NOVARTIS

Clinical Development & Medical Affairs

STI571, Imatinib, Gleevec

Clinical Trial Protocol CSTI571BUS282

A Phase II, non-randomized, open-label multicenter study of 5 year adjuvant imatinib mesylate (Gleevec®) in patients at significant risk for recurrence following complete resection of primary gastrointestinal stromal tumor (GIST)

Authors	[redacted]
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Table of contents

List of figures

List of tables

List of abbreviations

ACOSOG	American College of Surgeons Oncology
Group AE	adverse event
ALT	alanine aminotransferase/glutamic pyruvic transaminase/GPT
AST	aspartate aminotransferase/glutamic oxaloacetic
transaminase/GOT ANC	Absolute Neutrophils Count
AST	aspartate aminotransferase/glutamic oxaloacetic
transaminase/GOT AUC	Area Under Curve
CI	Confidence Interval
CR	Complete Response
CRF	Case Report/Record Form
CRO	Contract Research Organization
CSR	Clinical Study Report
CT (Scan)	Computer Tomography
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse
Event CYP	Cytochrome P
ESMO	European Society for Medical Oncology
EQ-5D	EuroQol EQ-5D
FAS	Full Analysis Set
FDA	Food & Drug Administration
FACT-G	Functional Assessment of Cancer Therapy-General
FPFV	First Patient First Visit
GCP	Good Clinical Practice
GI	Gastro Intestinal
GIST	Gastro Intestinal Stromal Tumor
HBcAb	Hepatitis B Core Antibody
HBsAb	Antibodies to Hepatitis B Surface Antigen
HBsAg	Hepatitis B Surface Antigen
HPFs	High Powered Fields
HR	Hazard Ratio
IA	Interim Analysis
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMS	Integrated Medical Safety
IN	Investigator Notification
IRB	Institutional Review Board
LC-MS/MS	Liquid Chromatography - tandem Mass Spectrometry
LLOQ	Lower Limit of Quantification
LPLT	Last Patient Last Treatment
LPLV	Last Patient Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
o.d.	omnia die/once a day
OS	Overall Survival

p.o.	per os/by mouth/orally
PD	Progressive Disease
PE	Physical Exam
PK	Pharmacokinetic
PPS	Per Protocol Set
PR	Partial Response
PRQs	Patient Reported Questionnaires
PSUR	Periodic Safety Update Report
qd	Quoque diem/once a day
REB	Research Ethics Board
RECIST	Response Evaluation Criteria in Solid Tumors
RFS	Recurrence-Free Survival
SAE	Serious Adverse Event
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SMC	Study Management Committee
SOP	Standard Operating Procedure
SPC	Summary Product Characteristics
SSG	Scandinavian Sarcoma Group
SST	Serum Separator
SUSAR	Suspected Unexpected Serious Adverse Reaction
TKI	Tyrosine Kinase Inhibitor
TTF	Time to Treatment Failure
TTP	Time to Progression
UNK	Unknown
ULN	Upper Limit Normal
VS	Vital Signs
WBC	White Blood Cells
WHO	World Health Organization
WOBC	Women of Child Bearing Potential
WT	Wild type

Amendment 6 (26-Jul-2016)

Amendment rationale:

The recruitment of this study has been completed (LPFV 05-01-2011) and 91 patients have been enrolled.

The primary purpose for the amendment is:

- To include hepatitis B virus testing as one of the study procedures, to identify study patients who may be at risk of hepatitis B reactivation. Reactivation of hepatitis B virus can occur in patients who are chronic carriers of this virus and are receiving a drug of the BCR-ABL TKI class such as imatinib. Some cases involving BCR-ABL TKI resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome. Patients may be tested by means of a local lab up until November 30, 2016.
- To terminate the 2 year follow-up phase of the trial. The primary objective of determining the recurrence-free survival following the complete resection of primary GIST in patients at significant risk who are treated with adjuvant imatinib for 5 years will still be evaluated. Last Patient Last Treatment occurred May 18, 2016 (all patients completed 5 years of treatment). Last Patient Last Visit date will occur December 30, 2016, this date will also serve as the study closure date.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

Changes to the protocol include:

- List of abbreviations updated
- Oncology clinical study protocol synopsis
  - Study design
  - Statistical methods and data analysis
- Section 1.3 History of Amendments
- Section 4 Study design
- Figure 4-1 Study design
- Section 6.4.2.3 Hepatitis B reactivation was added to provide information on next steps for patients tested positive for hepatitis B virus.
- Section 6.4.4 Study drug discontinuation/end of treatment
- Section 7 Visit Schedule and assessments
- Section 7-1 Study flow and visit schedule was updated to include the hepatitis B testing and remove follow-up
- Section 7.5 Post treatment follow up was removed
- Section 7.6.5.4 Hepatitis B testing was added

IRB/IEC/REB Approval

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/ IEC approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

Changes have been implemented throughout the protocol, a summary of previous amendments and history of Protocol Amendments is located in Section 1.3.

Oncology clinical study protocol synopsis

Investigational drug	STI571, Imatinib mesylate (Gleevec)
Protocol no.	CSTI571BUS282
Study phase	II
Study title	A Phase II, Non-Randomized, Open-Label Multicenter Study of 5 year Adjuvant Imatinib Mesylate (Gleevec®) in Patients at Significant Risk for Recurrence Following Complete Resection of Primary Gastrointestinal Stromal Tumor (GIST)
Background	Gastrointestinal stromal tumors (GIST) are mesenchymal neoplasms that are thought to arise from the interstitial cells of Cajal or their mesenchymal stem cell precursor. GIST is the most common sarcoma of the gastrointestinal tract. It can arise anywhere along the gastrointestinal tract, but it most commonly originates in the stomach or small intestine. The tumor occurs slightly more often in males and the median age at diagnosis is 58. GISTs are positive by immunohistochemistry for the CD117 antigen, an epitope of the KIT receptor tyrosine kinase (TK), in over 95% of cases (Corless and Heinrich 2008). Several studies have reported a small subgroup of KIT-negative GISTs (Tosoni 2004, Corless 2008). Activating mutations of KIT are the characteristic pathogenic feature of these tumors, being present in 80% to 85% of GISTs (Corless and Heinrich 2008). Among the GISTs without KIT mutations, a subgroup has mutations in the platelet-derived growth factor receptor α (PDGFRα) gene. The management of GIST has evolved very rapidly since its molecular pathogenesis was identified. The standard of care for patients with resectable primary GIST in the absence of metastasis is surgical resection. The risk of recurrence after resection of a primary GIST is a function of tumor size, mitotic rate, and tumor location (Ng 1992, DeMatteo 2000, Martin 2006, DeMatteo 2008). Patients with large (≥10 cm) tumors have a 5 year recurrence-free survival of about 45%. Patients with a mitotic rate of ≥ 5 mitoses/50 high power fields (HPF's) have a 5 year recurrence-free survival of 20%. Patients with small bowel tumors tend to do worse than those with gastric tumors. In an MDACC report, after long-term follow- up of all patients, only 10% were free of disease (Ng et al 1992). Recurrence after tumor rupture is not surprising but recurrence may also follow what appears to be complete resection, as a result of unsuspected microscopic tumor dissemination. The peritoneal surface and the liver are the predominant sites of initial recurrence. Conventional cytotoxic chemotherapy is ineffective for metastatic GIST, as response rates are only about 5% (DeMatteo et al 2002). Imatinib mesylate is the first-line therapy for metastatic or unresectable GIST with a median progression free survival reported between 18 months and 24 months in Phase III and II studies respectively and a median survival of 57 months (Verweij 2004, Blanke 2008a, Blanke 2008b). Imatinib mesylate achieves a partial response or stable disease in approximately 85% of patients with metastatic GIST (Demetri et al 2002). Nevertheless, the complete response rate is only approximately 5%. In about half of patients who acquire resistance to imatinib mesylate, the mechanism is due to the development of a second mutation in *KIT* (Heinrich 2003, Debiec-Rychter 2005, Heinrich 2006). The significant clinical effect of imatinib mesylate in the treatment of metastatic and/or unresectable GIST provided the rationale for investigating the effect of adjuvant imatinib mesylate in delaying or preventing recurrence following primary surgery in this disease with a high potential for recurrence. Currently, several trials are evaluating the benefits of adjuvant imatinib mesylate following the resection of primary GIST. A Phase II study (ACOSOG Z9000) accrued 106 evaluable patients at high risk of recurrent GIST after surgical resection. High risk was defined as tumor size ≥10 cm, intraperitoneal tumor rupture/bleeding, or primary tumor with < 5 peritoneal metastases. Patients were given 48 weeks of open-label imatinib mesylate 400 mg/day after surgical resection and were followed for recurrence and survival. The treatment was tolerated well (DeMatteo et al 2005). There were no grade 4 or grade 5 toxicities. There were 19 (17%) patients who had grade 3 toxicity, the most common being neutropenia (2%), dermatitis (2%), or increased ALT (2%). The most frequent toxicities of any grade were edema (55%), fatigue (43%), nausea (42%), diarrhea (42%), and dermatitis (27%). Overall, 83% of patients completed their prescribed therapy. After one, two and three years of follow up, progression free survival was 94%, 73% and 61% respectively. Overall survival after one year was 99%,

	and after two and three years overall survival was 97% (DeMatteo et al 2008b). A large randomized, double-blind, Phase III study (ACOSOG Z9001) compared the use of imatinib mesylate 400 mg/day for one year versus placebo in patients who had undergone primary surgical resection for cure of a KIT (CD117) positive GIST were recently reported (DeMatteo et al 2009). A total of 713 patients with primary GIST ≥3 cm and expressing KIT, who underwent complete gross resection, were randomly assigned to receive imatinib mesylate 400 mg daily or placebo for one year starting within 84 days of surgery. Relapse free survival at one year was 98% and 83% respectively (p<0.0001). Following this analysis the study was unblinded and patients on placebo were offered one year of imatinib. The Scandinavian Sarcoma Group (SSG) study XVIII is a randomized, open-label, Phase III study of short (12 months) versus long (36 months) duration of adjuvant treatment of imatinib 400 mg/day following resection of high risk primary or metastatic GIST. High risk for this trial is defined as: tumor > 10 cm, a mitotic rate of > 10/50 HPF's, tumor > 5 cm and a mitotic rate of > 5/50 HPF's fields or tumor rupture with spillage into the abdominal cavity. The primary endpoint is recurrence-free survival within the first five years following diagnosis and treatment with adjuvant therapy. This study closed enrollment on October 20, 2008. The EORTC study [62024] is a randomized, open-label study comparing 2 years of adjuvant imatinib 400 mg/day with no treatment following resection of intermediate or high risk GIST. High risk for this trial is defined as: tumor > 10 cm, a mitotic rate of >10/50 HPF's, tumor > 5 cm and a mitotic rate of > 5/50 HPF's fields. Intermediate risk for this trial is defined as: tumor < 5 cm and a mitotic rate of 6-10/50 HPF's fields or tumor 5-10 cm and a mitotic rate of < 5/50 HPF's. The primary endpoint is overall survival. This study closed enrollment in late 2008. From the ACOSOG Z9001 study, it is clear that some GIST patients at high risk of recurrence develop recurrent tumor after discontinuation of 1 year adjuvant imatinib mesylate. This is consistent with the finding that patients with stable metastatic GIST on imatinib mesylate rapidly developed disease progression when randomized to stop the drug (Le Cesne et al 2005). Thus, after it induces initial tumor death, imatinib mesylate is generally a static agent and not curative, at least in metastatic GIST. It is now widely accepted and stated in the American and European Consensus GIST Guidelines that imatinib mesylate should be continued indefinitely in metastatic GIST, unless tumor progression or drug intolerance occurs (Demetri 2004, Blay 2005). Since the dose (400 mg/day) of imatinib mesylate has already been established for most patients metastatic disease and has proven to be safe in the adjuvant Z9000 and Z9001 trials, the remaining critical questions for adjuvant imatinib mesylate use in GIST are treatment duration and patient selection. The duration of adjuvant therapy should first be established for patients at the highest risk of recurrence. This subset is most likely to benefit from long-term treatment and therefore potential toxicities can be justified. This trial will evaluate the benefit of long-term use of a targeted agent, imatinib mesylate. Determining the recurrence-free survival in patients at significant risk for recurrence will enable the planning of Phase III trials using long-term adjuvant imatinib mesylate therapy. The findings will have implications for the use of targeted agents in other diseases. The pharmacogenomic studies will advance our understanding of patient characteristics and optimize our use of imatinib mesylate in GIST.
Purpose/rationale	Imatinib is likely to be the dominant agent used in the treatment of GIST for at least the next 5 years. While other agents have been or are being tested, none has both the proven efficacy and low toxicity profile of imatinib. The rationale for adjuvant imatinib in patients at significant risk of tumor recurrence after surgical resection is to prevent or at a minimum delay recurrence. The optimal length of adjuvant treatment in GIST has yet to be determined. It is likely that data will not be available from the European trials until 2010 or beyond. Furthermore, regardless of the outcomes of these trials, a question remains whether 5 years of imatinib is better than 1, 2, or 3 years of treatment. Following the December 2008 approval of imatinib for adjuvant therapy in the United States, it would be difficult to randomize patients to different durations of imatinib therapy. Therefore we will explore the utility of five year adjuvant imatinib therapy to delay the time to recurrence, which may translate into an overall survival advantage. Long term treatment with adjuvant imatinib in GIST may emulate long-term hormonal therapy in breast cancer.

