I-STROKE II
IMATINIB IN ACUTE ISCHAEMIC STROKE

A PHASE 3, RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-ARM EFFICACY TRIAL OF IMATINIB IN ACUTE ISCHAEMIC STROKE

Sponsor/ Representative for sponsor	Karolinska Institutet / Niaz Ahmed, MD, PhD
Funder	The Swedish Research Council (Vetenskapsrådet) - Main The Swedish Heart-Lung Foundation (Hjärt-Lungfonden)
Coordinating/ Chief Investigator	Assoc. Prof. Niaz Ahmed, MD, PhD
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Protocol Code Number	I-StrokeII2016

1 Protocol Synopsis

PROTOCOL IDENTITY AND OBJECTIVES	
EudraCT Number:	2017-000075-85
Protocol Code Number	I-StrokeII2016
Protocol Title:	A phase 3, randomised, double-blind, placebo-controlled, parallel-arm efficacy trial of Imatinib in acute ischaemic stroke
Trial Objectives:	**Primary:** To investigate if Imatinib (800 mg / day) treatment initiated within 8 hours of symptom onset and given for 6 days improves functional outcome at three months after acute ischaemic stroke **Secondary:** 1) Investigate if Imatinib treatment improves functional outcome at three months in acute ischaemic stroke patients treated with iv thrombolysis 2) Investigate if Imatinib treatment improves neurological outcome at three months after acute ischaemic stroke 3) Investigate if Imatinib treatment improves neurological outcome at three months in acute ischaemic stroke patients treated with iv thrombolysis 4) Investigate if Imatinib reduces the frequency and grade of ICH in patients with acute ischaemic stroke treated with iv thrombolysis 5) Investigate if Imatinib reduces the frequency and grade of cerebral oedema in patients with acute ischaemic stroke treated with iv thrombolysis 6) Examine serious and non-serious adverse events in patients treated with Imatinib 7) Investigate if Imatinib reduces mortality at 3 months after acute ischaemic stroke 8) Investigate if Imatinib reduces mortality at 3 months in acute ischaemic stroke patients treated with iv thrombolysis
INVESTIGATIONAL MEDICINAL PRODUCT (IMP)	
Test Product:	Imatinib
Pharmaceutical Form:	Tablets, 400 mg Imatinib or matching placebo
Route of Administration:	Oral
METHODOLOGY	
Trial Design:	A phase 3, randomised, placebo-controlled, double-blind, parallel-arm prospective study to evaluate efficacy of Imatinib on functional independency at 3 months in acute ischaemic stroke
Dose/Duration treatment:	Day 1: 800 mg Imatinib or matching placebo as soon as possible after randomisation. Day 2-6: 400 mg Imatinib or matching placebo twice daily, total treatment duration: 6 days

Primary Endpoints:	Functional independency at 3 months as measured by modified Rankin Scale (mRS) Score 0-2. For a positive outcome, patients in the active group treated with Imatinib 800 mg per day will have statistically significant higher functional independency compared to the control group treated with placebo.
Secondary Endpoints:	1) Change in mRS score at 3 months, favourable shift of the scale in the Imatinib group compared to placebo 2) Neurological outcome at 24 h and at 7 days or discharge if occurs earlier and at 3 months 3) Frequency and grade of ICH and cerebral oedema on post-treatment imaging scan in patients undergoing IV thrombolysis and or endovascular thrombectomy, 4) Serious and non-serious adverse events 5) Mortality at 3 months
POPULATION OF TRIAL SUBJECTS	
Number of Subjects:	Imatinib/Placebo: 630/630, totally 1260 patients.
Description of Trial Subjects:	**Inclusion Criteria** 1) Clinical diagnosis of acute ischaemic stroke with a neurological deficit corresponding to 6 points or higher on the NIHSS score a) at the time of randomisation if no recanalisation therapy performed b) prior to iv thrombolysis therapy alone or prior to thrombectomy alone if performed c) prior to iv thrombolysis if both iv thrombolysis and thrombectomy performed Ischaemic stroke is defined as an event characterised by sudden onset of acute focal neurological deficit, presumed to be caused by cerebral ischaemia and an imaging scan excluding any intracranial haemorrhage. 2) Age 18-85 years 3) Patients should be randomised as soon as possible but not later than 8 hours of symptom onset. a) If the patient receives iv thrombolysis alone, patient should be randomised and study drug should be given within one hour after completion of iv thrombolysis infusion b) If the patient receives endovascular thrombectomy (with or without prior iv thrombolysis), patient should be randomised within two hours after completion of endovascular thrombectomy and study drug given as soon as possible after randomisation. 4) iv thrombolysis, if performed, is done in agreement with European Stroke Organisation guidelines and has been initiated within 4.5 hours of stroke onset (see below separate criteria for indications / contraindications) 5) Endovascular thrombectomy, if performed, is done in agreement with recently published American Stroke Association guidelines, and fulfilling the following criteria

