NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
April 2022

Leniolisib for previously untreated activated phosphoinositide 3-kinase delta syndrome

Company/Developer	Pharming Group NV

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 11618	NICE ID: 10657	UKPS ID: 660929

Licensing and Market Availability Plans

Currently in phase III/II clinical trials.

Summary

Leniolisib is in clinical development for patients with Activated Phosphoinositide 3-kinase Delta Syndrome (APDS). APDS is an inherited disorder where the patient is unable to fight infections because the immune system (the body's natural defences) does not work properly. APDS is caused by defects in the genes that control the production of a protein called phosphoinositide 3-kinase delta (PI3Kδ). Beginning in childhood, people with APDS develop recurrent infections, particularly in the lungs, sinuses, and ears. Over time, recurrent respiratory tract infections can lead to a condition called bronchiectasis, which damages the passages leading from the windpipe to the lungs (bronchi) and can cause breathing problems. Currently, treatment of APDS is limited to supportive therapies, with no therapy approved for the treatment of the disease.

Leniolisib is an oral medicine which targets the protein PI3Kδ within immune cells (B and T cells) and attenuates its action. This has been demonstrated to reduce the overactivity of the PI3Kδ pathway and its downstream targets, helping to restore normal development of B and T cells and their ability to fight infections, thereby reducing symptoms of APDS. If licensed, leniolisib will offer a treatment option for patients with APDS who currently have no effective therapies available.

Proposed Indication

Treatment for patients (12 years and older) with Activated phosphoinositide 3-kinase delta syndrome (APDS).[1]

Technology

Description

Leniolisib (CDZ173) is a selective phosphoinositide 3- kinase delta (PI3Kδ) inhibitor.[2] Phosphoinositide 3-kinases (PI3Ks) are a class of enzymes fundamental in the regulation of cell metabolism, proliferation and survival. PI3Kδ is one of four isoforms that comprise PI3Ks.[3] Leniolisib binds to PI3Kδ and attenuates its action. This has been demonstrated to reduce the overactive PI3Kδ pathway signalling, which helps to restore normal maturation of B and T cells, thereby reducing symptoms of ADPS, including a patient's ability to fight infections.[4]

Leniolisib is currently in clinical development for patients with APDS 12 years and older. In the phase II/III clinical trial (NCT02435173) which was composed of two parts, the first part was an open-label dose escalation study; and the second part was randomised, controlled and triple blinded. In Part 2 (the Phase III trial), patients were administered oral leniolisib 70mg twice a day for 12 weeks.[1,5]

Key Innovation

The central role of PI3Kδ is a secondary messenger, regulating numerous cellular functions, such as proliferation, differentiation and survival, of the adaptive immune system (B-cells and to a lesser extent T cells) as well as the innate immune system (neutrophil, mast cells, and macrophages). This strongly indicates that PI3Kδ is a valid and potentially effective therapeutic target for several immune diseases.[5]

Currently, treatment of APDS is limited to supportive therapies, such as antibiotics, antivirals and immunoglobulin replacement therapy, but there is no therapy approved for the treatment of the disease.[6] If licensed, leniolisib will offer a treatment option for patients with APDS who currently have no effective therapies available.

Regulatory & Development Status

Leniolisib does not currently have Marketing Authorisation in the EU/UK for any indication.

Leniolisib is in phase II clinical development for primary Sjögren's syndrome.[7]

Leniolisib was granted orphan drug designation in the EU in 2020 for the treatment of APDS.[4]

Additionally, in Q1 2022 MHRA accepted the paediatric investigation plan for leniolisib.[8]

Patient Group

Disease Area and Clinical Need

APDS is an inherited disorder where the patient is unable to fight infections because the immune system (the body's natural defences) does not work properly. It is caused by defects in the genes that control the

production of a protein called PI3Kδ. This protein is essential for the development of B and T cells, white blood cells that play a key role in the immune system. The defects make PI3Kδ overactive, interfering with the normal development of B and T cells and their ability to fight infections.[4] Beginning in childhood, people with APDS develop recurrent infections, particularly in the lungs, sinuses, and ears. Over time, recurrent respiratory tract infections can lead to a condition called bronchiectasis, which damages the passages leading from the windpipe to the lungs (bronchi) and can cause breathing problems. People with APDS may also have chronic active viral infections, commonly Epstein-Barr virus or cytomegalovirus infections.[9]

In 2020, APDS affected approximately 0.01 in 10,000 people in the European Union (EU), and this data includes patients in the UK. This was equivalent to a total of around 500 people.[4]

Recommended Treatment Options

Treatment for patients with APDS depends on their individual symptoms:[10]

- Infections should be managed quickly with antibiotic (bacterial infections) or antiviral (viral infections) drugs. If patients are at high risk of repeated infections, on-going antibiotic or antiviral drugs may be considered to prevent infections from occurring.
- For patients with poor antibody production, immunoglobulin replacement treatment may be used.
- Haematopoietic stem cell transplantation (HSCT) is the only curative option and, given the risks, may be considered for patients with severe APDS (including for those who have developed a lymphoma).
- Some drugs (such as steroids, sirolimus or the monoclonal antibody rituximab) are able to modify the response of the immune system so they are suitable for patients with features of autoimmunity such as low numbers of blood cells, kidney disease, arthritis, or inflammation of the colon.