Objectives	Primary objective ● To determine recurrence-free survival following the complete resection of significant risk primary GIST in patients who are treated with adjuvant imatinib for 5 years. Secondary objectives ● To determine overall survival***(The OS assessment period will include 5 years of adjuvant imatinib therapy and exclude the 2 year follow-up phase of the trial) .*** ● To assess the safety and tolerability of 5 years of adjuvant imatinib therapy. Exploratory objectives ● To explore the effect of chronic exposure to imatinib on pharmacokinetics through trough level at steady state for those patients in which data is available. ● To explore any relationship between KIT and PDGFR mutation status of primary tumor and recurrent tumors and related outcome. ● To explore pharmacogenomics of tumor tissue to advance our understanding of patient characteristics and optimize our use of imatinib mesylate in GIST. ● Explore quality of life assessment tool FACT-G in adjuvant GIST.
Endpoints (efficacy, safety)	Recurrence-free survival (RFS), defined as the time from the date of first dose of study drug to the date of the first documented disease recurrence or death due to any *cause*, is the primary efficacy variable. The recurrence of disease will be assessed by either a CT scan or MRI. The same method and the technique will be used throughout the study. The Full Analysis Set (FAS) will be used for the analysis of the primary efficacy variable. Overall survival defined as the time from the date of the first dose of study drug to the date of death from any cause **(The OS assessment period will include 5 years of adjuvant imatinib therapy and exclude the 2 year follow-up phase of the trial),** will be summarized and graphed using the product-limit (Kaplan-Meier) method. Patients who drop out will be treated as censored observations. The estimates of the 25th, median, 75th percentiles for the time of death and their 95% confidence intervals will be provided, if applicable.
Study design	This is a Phase II, non-randomized, open-label, multi-center study conducted only in the US. The primary endpoint is to evaluate the use of long term adjuvant imatinib mesylate in patients at significant risk for recurrence following complete resection of primary GIST. A total of 85 adult patients, ≥ 18 years of age, will be enrolled and exposed to a total of 5 years of imatinib therapy. Patients with a primary non-metastatic GIST will undergo R0 surgical resection of all gross disease. The patient will be deemed as having a significant risk of recurrence based on pathologic factors. Significant risk for this trial is defined as EITHER: ● Primary GIST (any site): ≥ 2 cm **and** a mitotic rate of ≥ 5/50 HPF's ● Non-gastric Primary GIST: ≥ 5 cm Primary tumor tissue will be submitted for central pathologic review prospectively to ensure the diagnosis of GIST. The inclusion of R1 resections will be reviewed on a case by case basis by the Study Management Committee. Imatinib will be administered 400 mg orally once a day (QD) for a total of 5 years. A physical exam will be performed at screening, baseline, weeks 2, 4, 16 and every 4 months for the first 3 years and every 6 months thereafter. Blood work will be required at screening, end of treatment and in the event of recurrence. Throughout the duration of the treatment period blood work should be performed per standard of care and at the discretion of the treating physician. Radiological assessments of the abdomen and pelvis will be performed at baseline and every 4 months for the first 3 years. Upon completion of three years on study, the radiological assessments (abdomen and pelvis) will be performed every 6 months thereafter. Radiological assessments of the chest will be performed at baseline and as clinically indicated. The same method and technique will be used thought the study. When there is radiologic evidence of recurrence, pathologic confirmation should be obtained whenever possible. Recurrence diagnosed without pathologic confirmation requires review by the study committee. When there is indeterminate evidence of recurrence based on radiologic studies and pathologic confirmation is not obtained, repeat cross-sectional imaging should be obtained in a minimum of 4 weeks. Further evaluation will be recommended by the Study Management Committee.

Population	The target population includes adult patients with primary GIST who have undergone surgical removal of all gross disease and have a significant risk for recurrence defined as EITHER: ● Primary GIST (any site): ≥ 2 cm **and** a mitotic rate of ≥ 5/50 HPF's ● Non-gastric Primary GIST: ≥ 5 cm A total of 85 patients 18 years of age or older will be enrolled and will have received no prior treatment for GIST with the exception of prior treatment with adjuvant imatinib ≤ 8 weeks after gross surgical resection
Inclusion/exclusion criteria	Inclusion criteria 1. Patients ≥ 18 years of age. 2. Patient must have a histologic diagnosis of primary GIST. 3. The tumor must express KIT (CD117) protein by immunohistochemistry performed by central pathology. 4. Patient must be at significant risk of tumor recurrence as defined by either: ● Primary GIST (any site): ≥ 2 cm **and** a mitotic rate of ≥ 5/50 HPF's ● Non-gastric primary GIST: ≥ 5cm 5. Patient must have undergone complete gross resection of a primary GIST within 12 weeks prior to first dose of imatinib study drug. The inclusion of R1 resections will be reviewed on a case by case basis by the Study Management Committee. 6. Patient must have no evidence of metastatic GIST on either 1) a post-operative CT of the abdomen and pelvis with intravenous and oral contrast or 2) MRI of the abdomen and pelvis with intravenous contrast. CT or MRI must be performed within 8 weeks prior to first dose of imatinib study drug. 7. Performance status 0 or 1 (ECOG) 8. Patient must have the following post-operative laboratory values confirmed within 14 days prior to first dose of imatinib study drug: ● total bilirubin < 1.5 x ULN ● ALT and AST < 2.5 x ULN ● creatinine < 1.5 x ULN ● ANC > 1.5 x 10^9/L ● platelets > 100 x 10^9/L 9. If patient is a cancer survivor, **ALL** of the following criteria apply: ● Patient has undergone potentially curative therapy for all prior malignancies. ● No evidence of any prior malignancies for at least 3 years with no evidence of recurrence (except for effectively treated basal cell or squamous carcinoma of the skin, carcinoma in-situ of the cervix that has been effectively treated by surgery alone, or lobular carcinoma in-situ of the ipsilateral or contralateral breast treated by surgery alone). ● Patient is deemed by their treating physician to be at low risk for recurrence from prior malignancies. 10. Female patients of childbearing potential must have negative pregnancy test within 7 days before initiation of study drug dosing. Postmenopausal women must be amenorrheic for at least 12 months to be considered of non-childbearing potential. Female patients of reproductive potential must agree to employ an effective barrier method of birth control throughout the study and for up to 7 days following discontinuation of study drug. 11. Written, voluntary informed consent. Exclusion criteria 1. Patient has metastatic GIST to the peritoneum, liver, lymph node, or other sites or recurrent GIST. 2. Prior treatment for GIST with the exception of prior treatment with adjuvant imatinib lasting ≤ 8 weeks following gross surgical resection. 3. Patient has received any other investigational agents within 28 days of first day of study drug dosing. 4. Patient with Grade III/IV cardiac problems as defined by the New York Heart Association Criteria. (i.e., congestive heart failure, myocardial infarction within 6 months of study) 5. Patients with severe and/or uncontrolled concurrent medical disease that in the opinion of the investigator could cause unacceptable safety risk or compromise compliance with the protocol (i.e., uncontrolled diabetes, chronic renal disease, chronic liver disease, or active uncontrolled infection).

	7. Patient receiving concurrent treatment with warfarin (acceptable alternative: low- molecular weight heparin). 8. Patient with any significant history of non-compliance to medical regimens or with inability to grant reliable informed consent.
Patient numbering	Study participants will be assigned patient numbers after baseline evaluations are complete and the entry criteria are met.
Investigational and control drugs	A Phase II, Non Randomized, Open-Label Imatinib Mesylate STI571, Imatinib Mesylate, Gleevec® = study drug Supplied as 100 mg and 400 mg tablets
Dose, regimen, treatment cycle	Imatinib 400 mg once a day for 5 years. Refer to Section 6.4.2.1 for dose modifications.
Supply, preparation, and administration	Imatinib will be labeled as Gleevec® (imatinib mesylate) and supplied by Novartis as 100 mg and 400 mg tablets. Not dosed by weight or body surface area. Patients will take imatinb orally with food and a large glass of water in the morning. The storage conditions for study drug will be described on the medication label.
Visit schedule and assessments	Refer to Section 7 for the evaluation schedule.
Efficacy assessment(s)	Tumor evaluation by CT or MRI (abdomen and pelvis) will be performed at baseline, permitted within 8 weeks prior to the first dose of imatinib study drug and every 4 months for the first 3 years. Upon completion of three years on study, the tumor evaluation by CT or MRI (abdomen and pelvis) will be performed every 6 months thereafter. Tumor evaluation of the chest by CT, MRI or X-Ray will be performed at baseline and as clinically indicated. The same method and technique will be used thought the study. When there is radiologic evidence of recurrence, pathologic confirmation should be obtained whenever possible. When there is indeterminate evidence of recurrence based on radiologic studies and pathologic confirmation is not obtained, repeat cross-sectional imaging should be obtained. Refer to Table 7-1 and Section 7.5.
Special safety assessment(s)	SAE reports, AE reports, laboratory profiles (hematology/chemistry), physical examinations and ECOG Performance Status.
Patient reported outcomes	Quality of life information will be collected using the Functional Assessment of Cancer Therapy-General (FACT-G). Refer to Section 7.9.
Pharmacokinetics	The pharmacokinetics of imatinib will be studied over the 5 year study period to address whether increased imatinib clearance after chronic exposure is a mechanism for the development of recurrent disease. Conversely, impaired clearance may correlate with imatinib toxicity. Therefore, imatinib trough levels will be tested at the conclusion of month 1 (day 29), month 4, month 12, month 24, month 36, month 48 and month 60. Refer to Section 7.10.
Biomarker assessments	Central pathologic review of formalin-fixed, paraffin-embedded tissue from the tumor is required for this study. The diagnosis of GIST and the presence of KIT protein expression will be assessed. Also, mitotic index and morphology (spindle cell or epithelioid) will be determined. Sites will be notified of the diagnosis. Only patients with confirmed diagnosis of GIST and KIT staining by immunohistochemistry will enroll and start imatinib therapy. When possible, tumor tissue samples will also be collected in the event of recurrence. Refer to Section 7.11.
Exploratory Biomarker pharmacodynamic studies involving tumor samples	Phenotypic and genetic analysis of the primary tumors will be performed and correlated to outcome. Genetic analysis of the primary tumors will be performed to identify *KIT* and *PDGFRA* mutations as described previously (Heinrich et al 2003). When possible, tumor tissue samples will also be collected in the event of recurrence. Refer to Section 7.11.2.
DSMB	N/A
Statistical methods and data analysis	It is planned that the data from all centers that participate in this protocol will be used, so that an adequate number of patients will be available for analysis. Unless otherwise specified, all statistical tests will be performed against a two-sided alternative hypothesis, employing a significance level of 0.05. The final analysis will be performed after the last

