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Newcastle University

Health Technology Briefing

October 2024

Ganaxolone for treating tuberous sclerosis complex-related epilepsy after 2 or more treatments

Company/Developer	Orion Pharma (UK) Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 29659	NICE ID: Not available	UKPS ID: 663745

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Ganaxolone is in clinical development for the treatment of tuberous sclerosis complex (TSC) - related epilepsy. TSC is a rare genetic condition that causes non-cancerous tumours to grow in various organs, including the brain, skin, kidneys, heart, eyes and lungs. These tumours result from changes in the TSC1 or TSC2 genes and can lead to epilepsy, a condition where the brain is prone to seizures, defined as, sudden bursts of electrical activity in the brain that disrupt normal functioning like behaviour, movement, feelings or consciousness. Approximately 50% of patients with TSC-related epilepsy become resistant to current anti-epileptic drugs, making new treatment options important.

Ganaxolone mimics the action of a substance in the body called allopregnanolone. It switches on so-called GABA receptors, which reduce excessive electrical activity in the brain, thereby lowering the number of seizures. Ganaxolone is unique because it binds to both intrasynaptic (at the synapse, where nerve cells connect) and extrasynaptic (outside the synapse) GABA receptors, unlike many common anti-epileptic drugs that target only intrasynaptic receptors. This dual action makes extrasynaptic receptors a promising therapeutic target. If approved, ganaxolone could provide an additional treatment option for epilepsy related to TSC.

Proposed Indication

Adjunctive treatment of children and adults with Tuberous Sclerosis Complex (TSC)-related Epilepsy.[1]

Technology

Description

Ganaxolone (Ztalmy, CCD-1042, GXN) is a synthetic analogue of the naturally occurring neurosteroid allopregnanolone, modified by the addition of a 3β-methyl group.[2] It is a selective high-affinity, positive allosteric modulator of the GABAA receptor complex that mimics the action allopregnanolone. It switches on so-called GABA receptors, which reduces excessive electrical activity in the brain and thus lowers the number of seizures.[3,4] By enhancing the inhibitory effects of GABAA receptors, neurosteroids such as ganaxolone have been associated with various effects, including anxiolytic, sedative, and anticonvulsant properties.[5]

Ganaxolone is in clinical development for the treatment of TSC-related epilepsy. In the phase III randomised controlled trial and related open label extension study (NCT05323734, NCT05604170), ganaxolone will be administered orally three times daily.[1,6] In the phase II clinical trial (NCT04285346) ganaxolone suspension (50mg/ml) was administered three times a day for 12 weeks with a 24 week extension period.[7]

Key Innovation

TSC-related epilepsy is often difficult to treat and refractory to multiple antiseizure medications.[8] Studies suggest that at least 50% of patients with TSC-related epilepsy develop drug resistance to anti-epileptic drugs.[9] Refractory TSC-associated epilepsy is associated with increased risk of neurodevelopmental comorbidities, including developmental delay, intellectual disability, autism spectrum disorder, and attention hyperactivity disorder.[8] Therefore, there is a need for an effective treatment option for this indication. Unlike benzodiazepines, ganaxolone modulates both synaptic and extrasynaptic GABAA receptors.[2] Ganaxolone has shown promising results in reducing 28-day seizure frequency in early clinical studies.[7] If licensed, ganaxolone will offer an additional treatment option for patients with TSC-related epilepsy who currently have few effective therapies available.

