Stock Data

Share Price:	0.25p
Market Cap.:	£5.37m
Shares in issue:	2,148.96m
52 week high/low:	0.30p/0.18p

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.

1-year share price performance

5-year share price performance

Source: *LSE*

Past performance is not an indication of future performance.

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TheraCryf plc

TheraCryf has announced positive top-line data from the first toxicology species in its lead Orexin-1 ('Ox-1') addiction programme. Dosing has completed in 28-day rodent studies, with initial data processed through developed analytical models demonstrating that the drug is well tolerated at amounts up to 100 times the expected requirements for human therapeutic use. This is well in excess of the tenfold safety margin indicated in FDA guidelines and suggests that full results across a range of doses, which may be available in June, are likely to be perfectly 'clean'. In pharmaceutical preclinical development of course, two animal species are required by regulatory authorities (FDA, EMA, ICH) for safety studies before initiating human clinical trials. Being able to pass candidates through different metabolic profiles is key to comprehensively test for any possible form of toxicity and accordingly, a second programme of dosing, this time most likely using mini pig, will get underway shortly. Theracryf is highly confident that the CRO, Pharmaron UK Limited, conducting its *in vivo* work will produce an outcome similarly positive to that delivered in the first round, with final data and associated analysis likely to be available in September. With all other remaining activities on schedule, this will be the final hurdle to negotiate before filing an Investigational New Drug ('IND') application (or equivalent in other countries) for Ox-1 early in Q4 2026. The commencement of a Phase 1 study in healthy human volunteers will undoubtedly represent a significant value inflection point for the Group and presently remains far from reflected in its valuation.

Orexins-based medications offer novel 'master switch'

Orexin-based medications are poised for an increasingly significant future role due to their novel 'master switch' ability to regulate sleep, wakefulness, reward and other neuropsychiatric diseases, moving beyond traditional sedatives or stimulants to offer more precise, tailored treatments for a wide range of psychiatric conditions. The orexin system effectively acts as a central conductor, making its modulation a 'blue sky opportunity' for such conditions.

Orexins, also known as hypocretins ('Hcrt'), are a pair of excitatory neuropeptides, namely Orexin-A (OxA/Hcrt-1) and Orexin-B (OxB/Hcrt-2), which are produced by a small population of neurons (c.50,000–80,000 in humans) in the lateral hypothalamus and perifornical area. Despite their limited number, these neurons project widely throughout the CNS to regulate arousal, sleep-wake cycles, feeding behaviour, reward and energy homeostasis. They exert their effects by binding to two G-protein coupled receptors, OX1R and OX2R, as detailed overleaf.

These two receptors are distributed differentially in the brain, suggesting specialized roles. OX1R is highly expressed in the locus coeruleus (noradrenergic neurons), ventromedial hypothalamic nucleus, amygdalohippocampal area, and raphe nuclei. It is strongly linked to reward, emotion and motivation. OX2R by contrast is primarily found in the tuberomammillary nucleus (histaminergic neurons), cerebral cortex, and hippocampus and is the dominant receptor for stabilising wakefulness. Both receptors are present in the ventral tegmental area and dorsal raphe. Binding of orexins to their receptors typically leads to neuronal excitation, most

frequently in terms of Gq Signalling, Ion Channels and Dimerization.

Comparison of Orexin Receptor Subtypes

Feature	OX1R	OX2R
Ligand Affinity	Orexin-A > Orexin-B	Orexin-A = Orexin-B
G-Protein	Gq/11	Gq/11, Gi/o
Major Role	Motivation, Reward, Emotion	Wakefulness, Sleep Stability
Key Location	Locus Coeruleus, Amygdala	Tuberomammillary Nucleus

