fourierLEGACY

Newsletter (UK)

Number 4. **Nov 2019**

Dear Colleagues,

We are pleased to announce that we are making slow but steady progress with the FOURIER LEGACY study. Thank you for all your help and support!

In the UK, we received initial ethics approval on 27 Sep 2019 with HRA/HCRW approval on 15 Oct 2019. We have now received Rec & HRA/HCRW approval for our substantial amendment on 21st Nov 2019, so are very nearly ready to get started.

We wish you and your teams a very happy festive season! 

Substantial amendment documents approved by REC & HRA/HCRW on 21 Nov 2019:

- Protocol v1.3
- UK Group-speciific appendix (GSA) v2.1
- PIS v2.1
- PIS v2.1 Northern Ireland version (this excludes any information on electronic health records as this is not applicable to Northern Ireland
- Letter for site to send to patients if all attempts at telephone contact have failed. This is to be sent with a copy of the PIS and a prepaid envelope to be returned to the study team at Imperial

New protocol

There is now a new version of the study protocol, v1.3 along with a new version of the patient information sheet.

The main changes are as follows: -

Section 11.2 Confidentiality

- The study results and anonymised database will be shared with TIMI and Amgen, for research and analysis.
- Added response option of 'Unsure' for consistency to the questions about lipid lowering therapy.

- Other minor editorial changes including addition of Study Schema, addition of sections on Data Handling/Record Keeping and Clinical Study Report

Revised Participant Information Sheet
The new version of the participant information sheet, incorporating the changes to data sharing in the new protocol is **v2.1** (Attached).

There is also a PIS specific to Northern Ireland (v2.1_Northern Ireland) without reference electronic health records, (as this section does not apply to N. Ireland).

CAG Approval
One of the issues with data collection in FOURIER LEGACY is how we may be able to obtain information on deaths that have occurred since the end of the FOURIER OUTCOMES study, as patients' consent for follow up ended at the end of the OUTCOMES trial.

In the UK, we have approached the Confidentiality Advisory Group (for England, Scotland and Wales) and the Privacy Advisory Committee (for Northern Ireland)

The responses that we received from both groups were positive. 'Death certificates are not usually considered to be confidential patient information as they are publicly available on request from the General Register's Office (GRO). A member of the CAG Chair Team reviewed the application and advised that requesting the death certificates from patient's GPs, rather than the GRO, does not affect the view that the certificates are not confidential patient information'.

UKCRN
We are pleased to announce that the Fourier Legacy Study has been approved by UKCRN and that the study will be registered on the National Portfolio. Investigators are invited to discuss with the study team how accruals to the programme will be managed.

Site Updates
1. <u>Organisation information document</u>

Candy has been working to put together the information packs, including the Organisation Information Documents (OID). As well as the standard content, these packs will also contain: -

- Signature and Delegation Log
- PI Verbal Consent Template (see below)
- PI Checklist 'Site to Patient Talking Points'. This will be a summary of the study broken down to talking points to help site staff discuss the study with potential participants.

2. <u>Documenting verbal consent</u>

Contact with participants should be recorded in the patient notes and verbal consent also recorded. In addition, we ask that sites complete a verbal consent form and return a copy of this

to the NCC, whilst filing the original in the site file. The verbal consent form will be sent with the information pack.
Verbal consent forms should be sent from an nhs.net email to our secure email address (to be provided).

3. Talking points

We will be providing a one-page summary of the study with talking points to help site staff introduce the study to new potential subjects. This will also be provided with the information packs.

4. Training sessions to be booked

Once OIDs have been received and signed, we will set up remote training sessions for site staff, which will act as a remote site initiation visit. A selection of dates and times will be sent out in due course to see which are suitable. In advance of this, we will send a template for site file structure.

Update on FOURIER Publications

The following papers have been published since the end of the trial:-

1. **Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease.** Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, Kuder JF, Wang H, Liu T, Wasserman SM, Sever PS, Pedersen TR; FOURIER Steering Committee and Investigators. *N Engl J Med*. 2017;376:1713-1722.

