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Liprotamase (Sollpura) for exocrine pancreatic insufficiency due to cystic fibrosis

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LAY SUMMARY

Liprotamase is a new drug for the treatment of exocrine pancreatic insufficiency (EPI), a condition where the pancreas does not produce enough enzymes for digesting fat, carbohydrates and proteins. EPI is common in patients who have cystic fibrosis (CF), which is the most common inherited disease in the UK.

Liprotamase works by replacing the lacking pancreatic enzyme, improving digestion and the absorption of nutrients from food. Other forms of pancreatic enzyme replacement therapy are available for use, but they do not work well in some patients with CF, require a large number of capsules to be taken, and are animal derived. Liprotamase would provide a new, non-animal derived form of therapy for these patients.

TARGET GROUP

- Exocrine pancreatic insufficiency (EPI) due to cystic fibrosis (CF)

TECHNOLOGY

DESCRIPTION

Liprotamase (Sollpura; ALTU-135; TheraCLEC-Total; Trizytek) is an orally administered, non-porcine form of pancreatic enzyme replacement therapy (PERT).[1] It consists of a fixed ratio of three active ingredients - crystalline lipase, crystalline protease and amorphous amylase - which are designed to improve fat, protein and carbohydrate absorption, respectively.[2]

Liprotamase is the first soluble, stable and non-pig derived PERT to offer a solution to patients who are either unable to swallow multiple pills or are forced to use gastric tubes in order to maintain appropriate nutritional health.[3]

Liprotamase is taken together with food to aid digestion. In phase III clinical trials, liprotamase dosage has been individually titrated over seven weeks (cf. Efficacy section).

Liprotamase does not currently have Marketing Authorisation in the EU for any indication. It is not in clinical trials for any other indication.

INNOVATION and/or ADVANTAGES

Although PERT is already a standard mode of therapy, if licensed, liprotamase will be the first biotech-derived form of PERT, and could improve digestion of nutrients as well as reducing treatment burden, with patients having to take fewer pills each day.

DEVELOPER

Anthera Pharmaceuticals (drug acquired from Eli Lilly and Co in 2014)[1]

AVAILABILITY, LAUNCH or MARKETING

Liprotamase has orphan drug status in the EU for the treatment of exocrine pancreatic insufficiency.[1] It previously also had an orphan drug designation in the USA for EPI, but this status was revoked in 2007 due to the patient population exceeding the numerical limit for the status.[4]

In 2011, the FDA made a decision not to approval Eli Lilly's New Drug Application for liprotamase, citing the need for further clinical trials.[5]

PATIENT GROUP

BACKGROUND

EPI is associated with diseases and conditions affecting the pancreas, such as chronic pancreatitis, pancreatic cancer, and CF.[6] The insufficient production of pancreatic enzymes leads to fat malabsorption and potential malnutrition, and if untreated, common symptoms of EPI include

steatorrhea, gastrointestinal symptoms, as well as poor growth in infants and children.[7] Reduced quality of life is also associated with EPI.[8]

In patients with CF, EPI is most commonly observed at birth or soon after, following in utero exocrine pancreatic damage.[8] During newborn screening, 63% of infants with CF are already exocrine insufficient and 30% of the remaining infants become exocrine insufficient over their first 36 months.[8]

CLINICAL NEED and BURDEN OF DISEASE

Prevalence of cystic fibrosis is 1 in 2,500 newborn infants.[9] In 2015, there were 10,810 individuals on the UK Cystic Fibrosis Registry.[10] The current median age at death for people with CF is 29 years and the median predicted survival is 36.6 years.[11]

In 2015-16, there were 13,580 hospital admissions, 86,986 bed days, and 15,716 finished consultant episodes associated with cystic fibrosis (ICD-10: E84.0 to E84.9).[12] Across the UK in 2008–12, 285 males and 313 females died from cystic fibrosis.[13]

Around 85 to 90% of people with cystic fibrosis also have EPI,[14] leading to an estimated UK prevalence (calculated based on the above-noted 2015 UKCFR population) of about 9,189 to 9,727.

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance. Lumacaftor–ivacaftor for treating cystic fibrosis homozygous for the F508del mutation (TA398). July 2016.
- NICE technology appraisal guidance. Colistimethate sodium and tobramycin dry powders for inhalation for treating pseudomonas lung infection in cystic fibrosis (TA 276). March 2013.
- NICE technology appraisal guidance. Mannitol dry powder for inhalation for treating cystic fibrosis (TA 266). November 2012.

- NICE guidance in development. Cystic fibrosis (GID-CGWAVE0736). Publication expected October 2017.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cystic Fibrosis (Adults). A01/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cystic Fibrosis (Children). A01/S/b.
- NHS England. 2013/14 NHS Standard Contract Paediatric Medicine: Respiratory.
- NHS Commissioning Board. Clinical commissioning policy: Ivacaftor for cystic fibrosis. March 2012.

