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Clinical Development

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GLIVEC/GLEEVEC

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An open label, multi-center imatinib roll-over protocol for patients who have completed a previous Novartis-sponsored imatinib study and are judged by the investigator to benefit from continued imatinib treatment

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List of abbreviations

AE	Adverse event
AP	Accelerated phase (of CML)
AUC	Area under the plasma concentration-time curve
AUC (0-24h)	Area under the plasma concentration-time curve during the dosing interval (0-24hours)
BC	Blast crisis (of CML)
CCyR	Complete cytogenetic response
CEL	Chronic eosinophilic Syndrome
Cmax	The maximum (peak) observed plasma drug concentration after oral dose administration (mass X volume-1)
Cmin	Minimum drug plasma (serum/blood) concentration
CML	Chronic myeloid leukemia
CMO&PS	Chief medical office and patient safety
CMR	Complete molecular response
CP	Chronic phase (of CML)
CRF	Case report/record form
CRO	Contract Research Organization
DFSP	Dermatofibrosarcoma protuberans
EC	European Commission
eCRF	Electronic case report/record form
EDC	Electronic Data Capture
EFS	Event free survival
EoT	End of treatment
FDA	Food and Drug Administration
FIP1L1-PDGFRα fusion kinase	FIP1L1 platelet-derived growth factor receptor alpha gene fusion kinase
GDD & GMA	Global Drug Development & Global Medical Affairs
GI	Gastrointestinal
GIST	Gastrointestinal stromal tumors
h	Hour
HBc Ab	Hepatitis B Core Antibody
HBs Ag	Hepatitis B Surface Antigen
HES	Hyper-eosinophilic syndrome
HR	Hazard ratio
HV	Healthy volunteers
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IUD	Intrauterine device
IUS	Intrauterine system
Ki	Inhibition constant
MMR	Major molecular response
o.d.	Omnia die/once a day
OC	Oral contraceptive
OOBR	Overall objective benefit rate

OS	Overall survival
p.o.	Per os/by mouth/orally
PFS	Progression-free survival
PDGFR- α	Platelet-derived growth factor receptors α
Ph	Philadelphia (chromosome)
PHI	Protected health information
PK	Pharmacokinetics
q.d.	quaque die/ once daily
REB	Research Ethics Board
RFS	Recurrence-free survival
RQ- PCR	Real-time quantitative reverse transcriptase polymerase chain reaction
SAE	Serious adverse event
STI571	Imatinib/Glivec/Gleevec
T1/2	The elimination half-life associated with the terminal slope of a semi logarithmic concentration-tine curve (time)
Tmax	The time to reach maximum (Cmax) plasma drug concentration after oral dose administration (time)

Glossary of terms

Dose level	The dose of drug given to the patient (total daily dose).
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol).
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in approved indication/dosage.
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study.
Other study treatment	Any drug administered to the patient as part of the required study procedures that were not included in the investigational treatment.
Parent study	The original Novartis-sponsored, Oncology Clinical Development & Medical Affairs study where the patient was first enrolled and received imatinib treatment.
Patient number	A unique identifying number assigned to each patient who enrolls in the study.
Personal Data	Patient information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes patient identifier information, study information and biological samples.
Roll-over study	A roll-over study allows patients from multiple parent studies spanning multiple indications to continue to be treated within one study after the completion of the parent study/ies
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient as part of the required study procedures, including placebo and active drug run-ins.
Withdrawal of consent	Withdrawal of consent from the study occurs only when a patient does not want to participate in the study any longer, and does not allow further collection of personal data.

Amendment 05 (3-Feb-2025)

Amendment rationale

CCI

[redacted]



IRBs/IECs/REBs

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

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

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 protocol amendment.

Amendment 04 (07-Nov-2019)

Amendment rationale

Protocol amendment 04 has been undertaken to provide clarification on study duration and to ensure that patients who are benefiting from study treatment will continue to receive study treatment as long as they have clinical benefit.