Regulatory & Development Status

Ganaxolone currently has Marketing Authorisation in the EU/UK for the adjunctive treatment of epileptic seizures associated with CDKL5 deficiency disorder in patients 2 to 17 years of age.[3]

Ganaxolone is in phase II/III clinical development for status epilepticus and CDKL5 deficiency disorder.[10]

Ganaxolone was granted orphan drug designation in the EU in 2019 for the treatment of CDKL5 deficiency disorder.[11]

Patient Group

Disease Area and Clinical Need

TSC is a rare genetic condition that is caused by mutations in either the TSC1 or TSC2 gene leading to mainly benign tumours to develop in different parts of the body.[12] The tumours most often affect the brain, skin, kidneys, heart, eyes and lungs. The tumours caused by tuberous sclerosis can result in a range of

associated health problems, including epilepsy (the most common neurological feature in TSC.)[12] It is thought that epilepsy occurs in TSC due to areas of abnormal brain development, called cortical tubers. Cortical tubers are disorganised areas of the brain that contain changes to nerve cells. Epilepsy is a neurological condition that means a person is more likely to have epileptic seizures.[13] Epileptic seizures happen because of a sudden increase in electrical activity in the brain, which temporarily disrupts how the brain would normally work.[13] There are many different types of epileptic seizures and people with TSC often develop different types as they age. These seizures include focal seizures, infantile spasms, absence seizures, atonic seizures, myoclonic seizures and tonic-clonic seizures. Although most epilepsy in TSC starts in children, it can also begin in adults.[13]

The prevalence of TSC in the UK was estimated to be 8.8 per 100,000 in 1998 and registry data demonstrates that an estimated 83.5% of patients with TSC experience TSC-related epilepsy.[14,15] In England, 2022-23, there were 321 finished consultant episodes (FCE) and 309 admissions for TSC (ICD-10 code Q85.1), which resulted in 437 FCE bed days and 247 day cases.[16]

Recommended Treatment Options

NICE recommend the following treatment for TSC-related epilepsy:[17]

- Cannabidiol as an add-on treatment for seizures caused by tuberous sclerosis complex in people aged 2 years and over, only if:
  - their seizures are not controlled well enough by 2 or more antiseizure medications (either used alone or in combination) or these treatments were not tolerated
  - seizure frequency is checked every 6 months, and cannabidiol is stopped if the frequency has not fallen by at least 30% compared with the 6 months before starting treatment
  - the company provides cannabidiol according to the commercial arrangement.

Clinical Trial Information

Trial	**TrustTSC; NCT05323734, EudraCT2021-003441-38, 1042-TSC-3001;** A Phase 3, Double-blind, Randomized, Placebo-controlled Trial of Adjunctive Ganaxolone (GNX) Treatment in Children and Adults With Tuberous Sclerosis Complex (TSC) Related Epilepsy **Phase III:** Active, not recruiting **Location(s):** Four EU countries, UK, USA, Canada and Israel **Primary completion date:** October 2024	**TrustTSC OLE; NCT05604170;** A Phase 3, Open-label Study of Adjunctive Ganaxolone (GNX) Treatment in Children and Adults With Tuberous Sclerosis Complex (TSC)-Related Epilepsy **Phase III –** Enrolling by invitation **Location(s):** Four EU countries, UK, USA, Canada, Australia, Israel and China **Primary completion date:** June 2027
Trial Design	Randomised, parallel assignment, triple masked	Open label, single group assignment
Population	N=128 (estimated); subjects with TSC-related epilepsy, refractory to at least 2 prior therapies; aged 1 to 65 years	N=132 (estimated); subjects with TSC-related epilepsy who completed Study 1042-TSC-3001 and continue to meet study requirements in Study 1042-

		TSC-2001; aged 1 to 65 years. Patients continuing on GNX after phase 2 trial invited to join this extension study
Intervention(s)	Ganaxolone administered by oral suspension 3 times a day	Ganaxolone administered by oral suspension 3 times a day
Comparator(s)	Matched placebo (as adjunct to standard of care)	No comparator
Outcome(s)	Primary outcome: • Double-blind phase: Percent change from baseline in 28-day seizure frequency during titration and maintenance period [time frame: baseline (day 1) through week 16] See trial record for full list of other outcomes	Primary outcome: • Percent change from baseline in 28-day seizure frequency through the end of 12-week treatment period [time frame: baseline and up to week 12] See trial record for full list of other outcomes
Results (efficacy)	-	-
Results (safety)	-	-

