been secured through investigator collaboration with the Erasmus Medical Centre, Rotterdam, the Netherlands ('Erasmus'). SFX-01 has also been out-licensed for neurodevelopmental disorders to STALICLA. TheraCryf retains the rights to all other indications worldwide and also enjoys a further academic collaboration with Sapienza (Universita de Roma), both of which continue to observe further evidence of its potential utility in cancers that have not previously been studied and represent high unmet medical needs.

Initial preclinical results collected by Erasmus were highly encouraging, as was the outcome of a Phase 1/1b healthy volunteer study. TheraCryf achieved orphan drug designation in the US for treatment of malignant glioma and blood cancer in late 2021. Regulatory scientific advice subsequently received from the Dutch Medicines Evaluation Board also confirmed there are no specific concerns regarding the clinical safety profile of SFX-01. Further preclinical formulation work is now expected to be completed within one year, leading to first dosing (in tablet form) of GBM patients in a Phase 0 study that is scheduled to get underway in H1 2026. This window of opportunity study aims to confirm that sulforaphane from SFX-01 enters the tumour while also being able to assess interactions of the agent with molecular targets in excised tissue. First GBM clinical data is expected to be released in H2 2026.

GBM has an incidence of 3.8 per 100,000 people. Prognosis with this severe form is poor with median survival of approximately 14 months and five-year survival of around 5% of diagnosed patients. With treatment options being limited to surgery followed by radiotherapy and only one drug approved for the condition, there is a high need for novel treatments. During FY2023/24, Erasmus was awarded a grant administered by the Dutch cancer society,

KWF, for a €1.1m total project value covering *in vitro* and *in vivo* preclinical experiments on SFX-01, followed by a window of opportunity clinical study in GBM patients. A Phase 1/1b study in healthy volunteers of the novel SFX-01 formulation was then completed later that year through a trial comprising three cohorts of 8 volunteers each, of which two in each cohort received a placebo. The trial was randomised and double-blinded. All participants had received their final dose on schedule by the end of January 2023. Analysis of the pharmacokinetic ('PK') data (i.e., how the drug is absorbed, distributed, metabolised and excreted by the human body) was completed, along with examination of the effects of SFX-01 administration on gene expression data on the entire genome of the volunteers on both active drug and placebo. Results indicated release in the small intestine, good protection by the enteric coat on the tablet and reliable conversion in the body to active metabolites. Laboratory samples found these concentrations sufficient for biological activity. There were no serious adverse events reported. Comprehensive pharmacodynamic data has since been collected although at this time, for the purpose of confidentiality, it has not been released.

Market Background Information – Autism Spectrum Disorder ('ASD') and Glioblastoma ('GBM')

Autism Spectrum Disorder	Glioblastoma
Therapeutic Market forecasts USD 3.78 billion 2021 – 5.15 billion 2028 (CAGR 4.5%), Fortune Business Insights; Autism Spectrum Disorder Therapeutics Market, 2021-2028 (Oct 2021) Treatment estimate $15-30k per patient per annum **Characteristics** Prevalence rate 1:100 children worldwide (WHO, 2022), 1:36 (US, CDC, 2020) Increasing rates of diagnosis (CDC) The major drivers of growth in the forecast period across the 8MM are: • Increasing incidence worldwide • Diagnosis and prescribing increases enabled by growing acceptance of telehealth during pandemic, and recognition of diagnostic tools such as Cognoa Inc's ASD Diagnosis Aid • Supportive regulatory environment to fast track therapeutic development programmes, as demonstrated by the achievement by HLR of an advanced therapy title from the FDA for Balovaptan The major barriers to growth in the forecast period in the 8MM are: • Competition Phase 2 onwards (Roche, Jazz, Zynerba, Impel) • Emergence of novel Digital Cognitive Therapies • Patient heterogeneity (Stalica claim to have a proprietary biomarker/enrichment technique) • Reluctance to submit paediatric population to long term therapeutic interventions	**Therapeutic Market forecasts** USD 549.1 million 2020 – 868.5 million 2030 (CAGR 4.7%), Global Data; GBM Global Drug Forecast and Market Analysis to 2030 (Dec 2021) Branded standard of care treatment, Temodar approx. $29k per patient per annum **Characteristics** Total 5 year prevalent population: 243,850 Total treated newly diagnosed (in 2020): 33,985 Total treated recurrent diagnosed (in 2020): 13,914 The major drivers of growth in the forecast period across the 8MM are: • Approvals and launches of high-priced therapeutics, including 2 cancer vaccines, 3 protein kinase inhibitors, and 3 small molecule chemotherapies • An increasing number of incident cases of GBM, particularly in the US (due to underlying population growth) and China (due to urbanization) • A high level of unmet need in GBM that warrants faster uptake of the pipeline agents expected to launch during the forecast window, as patients have few other treatment options The major barriers to growth in the forecast period in the 8MM are: • The patent expiration of Avastin and subsequent entry of biosimilars may reduce market traction, resulting in higher discounts from upcoming players such as Bio-Thera Solutions' BAT1706 for the biosimilar market • Increased cost-consciousness will limit reimbursement and the uptake rate of new market entrants, particularly in the 5EU. Moreover, China has made pledges to cut costs, likely to reduce prices further than anticipated in the forecast • A high failure rate has been historically observed for Phase III GBM trials and may impact the pipeline forecast and impede market growth