Some studies referenced in section 2.6 had incorrect study codes and were corrected.

Reference made to review board was removed from section 4.4 as there is no review board for the study.

In sections 5 and 7.1.4, definition of highly effective contraception has been updated to include total hysterectomy and "tubal ligation" has been revised to "bilateral tubal ligation"



IRBs/IECs/REBs

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

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

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 protocol amendment.

Summary of previous amendments

Amendment 03 (08-Apr-2019)

Amendment rationale

The primary purpose of the amendment is to provide further clarity to the end of study definition and trial timelines:

- The recruitment of this study has been completed (LPFV 01-Oct-2018) and 155 patients have been enrolled. In February 2019, 71 patients are ongoing in the study.
- End of study is defined as the date when all patients have completed their last assessment per protocol.
- CCI [redacted]





Amendment 02 (04-Aug-2017)

Amendment rationale

This roll-over study has been opened since 26-Mar-2013 with a total of 152 patients enrolled and 112 patients ongoing.

The main purpose of the amendment is:

- To correct an error in the language regarding male contraception and pregnancy outcome collection. Pregnancy outcomes from female partners of any males who took study treatment will not be collected in this study and males are not required to use contraception as imatinib is not genotoxic.
- To change the reference safety information for Glivec (imatinib).

Novartis has taken the decision to discontinue the use of the Investigator´s Brochure (IB) for Glivec® (imatinib), since Glivec has been on the market for more than 15 years (first registered in 2001) and has a well-established efficacy/safety profile. In addition, there is no further global clinical development planned for the compound. As of the dispatch of Glivec DSUR 006 in July 2017, the latest approved national/regional product label (e.g. in the EU Summary of Product Characteristics) will serve as the reference safety information (RSI) for the compound.

Additionally, this protocol is currently mandating quarterly visits for patients as opposed to the annual visit previously required in the original protocol. The sites have expressed concerns over the increase of the visit frequency. The concerns are based primarily on the amendment 01 being out of current NCCN recommendation for CML patient management. We would like to leave to the investigator's discretion whether the visit should be on-site or remote.





IRB / IEC 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.

Amendment 01 (07-Apr-2016)

Amendment rationale

The main purpose of the amendment is:

- To change the primary endpoint to safety to better characterize the long-term safety of imatinib
- 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.
- To include the collection of all AEs (including non-serious AEs) and an investigator attestation of continued clinical benefit.

This roll-over study has been opened since 26-Mar-2013 with a total of 152 patients' enrolled and 113 patients ongoing.




CCI



IRB / IEC 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.

Protocol summary:

