NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
June 2024

Iclepertin for treating cognitive impairment associated with schizophrenia in people aged 18 to 80 years

Company/Developer	Boehringer Ingelheim Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 13006	NICE ID: Not Available	UKPS ID: 667394

Licensing and Market Availability Plans

Phase III clinical development is ongoing.

Summary

Iclepertin is in clinical development for treating cognitive (thinking) impairment associated with schizophrenia (CIAS). Schizophrenia is a long-term mental health condition, which can be triggered by many different biological, social and psychological factors. The symptoms of schizophrenia are usually divided into positive symptoms (such as hallucinations and delusions), negative symptoms (such as emotional apathy, lack of drive, poverty of speech, social withdrawal, and self-neglect) and cognitive symptoms (such as working memory and executive function impairment). CIAS is a major burden for patients and negatively impacts many aspects of a patient's life, and there are currently no approved pharmacological therapies for these cognitive impairments.

Iclepertin when administered orally, is a new and powerful inhibitor that targets a specific protein called glycine transporter 1 (GlyT1). GlyT1 regulates the release and reabsorption of glycine, a neurotransmitter that supports brain signalling. This signalling has been linked to improved thinking. If licenced, iclepertin may provide a new treatment for CIAS.

Proposed Indication

Treatment of patients aged 18 to 50 years with cognitive impairment associated with schizophrenia (CIAS) and a clinically stable schizophrenia diagnosis.[1-5]

Technology

Description

Iclepertin (BI 425809) is a novel potent and selective glycine transporter 1 (GlyT1) inhibitor. GlyT1 is responsible for controlling the release and reuptake of glycine (a neurotransmitter that supports glutamatergic signalling in the forebrain, and glycinergic signalling in the hindbrain).[6] Glutamatergic signalling via N-methyl-d-aspartate (NMDA) receptors has been reported to improve cognition.[6,7]

Iclepertin is currently in development for the treatment of patients with CIAS.[8] In phase III clinical trials (CONNEX-3, NCT04860830; CONNEX-2, NCT04846881; and CONNEX-1, NCT04846868), participants received 10 mg of iclepertin once daily for 26 weeks.[1-3,6]

Key Innovation

CIAS consistently predict poor functional outcomes in patients with schizophrenia. However, there are currently no approved pharmacological therapies for these cognitive impairments.[7] Antipsychotic drugs, the standard-of-care (and only approved pharmacological option) treatment of schizophrenia, primarily address the positive symptoms, such as delusions and auditory hallucinations, but do not effectively treat negative symptoms, CIAS, or fully address daily functioning.[6] Consequently, there is an unmet clinical need to develop effective pharmacotherapies to improve CIAS and thereby potentially improve the quality of life and daily functioning among patients with schizophrenia.[6] Iclepertin has been reported to improve cognition in patients with schizophrenia at a daily dose of 10 mg and 25 mg administered orally for 12 weeks.[9] If licenced, iclepertin may provide a new treatment option for CIAS.

Regulatory & Development Status

Iclepertin does not currently have Marketing Authorisation in the EU or UK for any indication.

Iclepertin was awarded a Breakthrough Therapy Designation in May 2021, by the US Food and Drug Administration (FDA) for the treatment of schizophrenia.[10]

Patient Group

Disease Area and Clinical Need

Schizophrenia is a psychiatric disorder characterised by symptoms in three domains: positive (e.g. delusions, hallucinations), negative (e.g. social withdrawal, lack of motivation) and cognitive (e.g. working memory and executive function impairment). Cognitive impairment associated with schizophrenia (CIAS) is a major burden for patients and negatively impacts many aspects of a patient's life.[6,11] The risk factors for schizophrenia has been reported to include family history of the disease and pregnancy and birth complications. Also several triggers for schizophrenia has been reported to include drug abuse, and stress from divorce, bereavement, loss of job, physical, sexual and emotional abuse.[12]

In the UK the lifetime prevalence of schizophrenia and schizophrenia-related disorders is approximately 14.5 per 1000 people, although there is considerable variation between estimates.[13] CIAS is present in 80% of patients with schizophrenia and is a main determinant of functional disability and the indirect costs of the disease.[8,14] A key driver of health costs associated with schizophrenia is admission to hospital.

