

Statement from the STATIC team:

STATIC Trial Update: We have generated this message to explain the latest updates for the “STATIC trial”. First of all, Dr Tal Munir will be replacing Professor Peter Hillmen as the Chief Investigator for STATIC. Tal has been involved in the development of the trial concept and design of STATIC, as well as for FLAIR, and is now leading the CLL service in Leeds. Professor Hillmen will continue to be involved in STATIC to ensure a smooth transfer of responsibilities.

Secondly, we feel it is important to provide an update for potential STATIC participants, especially those who are awaiting accrual after finishing treatment with ibrutinib in the “FLAIR trial”. We are delighted to say that we are in the final stages of opening the STATIC trial. It has been a long road and the delay has been due to a multitude of factors including the Covid pandemic. We from the “STATIC” team would like to apologise for this frustrating delay as we understand the anxiety of FLAIR participants who have waited so long for the opening of this trial.

STATIC Trial Design: We have made some changes in the STATIC trial design due to a variety of reasons, including feedback from the funders of STATIC, the National Institute of Health Research Healthcare Technology Assessment Programme, but also with the emergence of the initial results from the FLAIR trial and other trials indicating the continuing risk of increasing toxicity with prolonged time on ibrutinib and that some patients stopping ibrutinib for toxicity have prolonged periods before needing further treatment. The principle modification in STATIC is that the patient choice group was felt to be inappropriate, particularly as any patient randomised to the intermittent treatment arm of STATIC would go back on ibrutinib at the first sign of their CLL returning. This modification was done with input from the UK CLL patient organisations as well as UK CLL experts. We want to reassure everyone wanting to take part in STATIC when they finish 6 years of ibrutinib treatment in FLAIR that STATIC includes a “randomisation trial” and “clinical need group”. The trial is designed in such a way that the participants who would not be considered appropriate for the randomisation trial, for example if their blood count is not at acceptable levels, could receive the drug in the “clinical need group”. The “randomisation trial” will be only recruiting participants who are in clinical remission as defined by the trial protocol. All participants from FLAIR trial who have already finished six years of ibrutinib will be able to participate in the trial, if they choose, with the same criteria as those patients from FLAIR still on treatment. For patients considering STATIC this means the following options are available:

For patients who have been treated in FLAIR:

- 1) Enter STATIC and be randomised to continuous ibrutinib or intermittent ibrutinib, as long as their CLL is under good control after six years of ibrutinib treatment in FLAIR. (note this is not stopping ibrutinib permanently but pausing ibrutinib – patients will re-start in STATIC at the first sign of their CLL reappearing)
- 2) Enter STATIC and be assigned to the “clinical need group” to stay on ibrutinib continuously as their CLL is not well controlled and would benefit from treatment with continuous ibrutinib
- 3) Not enter STATIC and remain off ibrutinib in follow-up in FLAIR (the patient will still remain under regular follow-up with their trials team)

For previously treated patients with CLL in STATIC: Patients who are receiving ibrutinib after at least one prior treatment for their CLL will also be eligible for STATIC in the randomisation trial, as long as their CLL is under good control after at least three years of ibrutinib treatment.

When will STATIC Open? Before we can open the STATIC trial, as with any clinical trial, it must be reviewed by an independent ethics committee. We have had a very positive meeting with the ethics committee, and the next step is to receive the formal feedback from this as well as from the Health Research Authority (HRA) and Medicines and Healthcare products Regulatory Agency (MHRA). Once the study is approved we can open the trial, and we expect this to be in October 2022. In the meantime, we have invited potential hospitals, including all those participating in FLAIR, to join the trial so that they can prepare to open to the study. Sites will open as and when they are ready to do so, depending on their local site timelines.

The STATIC trial asks increasingly important questions in terms of long-term therapy for patients with CLL and is one of very few trials addressing this issues. We would like to thank all the participants, investigators and trial teams from UK who have made FLAIR such a hugely successful and important trial. We expect that STATIC will answer important questions for CLL community including how to look after patients with CLL in the long-term.

Update provided by Dr Tal Munir and Professor Peter Hillmen on behalf of the STATIC trial team