Source: Academic papers, TPI estimates

The distinct therapeutic applications of each receptor, with OX1R recognised as a key target for behavioural/ metabolic conditions, plus potential for researchers to leverage their knowledge of the orexin system, suggests future focus will increasingly be on their independent (i.e. single orexin receptor antagonists or 'SORA'), rather than dual orexin receptor antagonists (or 'DORA') development. While suvorexant (Belsomra) and lemborexant (Dayvigo) were approved to treat insomnia by targeting OX1R and OX2R receptors to improve sleep initiation and maintenance, users have indicated that blocking both can sometimes induce or exacerbate symptoms such as cataplexy-like episodes and sleep fragmentation, rather than fully alleviating the conditions in all contexts. So, while nuanced approach to dual targeting may be assumed for enhancing arousal/treating hypersomnia, it appears selective targeting remains important for psychiatric and behavioural disorders. Note that in February 2026, the FDA accepted the New Drug Application ('NDA') and granted priority review for oveporexton (TAK-861) to treat narcolepsy type 1 ('NT1') by directly targeting the underlying orexin deficiency using just a potent OX2R agonist. In Phase 3 trials it significantly improved wakefulness and reduced cataplexy, demonstrating potential as a first-in-class and representing a further important move toward SORAs.

Comparison of FDA-Approved Dual Orexin Receptor Antagonists

Drug Name (Brand)	Developer	Mechanism	FDA Approval Date	Indication
Suvorexant (Belsomra)	Merck & Co.	Dual Orexin Receptor Antagonist (OX1R and OX2R)	August 13, 2014	Insomnia characterized by difficulties with sleep onset and/or sleep maintenance
Lemborexant (Dayvigo)	Eisai Co.	Dual Orexin Receptor Antagonist (OX1R and OX2R)	December 20, 2019	Insomnia characterized by difficulties with sleep onset and/or sleep maintenance
Daridorexant (Quviviq)	Idorsia Pharmaceuticals	Dual Orexin Receptor Antagonist (OX1R and OX2R)	January 7, 2022	Insomnia characterized by difficulties with sleep onset and/or sleep maintenance

Source: Market and Company data, TPI estimates

TheraCryf's Ox-1 programme demonstrates class-leading selectivity & high receptor occupancy

High selectivity (>100 fold) is considered critical for Ox-1 in order to permit the drug to specifically target addiction-related pathways while avoiding the side effects associated with inhibiting the orexin-2 receptor, including severe sedation or sleep disruption. By targeting only the Ox-1 receptor, the compound aims to treat daytime behaviours such as BED and AUD without affecting the normal sleep/wake cycle. This signals that the molecule has fully addressed issues that held back previous compounds (including a number of early GSK molecules) is particularly important, given that the side-effect profile of a drug often dictates its market viability.

In a 23 March 2026 update, TheraCryf had already reported that its Ox-1 blocker was well-tolerated at doses up to 1g/kg in regulatory toxicology studies. This is a critical indirect indicator of selectivity, given that if the drug had significant off-target binding to the OX2R at high concentrations, one would expect to see profound, dose-limiting sedation or sleep-like states *in vivo*. The fact that the drug was well-tolerated at such high doses provides good

evidence that it achieves a wide 'therapeutic window' (a high margin between the desired OX1R effect and the unwanted OX2R one). It also successfully demonstrated ability to bind to (i.e., block) a large percentage of orexin-1 receptors in the brain. With strong target engagement, high drug potency and potential for improved efficacy, Ox-1 has become significantly derisked. Based on these results, doses were selected for its pivotal 28-day toxicology studies. Given that all other activities remain on schedule, this should be considered the final important step on the path to IND/CTA readiness with final reporting scheduled for Q3 2026. In this respect, the valuation boost typically experienced by quoted pharmaceutical/biotech development companies in the months following their transition from preclinical development to Phase 1 trials, as pointed out for example by ScienceDirect, amounts to an uplift of approximately 87%. Wholly aware of this, acquisitive majors now keenly seeking opportunities in the Central Nervous System ('CNS') and Psychiatry space have already knocked on TheraCryf's door (as was reported on 14 April 2026). Rejection of their 'citing shot' might well produce a more realistic offer(s) in the relatively short term before others start taking a closer look at the highly impressive data delivered to date and the US$70 billion market opportunity being presented.

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