Trial	NCT04285346; A Phase 2 Open-label 12-Week Trial of Adjunctive Ganaxolone Treatment (Part A) in Tuberous Sclerosis Complex-related Epilepsy Followed by Long-term Treatment (Part B) **Phase II:** Completed **Location:** USA **Study completion date:** August 2022
Trial Design	Open label, single group assignment
Population	N=23 (actual); subjects with TSC-related epilepsy; refractory to at least 2 prior therapies; aged 2 to 65 years
Intervention(s)	Ganaxolone suspension (50mg/ml) administered 3 times a day for 12 weeks with 24-week extension period
Comparator(s)	No comparator
Outcome(s)	Primary outcome: • Percent change from baseline in 28-day seizure frequency through the end of 12-week treatment period [time frame: baseline and up to week 12] See trial record for full list of other outcomes
Results (efficacy)	See trial record
Results (safety)	See trial record

Estimated Cost

The cost of ganaxolone is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Cannabidiol for treating seizures caused by tuberous sclerosis complex (TA873). March 2023.
- NICE clinical guideline in development. Epilepsies in children, young people and adults (extraordinary review) (GID-NG10378). Expected date of issue to be confirmed.
- NICE clinical guideline. Epilepsies in children, young people and adults (NG217). April 2022.
- NICE quality standard. Epilepsies in children, young people and adults (QS211). December 2023.

NHS England (Policy/Commissioning) Guidance

- NHS England. Service Specification: Refractory Epilepsy Specialist Clinical Advisory Service. February 2020.
- NHS England. 2013/14 NHS Standard Contract for Neurosciences: Specialised Neurology (Adult). D04/S/a.
- NHS England. Clinical Commissioning policy: Everolimus for refractory focal onset seizures associated with tuberous sclerosis complex (ages 2 years and above). 170093P. December 2018.
- NHS England. Clinical Commissioning Policy: Deep Brain Stimulation for Refractory Epilepsy (all ages). 170036P. March 2018.

Other Guidance

- Specchio N, Nabbout R, Aronica E, Auvin S, Benvenuto A, de Palma LZ, et al. Updated clinical recommendations for the management of tuberous sclerosis complex associated epilepsy. 2023.[18]
- Northrup H, Aronow ME, Bebin EM, Bissler J, Darling TN, de Vries PJ, et al. Updated International Tuberous Sclerosis Complex Diagnostic Criteria and Surveillance and Management Recommendations. 2021.[19]
- Amin S, Kingswood JC, Bolton PF, Elmslie F, Gale DP, Harland C, et al. The UK guidelines for management and surveillance of Tuberous Sclerosis Complex. 2019.[20]

Additional Information

References

1 ClinicalTrials.gov. *Adjunctive GNX Treatment Compared With Placebo in Children and Adults With TSC-related Epilepsy*. *Trial ID: NCT05323734*. 2022. Status: Recruiting. Available from: https://clinicaltrials.gov/study/NCT05323734 [Accessed 20 August 2024].

2 Marinus Pharmaceuticals Inc. Ganaxolone: Mechanism of Action and Pharmacology. *74th American Epilepsy Society (Virtual)*. 2020. Available from: https://marinuspharma.com/wp-content/uploads/2020/12/1_AES2020_GNX-Mechanism-of-Action.pdf [Accessed 21 October 2024].