Cognitive impairment is linked to reduced adherence to treatment, a greater likelihood of hospital admission, and longer lengths of hospital stay.[15] In England (2022-23) there were 10,405 finished consultant episodes (FCEs) and 6,112 admissions for schizophrenia (ICD-10 code F20), which resulted in 37 day cases and 709,334 FCE bed days.[16]

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) recommend the following pharmacological treatment options for adults with schizophrenia:[17,18]

- The use of antipsychotic medication (e.g. clozapine, aripiprazole)
- And/or a mood stabiliser for psychosis with significant affective symptoms (e.g. lithium)
- And/or an antidepressant if there are significant depressive symptoms in adults with schizophrenia

Clinical Trial Information

Trial	**CONNEX-X; NCT05211947, EudraCT 2020-003745-11;** An Open Label, Single Arm, Extension Trial to Examine Long-term Safety of Iclepertin Once Daily in Patients With Schizophrenia Who Have Completed Previous Iclepertin Phase III Trials (CONNEX-X). **Phase III** – Recruiting **Location (s):** Fifteen EU countries, UK, US, Canada and others **Primary completion date:** February 2026
Trial Design	Interventional, single group assignment, open-label treatment
Population	N = 1401 (estimated); patients aged 18 to 51 years with a clinically stable schizophrenia diagnosis and who previously participated in a parent trial.
Intervention(s)	Oral administration of iclepertin tablet (10 mg), once daily for 1 year.[6]
Comparator(s)	No comparator
Outcome(s)	**Primary outcome measure:** Occurrence of treatment emergent adverse events (TEAEs) [Time Frame: up to 1 year and 12 days] See trial record for a full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	**CONNEX-3;** NCT04860830, EudraCT 2020-003726-23; A Phase III Randomized, Double-blind, Placebo-controlled Parallel Group Trial to Examine

	the Efficacy and Safety of Iclepertin Once Daily Over 26 Week Treatment Period in Patients With Schizophrenia (CONNEX-3). **Phase III** – Active, not recruiting **Location (s):** Nine EU countries, UK, US, and others **Primary completion date:** October 2024
Trial Design	Randomised, parallel assignment, quadruple masking, and placebo-controlled
Population	N = 609 (actual); patients aged 18 to 50 years with a clinically stable schizophrenia diagnosis.
Intervention(s)	Oral administration of iclepertin tablet (10 mg), once daily for 26 weeks.[6]
Comparator(s)	Matched placebo
Outcome(s)	**Primary outcome measure:** Change from baseline in overall composite T-score of the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) [Time Frame: After 26 weeks of treatment] See trial record for a full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	**CONNEX-2;** NCT04846881, EudraCT 2020-003744-84; A Phase III Randomized, Double-blinded, Placebo-controlled Parallel Group Trial to Examine the Efficacy and Safety of Iclepertin Once Daily Over 26 Week Treatment Period in Patients With Schizophrenia (CONNEX-2). **Phase III** – Active, not recruiting **Location (s):** Eight EU countries, US and others **Primary completion date:** October 2024
Trial Design	Randomised, parallel assignment, quadruple masking, and placebo-controlled
Population	N = 611 (actual); patients aged 18 to 50 years with a clinically stable schizophrenia diagnosis.
Intervention(s)	Oral administration of iclepertin tablet (10 mg), once daily for 26 weeks.[6]
Comparator(s)	Matched placebo
Outcome(s)	**Primary outcome measure:** Change from baseline in overall composite T-score of the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) after 26 weeks of treatment [Time Frame: at baseline and at week 26] See trial record for a full list of other outcomes
Results (efficacy)	-

Results (safety)	-

Trial	**CONNEX-1;** NCT04846868, EudraCT 2020-003760-11; A Phase III Randomized, Double-blind, Placebo-controlled Parallel Group Trial to Examine the Efficacy and Safety of Iclepertin Once Daily Over 26 Week Treatment Period in Patients With Schizophrenia (CONNEX-1). **Phase III** – Active, not recruiting **Location (s):** Five EU countries, US, Canada, Australia, and others **Primary completion date:** September 2024
Trial Design	Randomised, parallel assignment, quadruple masking, and placebo-controlled
Population	N = 620 (actual); patients aged 18 to 50 years with a clinically stable schizophrenia diagnosis.
Intervention(s)	Oral administration of iclepertin tablet (10 mg), once daily for 26 weeks.[6]
Comparator(s)	Matched placebo
Outcome(s)	**Primary outcome measure:** Change from baseline in overall composite T-score of the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) after 26 weeks of treatment [Time Frame: at baseline and at week 26] See trial record for a full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	NCT02832037, EudraCT 2016-000285-28; A Phase II Randomised, Double-blinded, Placebo-controlled Parallel Group Trial to Examine the Efficacy and Safety of 4 Oral Doses of BI 425809 Once Daily Over 12 Week Treatment Period in Patients With Schizophrenia. **Phase II** – Completed **Location (s):** Five EU countries, UK, US, Canada, and others **Study completion date:** January 2020
Trial Design	Randomised, parallel assignment, double masking, and placebo-controlled
Population	N = 509 (actual); patients aged 18 to 50 years with a clinically stable schizophrenia diagnosis.
Intervention(s)	Oral administration of iclepertin tablet (2 mg, 5 mg, 10 mg, or 25 mg), once daily for 12 weeks.[6]
Comparator(s)	Matched placebo
Outcome(s)	**Primary outcome measure:**

