National Institute for Health Research

NIHR Innovation Observatory
Evidence Briefing: September 2017

A4250 for progressive familial intrahepatic cholestasis

NIHRIO (HSRIC) ID: 13610 NICE ID: 9197

LAY SUMMARY

Progressive familial intrahepatic cholestasis (PFIC) is a rare, inherited condition that usually begins in infancy. The condition affects the liver, hindering or stopping the flow of bile from the liver. Bile flow is needed for fats, nutrients and vitamins to be absorbed into the body, and also to help the body get rid of toxins. Problems absorbing fats and nutrients can lead to poor weight gain and slower growth, and excess toxins in the body can lead to jaundice and itching, which can have a large impact on the quality of life of the patient and their family. There is no cure for this condition, and current treatments can only reduce the symptoms and slow down damage to the liver. It is not known how many people have this condition, but around 35 genetic tests are carried out each year for this condition.

The drug A4250 works in a new way that directly targets the part of the gut that allows bile to flow into the liver. By stopping bile from coming into the liver, bile levels are reduced, slowing down damage to the liver and reducing the symptoms of jaundice and itching. Because the drug acts directly on the gut, it has the potential to reduce the side-effects that occur with current medicines, such as problems with vitamin absorption. The drug is taken by mouth as a capsule.

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.

TARGET GROUP

Progressive Familial Intrahepatic Cholestasis (PFIC) – first line

TECHNOLOGY

DESCRIPTION

A4250 is a selective inhibitor of the ileal bile acid transporter (IBAT) that acts locally in the gut.[1] Ileum absorbs glyco-and taurine-conjugated forms of the bile salts. IBAT, sometimes also referred to as the apical sodium-dependent bile salt transporter (ASBT), is the first step in absorption at the brush-border membrane. A4250 works by decreasing the re-absorption of bile acids from the small intestine to the liver, which reduces the toxic levels of bile acids during the progression of the disease. It exhibits therapeutic intervention by checking the transport of bile acids.[2]

In the phase II clinical trial (NCT02630875), A4250 was administered orally to patients aged one to 17 years old. Five different doses of A4250 were evaluated, ranging from 10 µg/kg to 200 µg/kg, given over a four week treatment period.[3]

A4250 does not currently have Marketing Authorisation in the EU for any indication.

In addition to patients with PFIC, the phase II clinical trial NCT02630875 included patients with other paediatric cholestatic liver disease, including Alagille syndrome, biliary atresia or intrahepatic cholestasis.[3]

INNOVATION and/or ADVANTAGES

Ileal bile acid transporter (IBAT) inhibition is a novel therapeutic concept for cholestatic pruritus and the progression of cholestatic liver disease.[4] A4250 is a selective inhibitor of IBAT with minimal systemic exposure, thereby reducing the risk for systemic side effects. Studies show that A4250 has the potential to decrease the damage in the liver cells and the development of fibrosis/cirrhosis of the liver known to occur in PFIC.[2]

If licensed, A4250 will offer an additional treatment option for patients with PFIC, for whom there are few effective pharmacological therapies available.

The therapeutic choices are restricted to non-specific treatment of the symptoms and signs of the disease such as nutritional support, preventing vitamin deficiencies, and treatment of extrahepatic features. Medical treatment options include off-label use of ursodeoxycholic acid (UDCA), rifampin, antihistamines and naltrexone. A minority of patients respond to these medications and if so, only transiently. UDCA is commonly used off-label to reduce liver damage but not all patients respond.[5]

DEVELOPER

Albireo AB

AVAILABILITY, LAUNCH or MARKETING

A4250 is a designated orphan drug in the USA for October 2012.[2]

A4250 is a designated orphan drug in the EU for October 2016.[2]

A4250 was awarded PRIME status for PFIC by EMA in October 2016.[2]

The company expects to initiate a planned phase III trial of A4250 in patients with PFIC in the second half of 2017.[1]

PATIENT GROUP

BACKGROUND

PFIC is a class of chronic cholestasis disorders that begin in infancy and usually progress to cirrhosis within the first decade of life. The average age at onset is 3 months, although some patients do not develop symptoms until later childhood or adolescence. PFIC can progress rapidly and cause cirrhosis during infancy, or may progress slowly with minimal scarring well into adolescence. Few patients have survived into the third decade of life without treatment. PFIC is inherited in an autosomal recessive manner, and specific gene defects have been identified for three subtypes of PFIC, affecting bile acid secretion or phospholipid secretion.[6]