Source: TheraCryf, Investor Presentation January 2025

In October 2023, TheraCryf undertook a further *in vitro* study utilising research-quality SFX-01 on patient's sample tumour tissue which, as expected, also confirmed biological activity. Similarly, *in vivo* data presently being collected by Erasmus is expected to be released in Q2 2025. Following collation of all preclinical data and final formulation, approval from European regulatory authorities will be sought for the clinical study in GBM patients. Clinical trial preparations are expected to commence in Q4 2025, with first dosing (in tablet form) of GBM patients in a Phase 0 study scheduled to get underway in H1 2026 followed by release of clinical data in H2 2026.

SFX-01- Positive discussions continue to STALICLA regarding out-licensing payment

In late 2022, TheraCryf concluded a transaction worth up to US$160.5m in milestones, for the global rights for lead asset SFX-01 in neurodevelopmental disorders and schizophrenia, with STALICLA. STALICLA is a private Swiss biotech company that specialises in the identification of specific phenotypes of ASD using its proprietary precision medicine platform. TheraCryf retains the global rights for all other indications outside of neurodevelopmental disorders and schizophrenia. In February 2024, TheraCryf gave a notice of dispute to STALICLA, considering it had met the terms required to satisfy the second milestone in accordance with the License Agreement, and thus the payment due. Positive discussions continue regarding resolution, although no financial settlement of the dispute has been factored into any of the Group's current projections.

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SFX-01 – Enhancing the action of radiotherapy in cancer patients

Based on previous findings from preclinical work in glioma, in May 2022 TheraCryf commenced a collaboration with the Università Sapienza di Roma to investigate the hypothesis that SFX-01 could enhance the action of radiotherapy in cancer patients. The scientific work evaluated the anti-tumour activity of SFX-01 in two preclinical cellular models of rhabdomyosarcoma ('RMS') tumours, the most frequent soft tissue sarcoma in childhood.

In vitro data showed that SFX-01 reduced tumour cell growth by inducing G2 cell cycle arrest and triggering early apoptosis (cell death). In addition, the molecule was shown to be effective both as a single agent and in combination with radiotherapy where it was found to be synergistic. It created a more positive result than would have been expected from simply adding the two agents together. The results indicate that this can reduce tumour cell growth in clinically relevant radioresistant RMS cells and significantly inhibit the formation of cancer stem cell-derived tumourspheres (rhabdospheres). The results were presented in a poster at the ESMO Sarcoma and Rare Cancers Congress in March 2023. In 2024, these experiments were extended to *in vivo* mouse models whereby rhabdomyosarcoma cells are implanted into the animals allowing treatment effects to be evaluated in life in a more disease relevant condition. SFX-01 was shown to be effective in these models after oral administration, complementing the earlier *in vitro* results. These data were published in a peer reviewed journal, BMC Cancer in July 2024.

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