	a) Confirmed diagnosis on Computed Tomography Angiography (CTA) or Magnetic Resonance Angiography (MRA) of acute occlusion of either of the first two segments of the Middle Cerebral Artery (M1 or M2), terminal Carotid Artery, first segment of the Anterior Cerebral Artery (A1), or Basilar Artery, consistent with the clinical symptoms. b) thrombectomy has been initiated within 8 hours of symptom onset (defined *as start with femoral artery (groin) puncture)* 6) Patient is competent to make a decision and has provided informed consent with regard to participation in the study, retrieval and storage of data and follow up procedures **Exclusion Criteria** ***General*** 1) Imaging scans show signs of large current infarction as defined by more than 1/3 of the Middle Cerebral Artery territory or ½ of other vascular territories 2)) Known significant pre-stroke disability (mRS ≥2) 3) Severe comorbidities such as advanced dementia (estimate pre-stroke if otherwise healthy), terminal illness, and other severe medical conditions with anticipated life expectancy less than 6 months. 4) Acute pancreatitis 5) Severe hepatic dysfunction, including hepatic failure, cirrhosis, portal hypertension (oesophageal varices) and active hepatitis 6) Ongoing treatment with chemotherapy 7) Drugs which may increase the plasma concentration of Imatinib - ketokonazol, itrakonazol, erythromycin and claritomycin 8) Drugs which may decrease the plasma concentration of Imatinib: Dexametason, phenytoin, karbamazepin, rifampizin, phenobarbital, fosphenytoin, primidon, Hypericum perforatum (Johannesört, St John's wort) 9) Female patients with childbearing potential, if pregnancy cannot be excluded by pregnancy test (urine point-of-care pregnancy test). 10) Patient is participating in other interventional study ***Additional Exclusion criteria for patients treated with intravenous thrombolysis (IVT)*** 1) Severe stroke as assessed clinically by NIHSS>25 2) Administration of heparin within the previous 48 hours preceding the onset of stroke with an elevated activated thromboplastin time (aPTT) at presentation, or corresponding low-molecular heparin. 3) Patients receiving oral anticoagulants, e.g. warfarin sodium (INR>1.7) or direct oral anticoagulation: dabigatran (aPTT>40s), apixaban, rivaroxaban. 4) Platelet count below 100,000/mm^3. Significant bleeding disorder at present or within the past 6 months, known haemorrhagic diathesis.

