Press release 3 – Madrid, May 31st, 2014

82nd Annual Congress of the European Atherosclerosis Society (EAS)
May 31-June 3, Madrid, Spain

Very high cholesterol from birth: are target LDL cholesterol levels now achievable with new treatments?

- ***Novel treatments hold the key for improved management***

Familial hypercholesterolaemia (FH) is a common genetic condition that is characterised by elevated plasma low-density lipoprotein (LDL) cholesterol levels from birth. If left untreated, individuals with FH are at greatly increased risk of heart disease, especially if they are homozygous for this condition. The severity of atherosclerosis and heart disease in FH is proportional to the cumulative burden of elevated LDL cholesterol levels.

Clearly, the priority for clinical management of FH is to lower plasma LDL cholesterol to target levels, as recommended in the recent Consensus Statement of the European Atherosclerosis Society.[1] However, in many countries patients with FH are not diagnosed, and even when diagnosis is made, most patients do not achieve target LDL cholesterol levels.

'The cumulative LDL cholesterol burden in FH causes premature atherosclerosis. If untreated, people with homozygous FH, who have very high LDL cholesterol levels from birth, reach the threshold for heart disease at a young age, usually by the teenage years. It is critical to ensure LDL cholesterol lowering as close as possible to goal in these patients.'
– Dr Marina Cuchel, University of Pennsylvania, Philadelphia, USA

How common is FH?

Historically, it has been thought that about 1 in 500 people in the general population have heterozygous FH, and 1 in a million have homozygous FH.[2] However, recent research has challenged this. New data suggest that the prevalence of heterozygous FH may be as high as 1:200 to 1:250 people. These estimates are based on data from the Copenhagen General Population Study using the Dutch Lipid Clinic Network criteria for FH (the gold standard for diagnosis, see **Table 1**), as well as genetic testing.[1,3] Consequently, as many as 1 in 160,000 to 1 in 300,000 people are thought to have homozygous FH.[1,3]

Yet <1% of patients are diagnosed in most countries.[1] In part this is due to the lack of valid nationwide registries for FH, lack of screening strategies to detect index cases, as well as cost issues. Importantly, there is a lack of awareness of FH in primary care, the very clinicians who are usually the first to see such patients. Clearly, urgent action is needed to educate and improve diagnosis of FH.

What causes FH?

FH is caused by mutations that directly affect the rate at which LDL cholesterol is cleared from the circulation. Mutations in at least 3 genes cause FH:

- the LDL-Receptor gene (LDLR)
- the gene for apolipoprotein B (APOB), the major protein component of the LDL-cholesterol particle; and
- the gene for protein convertase subtilisin/kexin type 9 (PCSK9), which is an enzyme involved in degrading the LDL receptor protein in the lysosome of the cell and preventing it recycling.

In addition, mutations in a fourth gene, the gene for LDLR adapter protein 1 (*LDLRAP1)* causes a recessive form of FH, with a phenotype similar to homozygous FH. Mutations in the LDL-R gene account for most of the mutations identified to date.[4]

With the increased use of genetic testing comes the growing realisation that considerable heterogeneity exists in the clinical presentation of severe FH. In some patients identified by genetic testing as homozygous FH, LDL cholesterol levels may be lower than what is seen in clinically diagnosed homozygous FH, and may overlap with the levels seen in some patients with severe heterozygous FH.

How is FH currently treated?

The severity of atherosclerosis and heart disease in FH is proportional to the cumulative burden of elevated LDL cholesterol levels. If effective treatment is started from an early age and LDL cholesterol targets are met, this burden can be greatly reduced. Despite this, <5% of patients achieve the recommended LDL cholesterol targets. In these suboptimally treated patients with FH, coronary risk may be up to 13-fold higher than in those who attain recommended LDL cholesterol targets.[5]

The current mainstay of treatment is statin plus diet, started from the first visit to the clinician.[1] Combination treatment with ezetimibe and other lipid-lowering therapy provides incremental LDL cholesterol reduction.[1] While most patients with heterozygous FH can be successfully managed in primary care or with a shared care approach between primary and secondary care, those with severe heterozygous FH or homozygous FH, who are often refractory to treatment, as well as statin-intolerant patients, need specialist management.

Adjunctive lipoprotein apheresis, an extracorporeal procedure which involves the mechanical removal of LDL from the circulation, may be recommended in such patients. While LDL cholesterol levels may be reduced up to 80-90% at the end of a single treatment, there is a rebound effect due to accumulation of LDL cholesterol, and hence treatment needs to be repeated every 1-2 weeks. There are also issues relating to access, affordability and practical considerations.[6]

'The treatments that are available conventionally are not enough to reduce LDL cholesterol in these high risk patients.'- Dr Marina Cuchel

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New treatments: new hope

Recently, two novel treatments - lomitapide (for patients aged ≥18 years) and mipomersen (for patients aged ≥12 years) – have been approved as adjunct therapy for homozygous FH. Both of these treatments target the production and secretion of apolipoprotein B-containing lipoproteins via

novel mechanisms. Lomitapide, an oral treatment, inhibits microsomal triglyceride transport protein (MTP), which is responsible for loading triglycerides and phospholipids onto nascent chylomicrons in the intestine and very low-density lipoproteins in the liver, resulting in reduced secretion into the circulation.[7] Mipomersen, administered by subcutaneous injection, is a second generation antisense oligonucleotide, which targets the messenger ribonucleic acid (mRNA) of apolipoprotein B, leading in turn to reduced synthesis of apolipoprotein B by the ribosome.[8]

In clinical trials in patients with homozygous FH, these treatments have been shown to reduce LDL cholesterol levels by 25-50%, on top of current standards of care, including maximal statin therapy.[9,10] There are, however, recognised side effect issues, highlighting the need for a proper risk/benefit evaluation when considering initiation of these treatments.