	- Change From Baseline in Cognitive Function as Measured by the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) Overall Composite T-score After 12 Weeks of Treatment [Time Frame: Baseline, after 6 and 12 weeks of treatment] See trial record for a full list of other outcomes
Results (efficacy)	Pairwise comparisons showed greater mean improvement from baseline in MCCB overall composite T-score at week 12 with BI 425809 10 mg and 25 mg versus placebo (adjusted mean difference 1·98 [95% CI 0·43–3·53] for 10 mg and 1·73 [0·18–3·28] for 25 mg.[9]
Results (safety)	Balanced adverse events between iclepertin and placebo-controlled groups.[9]

Estimated Cost

The cost of iclepertin is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal awaiting development. Abilify MyCite for treating bipolar disorder 1 or schizophrenia (GID-TA10718). Expected publication date to be confirmed.
- NICE clinical guideline. Psychosis and schizophrenia in adults: prevention and management (CG178). February 2014.
- NICE guideline. Rehabilitation for adults with complex psychosis (NG181). August 2020.

NHS England (Policy/Commissioning) Guidance

- NHS England. Improving the physical health of people living with severe mental illness: Guidance for integrated care systems. Publishing reference: B1955. January 2024.
- NHS England. Implementing the early intervention in psychosis access and waiting time standard. Version 3. Publication reference: PR1954. February 2023.
- NHS England. Mental Health Implementation Plan 2019/20 - 2023/24. Publishing approval reference: 000830. July 2019.
- NHS England. Treatment of psychosis and schizophrenia algorithm. Version 2. Guideline number: 726FM. March 2018.

Other Guidance

- The American Psychiatric Association. Practice guideline for the treatment of patients with schizophrenia. 2021.[19]
- NHS Dorset. Service specifications. 05/MHLD/0010. 2016.[20]
- Scottish Intercollegiate Guidelines Network. Management of schizophrenia. 2013.[21]

Additional Information

References

1 ClinicalTrials.gov. *Clinical Trial of Iclepertin Effect on Cognition and Functional Capacity in Schizophrenia (CONNEX-1)*. 2021. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT04846868 [Accessed April 23, 2024].

2 ClinicalTrials.gov. *Clinical Trial of Iclepertin Effect on Cognition and Functional Capacity in Schizophrenia (CONNEX-2)*. 2021. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT04846881 [Accessed April 23, 2024].

3 ClinicalTrials.gov. *CONNEX-3: A Study to Test Whether Iclepertin Improves Learning and Memory in People With Schizophrenia*. 2021. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT04860830 [Accessed April 23, 2024].

4 ClinicalTrials.gov. *Clinical Trial of BI 425809 Effect on Cognition and Functional Capacity in Schizophrenia*. 2016. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT02832037 [Accessed April 23, 2024].

5 Wunderlich G, Blahova Z, Hake S, Ikezawa S, Marder S, Falkai P, Krystal JH. Efficacy and Safety of Iclepertin (BI 425809) in Patients With Schizophrenia: CONNEX, A Phase III Randomized Controlled Trial Program. *CNS Spectrums*. 2023;28(2):229-. Available from: https://doi.org/10.1017/S1092852923001530.

6 Rosenbrock H, Desch M, Wunderlich G. Development of the novel GlyT1 inhibitor, iclepertin (BI 425809), for the treatment of cognitive impairment associated with schizophrenia. *European Archives of Psychiatry and Clinical Neuroscience*. 2023;273(7):1557-66. Available from: https://doi.org/10.1007/s00406-023-01576-z.

7 Harvey PD, Bowie CR, McDonald S, Podhorna J. Evaluation of the Efficacy of BI 425809 Pharmacotherapy in Patients with Schizophrenia Receiving Computerized Cognitive Training: Methodology for a Double-blind, Randomized, Parallel-group Trial. *Clinical Drug Investigation*. 2020;40(4):377-85. Available from: https://doi.org/10.1007/s40261-020-00893-8.