The main symptom of PFIC is interruption or suppression of the flow of bile from the liver (cholestasis) due to defects within the liver, resulting in bile acids accumulating in the liver. Bile flow aids in digestion and absorption of dietary fats, vitamins and other nutrients, and aids in the elimination of excess cholesterol, waste and toxins from the body. Therefore, a problem with bile flow often results in malabsorption of vital nutrients and the accumulation of toxic materials in the body.[7]

Initial symptoms associated with PFIC may be foul smelling, greasy stools or watery diarrhoea, jaundice, pruritus (itching), failure to thrive, vitamin deficiencies and enlarged liver. PFIC subtypes 1 and 2 eventually progress to cause life-threatening complications including the formation of fibrous tissue (fibrosis) and liver regeneration with scarring (cirrhosis) in the liver, resulting in liver failure. Without surgical intervention, these complications may develop by the end of the first decade of life. Children with PFIC subtype 2 may have a greater risk of developing a form of liver cancer known as hepatocellular carcinoma, potentially before the age of one.[7]

CLINICAL NEED and BURDEN OF DISEASE

The population prevalence of PFIC is unknown, but the estimated prevalence at birth varies between 1 per 50,000 and 1 per 100,000.[8]

The UK Genetic Testing Network estimates that approximately 32 children per year may require genetic testing for PFIC (UK wide).[9]

There is no specific ICD-10 code for PFIC, and therefore it is not possible to identify hospital activity for these conditions.

Children with PFIC may require dietary treatment (including nasogastric feeding). One of the main symptoms is pruritus, which can lead to poor quality of life for the patient and their family and require multiple medications which show low effectiveness.[9]

All forms of PFIC are lethal in childhood unless treated[6], and even with treatment, patients usually develop fibrosis and end-stage liver disease before adulthood[8], and half of patients with PFIC will ultimately require liver transplantation.[10]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

No NICE guidance has been published on PFIC or related conditions.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract: Specialist Liver Disease Service (Children). E03/S(HSS)/d.
- NHS England. 2013/14 NHS Standard Contract: Metabolic Disorders (Children). E06/S/b.

OTHER GUIDANCE

- European Association for the Study of the Liver (EASL). EASL Clinical Practice Guidelines on the Management of Cholestatic Liver Diseases.

CURRENT TREATMENT OPTIONS

No specific therapy exists for individuals with PFIC. Treatment is directed towards the symptoms that are apparent in each patient. Treatment options include drug therapy, various surgical procedures, and in severe cases liver transplantation. Restoring vitamins and nutrients lost through malabsorption is necessary in many cases.[7]

The initial drug treatment is often ursodeoxycholic acid (UDCA), a hydrophilic bile acid that replaces toxic hydrophobic bile salts.[11] This treatment may improve liver function, and help to improve bile flow thus reducing jaundice and/or pruritus. Cholestyramine also helps to improve bile flow, although this drug must be taken with care as it may interfere with vitamin absorption. Rifampicin, a liver stimulant, may also reduce pruritus.[12]

Partial external biliary diversion may be considered if medical treatments fail to control pruritus, but this operation is only suitable for patients who have not developed cirrhosis. This procedure uses a short section of the bowel to make a channel for some of the bile to drain away into an external bag.

However, this may make malabsorption and vitamin deficiencies worse, and important body salts may also be lost.[12]

An alternative surgical intervention, internal ileal exclusion, creates a bypass around the distal ileum (the section of bowel where bile salts are usually reabsorbed), reducing the amount of bile salts reabsorbed into the bloodstream. Diarrhoea is a possible complication of this surgery.[12]

In cases where these surgeries have been unsuccessful, or the patient has progressed to cirrhosis or liver failure, liver transplantation may be required. This can demonstrate a dramatic improvement of symptoms[7], but patients must take anti-rejection medicines for the rest of their life and have regular medical follow-up.[12] Liver transplantation is currently the only definitive treatment available for PFIC.

