APPLICANT/ COORDINATING INVESTIGATOR	The Scandinavian Sarcoma Group (SSG)/ PD Dr. Peter Reichardt
CONDITION	Patients treated with adjuvant imatinib for 3 years after complete surgical removal of high-risk GIST and who are considered to be at a high risk of GIST recurrence despite 3 years of adjuvant imatinib.
OBJECTIVE(S)	**Primary:** •Recurrence-free survival (RFS) after randomisation. **Secondary:** •Overall survival. •GIST-specific survival. •Adverse events (Common Terminology Criteria for Adverse Events [CTCAE] version 3.0). •Quality of life **Exploratory:** •Effect of tumour site on RFS. •Effect of tumour mutation type on RFS. •Effect of imatinib dose at randomisation on RFS. •To evaluate tumour tissue and blood molecular markers in prediction of GIST recurrence.
INTERVENTION(S)	**Arm A: Imatinib** Imatinib mesylate will be administered at the dose of 400 mg/day. Dose escalation to doses greater than 400 mg/day is not allowed. Patients with KIT exon 9 mutation are an exception, and may be treated with a dose higher than 400 mg/day, but not higher than 800 mg/day. In case of toxicity, the dose may be reduced. In case imatinib needs to be discontinued for a time period longer than 28 days due to toxicity, imatinib treatment should be discontinued. **Arm B: No imatinib** No imatinib or other anti-cancer treatment will be administered in the adjuvant setting
KEY EXCLUSION CRITERIA	1. Presence of distant metastases or local recurrence of GIST. 2. Not willing to donate tumour tissue and/or blood samples for the study molecular studies. 3. Presence of a substitution mutation at PDGFRA codon D842 (usually D842V). 4. Administration of adjuvant imatinib longer than for 3 years is planned regardless of the result of randomisation, or “life long” imatinib administration is planned. 5. Prior adjuvant (+ neoadjuvant) therapy with imatinib mesylate for at least 35 months has not been completed, or the total duration of prior adjuvant (+ neoadjuvant) imatinib administration exceeds the total duration of 38 months. 6. Neoadjuvant imatinib for a duration that exceeds 12 months. 7. Longer than 4-week break during adjuvant imatinib administration. 8. The dose of imatinib at completion of 3 years of adjuvant imatinib was 200 mg per day or less or greater than 800 mg per day. 9. Patient has received any investigational anti-cancer agents during adjuvant imatinib or between completion of adjuvant imatinib and the date of randomisation. 10. Patient has been free of another malignancy for less than 5 years except if the other malignancy is not currently clinically significant nor requiring active

	intervention, or if the other malignancy is a basal cell skin cancer or a cervical carcinoma in situ, a small (2 cm or less in diameter) nodenegative breast cancer (pT1N0M0), a low Gleason score (<8) local (T1 or T2) prostate cancer. Recent existence of any other malignant disease is not allowed. 11. Patient with Grade III/IV cardiac disease as defined by the New York Heart Association Criteria (i.e., congestive heart failure, myocardial infarction within 6 months of study entry). 12. Female patients who are pregnant or breast-feeding. 13. Severe and/or uncontrolled medical disease (i.e., uncontrolled diabetes, severe chronic renal disease, or active uncontrolled infection). 14. Known diagnosis of human immunodeficiency virus (HIV) infection. 15. Patient with a significant history of non-compliance to medical regimens or with inability to grant reliable informed consent. 16. Patients with chronic or active hepatitis B. 17. Patients that have been committed to an institution by official or judicial order. 18. Patients that are dependent upon the sponsor, the trial site or the investigator.