	5) History or evidence or suspicion of intracranial haemorrhage including sub-arachnoid haemorrhage 6) Systolic blood pressure >185 mmHg or diastolic blood pressure >110 mmHg, in spite of repeated doses of i.v. medication to reduce blood pressure below these limits. 7) History of the following conditions: prior ischemic stroke within 3 months, intra-axial neoplasm, intracranial or spinal surgery within the prior 3 months, recent severe head trauma within 3 months or unruptured intracranial aneurysm>5 mm. 8) Major surgery or significant trauma in the past 10 days
Assessments and Procedures	Assessments and procedures are divided into following visits; Baseline (day 1), day after randomisation (day 2), daily visits day 3, 4, 5, 6 and 7 or discharge (whichever occurs first) and final follow-up at 3 months. Patients should preferably remain inpatients during the study medication period (total 6 days). If discharge occurs earlier than day 6, the patient should be contacted or, preferably, seen daily on an outpatient basis until day 6, the last day of study medication.
Variables:	Demographic and baseline data, time logistics (stroke onset, hospital arrival, initiation of intravenous thrombolysis and or mechanical thrombectomy if treated), medical history, pregnancy if childbearing potential. Stroke severity as measured by NIHSS at baseline and daily until day 7 (or at discharge if it occurs before day 7, this applies for all other day 7 parameters) and at 3 month. Blood pressure and pulse rate at baseline and daily until day 7. An imaging scan of the brain: at baseline and at 22 to 36 h after initiation of the first modality of recanalisation therapy if it was given, or whenever otherwise clinically indicated Lab tests at baseline and day 7 (or at discharge if it occurs before day 7): complete blood count (CBC), blood glucose, activated prothrombin time (aPTT), -INR, serum creatinine, serum sodium and potassium, serum amylase, AST and ALT, albumin. Other laboratory or point-of-care testing may be performed at the discretion of the attending physicians and team. Day 7 (or at discharge if it occurs before day 7) lab tests are only for selected number of centres and will be taken for at least 10% (N=126) of total study population. Concomitant medication at baseline, during the acute hospitalisation period and at day 7. Final stroke diagnosis and its subtypes are determined at day 7. Functional independency as measured by modified Rankin Scale at 3 months
Safety Parameters	Serious and non-serious adverse events, intolerable adverse events from randomisation to 3 month

TRIAL TIMETABLE	
First Subject In:	Q3 2018
Last Subject In:	Q3 2021
Last Subject Out:	Q4 2021

3 Administrative Information

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7 DESIGN

7.1 Outline

This is an academic driven, multicentre, prospective, randomised, double-blind, parallel-group, placebo-controlled, multicentre efficacy trial of Imatinib in acute ischaemic stroke. In Appendices 1, the study outline is presented as a flow chart.

Population: Patients with acute ischaemic stroke within 8 hours of symptom onset with a neurological deficit corresponding to 6 points or higher on the National Institutes of Health Stroke Scale (NIHSS) score
Intervention: Tablet Imatinib 800 mg per day orally for 6 days
Control: Matching placebo-treated group, randomised between Imatinib and placebo.
Outcome: Functional outcome scale at 3 months after treatment initiation using the mRS.

Treatment with approved criteria for intravenous thrombolysis and/or mechanical thrombectomy is permitted.

Patients with acute ischaemic stroke are screened as soon as possible. Randomisation occurs as soon as patients give consent and inclusions and exclusions criteria are fulfilled, through a computerised central randomisation service by means of a secure 24/7 web interface. The first dose (either 2 tablets of 400 mg of Imatinib or matching placebo) is administered orally as soon possible after randomisation (day 1) but not later than 1 hour after randomisation unless the patient is treated with iv thrombolysis and/ endovascular thrombectomy). In case the physician decides to treat the patient with recanalisation therapy (iv thrombolysis and/ endovascular thrombectomy), the study treatment should also be given as soon as possible (allowed also before the start of recanalisation therapy) without delaying the start of recanalisation therapy, but must occur not later than 1 hour of completion of the iv thrombolysis infusion and within 2 hours of completion of endovascular thrombectomy. Every effort should be made to give the study medication before the end of iv thrombolysis infusion. If the patient received thrombectomy treatment, study medication should be administered within 2 hours after the end of endovascular thrombectomy with or without prior iv thrombolysis treatment. Thereafter 400 mg Imatinib or matching placebo treatment is given twice daily (08.00 AM and 08.00PM) for additional 5 days, total treatment duration is 6 days. In patients with suspected swallowing difficulty, it is permitted to administer the study drug by nasogastric tube after the tablets are dispersed in a glass of still water (*see instruction section 9.1*).

Patients will be followed at the stroke unit during the treatment period, according to the standard monitoring protocol. Imaging scans (CT/ MRI) are performed according to the standard clinical protocol for the centre. Follow up imaging scan should be performed 22-36 hours after initiation of recanalisation therapy or earlier if clinically indicated.

Adverse effects, laboratory values, neurological score by NIHSS are documented according to the study protocol.

All patients' data are documented in the electronic case record form (eCRF) which will be developed before start of the study. Paper CRFs will be available for collecting data in case eCRF is not available at the time of data entry and will also be kept as study documentation.