Main paper showing that evolocumab reduced LDL-cholesterol by 59%. This was associated with a reduction in the primary endpoint of cardiovascular death, myocardial infarction, stroke, hospitalisation for unstable angina and coronary revascularisation, by 15% (p<0.001) and the key secondary endpoint of cardiovascular death, myocardial infarction and stroke, by 20% (p< 0.001).

2. **Cognitive Function in a Randomized Trial of Evolocumab.** Giugliano RP, Mach F, Zavitz K, Kurtz C, Im K, Kanevsky E, Schneider J, Wang H, Keech A, Pedersen TR, Sabatine MS, Sever PS, Robinson JG, Honarpour N, Wasserman SM, Ott BR; EBBINGHAUS Investigators. *N Engl J Med*. 2017;377:633-643.

Major substudy (Ebbinghaus) showing that compared with placebo, evolocumab had no adverse effects on cognitive function assessed by a variety of tests of memory and executive function.

3. **Cardiovascular safety and efficacy of the PCSK9 inhibitor evolocumab in patients with and without diabetes and the effect of evolocumab on glycaemia and risk of new-onset diabetes: a prespecified analysis of the FOURIER randomised controlled trial.** Sabatine MS, Leiter LA, Wiviott SD, Giugliano RP, Deedwania P, De Ferrari GM, Murphy SA, Kuder JF, Gouni-Berthold I, Lewis BS, Handelsman Y, Pineda AL, Honarpour N, Keech AC, Sever PS, Pedersen TR.

Lancet Diabetes Endocrinol. 2017 ;5:941-950.

Benefits of evolocumab in patients with diabetes similar to those observed in non-diabetic subjects. No evidence that evolocumab increased the risk of new-onset diabetes.

4. **Low-Density Lipoprotein Cholesterol Lowering With Evolocumab and Outcomes in Patients With Peripheral Artery Disease: Insights From the FOURIER Trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk).** Bonaca MP, Nault P, Giugliano RP, Keech AC, Pineda AL, Kanevsky E, Kuder J, Murphy SA, Jukema JW, Lewis BS, Tokgozoglu L, Somaratne R, Sever PS, Pedersen TR, Sabatine MS.
Circulation. 2018 ;137338-350.

Substantial benefits on cardiovascular outcomes seen with evolocumab in patients with peripheral vascular disease, including a 42% reduction in the risk of adverse limb events ($p<0.0093$).

5. **Clinical efficacy and safety of achieving very low LDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab: a prespecified secondary analysis of the FOURIER trial.**
Giugliano RP, Pedersen TR, Park JG, De Ferrari GM, Gaciong ZA, Ceska R, Toth K, Gouni-Berthold I, Lopez-Miranda J, Schiele F, Mach F, Ott BR, Kanevsky E, Pineda AL, Somaratne R, Wasserman SM, Keech AC, Sever PS, Sabatine MS; FOURIER Investigators.
Lancet. 2017;3901962-1971.

Highly significant relationship between low LDL-cholesterol levels and lower risk of cardiovascular endpoints extending to levels < 0.2 mmol/L. No safety concerns observed with achieving very low levels of cholesterol.

6. **Clinical Benefit of Evolocumab by Severity and Extent of Coronary Artery Disease.**
Sabatine MS, De Ferrari GM, Giugliano RP, Huber K, Lewis BS, Ferreira J, Kuder JF, Murphy SA, Wiviott SD, Kurtz CE, Honarpour N, Keech AC, Sever PS, Pedersen TR.
Circulation. 2018;138:756-766

Patients recruited into Fourier closer to their most recent myocardial infarction ,those with a history of multiple myocardial infarctions and those with multivessel coronary disease, were at high risk of cardiovascular events and experienced substantial reductions in cardiovascular endpoints.

7. **Clinical Efficacy and Safety of Evolocumab in High-Risk Patients Receiving a Statin: Secondary Analysis of Patients with Low LDL Cholesterol Levels and in Those Already Receiving a Maximal-Potency Statin in a Randomized Clinical Trial.** Giugliano RP, Keech A, Murphy SA, Huber K, Tokgozoglu SL, Lewis BS, Ferreira J, Pineda AL, Somaratne R, Sever PS, Pedersen TR, Sabatine MS.
JAMA Cardiol. 2017 ;2:1385-1391

Evolocumab was equally effective in reducing cardiovascular events in patients with stable atherosclerotic cardiovascular disease regardless of whether the baseline LDL-C was less than 70 or at least 70 mg/dL and whether the background statin was of maximal or submaximal potency.

