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CER-001 for familial primary hypoalphalipoproteinemia

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LAY SUMMARY

Familial primary hypoalphalipoproteinemia (FPHA), also known as familial high-density lipoprotein (HDL) deficiencies, are rare genetic disorders. HDL is a molecule that transports cholesterol and certain fats called phospholipids through the bloodstream from the body's tissues to the liver. Once in the liver, cholesterol and phospholipids are redistributed to other tissues or removed from the body. HDL is often referred to as "good cholesterol" because high levels of this substance reduce the chances of developing heart and blood vessel (cardiovascular) disease. FPHA is caused by changes in the ABCA1 or the APOA1 genes. These genes are responsible for HDL function, synthesis, and maturation. ABCA1 and APOA1 gene mutations decrease the amount of cholesterol or phospholipids available to form HDL, resulting in low levels of HDL in the blood. A shortage of HDL is believed to increase the risk of cardiovascular disease.

CER-001 is an engineered complex of the major structural protein of HDL, in combination with key phospholipids. Administered through intravenous (IV) infusion, CER-001 mimics the structure and function of natural HDL to stimulate the removal of excess cholesterol and other lipids. There is currently limited treatment options available specifically for FPHA. If licensed, CER-001 may offer a new treatment option for FPHA by aiding in the transport and elimination of excess cholesterol and other lipids in the liver.

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TARGET GROUP

Familial primary hypoalphalipoproteinemia (FPHA) (ABCA1/APOA1 deficiency)

TECHNOLOGY

DESCRIPTION

CER-001 is an engineered complex of recombinant human apoA-I, the major structural protein of high-density lipoprotein (HDL), and the phospholipids sphingomyelin and dipalmitoyl-phosphatidylglycerol.[1] CER-001 has been designed to mimic the structure and function of natural, nascent HDL, also known as pre-beta HDL. Its mechanism of action is to increase apoA-I and the number of HDL particles transiently, and to stimulate the removal of excess cholesterol and other lipids from tissues (including the arterial wall) for transport to the liver for elimination through a process called Reverse Lipid Transport (RLT).[2]

In the phase III trial (NCT02697136) subjects received 29 intravenous (IV) infusions of CER-001 given at weekly (9 infusions) and then biweekly (20 infusions) intervals. Further dosing information was not stated on the trial registry.[3]

CER-001 has completed phase II development for acute coronary syndrome (ACS).[4] While well tolerated, results showed no statistical difference between CER-001 and placebo and did not meet the primary efficacy endpoint of regression of atherosclerotic plaques in post-ACS patients.[5,6]

CER-001 does not currently have Marketing Authorisation in the EU for any indication.

INNOVATION and/or ADVANTAGES

Patients with familial primary hypoalphalipoproteinemia (FPHA) are at high risk of cardiovascular disease as a consequence of having inherited a virtually absent endogenous RLT system. Due to the specific characteristics of the disease and very limited available therapeutic approaches, FPHA remains an unmet medical need and a life-threatening condition.[7]

If licensed, CER-001 may offer a new treatment option for FPHA patients who currently have few well-tolerated effective therapies available.

DEVELOPER

Cerenis Therapeutics Inc

REGULATORY INFORMATION/ MARKETING PLANS

EU/UK regulatory information/marketing plans by the company are currently unknown.

CER-001 is a designated orphan drug in the EU for the treatment of ATP-binding cassette transporter A1 deficiency.[8]

PATIENT GROUP

BACKGROUND

Hypoalphalipoproteinemia (also known as low HDL) has historically been clinically defined as an HDL-cholesterol (HDL-C) less than 40 mg/dL (1.0 mmol/L) in men, and less than 50 mg/dL (1.3 mmol/L) in women. A number of aetiologies, often metabolic, can underlie a reduced circulating level of cholesterol in the HDL fraction such as diabetes, Metabolic Syndrome, obesity, and lack of physical activity (secondary hypoalphalipoproteinemia). In a very small percentage of the population, particularly among patients with the very lowest HDL-C values, there are patients who have a genetic defect (primary hypoalphalipoproteinemia) affecting either the constituent components of the pre-β particle, the process of pre-β particle synthesis, the steps leading to maturation into an alpha HDL particle, or the rates of catabolism – any of which alone or in combination can then result in an inherited condition of a very low circulating HDL particle number.[7]