Patients will be recruited from study centres across Sweden. Other countries will be invited to join the study depending on recruitment rate.

Patients will be followed until 3 months after stroke onset, with a final clinical visit and evaluation. All patients will have access to trial staff in case of any event during follow up.

7.3 SCHEDULE OF INVESTIGATIONAL EVENTS

Trial Period:	**Baseline/ Before randomisation**	**Next day after randomisation**	**Daily in stroke unit**	**Dis-charge[10] or days 7**	**Final follow up (3 Mo)**
Visit No:	**1**	**2**	**3,4,5,6[8]**	**7**	**8**
Day of visit:	**1**	**2**	**3-6**	**7**	**90 (80-110)**
Informed consent	X				
Incl-/excl criteria	X				
Date/ time of stroke onset	X				
Date/ time of Study drug administration	X	X	X		
Date/ time of iv thrombolysis start/end if given	X				
Date/ time of thrombectomy start/end if performed	X				
Demographic data	X				
Medical history	X				
Pregnancy excluded[1]	X				
Medications at stroke onset	X				
NIHSS	X[2,3]	X	X	X	X
Blood pressure, pulse rate	X	X	X	X	X
Lab tests[4]	X			X[11]	
Glucose test[5]	X				
Imaging scan (CT/MRI)	X[6]	X[7]			
ADR / SAE reporting	X	X	X	X	X
Treatments given from admission to discharge	X	X	X	X	
Final stroke diagnosis				X	
mRS	X[9]				X

Table 1. Visit schedule

[1]Pregnancy excluded by interview and/or pregnancy test

[2]at the time of randomisation if no recanalisation therapy performed

[3]prior to iv thrombolysis therapy alone or prior to thrombectomy alone or prior to iv thrombolysis if both iv thrombolysis and thrombectomy performed

[4] Serum and Plasma; complete blood count, blood glucose, aPTT, INR, serum creatinine, serum Na, serum K, amylase, AST, ALT, albumin

[5]Daily capillary blood glucose tests according to local practice,

[6]This CT/MRI is performed before randomisation.

[7]If patients treated with IV thrombolysis &/ thrombectomy (accepted interval 22-36 hours after initiation of the first recanalisation treatment) or if done due to clinical indication.

[8] Study treatment ends day 6, no study treatment on day 7.

[9]mRS before current stroke

[10]If discharge occurs before day 7

[11]. Day 7 lab tests are only for selected number of centres and will be taken for at least 10% (N=126) of total study population.

9 Treatment

9.1 Description of the Investigational Medicinal Product, Imatinib

Day of treatment	One tablet 400 mg Imatinib or matching placebo	Fluid (water, juice) *if tablets need to be dissolved*
1	*Asap* after randomisation*	200 ml
2	8 AM + 8 PM	200 ml
3	8 AM + 8 PM	200 ml
4	8 AM + 8 PM	200 ml
5	8 AM + 8 PM	200 ml
6	8 AM + 8 PM	200 ml

Table 2. Drug administration
** First dose will be 2 tablets*

Instructions to dissolve the tablet
Each tablet contains either of 400 mg Imatinib or the matching placebo. The time required to dissolve the tablet and the initial colour between the Imatinib and placebo may differ. So, the person who dissolves the tablet may realise the difference and guess that one of the tablet types contains active drug or placebo. To keep the blindness of the drugs, the tablet should only be dissolved by a delegated person who otherwise is not involved in the study. A list of delegated persons should be kept in each study centre and they will be thoroughly instructed before the start of the study. The delegated person should dissolve the tablet in a separate room where she/he is alone and dissolves the content as instructions above and wait for 10 minutes before return to patient's room. The appearance and smell of the fluid after dissolving the study drug (s) will not significantly differ.

9.3 Treatment Assignment

The patients are randomised to one of two alternative groups, Imatinib 400 mg or matching placebo by oral administration. Randomization will be performed through a computerised central randomisation service.

9.5 Concomitant Medication

Imatinib may increase the plasma concentration for ciclosporin, pimozid, simvastatin, calcium antagonists of dihydropyridine type, and statins.