Clinical Trial Information

Trial	NCT02859727, EudraCT-2016-000468-41; An Open-label, Non-randomized Extension Study to Evaluate the Long Term Safety, Tolerability, Efficacy and Pharmacokinetics of CDZ173 in Patients With APDS/PASLI (Activated Phosphoinositide 3-kinase Delta Syndrome/p110δ-activating Mutation Causing Senescent T Cells, Lymphadenopathy and Immunodeficiency) **Phase II/III** - active, not recruiting **Location(s):** four EU countries, USA, Belarus and Russian Federation **Primary completion date:** October 2026
Trial Design	Single group assignment, open label
Population	N=37; Subjects 12 to 75 years who participated in the study CCDZ173X2201 or were treated previously with PI3Kδ inhibitors other than leniolisib
Intervention(s)	Oral leniolisib 140 mg/day
Comparator(s)	No comparator
Outcome(s)	Primary outcome measure: Long term safety and tolerability of leniolisib in patients with APDS/PASLI (p110 delta-activating mutation causing senescent T cells, lymphadenopathy, and immunodeficiency) [time frame: 6 years 3 months]

	See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information	
Trial	NCT02435173, EudraCT-2014-003876-22; An Open-label, Non-randomized, Within-patient Dose-finding Study Followed by a Randomized, Subject, Investigator and Sponsor-blinded Placebo Controlled Study to Assess the Efficacy and Safety of CDZ173 (Leniolisib) in Patients With APDS/PASLI (Activated Phosphoinositide 3-kinase Delta Syndrome/ p110δ-activating Mutation Causing Senescent T Cells, Lymphadenopathy and Immunodeficiency) **Phase II/III** - completed **Location(s):** five EU countries, UK, USA, Belarus and Russian Federation **Study completion date:** August 2021
Trial Design	Randomised, parallel assignment, triple-blinded, placebo controlled
Population	N=37; Subjects 12 to 75 years who have a documented APDS/PASLI-associated genetic PI3Kδ mutation
Intervention(s)	• Part I: oral leniolisib 10mg twice a day from day 1 to day 28; 30mg twice a day from day 29 to day 56; and 70 mg twice a day from day 57 to day 84 • Part II: oral leniolisib 70mg twice a day from day 1 to day 85
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome measures: • Part I: Number of participants with Adverse Events (AEs) and Serious Adverse Events (SAEs) [time frame: from the start of treatment to 30 days after end of treatment, assessed up to maximum duration of 114 days] • Part I: CDZ173 Dose Concentration [Time Frame: Days 1, 29 and 57 (0.25 and 3 h post morning dose) and Day 84] • Part I: Percentage of Inhibition of Unstimulated and Stimulated pAkt Levels in B Cells [Time Frame: Baseline, days 29 and 57 (3 and 12 h post-dose) and day 84] • Part II: Change from baseline in the log10 transformed sum of product of diameters (SPD) in the index lesions [time frame: Baseline and Day 85] • Part II: Change from baseline in percentage of naïve B cells out of total B cells [time frame: Baseline and Day 85] See trial record for full list of other outcomes
Results (efficacy)	See trial record
Results (safety)	See trial record

Estimated Cost

Cost of leniolisib was confidential at the time of producing this briefing.

Relevant Guidance

NICE Guidance

No relevant guidance identified.

NHS England (Policy/Commissioning) Guidance

No relevant guidance identified.

Other Guidance

- International Patient Organisation for Primary Immunodeficiencies (IPOPI). APDS - activated PI3K delta syndrome. 2020.[10]

Additional Information

References

1 ClinicalTrials.gov. *Study of Efficacy of CDZ173 in Patients With APDS/PASLI.* 2021. Available from: https://clinicaltrials.gov/ct2/show/NCT02435173 [Accessed 8 March 2022].

2 Specialist Pharmacy Service (SPS). *Leniolisib.* 2021. Available from: https://www.sps.nhs.uk/medicines/leniolisib/ [Accessed 8 March 2022].

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6 PharmTech. *Pharming Reveals Positive Trial Results for Leniolisib Study.* 2022. Available from: https://www.pharmtech.com/view/pharming-reveals-positive-trial-results-for-leniolisib-study [Accessed 8 March 2022].

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9 MedlinePlus. *Activated PI3K-delta syndrome.* 2014. Available from: https://medlineplus.gov/genetics/condition/activated-pi3k-delta-syndrome/ [Accessed 8 March 2022].

10 International Patient Organisation for Primary Immunodeficiencies (IPOPI). *APDS - activated PI3K delta syndrome.* 2020. Available from: http://www.immunodeficiencyuk.org/static/media/up/IPOPIADPS.pdf [Accessed 8 March 2022].

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