Protocol number	CSTI571A2406
Title	An open label, multi-center imatinib roll-over protocol to better characterize the long-term safety in patients who have completed a previous Novartis-sponsored imatinib study and are judged by the investigator to benefit from continued imatinib treatment.
Sponsor and Clinical Phase	Novartis, IV.
Investigation type	Drug.
Study type	Interventional.
Purpose and rationale	The purpose of this study is to better characterize the long-term safety of imatinib in patients who are on imatinib treatment in a Novartis-sponsored, Oncology Global Development & Global Medical Affairs (OGD&GMA) study and are benefiting from the treatment as judged by the investigator.
Primary Objective	To evaluate long term safety data (SAEs and AEs)
Secondary Objective	To evaluate clinical benefit as assessed by the investigator.
Study design	This is a multi-center, open label study to provide continued supply of imatinib to patients currently being treated in Novartis-sponsored Oncology OGD&GMA studies and who are benefiting from treatment with imatinib. There will be no screening period for this study. Eligible patients are to be consented and can start their treatment with imatinib as soon as they enter the study. All patients must report to the study site for their first visit at which time, a 6 month supply of imatinib can be dispensed to the patient. It is recommended that patients return to the study center on a quarterly basis (12wks+/- 1wk), however the method of evaluation, whether on-site or remote is at the discretion of the investigator. At every quarterly visit, the investigator is required to confirm that the patient continues to have clinical benefit and may continue receiving study treatment. Patients must return to the study center on a 6 month basis (24 weeks +/- 1 week) for resupply of study medication at which time drug dispensing information will be collected. Patients will continue to be treated until they are no longer benefiting from imatinib treatment, develop unacceptable toxicities, withdraw consent, are non-compliant to the protocol, the investigator feels it is no longer in the patient's best interest to continue imatinib therapy or the patient dies, whichever comes first. CCI [redacted] A patient will reach the end of study when imatinib treatment is permanently discontinued and the end of treatment visit has been performed. All patients must be followed up for safety evaluations for 30 days after the last dose of study treatment. Following this there are no further follow-up study visits.
Population	Male and female patients who are currently enrolled in a Novartis-sponsored, Oncology OGD&GMA imatinib study, are benefiting from treatment with imatinib CCI [redacted] All objectives of the parent study must have been reached, and the study must be in the process of being completed & reported. Approximately 200 patients may enroll into this study.
Inclusion criteria	Patient must meet all of the criteria: Patient is currently enrolled in a Novartis- sponsored, Oncology Global Development & Global Medical Affairs study receiving imatinib and has fulfilled all their requirements in the parent study. Patient is currently benefiting from the treatment with imatinib, as determined by the investigator. Patient has demonstrated compliance, as assessed by the investigator, with the parent study protocol requirements.

Exclusion criteria	Patient must not meet any of the criteria: Patient has been permanently discontinued from imatinib, study treatment in the parent study, due to unacceptable toxicity, non-compliance to study procedures, withdrawal of consent or any other reason. Patient has participated in a Novartis sponsored combination trial where imatinib was dispensed in combination with another study medication and is still receiving combination therapy.
Investigational and reference therapy	Imatinib, 100 - 800 mg/day.
Efficacy assessments	It recommended that patients return to the study center on a quarterly basis (12wks+/- 1wk), however, the method of evaluation, whether on-site or remote is at the discretion of the investigator.. At every quarterly visit, the investigator is required to confirm that the patient continues to have clinical benefit and may continue receiving study treatment. It is the physician's discretion as to whether the follow up would be remote or on-site. In case of remote follow-up, the enrolling physician may consult with the physician on the phone or follow up with a local physician who might physically evaluate the patient and then communicate their assessment to the enrolling physician. The site PI may order labs as needed. The protocol, however, does not mandate any of these approaches as long as the enrolling physician provides the information requested on the CRF.
Safety assessments	All adverse events and SAEs will be collected continuously moving forward. Patients will be tested once for the following hepatitis B serologic markers: hepatitis B surface antigen (HBs Ag) and antibodies to hepatitis B core antigen (HBc Ab / anti HBc).
Other assessments	Not applicable.
Data analysis	The assessment of safety will be based mainly on the frequency of AEs and SAEs. Proportion of patients with clinical benefit as assessed by the investigator will be summarized at scheduled visits. As needed, safety information on patients from this protocol will link to the patient identifiers from the parent protocol.
Key words	Glivec/Gleevec, roll-over study, Managed Access

1 Background

1.1 Overview of gastrointestinal stromal tumors (GIST)

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal (GI) tract and are thought to originate from the interstitial cells of Cajal. GISTs are malignant tumors most commonly resulting from activating mutations in the receptor tyrosine kinase KIT (CD117) or the platelet-derived growth factor receptors α (PDGFRα) (Demetri et al 2010). Approximately 85% of KIT (CD117)-positive GISTs harbors an activating mutation in the KIT oncogene and 5-8% of GISTs have mutated PDGFRα gene. Mutations in KIT exon 11 are the most common (67%) while KIT exon 9 mutations are found in 10-12% of GISTs. Mutations in KIT exons 13 and 17 are rare. The remaining cases harbor no mutation and are referred to as "Wildtype" GIST (Corless and Heinrich 2008).