	enrolled patient has been treated with imatinib for 5 years. Full Analysis Set (FAS): consists of all patients who received at least one dose of study drug. The FAS will be the primary set for efficacy analyses. Safety Set (SS): consists of all patients who received at least one dose of study drug and had at least one post-baseline safety assessment. Per Protocol Set (PPS): consists of all FAS patients without a major protocol violation, who are evaluable for efficacy and who have either completed a minimum of 4.5 years of treatment or who have discontinued due to disease recurrence or have died. The PPS will be identified prior to database lock. The set for the pharmacokinetic analyses will include all patients in the FAS with a sufficient number of evaluable blood samples. The primary objective of the study is to determine recurrence-free survival following the complete resection of significant risk primary GIST in patients who are treated with adjuvant imatinib for 5 years. Recurrence-free survival (RFS) defined as the time from the date of first dose of study drug to the date of the first documented disease recurrence or death due to any cause**,** is the primary efficacy variable. The recurrence of disease will be assessed by either a CT scan or MRI. The FAS will be used for the analysis of the primary efficacy variable. The primary efficacy variable will be summarized and graphed using the product-limit (Kaplan-Meier) method. Patients who drop out will be treated as censored observations. The estimates of the 25th, median, 75th percentiles for the time first recurrence or death and their 95% confidence intervals will be provided, if applicable. Patients who discontinue from the study before completing ≥ 4.5 years of study treatment and do not have documented disease recurrence or death will be censored at the last assessment. A secondary objective of the study is to evaluate overall survival. Overall survival, defined as the time from the date of the first dose of study drug to the date of death from any cause ***(The OS assessment period will include 5 years of adjuvant imatinib therapy and exclude the 2 year follow-up phase of the trial),*** will be summarized and graphed using the product-limit (Kaplan-Meier) method. Patients who drop out will be treated as censored observations. The estimates of the 25th, median, 75th percentiles for the time of death and their 95% confidence intervals will be provided, if applicable. Overall survival will be analyzed in both the FAS and PPS. Interim analyses for efficacy will be performed after all enrolled patients have completed 1 and 3 years. No decision to terminate the study early or alter the sample size will be made based on the results of these interim efficacy analyses. The sample size of the study is based on the assumption that the 5-year RFS in this study will be at least 80%. To test the null hypothesis of 65% RFS survival at 5 years (estimated from ACOSOZ9001 Study) against the alternative hypothesis of 80% RFS survival with a one-sided significance level of 5% and 80% power, 51 evaluable patients are required. To allow for a 40% drop-out rate, 85 patients will be enrolled into the study. The sample size is calculated using Southwest Oncology Group One Sample Survival calculator (swogstat.org/stat/public/one_survival.htm). The sample size formula of this calculator is based on an approximation described in chapter 3 of Statistical Models and Methods for Lifetime Data by J. Lawless, John Wiley and Sons, 1982.

1 Background

1.1 Overview of gastrointestinal stromal tumors (GIST)

Gastrointestinal stromal tumors (GIST) are mesenchymal neoplasms that are thought to arise from the interstitial cells of Cajal or their mesenchymal stem cell precursor. GIST is the most common sarcoma of the gastrointestinal tract. It can arise anywhere along the gastrointestinal tract, but it most commonly originates in the stomach or small intestine. The tumor occurs slightly more often in males and the median age at diagnosis is 58. GISTs are positive by immunohistochemistry for the CD117 antigen, an epitope of the KIT receptor tyrosine kinase (TK), in over 95% of cases (Corless and Heinrich 2008). Several studies have reported a small subgroup of KIT-negative GISTs (Tosoni 2004, Corless 2008). Activating mutations of KIT are the characteristic pathogenic feature of these tumors, being present in 80% to 85% of GISTs (Corless and Heinrich 2008). Among the GISTs without KIT mutations, a subgroup has mutations in the platelet-derived growth factor receptor α (PDGFRα) gene.

The management of GIST has evolved very rapidly since its molecular pathogenesis was identified. The standard of care for patients with resectable primary GIST in the absence of metastasis is surgical resection. The risk of recurrence after resection of a primary GIST is a function of tumor size, mitotic rate, and tumor location (Ng 1992, DeMatteo 2000, Martin 2006, DeMatteo 2008a). Patients with large (≥10 cm) tumors have a 5 year recurrence-free survival of about 45%. Patients with a mitotic rate of ≥ 5 mitoses/50 high power fields (HPF's) have a 5 year recurrence-free survival of 20%. Patients with small bowel tumors tend to do worse than those with gastric tumors. In an MDACC report, after long-term follow-up of all patients, only 10% were free of disease (Ng et al 1992). Recurrence after tumor rupture is not surprising but recurrence may also follow what appears to be complete resection, as a result of unsuspected microscopic tumor dissemination. The peritoneal surface and the liver are the predominant sites of initial recurrence. Conventional cytotoxic chemotherapy is ineffective for metastatic GIST, as response rates are only about 5% (DeMatteo et al 2002).

Imatinib mesylate is the first-line therapy for metastatic or unresectable GIST with a median progression free survival reported between 18 months and 24 months in Phase III and II studies respectively and a median survival of 57 months (Verweij 2004, Blanke 2008a, Blanke 2008b). Imatinib mesylate achieves a partial response or stable disease in approximately 85% of patients with metastatic GIST (Demetri et al 2002). Nevertheless, the complete response rate is only approximately 5%. In about half of patients who acquire resistance to imatinib mesylate, the mechanism is due to the development of a second mutation in *KIT* (Heinrich 2003, Debiec-Rychter 2005, Heinrich 2006).

The significant clinical effect of imatinib mesylate in the treatment of metastatic and/or unresectable GIST provided the rationale for investigating the effect of adjuvant imatinib mesylate in delaying or preventing recurrence following primary surgery in this disease with a high potential for recurrence. Currently, several trials are evaluating the benefits of adjuvant imatinib mesylate following the resection of primary GIST. A Phase II study (ACOSOG Z9000) accrued 106 evaluable patients at high risk of recurrent GIST after surgical resection. High risk was defined as tumor size ≥10 cm, intraperitoneal tumor rupture/bleeding, or

primary tumor with < 5 peritoneal metastases. Patients were given 48 weeks of open-label imatinib mesylate 400 mg/day after surgical resection and were followed for recurrence and survival. The treatment was tolerated well (DeMatteo et al 2005). There were no grade 4 or grade 5 toxicities. There were 19 (17%) patients who had grade 3 toxicity, the most common being neutropenia (2%), dermatitis (2%), or increased ALT (2%). The most frequent toxicities of any grade were edema (55%), fatigue (43%), nausea (42%), diarrhea (42%), and dermatitis (27%). Overall, 83% of patients completed their prescribed therapy. After one, two and three years of follow up, progression free survival was 94%, 73% and 61% respectively. Overall survival after one year was 99%, and after two and three years overall survival was 97% (DeMatteo et al 2008b).

A large randomized, double-blind, Phase III study (ACOSOG Z9001) compared the use of imatinib mesylate 400 mg/day for one year versus placebo in patients who had undergone primary surgical resection for cure of a KIT (CD117) positive GIST were recently reported (DeMatteo et al 2009). A total of 713 patients with primary GIST ≥3 cm and expressing KIT, who underwent complete gross resection, were randomly assigned to receive imatinib mesylate 400 mg daily or placebo for one year starting within 84 days of surgery. Relapse free survival at one year was 98% and 83% respectively ($p<0.0001$). Following this analysis the study was unblinded and patients on placebo were offered one year of imatinib.

The Scandinavian Sarcoma Group (SSG) study XVIII is a randomized, open-label, Phase III study of short (12 months) versus long (36 months) duration of adjuvant treatment of imatinib 400 mg/day following resection of high risk primary or metastatic GIST. High risk for this trial is defined as: tumor > 10 cm, a mitotic rate of > 10/50 HPF's, tumor > 5 cm and a mitotic rate of > 5/50 HPF's fields or tumor rupture with spillage into the abdominal cavity. The primary endpoint is recurrence-free survival within the first five years following diagnosis and treatment with adjuvant therapy. This study closed enrollment on October 20, 2008.

The EORTC study [62024] is a randomized, open-label study comparing 2 years of adjuvant imatinib 400 mg/day with no treatment following resection of intermediate or high risk GIST. High risk for this trial is defined as: tumor >10 cm, a mitotic rate of > 10/50 HPF's, tumor > 5 cm and a mitotic rate of > 5/50 HPF's fields. Intermediate risk for this trial is defined as: tumor < 5 cm and a mitotic rate of 6-10/50 HPF's fields or tumor 5-10 cm and a mitotic rate of < 5/50 HPF's. The primary endpoint is overall survival. This study closed enrollment in late 2008.

From the ACOSOG Z9001 study, it is clear that some GIST patients at high risk of recurrence develop recurrent tumor after discontinuation of 1 year adjuvant imatinib mesylate. This is consistent with the finding that patients with stable metastatic GIST on imatinib mesylate rapidly developed disease progression when randomized to stop the drug (Le Cesne et al 2005). Thus, after it induces initial tumor death, imatinib mesylate is generally a static agent and not curative, at least in metastatic GIST. It is now widely accepted and stated in the American and European Consensus GIST Guidelines that imatinib mesylate should be continued indefinitely in metastatic GIST, unless tumor progression or drug intolerance occurs (Demetri 2004, Blay 2005).

Since the dose (400 mg/day) of imatinib mesylate has already been established for most patients with metastatic disease and has proven to be safe in the adjuvant Z9000 and Z9001

trials, the remaining critical questions for adjuvant imatinib mesylate use in GIST are treatment duration and patient selection. The duration of adjuvant therapy should first be established for patients at the highest risk of recurrence. This subset is most likely to benefit from long-term treatment and therefore potential toxicities can be justified.

This trial will evaluate the benefit of long-term use of a targeted agent, imatinib mesylate. Determining the recurrence-free survival in patients at significant risk for recurrence will enable the planning of Phase III trials using long-term adjuvant imatinib mesylate therapy. The findings will have implications for the use of targeted agents in other diseases. The pharmacogenomic studies will advance our understanding of patient characteristics and optimize our use of imatinib mesylate in GIST.

1.2 Overview of imatinib mesylate

Imatinib (Glivec®/Gleevec®, imatinib mesylate, formerly STI571) is a small molecule protein tyrosine kinase inhibitor. It inhibits the activity of several tyrosine kinases: c -KIT, the receptor for stem cell factor coded by the c-Kit proto-oncogene, the platelet-derived growth factor receptors α and β (PDGFRα and PDGFRβ), the Abl family of non-receptor tyrosine kinases consisting of Abl and Arg (the Abl-related gene), and c-Fms, the receptor for macrophage-stimulating factor.

Imatinib received worldwide approval for the treatment of adult patients with KIT (CD117) positive unresectable and/or metastatic malignant GIST as it significantly changed the prognosis for this life threatening disease by prolonging the overall survival (Section 1.1 and [Summary of Product Characteristics SPC]). Imatinib was approved by the US FDA in December 2008 for the adjuvant treatment of adult patients following complete surgical removal of Kit-positive gastrointestinal stromal tumors (GIST). The majority of adverse events in patients with GIST treated with imatinib in both Novartis sponsored and non-sponsored studies were of mild to moderate grade. The most frequently reported drug-related adverse events were nausea, vomiting, edema, and muscle cramps. Edema was most frequently periorbital or in lower limbs and was managed with diuretics, other supportive measures, or by reducing the dose of imatinib. The frequency of severe edema was 2-5%. A variety of adverse events were observed representing local or general fluid retention including pleural effusion, ascites, pulmonary edema and rapid weight gain with or without superficial edema. Treatment with imatinib has been associated with neutropenia or thrombocytopenia. Treatment was discontinued permanently because of liver laboratory abnormalities in less than 0.5% of patients [SPC].