The third novel treatment showing promise for the management of FH is PCSK9 monoclonal antibody therapy, which acts to increase LDL clearance. Clinical trials in heterozygous FH have shown effective LDL cholesterol lowering (> 50%) with both alirocumab and evolocumab on top of current standards of care. Treatment was also well tolerated for up to 12 months.[11-14]

Furthermore, there is evidence from a proof of concept study with evolocumab that PCSK9 inhibitors given on top of standard of care reduce LDL cholesterol levels (by up to 26%) in patients with homozygous FH with residual LDL activity*.[15] However, PCSK9 inhibitors are not effective in patients with homozygous FH with receptor defective* phenotype.

In addition to the obvious LDL lowering effect, there are two potential advantages with this treatment strategy in FH.

'First, in this age where we stress the importance of personalised medicine, PCSK9 inhibitors offer the possibility of treating people with FH due to PCSK9 mutations with an agent that specifically targets this mutation.

Second, there are data showing that PCSK9 levels are very high in patients with severe FH, and levels are further increased by statin therapy. Therefore, adding a PCSK9 inhibitor to statin treatment may counteract this effect.' -

In conclusion, Dr Marina Cuchel commented:

'The future looks promising for the management of FH, with an armamentarium of new treatments, two of which are currently licensed. Added to current standards of care, these novel treatments offer potential for achieving LDL cholesterol goal and improving prognosis in these difficult to treat patients.'

* The severity of the homozygous FH phenotype depends on residual LDL receptor activity, which is measured by in vitro assays using the patient's cultured fibroblasts. This is conventionally classified as either receptor-negative (<2% residual activity) or receptor-defective (2-25% residual activity).

Details of Congress Sessions:

***Oral presentation - Clinical and Late Breaking Session I: Phase III placebo-controlled multicentre trial of a PCSK9 monoclonal antibody (evolocumab) (Sunday June 1st, 16:11 pm).**

***Poster presentation- EAS-0758 09 - Hypolidaemic drugs present and future: Relationship between alirocumab, PCSK9, and LDL-C levels: results from the ODYSSEY MONO Phase 3 trial of alirocumab 75 mg every 2 weeks**

***Workshop: Optimising treatment of FH (Tuesday 3rd June, 11:45-12:30)**

***Aegerion Educational Symposium: Bridging the treatment gap In Homozygous FH (Saturday May 31st, 16:00-17:30)**

***Amgen Educational Symposium: Addressing the needs of high-risk patients in hyperlipidemia management: the therapeutic horizon (Monday June 2nd, 13:00-14:30)**

***Sanofi-Regeneron Educational Symposium: PCSK9: From genomics to customised lipid lowering approaches (Monday June 2nd, 17:00-18:30)**

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Notes for editors:

For further information about FH refer to: http://www.fh-foundation.org/.

About the EAS Consensus Panel

The EAS Consensus Panel is comprised of internationally renowned experts in atherosclerosis and cardiovascular disease, and is co-chaired by Professor John Chapman (INSERM U939, Pitié-Salpetriere University Hospital, Paris, France) and Professor Henry Ginsberg (Columbia University, New York, USA). The Panel was first convened in November 2009 to consider the evidence for non-LDL lipids as risk factors for cardiovascular disease. Subsequent Consensus Panels have focused on familial hypercholesterolaemia, hypertriglyceridaemia, and the role of foods supplemented with plant sterols/stanols in dyslipidaemia management and cardiovascular disease prevention.

Table 1. Dutch Lipid Clinic Network criteria for diagnosis of FH in adults

	Points
Group 1 Family history	
First degree relative with	
• Known premature CHD (<55 years in men, <60 years in women)	1
OR	
• Known LDL cholesterol >95th percentile by age and gender for country	1
• Tendon xanthoma and/or corneal arcus	2
OR	
• Children <18 years with LDL cholesterol >95th percentile by age and gender for country	2
Group 2 Clinical history	
Subject with	
• Premature CHD (as defined above)	2
• Premature cerebral or peripheral vascular disease (as defined above)	1
Group 3 Clinical examination	
• Tendon xanthoma	6
• Corneal arcus in a person <45 years	4
Group 4 Biochemistry (LDL cholesterol)	
• >8.5 mmol/L (>325 mg/dL)	8
• 6.5-8.5 mmol/L (251-325 mg/dL)	5
• 5.0-6.4 mmol/L (191-250 mg/dL)	3
• 4.0-4.9 mmol/L (155-190 mg/dL)	1
Group 5 Molecular genetic testing	
• Causative mutation in the *LDLR, APOB*, or *PCSK9* genes	8
The highest single score in each group is considered.	
Score >8 definite FH; 6-8 probable FH; 3-5 possible FH; 0-2 unlikely FH	

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