Survival in PFIC patients not undergoing surgical diversion or liver transplant is 50% at the age of 10 and almost none at the age of 20 years, highlighting the rate of progression and life-threatening nature of the disease.[13]

In summary, PFIC is a fatal disorder associated with significant morbidity where the treatment options of off-label medicines, permanent diversion surgery or liver transplant are insufficient.

EFFICACY and SAFETY

Trial	A4250-005; A4250; phase III
Sponsor	Albireo AB
Status	Not started
Source of Information	Albireo AB
Location	Not stated
Design	Randomised, double-blind, placebo-controlled
Participants	N=60; aged 6 mths - 18 yrs; PFIC 1 and 2
Schedule	2 doses of A4250 will be evaluated: 40 µg/kg and 120 µg/kg, or placebo. Patients will be treated for 6 months.
Follow-up	Patients will be able to roll over into an extension study, A4250-008, to be treated for an additional 18 mths. Long term safety and outcomes will be evaluated in this open label phase, including time to PEBD surgery and/or listing for liver transplantation, growth, and biomarkers for progression of liver disease.

Primary Outcomes	Primary efficacy endpoint is proportion of patients experiencing at least a 70% reduction in fasting serum bile acid levels (s-BA) or reaching a level ≤70 µmol/L compared to placebo.
Secondary Outcomes	Change in pruritus score as indexed by caregiver-reported observed scratching score compared to placebo Change from Baseline to Wk 24 in fasting s-BA compared to placebo Change from baseline to Wk 24 in patient reported itch severity compared to placebo Change from Baseline to Wk 24 in ALT compared to placebo Change from Baseline to Wk 24 in IGF-1 compared to placebo Change in growth from start of active treatment to Wk 24 compared to placebo Proportion of patients achieving meaningful reduction in caregiver-reported observed scratching at Wk 24 compared to placebo Change from Baseline to Wk 24 in sleep parameters measured with the Albireo PRO and ObsRO instruments compared to placebo Number of patients undergoing biliary diversion surgery or being listed for liver transplantation compared to placebo Change from Baseline to Wk 24 in quality of life (QoL) compared to placebo
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Not stated

Trial	NCT02630875, A4250-003; A4250; phase II[14]
Sponsor	Albireo AB
Status	Published in extract
Source of Information	European Association for the Study of the Liver[15], ClinicalTrials.gov[14]
Location	5 EU countries, incl UK
Design	Non-randomised, open-label, single group assignment
Participants	N=19; aged 1-17 years; pruritus due to chronic cholestasis
Schedule	Five different doses of A4250 ranging from 10 µg/kg to 200 µg/kg were evaluated. Subjects received A4250 at a dose of 0.01, 0.03, 0.06, 0.1, 0.2, 0.3 mg/kg. Participants were initially given a single dose, then given the drug in capsule form for four wks.

Follow-up	Not reported
Primary Outcomes	Primary efficacy endpoint is change in total serum bile acids at end of four-wk treatment. Primary safety endpoint is the occurrence of treatment-emergent serious adverse events (TEAEs) during the four treatment wks.
Secondary Outcomes	VAS-itch (Visual Analogue Scale) at end of four-wk treatment Whitington itching score at end of four-wk treatment Pharmacokinetics at end of four-wk treatment Liver biochemistry evaluation at end of four-wk treatment Occurrence of TEAEs during the whole study period Description and severity of any AE also reported at end of four-wk treatment Secondary efficacy aims: Demonstrate the efficacy of A4250, orally administered during a four-wk treatment period, on liver biochemistry variables and on pruritus parameters Evaluate the pharmacokinetic properties of A4250 orally administered as a single dose and then after a four-wk treatment period Evaluate changes in VAS-itching score after a four week treatment period
Key Results	Pruritus improved in 14 of 19 cases as assessed by VAS-itch (scale 0-10). The dose with the greatest improvement demonstrated a mean decrease of 2.86 points from baseline for VAS-itch. Mean levels of serum bile acids were reduced at all doses. Overall, the reductions in serum bile acids exhibited high variability which was due to the wide range of doses and to the various diseases and disorders represented and variability in baseline serum bile acid levels within and across cohorts in the trial. The sub-population of PFIC patients (n=9) had a greater mean reduction in serum bile acids than patients in the trial with other cholestatic liver diseases. In this cohort, reductions ranged from 43% to 98%.
Adverse effects (AEs)	There were no serious AEs or patient dropouts, and the drug exhibited a favourable overall tolerability profile. Most side effects were mild and transient and considered to be unrelated to the drug.
Expected reporting date	-