Preliminary evidence may suggest that in metastatic disease there is a correlation between imatinib plasma exposure and clinical outcome parameters (von Mehren et al 2008). However, there are no such data between exposure and clinical outcome in the adjuvant setting.

1.3 History of Amendments

Amendment 5

The purpose of Amendment 5 is to align CT/MRI scans and patient visits. The amendment will reduce the number of patient visits from every 4 months to every 6 months after the patient has completed three years on study.

Amendment 4

The purpose of Amendment 4 is to resolve patient radiation exposure concerns. The amendment will reduce the number of CT/ MRI scans of the Abdomen and Pelvis from every 4 months to every 6 months after the patient has completed three years on study.

Amendment 3

The purpose of Amendment 3 is to change the sample size to 85 patients enrolled and discontinue PK assessments after August 31, 2011. Editorial changes have been made to clarify relevant sections.

Amendment 2

The purpose of Amendment 2 is to provide 400 mg imatinib tablets, reduce the follow up period, reduce the number of PK assessments, reduce the number of required laboratory assessments, remove reference to a visit at 8 weeks, remove the EQ-5D quality of life assessment tool, remove reporting requirements in the event of a pregnant partner. Editorial changes have been made to clarify particular sections.

Amendment 1

The purpose of amendment 1 is to clarify CT/MRI procedures at baseline, the scope and review procedures of Study Management Committee, modify the supply of study drug, and editorial changes have been made to clarify particular sections.

2 Study rationale/purpose

Imatinib is likely to be the dominant agent used in the treatment of GIST for at least the next 5 years. While other agents have been or are being tested, none has both the proven efficacy and low toxicity profile of imatinib. The rationale for adjuvant imatinib in patients at significant risk of tumor recurrence after surgical resection is to prevent or at a minimum delay recurrence. The optimal length of adjuvant treatment in GIST has yet to be determined. It is likely that data will not be available from the European trials until 2010 or beyond. Furthermore, regardless of the outcomes of these trials, a question remains whether 5 years of imatinib is better than 1, 2, or 3 years of treatment.

Following the December 2008 approval of imatinib for adjuvant therapy in the United States, it would be difficult to randomize patients to different durations of imatinib therapy. Therefore we will explore the utility of five year adjuvant imatinib therapy to delay the time

to recurrence, which may translate into an overall survival advantage. Long term treatment with adjuvant Imatinib in GIST may emulate long-term hormonal therapy in breast cancer.

3 Objectives

3.1 Primary objective

To determine recurrence-free survival following the complete resection of significant risk primary GIST in patients who are treated with adjuvant imatinib for 5 years.

3.2 Secondary objectives

- To determine overall survival ***(The OS assessment period will include 5 years of adjuvant imatinib therapy and exclude the 2 year follow-up phase of the trial).***
- To assess the safety and tolerability of 5 years of adjuvant imatinib therapy.

3.3 Exploratory objectives

- To explore the effect of chronic exposure to imatinib on pharmacokinetics through trough level at steady state for those patients in which data is available.
- To explore any relationship between KIT and PDGFR mutation status of primary tumor and recurrent tumors and related outcome.
- To explore pharmacogenomics of tumor tissue to advance our understanding of patient characteristics and optimize our use of imatinib mesylate in GIST.
- Explore quality of life assessment tool FACT-G in adjuvant GIST.

4 Study design

This is a Phase II, non-randomized, open-label, multi-center study conducted only in the US. The primary endpoint is to evaluate the use of long term adjuvant imatinib mesylate in patients at significant risk for recurrence following complete resection of primary GIST. A total of 85 adult patients, ≥ 18 years of age, will be enrolled and exposed to a total of 5 years of imatinib therapy.

Patients with a primary non-metastatic GIST will undergo R0 surgical resection of all gross disease. The patient will be deemed as having a significant risk of recurrence based on pathologic factors. Significant risk for this trial is defined as EITHER:

- Primary GIST (any site): ≥ 2 cm **and** a mitotic rate of ≥ 5/50 HPF's
- Non-gastric Primary GIST: ≥ 5 cm

Primary tumor tissue will be submitted for central pathologic review prospectively to ensure the diagnosis of GIST. The inclusion of R1 resections will be reviewed on a case by case basis by the Study Management Committee.

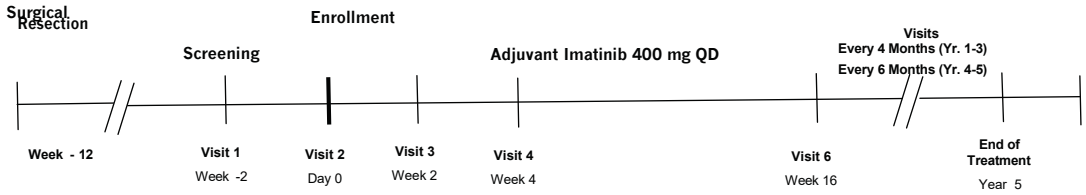
Patients must start imatinib study drug within 12 weeks of surgery. With the exception of radiological assessments, all screening assessments must be completed between baseline and day -14. Radiological assessments are permitted within 8 weeks prior to the first dose of imatinib study drug. Up to 8 weeks of prior treatment with adjuvant imatinib is permitted.

Imatinib will be administered 400 mg orally once a day (QD) on a continuous schedule for a total of 5 years. A physical exam will be performed at screening, baseline, weeks 2, 4, 16 and every 4 months for the first 3 years and every 6 months thereafter. Blood work will be required at screening, end of treatment and in the event of recurrence. Throughout the duration of the treatment period blood work should be performed per standard of care and at the discretion of the treating physician. Radiological assessments of the abdomen and pelvis will be performed at baseline and every 4 months for the first 3 years. Upon completion of three years on study, the radiological assessments (abdomen and pelvis) will be performed every 6 months thereafter. Radiological assessments of the chest will be performed at baseline and as clinically indicated. The same technique and method will be used throughout the study.

When there is radiologic evidence of recurrence, pathologic confirmation should be obtained whenever possible. Recurrence diagnosed without pathologic confirmation requires review by the Study Management Committee. When there is indeterminate evidence of recurrence based on radiologic studies and pathologic confirmation is not obtained, repeat cross -sectional imaging should be obtained in a minimum of 4 weeks. Further evaluation will be recommended by the Study Management Committee.

Patients with confirmed progression will be discontinued from study treatment.

Figure 4-1 Study design



4.1 Study Management Committee

In order to monitor study conduct, a Study Management Committee (SMC) will evaluate recommendations regarding safety and efficacy and provide decisions on study conduct. The SMC will provide a written response indicating the proposed actions, i.e., accept, reject or modify the recommendations. The SMC will consider patient cases where further discussions of patient management are required. The SMC will consist of five members all of whom are GIST specialists. In addition, this committee will include a sponsor representative(s) who will facilitate communication between the SMC and the sponsor.

The SMC will also be responsible for the general oversight of the study and will advise and contribute to publications. In addition, the SMC will be responsible for reviewing the inclusion of patients with R1 margins, reviewing disease recurrence diagnosed without pathologic confirmation, protocol amendments and for the final analysis of the data and clinical study report.

4.1.1 Review of the inclusion of R1 margins and recurrence without pathologic confirmation

The SMC will review the following cases:

- the inclusion of patients with R1 margins
- recurrence without pathologic confirmation

For each case, the study center will submit the request by fax or email to Novartis. The request will consist of relevant surgical, pathology and radiology reports that have been blinded of all patient identifiers and Case Report Form (CRF) pages. Drug Administration Record pages and Concomitant Medication/Therapies pages should be provided. Comments CRF pages if the investigator would like to provide additional information should also be sent. Accompanying the CRF pages will be a cover page with center and patient identification numbers and the request. Novartis will summarize the case and forward the information to all SMC members with the center identification blinded.

The SMC members and relevant Novartis representatives will communicate as needed using email and teleconferences. The SMC will review and approve the requests. At least 3 out of 5 members need to be available and the final decision will be based on a consensus. Whenever appropriate, the case request may also be discussed with the investigator who issued it.

The decision to approve or not approve the request will be forwarded by Novartis to the study center, within 14 days, whenever possible.

The requests coming from any center where one of the SMC members is an investigator will be handled similarly, with the exception that the investigator concerned will not be involved in the review/approval process.

4.1.2 Review of safety and efficacy analyses

The SMC will review the planned interim analyses results. Interim analyses will be conducted after all enrolled patients have completed 1 and 3 years of treatment.

5 Population

The target population includes adult patients with primary GIST who have undergone surgical removal of all gross disease and have a significant risk for recurrence defined as EITHER:

- Primary GIST (any site): ≥ 2 cm **and** a mitotic rate of ≥ 5/50 HPF's
- Non-gastric primary GIST: ≥ 5 cm

A total of 85 adult patients 18 years of age or older will be enrolled.

Inclusion/exclusion criteria

The investigator or his/her designee must ensure that all patients who meet the following inclusion and exclusion criteria are offered enrollment in the study.

5.1 Inclusion criteria

1. Patients ≥ 18 years of age.
2. Patient must have a histological diagnosis of primary GIST.
3. The tumor must express KIT (CD117) protein by immunohistochemistry performed by central pathology.
4. Patient must be at significant risk of tumor recurrence as defined by either:
   - Primary GIST (any site): ≥ 2 cm **and** a mitotic rate of ≥ 5/50 HPF's
   - Non-gastric primary GIST: ≥ 5cm
5. Patient must have undergone complete gross resection of a primary GIST within 12 weeks prior to first dose of imatinib study drug. The inclusion of R1 resections will be reviewed on a case by case basis by the Study Management Committee.
6. Patient must have no evidence of metastatic GIST on either 1) a post-operative CT of the abdomen and pelvis with intravenous and oral contrast or 2) MRI of the abdomen and pelvis with intravenous contrast. CT or MRI must be performed within 8 weeks prior to first dose of imatinib study drug.
7. Performance status 0 or 1 (ECOG)
8. Patient must have the following post-operative laboratory values confirmed within 14 days prior to first dose of imatinib study drug:
   - total bilirubin < 1.5 x ULN **NOTE:** Patients with elevated bilirubin secondary to Gilbert's disease are eligible to participate in the study.
   - ALT and AST < 2.5 x ULN
   - creatinine < 1.5 x ULN
   - ANC > 1.5 x 10^9/L
   - platelets > 100 x 10^9/L
9. If patient is a cancer survivor, **ALL** of the following criteria apply:
   - Patient has undergone potentially curative therapy for all prior malignancies.
   - No evidence of any prior malignancies for at least 3 years with no evidence of recurrence (except for effectively treated basal cell or squamous carcinoma of the skin, carcinoma in-situ of the cervix that has been effectively treated by surgery alone, or lobular carcinoma in-situ of the ipsilateral or contralateral breast treated by surgery alone).
   - Patient is deemed by their treating physician to be at low risk for recurrence from prior malignancies.
10. Female patients of childbearing potential must have negative pregnancy test within 7 days before initiation of study drug dosing. Postmenopausal women must be amenorrheic for at least 12 months to be considered of non-childbearing potential. Female patients of reproductive potential must agree to employ an effective barrier method of birth control throughout the study and for up to 7 days following discontinuation of study drug.
11. Written, voluntary informed consent.