8 Boehringer Ingelheim. *Iclepertin: GlyT1 inhibitor*. 2024. Available from: https://www.boehringer-ingelheim.com/science/human-pharma/clinical-pipeline/cns/iclepertin [Accessed April 23, 2024].

9 Fleischhacker WW, Podhorna J, Gröschl M, Hake S, Zhao Y, Huang S, et al. Efficacy and safety of the novel glycine transporter inhibitor BI 425809 once daily in patients with schizophrenia: a double-blind, randomised, placebo-controlled phase 2 study. *Lancet Psychiatry*. 2021;8(3):191-201. Available from: https://doi.org/10.1016/s2215-0366(20)30513-7.

10 PR Newswire. *Boehringer Ingelheim's Investigational Treatment for Cognitive Impairment Associated with Schizophrenia Receives FDA Breakthrough Therapy Designation*. 2021. Available from: https://www.prnewswire.com/news-releases/boehringer-ingelheims-investigational-treatment-for-cognitive-impairment-associated-with-schizophrenia-receives-fda-breakthrough-therapy-designation-301297651.html [Accessed April 24, 2024].

11 National Health Service (NHS). *Symptoms - Schizophrenia*. 2023. Available from: https://www.nhs.uk/mental-health/conditions/schizophrenia/symptoms/ [Accessed April 24, 2024].

12 National Health Service (NHS). *Causes - Schizophrenia*. 2023. Available from: https://www.nhs.uk/mental-health/conditions/schizophrenia/causes/ [Accessed April 24, 2024].

13 National Institute for Health and Care Excellence (NICE). *Psychosis and schizophrenia in children and young people: recognition and management* 2024. Available from: https://www.nice.org.uk/guidance/cg155/resources/psychosis-and-schizophrenia-in-children-and-young-people-final-scope2#:~:text=In%20the%20UK%20the%20lifetime,is%20considerable%20variation%20between%20estimates. [Accessed April 24, 2024].

14 Harvey PD, Bosia M, Cavallaro R, Howes OD, Kahn RS, Leucht S, et al. Cognitive dysfunction in schizophrenia: An expert group paper on the current state of the art. *Schizophrenia Research: Cognition*. 2022;29:100249. Available from: https://doi.org/10.1016/j.scog.2022.100249.

15 McCutcheon RA, Keefe RSE, McGuire PK. Cognitive impairment in schizophrenia: aetiology, pathophysiology, and treatment. *Molecular Psychiatry*. 2023;28(5):1902-18. Available from: https://doi.org/10.1038/s41380-023-01949-9.

16 National Health Service (NHS) Digital. *Hospital Admitted Patient Care Activity, 2022-23*. 2023. Available from: https://view.officeapps.live.com/op/view.aspx?src=https%3A%2F%2Ffiles.digital.nhs.uk%2F34%2FC4E943%2Fhosp-epis-stat-admi-diag-2022-23-tab.xlsx&wdOrigin=BROWSELINK [Accessed 22 May, 2024].

17 National Institute for Health and Care Excellence (NICE). *Psychosis and schizophrenia in adults: prevention and management (CG178)*. 2014. Available from: https://www.nice.org.uk/guidance/cg178/chapter/recommendations#choice-of-antipsychotic-medication [Accessed May 09, 2024].

18 National Institute for Health and Care Excellence (NICE). *Rehabilitation for adults with complex psychosis (NG181)*. 2020. Available from: https://www.nice.org.uk/guidance/ng181/chapter/recommendations#pharmacological-treatments [Accessed May 09, 2024].

19 The American Psychiatric Association. *Practice guideline for the treatment of patients with schizophrenia*. 2021. Available from: https://psychiatryonline.org/doi/pdf/10.1176/appi.books.9780890424841 [Accessed April 24, 2024].

20 National Health Service (NHS) Dorset. *Service Specifications: 05/MHLD/0010* 2016. Available from: https://nhsdorset.nhs.uk/Downloads/aboutus/finance/05_MHLD_0010%20Assertive%20Outreach%20v1.1.pdf [Accessed April 24, 2024].

21 Scottish Intercollegiate Guidelines Network (SIGN). *Management of schizophrenia*. 2013. Available from: https://www.sign.ac.uk/media/1069/sign131.pdf [Accessed April 24, 2024].

NB: This briefing presents independent research funded by the National Institute for Health and Care Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.