Regional Ethical Review Board in Stockholm

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Stockholm, 21 December 2015

Amendment 5 for the EFFECTS study, and
Annual safety report for EFFECTS EFFECTS: ESTABLISHING THE EFFECTS(S) AND SAFETY OF FLUOXETINE INITIATED IN THE ACUTE PHASE OF STROKE. Relates to the period 20 October 2014 to 31 October 2016

EudraCT no.: 2011-006130-16
EPN no.: Ref. no.: 2013/1265-31/2. Date 30 September 2013
Amendment 1: Date: 15 April 2015
Amendment 2: Ref. no.: 2015/991-32. Date 10 June 2015
Amendment 3: Ref. no.: 2015/20156-32. Date 30 November 2015
Amendment 4: Ref. no.: 2016/1191-32. Date 14 June 2016

This is amendment 5 for EFFECTS. It includes year 2 of the annual safety report. This is a copy of the safety report that is sent to the Swedish Medical Products Agency. It also includes some amendments, **points A-C below**. The report covers the period since the study started (20 October 2014). In addition to the Swedish Medical Products Agency and the Ethical Review Board, the safety report has also been sent to the steering group and the Safety Committee for EFFECTS, the heads of the Department of Clinical Sciences at Danderyd Hospital and the Department of Clinical Neuroscience (CNS) at Karolinska Institutet, Professor Erik Näslund and Jan Hillert, and our monitors at Karolinska Trial Alliance.

During the year, the Safety Committee has held two meetings and has notified the Chief Investigator that EFFECTS can continue as planned since the study meets the necessary safety requirements.

A:

As an addition to the previously approved application, resource letters are submitted for:

1. Norra Älvsborg County Hospital Trollhättan, Bromma Geriatric Clinic and Västmanland Hospital Västerås

Additional centres that may be included during 2017 are: Lindesberg (will be included), Dalen Hospital, Sollefteå Hospital, Enköping, Kalmar, Eksjö, Värnamo, Östra Hospital, Borås, Sunderby Hospital, Skellefteå, Karlstad, Södertälje, Kullbergska, Jönköping, Karlskrona, Karlshamn and Varberg.

We have previously submitted resource letters for: Danderyd Hospital, Karolinska Hospital (Solna), Hässleholm, Skaraborg Hospital Skövde, Uppsala University Hospital, Karolinska Hospital (Huddinge), Capio St Göran's Hospital, Mora General Hospital, Falu General Hospital, Lidköping, Norrtälje, Kristianstad, Rehab Station Stockholm, Mälar Hospital Eskilstuna, Halland Hospital Halmstad, Skåne University Hospital Malmö, Helsingborg General Hospital, Skåne University Hospital, Lund, Norrland University Hospital Umeå, Visby General Hospital, Sundsvall Hospital, Sahlgrenska Hospital, Gothenburg, Högsbo Hospital, Gothenburg, Stora Sköndal, Östersund Hospital, Alingsås Hospital, Ängelholm Hospital, Stockholm Nursing Home and Örebro University Hospital Rehabilitation Medicine Clinic.

B:

Major amendments, updates in the Research Protocol to version 4.8

1. The company that manufactures fluoxetine has updated its SPC. They now state that if metoprolol is used in the case of heart failure, fluoxetine is contraindicated. EFFECTS' Steering Committee and Safety Committee have made the assessment that this applies to serious heart failure, that it may be clinically significant in the case of more advanced heart failure (NYHA Grad IIB – IV) and especially in higher doses, and that in the case of simultaneous treatment with metoprolol and fluoxetine one should be attentive to the interaction and should follow up on the patient soon after inclusion with clinical monitoring including ECG. In the annual safety report to the Swedish Medical Products Agency, we have carried out a thorough analysis in relation to this problem, and it does not recur here. In summary, EFFECTS' steering group is of the opinion that this did not give cause for any change to the study, as this falls under the exclusion criterion *pharmaceuticals that have significant interactions with SSRIs*. All centres have been notified of this serious interaction, and we have clarified this exclusion criterion through the following addition to our research plan.

   "Fluoxetine is contra-indicated in combination with metoprolol used in cardiac failure New York Heart Association Grade IIIB and IV. At higher doses of metoprolol used in heart failure indication one should be vigilant of the interaction and early after enrollment monitor the patient with clinical monitoring including ECG."

   Page 25 in the Research Plan

2. We have previously written that participation in another CTIMP does not automatically rule out participation in EFFECTS, but that it is important not to overburden patients with studies. In the section about co-enrolment, we now mention the TIMING study and write:

   "It is allowed to co-enroll patients in EFFECTS and the TIMING study. The intervention in TIMING is early vs delayed start of NOAC in patients with acute stroke and atrial fibrillation. Thus, all patients would receive NOAC either <=4 days or > 5 days from the acute stroke."

   Page 26 in the Research Plan

3. We have noted that our protocol has not specified how long we recommend stopping in the event of suspected side effects and whether we will permit restarting medication after a longer stop. We have now clarified this in the updated version. We write:

"We recommend coming off IMP for 14 days to see if the symptoms resolve. If they do then ideally they would restart to see if symptoms return. However, we recognize very few patients are prepared to do so. All stops (temporary and permanent) of the IMP must be registered in the e-CRF. There is not any limit for how long a temporary stop might be."

Page 25 in the Research Protocol.

C:

Minor amendments, updates to version 4.8

Page 1
Added reference number and EFFECTS study number in the Clinicaltrials.gov database to Amendments 3 and 4. Changed the protocol version to version 4.8 and the date to 21 December 2016.

Page 52
In the protocol, we clarify that the amendment of a centre in the study does not need to be sent out to all centres as a protocol amendment. This is communicated in connection with major protocol changes and electronically via the weekly newsletter and on the study's website (www.effects.sehttp://www.effects.se/). We write:

"Amendment relating to the addition of centers in the study do not need to be sent out to all centers as a protocol amendment. This is communicated in connection with major protocol changes and electronically via the newsletter and on the study website (www.effects.se)."

A fee of SEK 2,000 will be paid this week, stating the reference:
Amendment 5 EFFECTS/Lundström

APPROVED 4 January 2017

[signed]
Erik Lundström
Chief Investigator EFFECTS

[signed]
Pär Sparén
Scientific secretary
Regional Ethical Review Board in Stockholm

Appendices:

Copies of Resource certification for new centres
Arlig_sakerhetsrapport_EFFECTS_2016 including 2 appendices marked with *
* Appendix 1 EFFECTS 2016
* Appendix 2 EFFECTS 2016
EFFECTS Protocol version 4 8 EU no. 2011-006130-16