5.2 Exclusion criteria

1. Patient has metastatic GIST to the peritoneum, liver, lymph node, or other sites or recurrent GIST.
2. Prior treatment for GIST with the exception of prior treatment with adjuvant imatinib lasting ≤ 8 weeks following gross surgical resection.
3. Patient has received any other investigational agents within 28 days of first day of study drug dosing.
4. Patient with Grade III/IV cardiac problems as defined by the New York Heart Association Criteria. (i.e., congestive heart failure, myocardial infarction within 6 months of study)
5. Patients with severe and/or uncontrolled concurrent medical disease that in the opinion of the investigator could cause unacceptable safety risk or compromise compliance with the protocol (i.e., uncontrolled diabetes, chronic renal disease, chronic liver disease, or active uncontrolled infection).
6. Patient has a known diagnosis of human immunodeficiency virus (HIV) infection.
7. Patient receiving concurrent treatment with warfarin (acceptable alternative: low-molecular weight heparin).
8. Patient with any significant history of non-compliance to medical regimens or with inability to grant reliable informed consent.

6 Treatment

6.1 Investigational drugs

Study Drug (open-label): STI571, Imatinib mesylate, Gleevec

6.1.1 Known undesirable effects of study drug

Imatinib mesylate (labeled as Gleevec)

Please refer to Section 1.2.

6.1.2 How supplied

Each study site will be supplied with the medication by Novartis. Imatinib will be provided as 100 mg and 400 mg tablets for oral use, packaged in bottles. Patients will receive imatinib on an outpatient basis. The supplied bottles will be labeled with Gleevec® (imatinib mesylate) for imatinib and will comply with legal requirements of the U.S.

6.1.3 Preparation and storage

The storage conditions for study drug will be described on the medication label. The study medication is to be stored in a secure locked area while under the responsibility of the investigator. Receipt and dispensing of study medication must be recorded by an authorized person at the investigator's site.

6.2 Treatment arms

All patients will receive imatinib (STI571): 400 mg once daily

6.3 Patient numbering

Each patient in the study is uniquely identified by a **9 digit patient number** which is a combination of his/her **4-digit center number** and **5-digit subject number**. The center number is assigned by Novartis to the investigative site.

Upon signing the informed consent form, the patient is assigned a patient number by the investigator. At each site, the first patient is assigned patient number XXXX_00001, and subsequent patients are assigned consecutive numbers (e.g. the second patient is assigned patient number XXXX_00002, the third patient is assigned patient number XXXX_00003). Once assigned to a patient, the patient number will not be reused.

In addition, the CRF titled "Screened subjects who did not take study drug", which includes demographic information, should be completed for any patient who is screened but not treated in this study.

6.4 Treating the patient

Study drug will be dispensed by the pharmacist at the investigator's institution. Records of drug formulation, number of bottles, tablets dispensed, received, and returned must be recorded. Patients will be asked to return all unused imatinib study drug at each visit (to check compliance) and at the discontinuation of treatment.

6.4.1 Study drug administration

Therapy with imatinib will be continued for up to 5 years or until progression, relapse, or the development of intolerance of treatment, or as long as they have not been discontinued from this study.

Patients will take imatinib orally with food and a large glass of water in the morning. Patients should be instructed to swallow tablets whole and not to chew them. Every attempt should be made to take medication approximately in the same time period daily.

All patients must avoid grapefruit, star fruit, pomegranate, and Seville oranges during the study as this can enhance and prolong their exposure to the study drug. The juices and products containing these fruits must also be avoided. Vomited doses should not be repeated, missed or forgotten doses should not be replaced and the patients should take the next dose at the schedule time.

The investigator should instruct the patient to take imatinib exactly as prescribed (promote compliance). All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record CRF.

6.4.2 Permitted study drug adjustments

For patients who are unable to tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to keep the patient on study drug. Please refer to Section 6.4.2.1.

These changes must be recorded on the Dosage Administration Record CRF.

6.4.2.1 Dosing modifications

This study will use the most recent version of the CTCAE (NCI Common Terminology Criteria for Adverse Events) for toxicity and adverse event reporting. NCI Common Toxicity Criteria 4.0 can be downloaded as a PDF file from the following website: ctep.info.nih.gov/reporting/ctc.html. If multiple dose-reducing toxicities are present, the greatest dose reduction schedule should be used.

During the five years of study treatment, patients will be receiving imatinib 400 mg/day. For patients who are unable to tolerate the protocol-specified dosing schedule due to drug-related toxicity, certain dose adjustments are permitted in order to keep the patient on study drug. Please refer to Table 6-1.

Dose reduction

- No dose reductions will be performed for hematological toxicities Grade 1 or 2 and non-hematological toxicities grade 1.

Please refer to Table 6-1 for dose reduction steps and criteria for interruption and re-initiation of imatinib for drug-related toxicities.

Dose re-escalation

Every attempt to re-escalate the dose of study treatment to the initial dose level should be made. This applies to either dose reductions due to hematological or non-hematological toxicities. The dose should be re-escalated if the following criteria are met at least one month after dose reduction:

- All ≥ Grade 2 non-hematologic toxicities have resolved to ≤ Grade 1
- All ≥ Grade 3 hematologic toxicities have resolved to ≤ Grade 1
- Or alternatively, all ≥ Grade 3 hematological and non-hematological toxicities have resolved to ≤ Grade 2 and are manageable with supportive therapy

Table 6-1 Dose modification for imatinib

Hematologic toxicity	
≥ Grade 3	Hold therapy and resume imatinib at 400 mg QD after recovery to ≤ Grade 1, if recovery occurs within 14 days If toxicity persists for 15-28 days or recurs, hold therapy and resume at next lower dose level after recovery to ≤ Grade 1: I→ 300 mg QD If recurrence is seen at the reduced imatinib dose of 300 mg QD I→ discontinue. If recovery to ≤ Grade 1 is greater than 28 days, consult the Sponsor.
Note: No dose reductions will be performed for grade 3 or 4 anemia. The patient may receive blood transfusions. Use of erythropoietin alfa (EPO) is allowed at the discretion of the treating investigator. G-CSF or GM-CSF may not be used as a prophylactic but may be used as otherwise clinically indicated to support blood counts for patients in this study. Questions related to dose modification or stopping therapy should be addressed with Novartis.	
General non-hematologic toxicity	
Grade 2 (persisting > 7 days with optimal supportive care)	Hold therapy and resume imatinib at 400 mg QD after recovery to ≤ Grade 1 is seen. If toxicity recurs, hold therapy until recovery to ≤ Grade 1 is seen and then resume at next lower dose level I→ 300 mg QD If another recurrence is seen I→ discontinue. If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study.
≥ Grade 3	Hold therapy and resume imatinib at 400 mg QD after recovery to ≤ Grade 1 is seen If toxicity recurs, hold therapy until recovery to ≤ Grade 1 is seen and then resume imatinib at next lower dose level I→ 300 mg QD If another recurrence is seen I→ discontinue. If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study.

6.4.2.2 Follow-up for toxicities

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or abnormal laboratory value must be followed until resolution or stabilization of the event. A dose interruption of ≥ 28 days due to imatinib-related adverse events will require the patient to be discontinued from the study. Cases of dose interruptions of ≥ 28 days which are not imatinib-related may be presented to the SMC to decide if the patient may resume study therapy. Patients will continue to be followed for toxicity for 28 days following the last dose of study medication.

6.4.2.3 Hepatitis B reactivation

Hepatitis B virus testing should be performed to identify patients who may be at risk for Hepatitis B reactivation. Experts in liver disease and in the treatment of hepatitis B should be consulted for patients who test positive for hepatitis B virus during imatinib treatment. Carriers of hepatitis B virus who require treatment with imatinib should be closely monitored for signs and symptoms of active hepatitis B infection throughout therapy and for several months following termination of therapy.

6.4.3 Other concomitant medications

In general, concomitant medications and therapies deemed necessary for the supportive care and safety of the patient are allowed, provided their use is documented in the patient records and on the appropriate case report form. The administration of any other anti-cancer agents including, chemotherapy and biologic agents is not permitted. Use of erythropoietin alfa (EPO) is allowed at the discretion of the treating investigator. G-CSF or GM-CSF may not be used as a prophylactic but may be used as otherwise clinically indicated to support blood counts for patients in this study. The use of other concurrent investigational drugs is not allowed.

Drugs that may increase imatinib plasma concentrations

Caution is recommended when administering imatinib with inhibitors of the cytochrome P450 isoenzyme CYP3A4 family (e.g., ketoconazole, itraconazole, erythro mycin, and clarithromycin). Substances that inhibit CYP3A4 activity may decrease metabolism and increase imatinib concentrations. There was a significant increase in exposure to imatinib when the compound was co-administered with ketoconazole, a CYP3A4 inhibitor.

A list of cytochrome P450 isoenzymes and CYP3A4 inhibitors may be found at medicine.iupui.edu/flockhart. FDA classification of CYP3A4 inhibitors can be found at fda.gov/cder/drug/drugInteractions/tableSubstrates.htm#classInhibit. Novartis must be contacted if a patient needs to be started on any of these drugs during study treatment. Further information can also be found in the following reference (Venkatakrishnan Von Moltke and Greenblatt 2001).

Drugs that may decrease imatinib plasma concentrations

Substances that are inducers of CYP3A4 activity may increase metabolism and decrease imatinib plasma concentrations. Co-medications that induce CYP3A4 (e.g., dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital or St. John's Wort) may reduce exposure to imatinib. There was a significant decrease in exposure to imatinib when imatinib was co-administered with rifampicin, an inducer of CYP3A4.

Please see medicine.iupui.edu/flockhart for a list of CYP3A4 inducers. Novartis must be contacted if a patient needs to be started on any of these drugs during study treatment.

Drugs that may have their plasma concentration altered by imatinib

Imatinib increases the mean C_{max} and AUC of simvastatin (a CYP3A4 substrate) 2- and 3.5-fold, respectively, indicating inhibition of CYP3A4 by imatinib. Particular caution is recommended when administering imatinib with CYP3A4/5 substrates with a narrow therapeutic window (e.g., cyclosporine or pimozide). Imatinib will increase plasma concentrations of other CYP3A4 metabolized drugs (e.g., triazolo-benzodiazepines, dihydropyridine calcium channel blockers, certain HMG-CoA reductase inhibitors, etc.).

Since warfarin is metabolized by CYP2C9 and CYP3A4, patients who require anticoagulation should receive low-molecular weight or standard heparin, not warfarin.

In vitro, imatinib inhibits the activity of cytochrome P450 isoenzyme CYP2D6 at concentrations similar to those that affect CYP3A4/5 activity. Systemic exposure to substrates

of CYP2D6 is expected to be increased when co-administered with imatinib. No specific studies have been performed and caution is recommended.

A list of cytochrome P450 isoenzymes and CYP3A4 inhibitors may be found at medicine.iupui.edu/flockhart. FDA classification of CYP3A4 inhibitors can be found at fda.gov/cder/drug/drugInteractions/tableSubstrates.htm#classInhibit. Novartis must be contacted if a patient needs to be started on any of these drugs during study treatment. Further information can also be found in the following reference (Venkatakrishnan Von Moltke and Greenblatt 2001).

Patients should be warned to avoid or restrict the use of over-the-counter and prescription medicines containing acetaminophen (paracetamol).

Patients should also avoid Seville oranges or Seville oranges derivatives, grapefruit or grapefruit juice, star fruit or star fruit juice and other foods known to inhibit CYP3A4 while taking Gleevec.

The investigator should instruct the patient to notify the study site about any new medications and supplements he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient starts treatment with study drug must be listed on the Concomitant medications/Significant non-drug therapies CRF.

6.4.4 Study drug discontinuation/end of treatment

Patients who discontinue study drug should be considered withdrawn from the study after the end of treatment evaluations are performed or when it is clear that the patient will not return for these assessments.