Familial primary hypoalphalipoproteinemia (FPHA), also known as familial high-density lipoprotein (HDL) deficiencies, include patients with a heritable genetic defect in one of the key genes involved in HDL particle production or maturation.[7, 10] Mutations in the ABCA1 gene or the APOA1 gene cause FPHA. The proteins produced from these genes work together to remove cholesterol and phospholipids from cells. The ABCA1 gene provides instructions for making a protein that removes cholesterol and phospholipids from cells by moving them across the cell membrane. The movement of these substances across the membrane is enhanced by another protein called apolipoprotein A-I (apoA-I), which is produced by the APOA1 gene.[10]

Familial HDL deficiency is inherited in an autosomal dominant pattern, where an alteration in one copy of either the ABCA1 or the APOA1 gene in each cell is sufficient to cause the disorder. People with alterations in both copies of the ABCA1 gene develop the related disorder Tangier disease.[9] Clinically, subjects with apoA-I deficiency present corneal opacities, xanthomas, and cardiovascular diseases caused by atherosclerosis. Less frequently, apoA-I deficiency may lead to neurosensory symptoms like hearing loss, systemic amyloidosis, or even hepatic or renal failure. Heterozygous apoA-I mutations span a range from no to severe symptoms equalling the homozygous state, depending on the location of the mutation(s). A shortage (deficiency) of HDL is believed to increase the risk of cardiovascular disease.[7]

CLINICAL NEED and BURDEN OF DISEASE

The prevalence of FPHA is largely unknown.[10] In 2014, ABCA1 deficiency was estimated to affect less than 0.01 in 10,000 people in the EU (a total of fewer than 500), while APOA1 deficiency has only been described in approximately 30 families worldwide.[8,11]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- No relevant guidance identified.

NHS ENGLAND and POLICY GUIDANCE

- No relevant guidance identified.

OTHER GUIDANCE

- Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice, 2005.[12]

CURRENT TREATMENT OPTIONS

To date, there is no specific treatment addressing deficiencies in APOA1 or ABCA1. The treatment strategy is to reduce the risk of atherosclerosis, which is the main mechanism of increased morbidity and mortality.[7]

EFFICACY and SAFETY

Trial	TANGO, NCT02697136, EudraCT-2015-003713-23; CER-001 for genetically defined familial primary hypoalphalipoproteinemia; phase III
Sponsor	Cerenis Therapeutics
Status	Ongoing
Source of Information	Trial registry[3]
Location	EU (not incl UK), USA, Canada, and Israel
Design	Randomised, parallel assignment, quadruple masking (participant, care provider, investigator, outcomes assessor)
Participants	n=30(planned); aged ≥18 years; genetically confirmed HDL-c deficiency due to defects in genes coding for ABCA1 and/or ApoA-1; ApoA-I < 70 mg/dL; symptomatic or asymptomatic cardiovascular disease; stable doses of lipid lowering therapies for at least 6 weeks prior to baseline procedures
Schedule	Randomised (2:1) to receive 29 intravenous (IV) infusions of CER-001 given at weekly (9 infusions) and biweekly (20 infusions) intervals. Further dosing information was not stated on the trial registry.
Follow-up	Subjects will be required to have acceptable baseline 3TMRI imaging of carotid arteries. 3TMRI imaging of the carotid and femoral arteries will be performed at Week 8, Week 24 (primary endpoint) and Week 48. The total study duration from randomization can range from 50 to 54 weeks for patients completing the study as designed.
Primary Outcomes	• Change in mean vessel wall area (MVWA) of the carotid artery [Time Frame: Baseline to Week 24] - change from baseline to Week 24 carotid MVWA; CER-001 versus placebo; measured by 3TMRI

Secondary Outcomes	• Change in mean vessel wall area (MVWA) of the carotid artery [Time Frame: Baseline to Week 8] - change from baseline to Week 8 carotid MVWA; CER-001 versus placebo; measured by 3TMRI • Change in mean vessel wall area (MVWA) of the carotid artery [Time Frame: Baseline to Week 48] - change from baseline to Week 48 carotid MVWA; CER-001 versus placebo; measured by 3TMRI • Change in Target to Background Ratio (TBR) of the carotid artery [Time Frame: Baseline to Week 24] - change from baseline to Week 24 in carotid TBR; CER-001 versus placebo; measured by FDG-PET • Other outcome measures: Change in femoral MVWA [Time Frame: Baseline, Weeks 8, 24 and 48] - assessed by 3TMRI; change from baseline; CER-001 versus placebo
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Previously reported as Dec 2017.

ESTIMATED COST and IMPACT

COST

The cost of CER-001 is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☐ 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

☒ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☒ Other: uncertain unit cost compared to existing treatments

☐ None identified

OTHER ISSUES

☒ None identified

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