3 European Medicines Agency (EMA). *Ztalmy*. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/ztalmy [Accessed 20 August 2024].
4 Lamb YN. Ganaxolone: First Approval. *Drugs*. 2022;82(8):933-40. Available from: https://doi.org/10.1007/s40265-022-01724-0.
5 DrugBank. *Ganaxolone*. Available from: https://go.drugbank.com/drugs/DB05087 [Accessed 20 August 2024].
6 ClinicalTrials.gov. *Open-label Study of Adjunctive GNX Treatment in Children and Adults With TSC-related Epilepsy*. *Trial ID: NCT05604170*. 2022. Status: Enrolling by invitation. Available from: https://clinicaltrials.gov/study/NCT05604170 [Accessed 20 August 2024].
7 ClinicalTrials.gov. *Adjunctive Ganaxolone Treatment (Part A) in TSC Followed by Long-term Treatment (Part B) (TSC)*. *Trial ID: NCT04285346*. 2020. Status: Completed. Available from: https://clinicaltrials.gov/study/NCT04285346 [Accessed 20 August 2024].
8 Singh A, Hadjinicolaou A, Peters JM, Salussolia CL. Treatment-Resistant Epilepsy and Tuberous Sclerosis Complex: Treatment, Maintenance, and Future Directions. *Neuropsychiatr Dis Treat*. 2023;19:733-48. Available from: https://doi.org/10.2147/ndt.S347327.
9 Liu S, Yu T, Guan Y, Zhang K, Ding P, Chen L, et al. Resective epilepsy surgery in tuberous sclerosis complex: a nationwide multicentre retrospective study from China. *Brain*. 2020;143(2):570-81. Available from: https://doi.org/10.1093/brain/awz411.
10 ClinicalTrials.gov. *Other terms: ganaxolone | Not yet recruiting, Recruiting, Active, not recruiting, Enrolling by invitation studies | Phase: 2, 3*. Available from: https://clinicaltrials.gov/search?term=ganaxolone&aggFilters=phase:2%203,status:not%20rec%20enr%20act [Accessed 20 August 2024].
11 European Medicines Agency (EMA). *EU/3/19/2224 - orphan designation for treatment of CDKL5 deficiency disorder*. 2019. Available from: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu-3-19-2224 [Accessed 20 August 2024].
12 National Health Service (NHS). *Tuberous sclerosis*. Available from: https://www.nhs.uk/conditions/tuberous-sclerosis/ [Accessed 20 August 2024].
13 Tuberous Sclerosis Association. *Epilepsy*. Available from: https://tuberous-sclerosis.org/tsc_affects_the_body/epilepsy/ [Accessed 20 August 2024].
14 Kingswood JC, d'Augères GB, Belousova E, Ferreira JC, Carter T, Castellana R, et al. TuberOus SClerosis registry to increase disease Awareness (TOSCA) - baseline data on 2093 patients. *Orphanet J Rare Dis*. 2017;12(1):2. Available from: https://doi.org/10.1186/s13023-016-0553-5.
15 O'Callaghan FJK, Shiell AW, Osborne JP, Martyn CN. Prevalence of tuberous sclerosis estimated by capture-recapture analysis. *The Lancet*. 1998;351(9114):1490. Available from: https://doi.org/10.1016/S0140-6736(05)78872-3.
16 NHS Digital. *Hospital Admitted Patient Care Activity, 2022-23*. 2023. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2022-23 [Accessed 24 May 2024].
17 National Institute for Health and Care Excellence (NICE). *Cannabidiol for treating seizures caused by tuberous sclerosis complex* (*TA873)*. Available from: https://www.nice.org.uk/guidance/ta873/chapter/1-Recommendations [Accessed 04 October 2024].
18 Specchio N, Nabbout R, Aronica E, Auvin S, Benvenuto A, de Palma L, et al. Updated clinical recommendations for the management of tuberous sclerosis complex associated epilepsy. *European Journal of Paediatric Neurology*. 2023;47:25-34. Available from: https://doi.org/10.1016/j.ejpn.2023.08.005.

19 Northrup H, Aronow ME, Bebin EM, Bissler J, Darling TN, de Vries PJ, et al. Updated International Tuberous Sclerosis Complex Diagnostic Criteria and Surveillance and Management Recommendations. *Pediatric Neurology*. 2021;123:50-66. Available from: https://doi.org/10.1016/j.pediatrneurol.2021.07.011.

20 Amin S, Kingswood JC, Bolton PF, Elmslie F, Gale DP, Harland C, et al. The UK guidelines for management and surveillance of Tuberous Sclerosis Complex. *QJM: An International Journal of Medicine*. 2018;112(3):171-82. Available from: https://doi.org/10.1093/qjmed/hcy215.

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