All patients must be followed for 28 days for AEs. Patients who discontinue the study due to a study drug-related adverse event must be followed weekly for 4 weeks, or until resolution or stabilization of the event, whichever occurs first.

Treatment interruption

If treatment with imatinib is interrupted for a reason other than toxicity, every effort should be made to reinstate treatment as soon as possible and medically acceptable. If a patient is off treatment they should still continue the protocol visit schedule and comply with study procedures.

End of treatment

Patients may stop imatinib if one of the following occurs:

1. adverse event(s)
2. abnormal laboratory value(s)
3. abnormal test procedure result(s)
4. unsatisfactory therapeutic effect (including disease progression/relapse)
5. treatment duration completed per protocol
6. protocol deviation
7. subject withdrew consent
8. lost to follow-up
9. administrative problems
10. death

End of treatment evaluations must be collected within 7 days of the last dose of study drug for any patient discontinuing prematurely (before completing 5 years of study treatment). These evaluations include recording of adverse events, concomitant medications, physical examination, vital signs, ECOG performance status, biochemistry, hematology, radiological assessment, FACT-G and 28 days follow up for adverse events. PK will be collected if the visit occurs on or before August 31, 2011.

The completion of the End of Treatment CRF page will be required at any time a patient discontinues from the study, giving the date and reason for stopping imatinib. If an End of Treatment evaluation had been performed within 7 days of study discontinuation, it does not need to be repeated.

6.4.5 Premature patient withdrawal

See Section 6.4.4.

6.4.6 End of study

The end of study will be December 30, 2016. The Study Evaluation Completion CRF page will be required to be completed after the time that survival follow up has ended or no additional information regarding survival can be obtained.

Patients may voluntarily withdraw from the study at any time. If such withdrawal occurs, or if the patient fails to return for visits, the investigator should make every effort to determine the primary reason for premature withdrawal and record this information on the End of Treatment CRF and Study Evaluation Completion CRF.

For patients who are lost to follow-up, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

7 Visit schedule and assessments

Table 7-1 lists all of the assessments and indicates with an "X" the visits when they are performed. All data obtained from these assessments must be supported in the patient's source documentation.

Screening evaluations

Written informed consent must be obtained before any study specific medical procedures are performed. Informed consent and Central Pathology assessments to be performed within 1 month prior to the first dose of imatinib study drug.

Study evaluation visit windows

In the event that an evaluation is performed within the 48 hours prior to the first dose of study drug treatment as part of the baseline evaluations, the evaluation will not be required to be repeated on Day 1. Radiological assessments performed within 8 weeks prior to the first dose of imatinib study drug do not need to be repeated on Day 1. During Cycle 1, all routine assessments must be performed within ± 3 days of the day indicated on the visit evaluation schedule. All routine assessments for Cycles 2 through the end of Cycle 60 must be performed ± 14 days of the day indicated on the visit evaluation schedule. Post treatment follow up must be performed ± 30 days of the day indicated on the visit evaluation schedule.

Hepatitis B testing will be performed once and only once at an unscheduled visit and before November 30, 2016.

Table 7-1 Visit evaluation schedule

	Screening	Month 1			Years 1 - 5 Q4 Months (yr. 1-3) Q6 Months (yr. 4-5)	Recurrence ≤ 5 yrs	Month 60/ End of Treatment		End of Study Evaluation
Visit no.	**1[1]**	**2**	**3**	**4**	**5-18**	**999**	**19 (777)**		**23 (778)**
Day/Month[12]	**D -14 to -1**	**D 1** Baseline	**D 15**	**D 29**	**M 4, 8, 12, 16, 20, 24, 28, 32, 36, 42, 48, & 54**				
Informed Consent	X[10]								
Inclusion/exclusion criteria[2]	X								
Demographic	X								
Relevant medical history/current medical conditions	X								
Prior/concomitant medications	X								
Disease History	X								
Prior antineoplastic therapy	X								
Physical examination, Weight, Vital Signs, ECOG Performance Status	X	X	X	X	X	X	X		
Height	X								
Hematology/Biochemistry[11]	X					X	X		
Serum pregnancy test (WOBC)	X								
Serology- Hepatitis B Testing	X ONLY once after patient is consented to amendment 06								
Pre Dose Urine pregnancy test (WOBC)		X							
CT or MRI of the Abdomen and Pelvis[3,4]	X	X[9]			X – Q4 mo Year 1-3, then Q6 mo Year 4-5	X	X		
CT, MRI or X-Ray of the Chest[5]	X								

	Screening	Month 1			Years 1 - 5 Q4 Months (yr. 1-3) Q6 Months (yr. 4-5)	Recurrence ≤ 5 yrs	Month 60/ End of Treatment		End of Study Evaluation
Visit no.	**1[1]**	**2**	**3**	**4**	**5-18**	**999**	**19 (777)**		**23 (778)**
Day/Month[12]	**D -14 to -1**	**D 1** Baseline	**D 15**	**D 29**	**M 4, 8, 12, 16, 20, 24, 28, 32, 36, 42, 48, & 54**				
PK blood sampling for visits occurring on or before August 31, 2011				X	X[6]	X	X		
Tumor Sampling	X[10]					X[7]			
Pharmacogenomics	X					X			
Imatinib dosing 400 mg and Compliance		X	X	X	X	X[8]	X		
Dose Administration Record		X	X	X	X	X	X		
Quality of Life assessment - FACT-G	X	X			X	X	X		
Adverse events		X	X	X	X	X	X		
Concomitant Medications/Therapies		X	X	X	X	X	X		
End of Treatment							X		
Status of Response									X
Status of Recurrence									X
Antineoplastic Treatments									X
Survival									X
Study Completion Evaluation									X

1.Patients must start imatinib study drug within 12 weeks of resection. Screening assessments must be completed between baseline and day -14, with the exception of Radiological assessments which are permitted within 8 weeks prior to the first dose of imatinib study drug.
2.All inclusion criteria must be fulfilled and eligibility of the patient confirmed before enrollment.
3.CT with IV and PO contrast or MRI with IV contrast is to be performed with cuts of 10 mm or less in slice thickness contiguously. The same method of assessment and same technique should be used for each imaging procedure through the study. Refer to Section 7.6.1.
4.CT or MRI of the Abdomen and Pelvis; upon completion of three years on study, the tumor evaluation by CT or MRI will be performed every 6 months thereafter.
5.CT, MRI or X-Ray of the chest should performed at baseline and as clinically indicated. The same method of assessment and same technique should be used whenever possible.
6.PK will be drawn at visits occurring on or before August 31, 2011 at Month 4/Visit 5, Month 12/Visit 7, Month 24/Visit 10, Month 36/Visit 13 and Month 48/Visit 16. Refer to Table 7-3.
7.When possible, biopsy samples should be submitted upon recurrence.

	Screening	Month 1			Years 1 - 5 Q4 Months (yr. 1-3) Q6 Months (yr. 4-5)	Recurrence ≤ 5 yrs	Month 60/ End of Treatment		End of Study Evaluation
Visit no.	**1[1]**	**2**	**3**	**4**	**5-18**	**999**	**19 (777)**		**23 (778)**
Day/Month[12]	**D -14 to -1**	**D 1** Baseline	**D 15**	**D 29**	**M 4, 8, 12, 16, 20, 24, 28, 32, 36, 42, 48, & 54**				

8.When there is radiologic evidence of recurrence, pathologic confirmation should be obtained whenever possible. Recurrence diagnosed without pathologic confirmation requires review by the Study Management Committee. When there is indeterminate evidence of recurrence based on radiologic studies and pathologic confirmation is not obtained, repeat cross-sectional imaging should be obtained in a minimum of 4 weeks. Further evaluation will be recommended by the Study Management Committee. See Section 4.
9.Radiological assessments performed within 8 weeks prior to the first dose of imatinib study drug do not need to be repeated on Day 1.
10.Informed consent and Central Pathology assessments to be performed within 1 month prior to the first dose of imatinib study drug.
11.Blood work will be required as noted in Table 7-1. Throughout the duration of the treatment period blood work should be performed per standard of care and at the discretion of the treating physician. When abnormal laboratory values or test results constitute an adverse event they must be recorded on the Adverse Events CRF.
12. A physical exam will be performed at screening, baseline, weeks 2, 4, 16 and every 4 months for the first 3 years and every 6 months thereafter.

7.1 Information to be collected on screening failures

The demographics of patients who are screen failures, as well as the reason the patient did not qualify for the study will be captured in the CRF titled, "Screened subjects who did not take study drug".

7.2 Patient demographics/other baseline characteristics

Patients will have received no prior treatment for GIST with the exception of prior treatment with adjuvant imatinib lasting ≤ 8 weeks following gross surgical resection

7.2.1 Inclusion/exclusion criteria

Patient eligibility is to be established by confirming all inclusion/exclusion criteria. A relevant record (e.g. checklist) must be stored with the source documentation at the study site. Violation of any entry criterion excludes a subject from enrollment into the study.

7.2.2 Demographics

The patient's date of birth, sex, predominant race and predominant ethnicity, will be recorded on the Demography CRF.

7.2.3 Relevant medical history/current medical conditions

Relevant medical history and current medical conditions, including those symptoms related to GIST are recorded on the respective CRF until the start of the study drug.

7.2.4 Prior treatments

Prior anti-neoplastic medications, radiotherapy, and surgeries, including surgical biopsies, will be collected.

7.2.5 Disease history

Relevant information related to the disease history will be collected including, date of initial diagnosis of GIST.

7.3 Treatments

Compliance will be assessed by the investigator and/or study personnel at each visit using pill counts and information provided by the patient or the caregiver. This information should be captured in the source document at each visit.

7.3.1 Dosage administration record

Date of imatinib dose administration will be recorded on the Dosage administration record CRF. The date and time of imatinib dose administration will be recorded on the Blood collection - imatinib CRF page for pharmacokinetic evaluations as appropriate.

Any changes in study drug dose administration including, interruption or reduction in dosing due to an adverse event must be reflected on the Dosage administration record CRF

7.3.2 Concomitant medications/significant non-drug therapies

All concomitant medication, including over-the-counter medications, taken within 28 days prior to the start of study drug and during the course of the study must be recorded on the Concomitant Medications/Significant Non-Drug Therapies CRF. Medication entries should include the trade name, the start and discontinuation dates and the reason for therapy.

7.4 End of treatment

Information on the subject's completion or discontinuation of the study including the reason for discontinuation of the study and the last dose of study drug will be recorded in a CRF.

7.5 Efficacy

7.5.1 Radiological assessment

A CT scan with IV and PO contrast or MRI with IV contrast (in patients with CT contrast allergy) of the abdomen and pelvis at baseline and every 4 months (± 14 days) for the first 3 years. Upon completion of three years on study, a CT scan with IV and PO contrast or MRI with IV contrast (in patients with CT contrast allergy) of abdomen and pelvis will be performed every 6 months thereafter. CT and MRI is to be performed with cuts of 10 mm or less in slice thickness contiguously. The same method of assessment (either CT or MRI) and the same technique should be used for each imaging procedure throughout the study.

Radiological assessment of the chest will be performed at baseline and as clinically indicated. CT, MRI and X-Ray are all acceptable methods, the same method of assessment and the same technique should be used throughout the study.

7.5.2 Recurrence-free survival

Recurrence-free survival (RFS) defined as the time from the date of first study drug to the date of the first documented disease recurrence or death due to any cause ***(The RFS assessment period will include 5 years of adjuvant imatinib therapy and exclude the 2 year follow-up phase of the trial)***.

7.5.3 Overall survival

Overall survival defined as the time from the date of the first dose of study drug imatinib to the date of death from any ***cause (The OS assessment period will include 5 years of adjuvant imatinib therapy and exclude the 2 year follow-up phase of the trial)***.

7.6 Safety

7.6.1 Adverse events

An adverse event for the purposes of this protocol is the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) occurring the first dose of study drug even if the event is not considered to be related to the study drug(s). Please refer to Section 6.1 for the protocol-specific definitions of study drug and study treatment.

