Health Technology Briefing
July 2024

Norucholic acid for treating primary sclerosing cholangitis

Company/Developer	Dr Falk Pharma UK Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 13018	NICE ID: 10333	UKPS ID: 653985

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Norucholic acid (NCA), (previously known as norursodeoxycholic acid (norUDCA) is in clinical development for treating primary sclerosing cholangitis (PSC). PSC is a rare and progressive chronic liver disease. In PSC the bile ducts (tubes which allow the liquid produced by the liver (bile) to flow from the liver to the small intestine where it helps with digestion of fat) become inflamed and scarred, causing them to narrow and block. This causes bile to build up in the liver which slowly damages and scars the liver. The cause of PSC is unknown but potential causes may originate from genetics, immune system problems and bacteria or viruses. The main symptoms of PSC include itching, tiredness and yellowing of the skin and eyes. There is no cure for PSC and there are few treatments available.

NCA is a modified form of ursodeoxycholic acid, a bile acid found in small amount in human bile and which is already authorised for the treatment of primary sclerosing cholangitis. NCA, once taken by the patient, is thought to enter repeated cycles in which it is secreted by the liver cells, partially re-absorbed by the cells of the bile ducts, and then re-enters the liver cells. These cycles are thought to 'flush' the bile ducts. By 'flushing' the biliary system, this medicine is expected to prevent the build-up of bile acids in the liver and therefore the damage to the liver tissue. If licensed, NCA would offer the first approved medicinal product for the treatment of PSC.

Proposed Indication

Primary sclerosing cholangitis (PSC).[1]

Technology

Description

Norucholic acid (NCA) is a side-chain-shortened synthetic analogue of ursodeoxycholic acid with relative resistance to amidation, which enables its cholehepatic shunting.[2] Dysregulated T cells including $CD8^+$ T cells are thought to contribute to the immunopathogenesis of PSC.[3] Norucholic acid, once taken by the patient, is thought to enter repeated cycles in which it is secreted by the liver cells, partially re-absorbed by the cells of the bile ducts, and then re-enters the liver cells. These cycles are thought to 'flush' the bile ducts. By 'flushing' the biliary system, this medicine is expected to prevent the build-up of bile acids in the liver and therefore the damage to the liver tissue.[4]

NCA is currently in phase III clinical development for the treatment of PSC. In the phase III clinical trial (NCT03872921), NCA is administered orally in 250mg capsules, 6 capsules a day for 2 years. [1]

Key Innovation

Currently, no cure or effective treatments for PSC exist. Hence, a need for urgent and innovative drugs for the treatments of PSC. NCA, a side chain-shortened derivative of ursodeoxycholic acid, NCA, has been shown to significantly reduced serum alkaline phosphatase levels in a dose-dependent manner during a 12-week treatment in addition to an excellent safety profile. If licensed, NCA would offer the first approved medicinal product for the treatment of PSC.[5]

Regulatory & Development Status

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

NCA is currently in phase 2 clinical development for non-alcoholic steatohepatitis (NASH),[6] and primary biliary cholangitis (PBC).[7]

NCA has the following regulatory designations/awards:

- An orphan drug designation in the USA in 2021 for the treatment of PSC.[8]
- An orphan drug designation in the EU in 2014 for the treatment of PSC.[9]

Patient Group

Disease Area and Clinical Need

PSC is a rare, chronic liver disease in which the bile ducts inside and outside the liver progressively decrease in cross-sectional area due to inflammation and scarring (fibrosis). The disease may occur alone, but in the majority of patients is associated with inflammatory diseases of the colon, especially chronic ulcerative colitis.[10] The cause of PSC remains unknown. Liver damage and cirrhosis is often presumed to be caused by drinking too much alcohol, however, PSC is not related to alcohol in any way. Current evidence suggests that the disease may be triggered by an unknown bacteria or virus in people who are genetically programmed to get the disease. The common viruses known to cause hepatitis have not been associated with it. The frequent occurrence of PSC in association with inflammatory bowel disease suggests that a

common cause for both diseases may exist or that the inflamed colon allows toxins or infections to be absorbed into the body and this can cause the bile duct inflammation. The disease affects both genders, although two male patients are affected for every female patient and it can affect all ages.[11] The common early symptoms of PSC are tiredness and some abdominal discomfort in the right upper abdomen. The late symptoms include: itching, jaundice and episodes of fever. Many people have no symptoms at first and the disease is only discovered because of abnormal results of routine blood tests in patients with ulcerative colitis or Crohn's disease. In some people PSC does not produce any symptoms. Most people have few or no symptoms for many years.[11]