Warfarin should not be given together with Imatinib, low molecular weight or unfractionated heparin should be used.

The effect of paracetamol may increase, high doses of paracetamol should be avoided

The effect of metoprolol can increase during treatment with Imatinib, and careful monitoring of these patients is recommended while on Imatinib

Concomitant medication will be documented in the study database.
medication and other parameters.

10 Assessment of Safety and efficacy

10.1 Clinical & Laboratory Safety Assessments

Usual adverse events of Imatinib
Known usual adverse effects *in long term treatment* will be listed in the CRF and checked for present or non-present:

1. Headache	2. Nausea
3. Vertigo	4. Diarrhoea,
5. Vomiting	6. Dyspepsia
7. Flatulence	8. Cough
9. Abdominal pain	10. Periorbital oedema
11. Dermatitis	12. Eczema
13. Itching	14. Nocturnal hyperhidrosis
15. Muscular spasms	16. Muscular & skeletal pain (e.g. myalgia, arthralgia)
17. Fluid retention	18. Oedema (e.g. eye lid, facial or wide-spread)
19. Tiredness	20. Insomnia
21. Weakness	

Any other event not listed above will be described as a free text entry.

11 Safety Assessments

11.3.1 You should NOT report to the trial sponsor:

Any Adverse Events that are part of the natural history of the primary event of stroke or expected complications of stroke should NOT be reported to the trial sponsor. These include:

- Falls
- Fracture
- Painful shoulder syndromes
- Pressure sores
- Spasticity or contractures
- Any other known complications of stroke which has no association with the IMP according to the judgment of the treating physician.

Reporting these events is unlikely to be informative and places an unnecessary burden on the local researchers which would compromise the practicality of this investigator lead trial.

11.3.2 You SHOULD report to the Sponsor

The following Adverse Events should be reported to the Trial Co-ordinating Centre on the discharge form. These events will also be collected during the 3 months of follow up providing they meet the criteria of a Serious Adverse Event as defined in section 11.1.

- Any SAE
- all-cause mortality
- stroke/TIA
- myocardial infarction
- upper gastrointestinal bleeding
- epilepsy/seizures
- Liver or renal dysfunction

- Neutropeni, trombocytopeni, anemi, Pancytopeni,
- Pneumoni

13 Quality Control and Quality Assurance

13.1 Source Data

A note of participation in the trial must be entered in the patient health record file. The note will contain:
Study title
Randomisation number
Information that an informed consent form has been signed and is kept with the study documentation
Medically responsible study doctor and study nurse, with contact details.

13.2 Monitoring

The Sponsor has appointed Karolinska Trial Alliance (KTA) to perform independent monitoring for quality control of the study. Monitoring will be performed before, during and after study completion in accordance with the ICH GCP guidelines. The extent of monitoring will be described in a monitoring plan, which will be approved by the Sponsor. Study conductance, source data, drug accountability, adherence to GCP, and regulatory requirements will be monitored.
Authorization, CTA, is obtained from the MPA. A favourable ethical opinion will be obtained from IEC prior to the commencement of this study.

20 Sub-study: Post-stroke epilepsy

20.2 Objective

To investigate whether the administration of Imatinib according to the primary clinical trial protocol, can affect the development of epileptic seizures in stroke patients, both in the acute setting as well as within 1-year post-stroke.

20.3 Procedure

No new methods, invasive procedures or treatments will be administered/performed, merely registration of additional data as follows:

1. Registration of history of pre-stroke epilepsy and treatments.
2. Registration of clinical and/or EEG verified epileptic seizures during the acute setting (within 1 week after stroke). The seizures will be classified according to standard definitions, see appendices 4.
3. Registration of antiepileptic medications used within the first week after the stroke.

At an extra follow-up meeting/phone call at 1 year after inclusion, AND through review of the patient records, we will assess whether the patients have developed a post-stroke epilepsy. The seizures will be classified according to the semiology of the epileptic seizures, see appendices 4. An epilepsy diagnosis (at least one unprovoked seizure post-stroke in a previously seizure-free individual) will always be designated a post-stroke epilepsy, without any further specification. Any antiepileptic medications and the period in which they were used will be documented.