Adverse events will be assessed according to the most current version of the Common Toxicity Criteria for Adverse Events (CTCAE). This can be downloaded as a PDF file from the following website: ctep.info.nih.gov/reporting/ctc.html. If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, or grades 1 - 4 will be used. CTCAE grade 5 (death) will not be used in this study; rather, this information will be collected in the End of Treatment or Survival Information CRF page. Adverse event monitoring should be continued for at least 4 weeks following the last dose of study treatment.

Adverse events (but not serious adverse events) occurring before starting study treatment but after signing the informed consent form are recorded on the Medical History/Current Medical Conditions Electronic Case Report Form. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant or require therapy (e.g., any hematologic abnormality that requires transfusion or cytokine treatment); and should be recorded on the Adverse Events CRF under the signs, symptoms or diagnosis associated with them. In addition, isolated abnormal laboratory values that are considered clinically significant (e.g., cause study discontinuation or constitutes in and of itself a Serious Adverse Event) should be recorded on the Adverse Events CRF. SAEs occurring after the first dose of study drug are recorded on the Adverse Event CRF.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE grade 1-4)
2. Its relationship to imatinib (suspected/not suspected)
3. Its duration (start and end dates or if continuing at final exam)
4. Action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)
5. Whether it is serious, where a serious adverse event (SAE) is defined as one which:
    - Is fatal or life-threatening
    - Results in persistent or significant disability/incapacity
    - Constitutes a congenital anomaly/birth defect
    - Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
        - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
        - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
        - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
        - Social reasons and respite care in the absence of any deterioration in the patient's general condition

- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see Section 8.1.

All adverse events should be treated appropriately. Such treatment may include changes in study drug treatment including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalization, or any other medically required intervention. Once an adverse event is detected, it should be followed until its resolution, an assessment should be made at each visit (or more frequently, if necessary) of any changes in its severity, its suspected relationship to the study drug(s), any of the interventions required to treat it, and its outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

7.6.2 Physical examination, weight, height

A complete physical examination will be performed and will be collected by the investigator according to the Visit schedule (refer to Table 7-1). Information about the physical examination findings will be present in the source documentation at the study site. Significant findings that are present prior to the start of study drug must be included on the Relevant Medical History/Current Medical Conditions pages of the CRF. Significant findings made after the start of study drug which meet the definition of an Adverse Event must be recorded on the Adverse Event part in the CRF.

There are no case report forms to capture routine normal findings from physical examinations; however these findings must be present in the patient's source documents.

7.6.3 Vital signs

Sitting pulse rate, blood pressure, and weight will be measured as specified in Table 7-1 and must be present in the patient's chart, and captured on the CRF. Height will be measured only at screening and recorded on the CRF.

Patients should be monitored for signs and symptoms of fluid retention. An unexpected rapid weight gain should be carefully investigated and appropriate treatment provided.

7.6.4 Performance status

Performance status will be recorded in the CRF according to Table 7-1 and as defined by the by the Eastern Cooperative Oncology Group performance status scale in Table 7-2.

Table 7-2 Eastern Cooperative Oncology Group performance status scale

Grade	Description
0	Fully active, able to carry on all pre-disease activities without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g. light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

7.6.5 Laboratory evaluations

The research site/institution will perform laboratory analyses according to the Visit Schedules (refer to Table 7-1). The Sponsor must be provided with a copy of the laboratory's certification, and a tabulation of the normal ranges and units for each parameter required. Additionally, if at any time a patient has laboratory parameters obtained from a different outside laboratory, the Sponsor must be provided with a copy of the certification and a tabulation of the normal ranges for that laboratory.

The investigator is responsible for reviewing all laboratory reports for patients in this study and evaluating any abnormalities for clinical significance.

At any time during the study, abnormal laboratory parameters which are clinically relevant (e.g. require dose modification and/or interruption of study drug, lead to clinical symptoms or signs or require therapeutic intervention), whether specifically requested in the protocol or not, must be recorded on the appropriate comment CRF page.

When abnormal laboratory values or test results constitute an adverse event (i.e., induces clinical signs/symptoms or requires therapy) they must be recorded on the Adverse Events CRF.

7.6.5.1 Hematology

Hematology includes assessment of hemoglobin, platelets count, total white blood cell count (WBC) and differential count including neutrophils, bands, lymphocytes, monocytes, eosinophils and basophils. Hematology assessments will be performed according to the Visit schedule (refer to Table 7-1).

7.6.5.2 Biochemistry

Biochemistry includes sodium, potassium, creatinine, glucose, blood urea nitrogen -BUN (or urea), albumin, AST (SGOT), ALT (SGPT), total bilirubin with fractionation into direct and indirect (if total bilirubin elevated), alkaline phosphatase, total calcium, magnesium, and phosphorus. Biochemistry assessments will be performed according to the Visit schedule (refer to Table 7-1).

7.6.5.3 Pregnancy test

A serum pregnancy test is mandatory at screening, and urine pregnancy test is mandatory at baseline prior to first study drug administration, for women of child bearing potential

(WOBC). Post-menopausal women must be amenorrheic for at least 12 months to be considered of non-childbearing potential; documentation must be available.

To ensure patient safety, each pregnancy in a patient on study drug must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the local Novartis Integrated Medical Safety Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Novartis study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

7.6.5.4 Hepatitis B testing

All patients will be tested once for the following hepatitis B serologic markers: hepatitis B surface antigen (HBsAg), antibodies to hepatitis B core antigen (HBsAb) and antibodies to hepatitis B core antigen (HBcAb). All patients should have testing performed at an unscheduled visit and before November 30, 2016. Radiological examinations

Radiological assessments by CT or MRI of the abdomen and pelvis will be performed at baseline within 8 weeks of the first dose of imatinib study drug and every 4 months for the first 3 years. Upon completion of three years on study, the radiological assessments (abdomen and pelvis) will be performed every 6 months thereafter. When there is radiologic evidence of recurrence, pathologic confirmation should be obtained whenever possible. Recurrence diagnosed without pathologic confirmation requires review by the study committee. When there is indeterminate evidence of recurrence based on radiologic studies and pathologic confirmation is not obtained, repeat cross-sectional imaging should be obtained in a minimum of 4 weeks. Further evaluation will be recommended by the Study Management Committee.

Radiological assessments of the chest by CT, MRI or X-Ray will be performed at baseline and as clinically indicated.

Refer to Table 7-1 and Section 7.4.

7.7 Tolerability

No additional measurements of tolerability, other than safety measurements.

7.8 Resource utilization

Health Resource Utilization data will not be collected in this study.

7.9 Patient-reported outcomes

7.9.1 Functional Assessment of Cancer Therapy-General (FACT-G)

The FACT-G is designed for patient self-administration and will be completed by the patient. The Functional Assessment of Cancer Therapy (FACT) questionnaires have been widely used

to assess quality of life of cancer patients in numerous clinical trials. These instruments consist of a general quality of life component (FACT-G) and several site-specific and treatment-specific subscales. The core quality of life instrument (FACT-G), which consists of 27 items which cover 4 primary domains: Physical Well-being, Social/Family Well-being, Emotional Well-being, and Functional Well-Being, has been rigorously tested and validated. This scale provides a two-fold purpose. Pages 1 and 2 collect information on overall quality of life including physical, social, emotional and functional well-being while page 3 collects information on additional concerns directly related to the symptom of diarrhea associated with the disease.

General administration guidelines for patient reported questionnaires (PRQs):

The patient reported questionnaires (PRQs) will be given to patients to complete upon the patient's arrival at the clinic, i.e. before any other assessments are performed and before the patient meets with the physician. This is to ensure that the patients' recordings are not influenced by any discussions with the physicians during the visit. Patients should be instructed to read the brief instructions at the top of the page. Patients should be encouraged to complete every item in order without skipping any. Patients should be encouraged to circle the response most applicable. If for whatever reason the patient does not complete the questionnaire at the scheduled assessment, time and reason should be recorded. Patients need to initial and date the last page of each questionnaire completed. The study personnel is responsible for collecting the forms from the patient at each visit. The field monitor is responsible for collecting all complete and incomplete forms from the site and to forward them to Novartis or the designated CRO.

The FACT-G will be completed at Visit 1, Visits 5-19 and upon recurrence.

7.10 Pharmacokinetics

The pharmacokinetics of imatinib will be studied through August 31, 2011 to address whether increased imatinib clearance after chronic exposure is a mechanism for the development of recurrent disease. Conversely, impaired clearance may correlate with imatinib toxicity. Therefore, imatinib trough levels will be tested at the following visits occurring on or before August 31, 2011: prior to dosing on: at the conclusion of month 1 (day 29), Month 4/Visit 5, Month 12/Visit 7, Month 24/Visit 10, Month 36/Visit 13, Month 48/Visit 16 and Month 60/Visit 19. Refer to Table 7-3.

It is important that patients DO NOT take imatinib before this blood sample is drawn. The exact 24:00 hr clock time of dosing of the dose prior to PK sampling as well as the morning dose of imatinib should be recorded together with the actual sample collection date and time on the imatinib PK blood collection CRF page. Sampling problems will be noted in the Comments section of the CRF page. Record of drug doses at the time of trough PK sampling should also be maintained. If there were any dose changes less than 7 days prior to obtaining the PK trough samples, information with regard to the prior dose and current dose should be reflected in the CRF.

If a patient withdraws prematurely from the study or has confirmed recurrence, a pharmacokinetic sample should be obtained as close as possible to the last dose of imatinib.

Refer to Table 7-1 for the visit schedule and Table 7-3 for PK sampling schedule.

Table 7-3 PK sampling schedule for imatinib, visits occurring on or before August 31, 2011

PK Collection No	Visit	Month	Time point
2	4	1	Day 29
3	5	4	Month 4
5	7	12	Month 12
8	10	24	Month 24
9	13	36	Month 36
10	16	48	Month 48
11	19	60	Month 60/End of Treatment
12	Unscheduled**		
* Unscheduled sample at Confirmed Recurrence All PK samples will be 3 mLs in volume and drawn prior to the daily dose of imatinib.			

7.10.1 Procedures of blood sample collection

All blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein. For the determination of imatinib concentration in plasma, blood samples (3 mL) will be collected into an EDTA vacutainer tubes (lavender top) and gently inverted 8-10 times and immediately placed in the ice bath. Within 30 minutes, however up to 1 hour is acceptable, plasma will be prepared by centrifugation (ca 1100 x g for 10 min). Following centrifugation, the plasma will be transferred by pipette into polypropylene, cryogenic, freezing vials and stored frozen at = -20°C until shipped to TDM Pharmaceutical Research for sample analyses.

7.10.2 Sample handling and shipment of pharmacokinetic samples

Analysis of PK samples will be performed by TDM Pharmaceutical Research. Detailed instructions for the PK sample preparation, labeling, shipment and relevant contact information are included in the study specific lab manual.

7.10.3 Analytical methods

Plasma concentrations of imatinib will be determined using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay with a lower limit of quantification (LLOQ) of approximately 10 ng/mL. Any results below the lower limit of quantification (BLLOQ) and any missing samples will be labeled accordingly.

7.11 Biomarkers

7.11.1 Tumor characterizations

Central pathologic review of formalin-fixed, paraffin-embedded tissue from the tumor is required for this study. Specifically, twenty unstained slides (3 or 5 micron sections) or a representative paraffin block of the tumor, bearing the pathology accession number must be submitted for analysis. A copy of the original pathology report, corresponding to the pathology accession number must accompany the sample. The central pathologic review will be performed prospectively and will determine the entry into the trial. The diagnosis of GIST

and the presence of KIT protein expression will be assessed. Also, mitotic index and morphology (spindle cell or epithelioid) will be determined. Sites will be notified of the diagnosis. Only patients with confirmed diagnosis of GIST and KIT staining by immunohistochemistry will enroll and start imatinib therapy.