PSC affects approximately 7 people per 10,000 in the UK.[12] In England, 2022-2023, there were 11,050 finished consultant episodes (FCE) and 5,881 admissions for cholangitis (ICD-10 code K83.0), of which PSC makes up a subset, which resulted in 45,880 FCE bed days and 675 day cases.[13]

Recommended Treatment Options
Currently, there is no treatment option recommended by NICE for PSC. PSC patients may undergo an endoscopic retrograde cholangiopancreatography (ECRP) procedure or receive a liver transplant for advanced disease.[14]

Clinical Trial Information

Trial	**NUC-5**, NCT03872921, Double-blind, Randomized, Placebo-controlled, Phase III Study Comparing norUrsodeoxycholic Acid Capsules With Placebo in the Treatment of Primary Sclerosing Cholangitis. **Phase 3:** Unknown status **Locations:** 2 EU countries **Primary completion date:** April 2021
Trial Design	Randomised, Parallel Assignment, double-blind
Population	N=302 (actual). Adults aged 16-75 with a verified diagnosis of PSC.
Intervention(s)	Norucholic acid (orally administered)
Comparator(s)	Matched placebo (orally administered)
Outcome(s)	Primary outcome measures: • Superiority of norursodeoxycholic acid (norUDCA) compared to placebo in the treatment of Primary Sclerosing Cholangitis (PSC) [Time Frame: 2 years] • Show superiority of norursodeoxycholic acid (norUDCA) compared to placebo in the treatment of Primary Sclerosing Cholangitis (PSC) [Time Frame: 2 years] See trial record for full list of outcomes
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information

Trial	**NUC-3**, NCT01755507, EudraCT2016-003367-19, Double-blind, Randomized, Placebo-controlled, Phase II Dose-finding Study Comparing Different Doses of Norursodeoxycholic Acid Capsules With Placebo in the Treatment of Primary Sclerosing Cholangitis **Phase 2:** Completed **Locations:** 3 EU countries. **Study completion date:** October 2015
Trial Design	Randomised, Parallel Assignment, double-blind
Population	N=159 (actual). Adults aged 18-80 with verified diagnosis of PSC.
Intervention(s)	Norucholic acid (orally administered)
Comparator(s)	Matched placebo (orally administered)
Outcome(s)	Primary outcome measures: • Change in serum AP levels during treatment [Time Frame: 12 weeks] See trial record for full outcome list
Results (efficacy)	Norucholic acid reduced Alkaline phosphate (ALP) levels by −12.3%, −17.3%, and −26.0% in the 500, 1,000, and 1,500 mg/d groups (p = 0.029, p = 0.003, and p <0.0001 when compared to placebo), respectively, while a +1.2% increase was observed in the placebo group. Similar dose-dependent results were found for secondary endpoints, such as ALT, AST, γ-GT, or the rate of patients achieving ALP levels <1.5× ULN.[5]
Results (safety)	Serious adverse events occurred in seven patients in the 500 mg/d, five patients in the 1,000 mg/d, two patients in the 1500 mg/d group, and three in the placebo group. There was no difference in reported pruritus between treatment and placebo groups.[5]

Estimated Cost

The cost of NCA is currently unknown.

Relevant Guidance

NICE Guidance

There is no relevant NICE guidance identified.

NHS England (Policy/Commissioning) Guidance

There is no relevant NHS guidance identified.

Other Guidance

- Chapman MH, Thorburn D, Hirschfield DM, et al. British Society of Gastroenterology and UK-PSC guidelines for the diagnosis and management of primary sclerosing cholangitis. 2019.[14]
- Isayama H, Tazuma S, Kokudo N, et al. Clinical guidelines for primary sclerosing cholangitis. 2017.[15]
- Lindor K, Kowdley KV, Harrison EM. ACG Clinical Guideline: Primary sclerosing cholangitis. 2015.[16]

Additional Information

References

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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.