KEY INCLUSION CRITERIA	1. Age ≥ 18 years. 2. Morphological and immunohistological documentation of GIST (immunostaining for KIT [CD117] and/or DOG-1 positive, or mutation of KIT or PDGFRA present in tumour tissue). 3. Macroscopically complete surgical resection of GIST (either R0 or R1 resection). 4. Mutation analysis of KIT and PDGFR genes has been carried out. 5. A high risk of GIST recurrence, either 1) gastric GIST with mitotic count >10/50 HPFs, or 2) non-gastric GIST with mitotic count >5/50 HPFs, or 3) non-gastric GIST treated with neoadjuvant imatinib and initially larger than 10 cm 4) tumour rupture Tumour rupture (spillage of the tumour contents into the abdominal cavity) may have occurred either before or at surgery. 6. ECOG performance status ≤ 2. 7. Adequate organ function, defined as serum total bilirubin <1.5 x ULN (upper limit of normal), serum AST (SGOT) and ALT (SGPT) <2.5 x ULN, creatinine <1.5 x ULN; blood ANC (neutrophil count) ≥1.0 x 109/L, platelet count ≥100 x 109/L. 8. Female patients of childbearing potential must have a negative pregnancy test within 14 days before initiation of study drug dosing. Postmenopausal women must have amenorrhoea for at least 12 months to be considered of non-childbearing potential. Male and female patients of reproductive potential must agree to employ an effective barrier method of birth control throughout the study and for up to 3 months following discontinuation of study drug. For females, a highly effective method for birth control must be used, which means that the method can achieve a failure rate of less than 1% per year when used consistently and correctly. All females of child-bearing potential must be informed of such methods, and must also, if sexually active, accept a monthly pregnancy test during treatment if randomized to prolonged imatinib use. 9. Patient willing to be followed up at the study site regardless of the result of randomisation. 10. Patient has provided a written, voluntary informed consent prior to study-specific screening procedures.
OUTCOME(S)	**Primary:**

	• Recurrence-free survival (RFS) is defined by the time interval between the date of randomisation and the date of first detection of GIST recurrence or death, whichever occurs first. **Secondary:** • Overall survival (the time period between the date of randomisation and the date of death). • GIST-specific survival (the time period between the date of randomisation and the date of death considered to be caused by GIST; patients who die from other causes are censored on the date of death). • Safety (Common Terminology Criteria for Adverse Events [CTCAE] version 3.0). • Quality of Life (EQ-5D instrument). **Exploratory:** • Effect of the tumour mutation type on RFS. • Effect of tumour site on RFS. • Effect of the imatinib dose at randomisation on RFS. • Tumour tissue and blood molecular markers in prediction of GIST recurrence.
STUDY TYPE	Open-label, 2-arm, prospective, randomised, multicentre phase III trial. Patients diagnosed with GIST who have completed 3 years of adjuvant imatinib, who are free from GIST recurrence after 3 years of adjuvant imatinib, and who have a high risk of recurrence despite 3 years of adjuvant imatinib will be randomly allocated to one of the following 2 arms in a 1:1 ratio: **A.** to further 24 months of adjuvant imatinib (i.e. the planned total duration of adjuvant imatinib is 5 years) **B.** to stop imatinib (i.e. the planned total duration of adjuvant imatinib is 3 years) The study participants will be followed up for a minimum of 10 years post-randomisation or until death.
STATISTICAL ANALYSIS	This is a superiority study regarding the main endpoint (RFS). Based on the estimates from the SSG XVIII, the survival estimates from year 1 to 5 after the randomisation are assumed to be 81.2%, 64.8%, 44.2%, 36.2% and 31.1% in the 3-year imatinib treatment arm, assuming an exponential survival function fitted to the estimates extracted from SSG XVIII. In the 5-year arm, the corresponding estimates are assumed to be 91.5%, 87.7%, 71.8%, 53.0% and 39.1%. Based on simulations using log-rank tests (2-sided significance level of 0.05), 137 patients in each treatment arm are required to achieve a power of 80%. To allow for a drop-out rate of 10%, 150 patients per group will be randomised (power 0.8, 2-sided alpha 0.05, 1:1 randomisation).
SAMPLE SIZE	300 patients to be randomised in 1:1 ratio, 150 to imatinib for further 24 months and 150 to stop imatinib
TRIAL DURATION	2 years of recruitment followed by 10 years follow up after randomization