When possible, tumor tissue samples will also be collected in the event of recurrence.

Refer to Table 7-1.

7.11.2 Pharmacogenomics

Phenotypic and genetic analysis of the primary tumors will be performed and correlated to outcome. Genetic analysis of the primary tumors will be performed to identify *KIT* and *PDGFRA* mutations as described previously (Heinrich et al 2003).

When possible, tumor tissue samples will also be collected in the event of recurrence.

Refer to Table 7-1.

7.11.3 Sample handling and shipment of pathology samples

All pathology and pharmacogenomic studies will be performed by Christopher Corless, MD, PhD at Oregon Health & Science University (OHSU). Detailed instructions for the pathology sample preparation, labeling, shipment and relevant contact information are included in the study specific lab manual.

8 Safety monitoring

8.1 Serious adverse event reporting

To ensure patient safety, every SAE, **regardless of suspected causality**, occurring after the patient begins taking study drug and until 4 weeks after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after this 4-week period should only be reported to Novartis if the investigator suspects a causal relationship to the study drug. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form. The investigator must assess and record the relationship of each SAE to each specific study drug (if there is more than one study drug), complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the local Integrated Medical Safety Department.

The telephone and telefax number of the contact persons in the local department of Integrated Medical Safety, specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Package Insert (new occurrence) and is thought to be related to the Novartis study drug, a Integrated Medical Safety Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

8.2 Pregnancies

To ensure patient safety, each pregnancy in a patient on study drug must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the local Novartis Integrated Medical Safety Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Novartis study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

9 Data review and data management

9.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis/Contract Research Organization (CRO) representative will review the protocol and CRFs with the investigators and their staff. During the study, the CRO field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the

patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

9.2 Data collection

Designated investigator staff must enter the information required by the protocol onto the Novartis CRFs that are printed on 3-part, non-carbon-required paper. Field monitors will review the CRFs for completeness and accuracy and instruct site personnel to make any required corrections or additions. The CRFs are forwarded to the CRO by CRO field monitors or by the investigational site, one copy being retained at the investigational site. Once the CRFs are received by the CRO, their receipt is recorded, the original copy is placed in the CRO's Central Files, and the non-carbon-required copy is forwarded to the responsible medical data management staff for processing.

9.3 Database management and quality control

Data from the CRFs are entered into the study database by Contract Research Organization staff following their own internal standard operating procedures that have been reviewed and approved by Novartis.

Subsequently, the entered data are systematically checked by Data Management staff, using error messages printed from validation programs and database listings. Obvious errors are corrected by Data Management personnel. Other errors or omissions are entered on Data Query Forms, which are returned to the investigational site for resolution. Copies of the signed and resolved Data Query Forms are kept with the CRF at the investigator site, and the original is sent to the CRO so the resolutions can be entered into the database. Quality control audits of all key safety and efficacy data in the database are made prior to locking the database.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples for Pharmacogenomics will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Imatinib PK samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

The occurrence of any protocol violations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked.

Any changes to the database after that time can only be made by joint written agreement between the Head of Oncology US Franchise and Head of Oncology US CD&MA.

10 Statistical methods and data analysis

A designated Clinical Research Organization (CRO) will perform the statistical analysis.

It is planned that the data from all centers that participate in this protocol will be used, so that an adequate number of patients will be available for analysis.

Unless otherwise specified, all statistical tests will be performed against a one-sided alternative hypothesis, employing a significance level of 0.05.

The final analysis will be performed after the last enrolled patient has been treated with imatinib for 5 years. Any data collected during the 2-year follow-up period will only be summarized descriptively.

10.1 Sets for analysis

Full Analysis Set (FAS): consists of all patients who received at least one dose of study drug.

The FAS will be the primary set for efficacy analyses.

Safety Set (SS): consists of all patients who received at least one dose of study drug and had at least one post-baseline safety assessment.

Please note: the statement that a patient had no adverse events (on the Adverse Event CRF) constitutes a safety assessment. Patients who have received at least one dose of study drug but who have no post-treatment safety data of any kind would be excluded from the safety set.

Per Protocol Set (PPS): consists of all FAS patients without a major protocol violation, who are evaluable for efficacy and who have either completed a minimum of 4.5 years of treatment or who have discontinued due to disease recurrence or have died. The PPS will be identified prior to database lock.

The set for the pharmacokinetic analyses will include all patients in the FAS with a sufficient number of evaluable blood samples.

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data including age, gender, height, weight, ECOG status, medical conditions etc. will be summarized descriptively for the FAS and the PPS. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, 25^{th} and 75^{th} percentiles, minimum and maximum will be presented.

10.3 Treatments (study drug, concomitant therapies, compliance)

The actual daily dose and duration of study drug will be summarized using descriptive statistics.

Concomitant medications and significant non-drug therapies prior to and after the start of the study drug will be summarized.

10.4 Primary objective

The primary objective of the study is to determine recurrence-free survival following the complete resection of significant risk primary GIST in patients who are treated with adjuvant imatinib for 5 years.

10.4.1 Variable

Recurrence-free survival (RFS) defined as the time from the date of first dose of study drug to the date of the first documented disease recurrence or death due to any cause ***(The RFS assessment period will include 5 years of adjuvant imatinib therapy and exclude the 2 year follow-up phase of the trial),*** is the primary efficacy variable. The recurrence of disease will be assessed by either a CT scan or MRI.

The FAS will be used for the analysis of the primary efficacy variable.

10.4.2 Statistical hypothesis, model, and method of analysis

The primary efficacy variable will be summarized and graphed using the product-limit (Kaplan-Meier) method. Patients who drop out will be treated as censored observations. The estimates of the 25th, median, 75th percentiles for the time first recurrence or death and their 95% confidence intervals will be provided, if applicable.

10.4.3 Handling of missing values/censoring/discontinuations

Patients who discontinue from the study before completing ≥ 4.5 years of study treatment and do not have documented disease recurrence or death will be censored at the last assessment.

10.4.4 Supportive analyses

Analyses using Cox's Proportional Hazards Model will be performed to assess the effects of appropriate covariates including primary GIST status (Gastric vs. Non-gastric).

The primary efficacy variable time to RFS will be analyzed as sensitivity analysis in the PPS.

10.5 Secondary and exploratory objectives

A secondary objective of the study is to evaluate overall survival.

Overall survival, defined as the time from the date of the first dose of study drug to the date of death from any cause ***(The OS assessment period will include 5 years of adjuvant imatinib therapy and exclude the 2 year follow-up phase of the trial),*** will be summarized and graphed using the product-limit (Kaplan-Meier) method. Patients who drop out will be treated as censored observations. The estimates of the 25th, median, 75th percentiles for the time of death and their 95% confidence intervals will be provided, if applicable.

The exploratory objectives of the study are:

- To explore the effect of chronic exposure to imatinib on pharmacokinetics through trough level at steady state for those patients in which data is available.
- To explore any relationship between KIT and PDGFR mutation status of primary tumor and recurrent tumors and related outcome.

- To explore pharmacogenomics of tumor tissue to advance our understanding of patient characteristics and optimize our use of imatinib mesylate in GIST.
- Explore quality of life assessment tool FACT-G in adjuvant GIST.

Details of the analyses to address the exploratory objectives will be described in the statistical analyses plan before data base lock.

Sets and grouping for the analyses

Overall survival will be analyzed in both the FAS and PPS.

10.5.1 Safety assessments and analyses

The assessment of safety will be based mainly on the frequency of adverse events and on the number of laboratory values that fall outside of pre-determined ranges. Other safety data (e.g., electrocardiogram, vital signs, etc.) will be also be summarized. All safety data will be summarized and listed by dose level if necessary.

10.5.2 Adverse events (AE)

All adverse events recorded during the study will be summarized. The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class, severity (based on CTC grades), type of adverse event, relation to the study drug. The adverse events which result in death, discontinuation of the treatment or are otherwise classified as dose limiting will be presented separately.

10.5.3 Laboratory abnormalities

All laboratory values will be converted into SI units and the severity grade calculated using appropriate common toxicity criteria (CTC).

A listing of laboratory values will be provided by laboratory variable, patient, and dose level. A separate listing will display notable laboratory abnormalities (i.e., newly occurring CTC grade 3 or grade 4 laboratory toxicities). The frequency of laboratory abnormalities will be displayed by variable, cycle and study arm. Laboratory data will be summarized by presenting shift tables.

10.5.4 Other safety data

Data from other tests (e.g., electrocardiogram or vital signs) will be summarized and listed, notable values will be flagged, and any other information collected will be listed as appropriate. Any statistical tests performed to explore the data will be used only to highlight any interesting comparisons that may warrant further consideration.

10.5.5 Tolerability

N/A

10.5.6 Resource utilization

N/A

10.5.7 Patient-reported outcomes

N/A

10.5.8 Functional Assessment of Cancer Therapy-General (FACT-G)

For the FACT-G Quality of Life Index, the total score is defined as the sum of the four sub-scales (physical, functional, social, and emotional). Change from baseline in FACT-G total scores will be the primary endpoint for the Quality of Life Index. Changes from baseline in FACT-G total scores and the four sub-scales will be evaluated at 1, 3, 5, 10 and after recurrence using paired t-tests.

10.5.9 Pharmacokinetics

The PK objectives for this study are to explore the relationship between pharmacokinetics and disease recurrence and to explore the effect of chronic exposure to imatinib on pharmacokinetics through trough level at steady state for those patients in which data is available. Any findings will be summarized descriptively.

10.5.10 Biomarkers

N/A

10.5.11 Tumor characterization

See Section 10.5.

10.5.12 Pharmacogenomics

See Section 10.5.

10.6 Interim analysis

Interim analyses for recurrence-free survival and efficacy will be performed after all enrolled patients have completed 1 and 3 years. No decision to terminate the study early or alter the sample size will be made based on the results of these interim recurrence-free survival and efficacy analyses.

10.7 Sample size calculation

The sample size of the study is based on the assumption that the 5-year RFS in this study will be at least 80%. To test the null hypothesis of 65% RFS survival at 5 years (observed in ACOSOGZ9001 Study) against the alternative hypothesis of 80% RFS survival with a one-sided significance level of 5% and 80% power, 51 evaluable patients are required. To allow for a 40% drop-out rate, 85 patients will be enrolled into the study. The sample size is calculated using Southwest Oncology Group One Sample Survival calculator (swogstat.org/stat/public/one_survival.htm). The sample size formula of this calculator is based on an approximation described in chapter 3 of Statistical Models and Methods for Lifetime Data by J. Lawless, John Wiley and Sons, 1982.

10.8 Power for analysis of critical secondary variables

N/A

11 Administrative procedures

Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the protocol, the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to Novartis before study initiation. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

Informed consent

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC/REB approval.

Women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC/REB at the study site should be informed within 10 working days.

Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical trial agreement.

Study drug supply and resupply, storage, and tracking/drug accountability

Study drug must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. Upon receipt, Gleevec® (imatinib mesylate) should be stored according to the instructions specified on the drug label. Clinical supplies are to be dispensed only in accordance with the protocol.

The medication label will comply with the legal requirements of the US. The label will include storage conditions for the drug and the patient number but no other patient information is printed.

The investigator must maintain an accurate record of the shipment and dispensing of study drug in a drug accountability ledger. Drug accountability will be noted by the field monitor during site visits and at the completion of the trial. Patients will be asked to return all unused study drug and packaging at the end of the study or at the time of study drug discontinuation.

At the conclusion of the study, and, as appropriate during the course of the study, the investigator will return all used and unused study drug, packaging, drug label, and a copy of the completed drug accountability ledger to the CRO monitor or to the Novartis address provided in the investigator folder at each site.

12 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the trial to request approval of a protocol deviation, as no authorized deviations are permitted. If

the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

13 References (available upon request)

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