OTHER GUIDANCE

- Clinical Guidelines: Care of Children with Cystic Fibrosis (7th edition). Available at: http://www.rbht.nhs.uk/EasySiteWeb/GatewayLink.aspx?alId=1851660
- Cystic Fibrosis Trust. Consensus documents. Available at: https://www.cysticfibrosis.org.uk/the-work-we-do/clinical-care/consensus-documents

CURRENT TREATMENT OPTIONS

Current standard therapy for the treatment of EPI is pancreatic enzyme replacement therapy (PERT), with other features of EPI management being vitamin supplementation and lifestyle modifications (such as avoidance of fatty foods).[15] PERT uses products that contain porcine pancreatin or pancrelipase.[16] The enteric coating of these products often leads to delayed release of the enzyme in CF patients due to their more acidic duodenum.[16] The capsules must often also be taken in large numbers due to their low specific activity.[16]

EFFICACY and SAFETY

Trial	RESULT; NCT03051490; non-inferiority of liprotamase (Sollpura) vs PERT; phase III
Sponsor	Anthera Pharmaceuticals
Status	Planned; not yet open for recruitment
Source of Information	Trial registry,[17] company news release[18]
Location	TBC
Design	randomised, open-label, non-inferiority, active-comparator trial
Participants	Estimated n=150; ages 7 and older; diagnosis of CF; good disease control with porcine PERT prior to enrolment; good nutritional status
Schedule	Individually-optimised dose to be administered orally
Follow-up	6 months
Primary Outcomes	Coefficient of Fat Absorption (CFA) at week 8
Secondary Outcomes	Coefficient of Nitrogen Absorption (CNA), AEs
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Topline data from the RESULT study is expected around the end of 2017 or early 2018.

Trial	SOLUTION; NCT02279498; GDC40002433; phase III; non-inferiority of liprotamase (Sollpura) vs PERT (Pancreaze)	EASY; NCT02823964; phase III/IV extension study
Sponsor	Anthera Pharmaceuticals	Anthera Pharmaceuticals
Status	Topline results published	Ongoing
Source of Information	Trial registry,[19] company press releases[20] [21]	Trial registry,[22] company news release[18]
Location	EU (not incl UK), USA, Canada, Israel	EU (not incl UK), USA, Israel
Design	Randomised, active-controlled	Open-label extension study (long-term efficacy)
Participants	N=126; ages 7 and older; diagnosis of CF; minimum CFA at screening while on stable PERT therapy; good nutritional status	Estimated n=70; provides continued access to liprotamase (Sollpura) for patients who complete the SOLUTION study. EASY study will also be offered to subjects completing the RESULT and SIMPLICITY studies.
Schedule	Individually-optimized dose; administered orally; 8 weeks	n/a
Follow-up	18-20 weeks	Manufacturer plans to continue the EASY study until the Biologic License Application for liprotamase (Sollpura) is approved by the FDA.
Primary Outcomes	Coefficient of Fat Absorption (CFA) An additional extension period designed as an observational analysis of long-term effects of Sollpura and Pancreaze on weight, height, BMI, and safety.	Safety, as measured by number of participants with adverse events including clinical or laboratory abnormalities
Secondary Outcomes	Safety, AEs	Weight, height, BMI, malabsorption score
Key Results	The study narrowly missed the CFA non-inferiority margin of the primary modified Intent to Treat (mITT) analysis. In additional pre-specified analyses of CFA, Sollpura met the non-inferiority criterion. Ratio of the three enzymes in Sollpura demonstrated an appropriate response in the coefficient of nitrogen absorption (CNA).	-

	During the extension period (Week 7 through Week 20), all patients treated with Sollpura maintained their weight. Both groups showed small increases in height. A modest decrease in body mass index (BMI) was observed in both treatment groups. In paediatric patients less than 17 years of age, the key age group for growth and development, similar trends in weight and height were observed in both treatment groups	
Adverse effects (AEs)	Sollpura was generally well tolerated compared to Pancreaze, although symptoms related to malabsorption were generally modestly more frequent in the Sollpura arm. Extension: Proportions of patients experiencing mild, moderate, or serious events in the Sollpura vs Pancreaze arm were 27.7% vs 41.3%, 9.2% vs 11.1% and 3.1% vs 1.6%, respectively. The rate of serious adverse events was 4.6% for Sollpura and 6.3% for Pancreaze with no discontinuations in either arm.	-
Expected reporting date	-	Estimated primary completion date reported as September 2017.

ESTIMATED COST and IMPACT

COST

The cost of liprotamase is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS and CARERS

☐ Reduced mortality/increased length of survival ☒ Reduced symptoms or disability

☒ Other: *potential improvement in quality of life* ☐ 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: *unknown cost of new therapy*	☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified: *specify*	☒ None identified

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