8. **Cost-effectiveness of Evolocumab Therapy for Reducing Cardiovascular Events in Patients with Atherosclerotic Cardiovascular Disease.** Fonarow GC, Keech AC, Pedersen TR, Giugliano RP, Sever PS, Lindgren P, van Hout B, Villa G, Qian Y, Somaratne R, Sabatine MS.
JAMA Cardiol. 2017 ;2:1069-1078

Initial cost effectiveness analyses of evolocumab based on Fourier data.

9. **Inflammatory and Cholesterol Risk in the FOURIER Trial.** Bohula EA, Giugliano RP, Leiter LA, Verma S, Park JG, Sever PS, Lira Pineda A, Honarpour N, Wang H, Murphy SA, Keech A, Pedersen TR, Sabatine MS.
Circulation. 2018 ;138;131-140

This paper addresses the question of whether the benefits of evolocumab are modified by baseline inflammatory risk as assessed by high sensitivity (hs) CRP. LDL-C reduction with evolocumab reduces cardiovascular events across hsCRP strata with greater absolute risk reductions in patients with higher-baseline hsCRP. Event rates were lowest in patients with the lowest hsCRP and LDL-C.

10. **Effect of the PCSK9 Inhibitor Evolocumab on Total Cardiovascular Events in Patients with Cardiovascular Disease: A Prespecified Analysis From the FOURIER Trial**. Murphy SA, Pedersen TR, Gaciong ZA, Ceska R, Ezhov MV, Connolly DL, Jukema JW, Toth K, Tikkanen MJ, Im K, Wiviott SD, Kurtz CE, Honarpour N, Giugliano RP, Keech AC, Sever PS, Sabatine MS.
JAMA Cardiol. 2019;4:613-619

This paper shows that when analyses incorporated all cardiovascular events occurring during the trial rather than time to first event analyses, more than double the number of events were recorded and the risk reductions associated with evolocumab were substantial.

11. **Lipoprotein(a), PCSK9 Inhibition, and Cardiovascular Risk**. O'Donoghue ML, Fazio S, Giugliano RP, Stroes ESG, Kanevsky E, Gouni-Berthold I, Im K, Lira Pineda A, Wasserman SM, Češka R, Ezhov MV, Jukema JW, Jensen HK, Tokgözoğlu SL, Mach F, Huber K, Sever PS, Keech AC, Pedersen TR, Sabatine MS.
Circulation. 2019 ;139:1483-1492

Higher levels of Lp(a) are associated with an increased risk of cardiovascular events in patients with established cardiovascular disease irrespective of low-density lipoprotein cholesterol. Evolocumab significantly reduced Lp(a) levels, and patients with higher baseline Lp(a) levels experienced greater absolute reductions in Lp(a) and tended to derive greater coronary benefit from PCSK9 inhibition.

12. **Efficacy and Safety of Evolocumab in Chronic Kidney Disease in the FOURIER Trial.**

Charytan DM, Sabatine MS, Pedersen TR, Im K, Park JG, Pineda AL, Wasserman SM, Deedwania P, Olsson AG, Sever PS, Keech AC, Giugliano RP; FOURIER Steering Committee and Investigators. *J Am Coll Cardiol.* 2019 ;73:2961-2970

LDL-C lowering and relative clinical efficacy and safety of evolocumab versus placebo were consistent across all CKD groups. Absolute reduction in the composite of cardiovascular death, MI, or stroke with evolocumab was numerically greater with more advanced CKD.

13. **Interindividual Variation in Low-Density Lipoprotein Cholesterol Level Reduction with Evolocumab: An Analysis of FOURIER Trial Data**. Qamar A, Giugliano RP, Keech AC, Kuder JF, Murphy SA, Kurtz CE, Wasserman SM, Sever PS, Pedersen TR, Sabatine MS. *JAMA Cardiol*. 2019;4:59-63

Paper shows highly consistent and robust reduction in LDL-cholesterol levels with evolocumab. Interesting variability in response demonstrated in both evolocumab and placebo groups

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