ESTIMATED COST and IMPACT

COST

The cost of A4250 is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☒ Improved quality of life for patients and their families

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☒ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other

☐ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☒ Reduced drug treatment costs

☐ Other increase in costs

☒ Other reduction in costs

☐ Other

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

REFERENCES

[1] Albireo. *A4250*. Available from: http://www.albireopharma.com/programs/a4250-program/ [Accessed 18 August 2017]

[2] GlobalData. *A-4250.* Available from: https://pharma.globaldata.com/ProductsView.aspx?ProductType=0,1&ProductID=228287 [Accessed 18 August 2017]. Login required

[3] Albireo. *Promising Pediatric Data for Albireo's A4250 to be presented at The International Liver Congress 2017.* Available from: http://www.albireopharma.com/2017/04/22/promising-pediatric-data-for-albireos-a4250-to-be-presented-at-the-international-liver-congress-2017/ [Accessed 18 August 2017]

[4] Baumann U, Lacaille F, Sturm E et al. The Ileal Bile Acid Transport inhibitor A4250 decreases pruritus and serum bile acids in cholestatic liver diseases – an ongoing multiple dose, open-label, multicentre study. *Journal of Heptatology.* 2017; 66: S63-S94. Available from: http://www.journal-of-hepatology.eu/article/S0168-8278(17)30445-2/pdf [Accessed 22 August 2017]

[5] Hori T, Nguyen JH, Uemoto S. Progressive familial intrahepatic cholestasis. *Hepatobiliary & Pancreatic Diseases International.* 2010;9(6):570-578.

[6] Medscape. *Progressive Familial Intrahepatic Cholestasis*. Available from: http://emedicine.medscape.com/article/932794-overview [Accessed 21 August 2017]

[7] National Organization for Rare Disorders. *Low Gamma-GT Familial Intrahepatic Cholestasis.* Available from: https://rarediseases.org/rare-diseases/low-gamma-gt-familial-intrahepatic-cholestasis/ [Accessed 21 August 2017]

[8] Orphanet. *Progressive familial intrahepatic cholestasis.* Available from: http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Expert=172 [Accessed 21 August 2017]

[9] UK Genetic Testing Network. *Proposal form for the evaluation of a genetic test for NHS Service Gene Dossier: Progressive familial intrahepatic cholestasis.* Available from: https://ukgtn.nhs.uk/uploads/tx_ukgtn/Cholestasis_1_ATP8B1_GD_Sept_11.pdf [Accessed 21 August 2017]

[10] Gonzales E, Spraul A, Jacquemin E. Clinical utility gene card for: Progressive familial intrahepatic cholestasis type 1. *European Journal of Human Genetics*. 2014 22, doi:10.1038. Available from: http://www.nature.com/ejhg/journal/v22/n4/full/ejhg2013186a.html [Accessed 21 August 2017]

[11] Srivastava A. Progressive Familial intrahepatic Cholestasis. *Journal of Clinical and Experimental Hepatology*. 2014 Mar;4(1): 25-36. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4017198/ [Accessed 22 August 2017]

[12] Children's Liver Disease Foundation. *Progressive Familial Intrahepatic Cholestasis (PFIC): a guide.* Available from: https://www.childliverdisease.org/Information/Medical-stuff/Information-on-liver-diseases/Progressive-Familial-Intrahepatic-Cholestasis [Accessed 22 August 2017]

[13] Pawlikowska L, Strautnieks S, Jankowska I, et al. Differences in presentation and progression between severe FIC1 and BSEP deficiencies. *Journal of Hepatology*. 2010;53(1):170-178.

[14] ClinicalTrials.gov. *A4250, an IBAT Inhibitor in Pediatric Cholestasis NCT02630875*. Available from: https://clinicaltrials.gov/ct2/show/record/NCT02630875?term=NCT02630875 [Accessed 18 August 2017]

[15] European Association for the Study of the Liver. *ILC 2017: New therapy has potential to be a significant advance for the treatment of paediatric cholestatic liver diseases*. Available from: https://ilc-congress.eu/wp-content/uploads/2017/04/LBO-004-Baumann.pdf [Accessed 21 August 2017]