GISTs can arise anywhere along the GI tract but are most common in the stomach and small intestine (Demetri et al 2010). The majority of KIT exon 9 mutations arise in small intestinal GISTs, while most PDGFRα mutations are found in gastric GISTs. KIT exon 11 mutations are distributed throughout the GI tract. Response to systemic therapies in the metastatic /inoperable disease setting is related to the identified activating mutations in GIST and the development of subsequent resistance mutations (Corless and Heinrich 2008).

The mainstay of therapy for patients with primary GIST is surgical resection. However, surgery alone is generally not curative; the 5-year disease specific survival is reported to be 54%. Recurrence rates exceeding 50% within 2 years of resection of primary GIST and approximating 90% after re-excision (DeMatteo et al 2000), underscored the need for effective postoperative treatment.

Imatinib received worldwide approval for the treatment of adult patients with KIT (CD117) and unresectable and/or metastatic GIST and dramatically changed the prognosis for such patients by prolonging the overall and the progression-free-survival (PFS) and increasing the 5-year survival rate (Zalcberg et al 2005, Blanke et al 2008). Imatinib at doses ranging from 400 mg/day to 800 mg/day is used worldwide for the treatment of patients with unresectable and/or metastatic KIT-positive GIST. In addition, imatinib 800 mg/day significantly improves progression-free survival (PFS) in patients with advanced GIST harboring KIT exon 9 mutations compared to 400 mg/day.

As a result of the efficaciousness of imatinib for the treatment of patients with unresectable and/or metastatic GIST, a double-blind, randomized phase III study (ACOSOGZ9001) was conducted to determine if adjuvant treatment of adult patients with GIST following complete resection with 400 mg/day of imatinib for 12 months improved recurrence-free survival (RFS) compared with placebo (DeMatteo et al 2009). The results of the study indicated that treatment with imatinib significantly prolonged RFS with a hazard ratio (HR) of 0.325 (p-value < 0.0001; 95% CI, 0.198- 0.534). Based on these data, imatinib at a dose of 400 mg/day was approved worldwide for the adjuvant treatment of adult patients following resection of GIST.

The SSGXVIII/AIO, a Phase III multicenter, open-label, randomized study confirmed and extended the results of the ACOSOGZ9001 study. In the SSGXVIII/AIO study, GIST patients at high risk of disease recurrence were randomized to either 3 years or 1 year of 400 mg imatinib. The study data revealed that 36 months of adjuvant therapy with imatinib is well

tolerated and superior to 12 months in prolonging RFS with a HR of 0.46 (p-value < 0.001; 95% CI: 0.32-0.65) and 5-year RFS 65.5% vs 47.9%, respectively and longer overall survival with a HR of 0.45 (p-value = 0.02; 95% CI: 0.22-0.89) and 5-year survival 92.0% vs 81.7%, respectively) in patients with GIST following surgical resection (Joensuu et al 2011).

1.2 Overview of chronic myeloid leukemia (CML)

Chronic myeloid leukemia (CML) is a hematological stem cell disorder associated with a specific chromosomal translocation known as the Philadelphia (Ph) chromosome detected in 95% of patients (Nowell and Hungerford 1960, Rowley 1973). The molecular consequence of the translocation is the fusion of the Abl proto-oncogene to the Bcr gene resulting in the production of an activated form of the Abl protein-tyrosine kinase (Bartram et al 1983, Heisterkamp et al 1983). Expression of the BCR-ABL protein is capable of inducing leukemias in mice, implicating the protein as the cause of these diseases (Daley et al 1990, Kelliher et al 1990). Clinically, CML progresses through three distinct phases of increasing refractoriness to therapy: chronic phase (median duration 3-4 years; median survival up to 10 years with allogeneic bone marrow transplant and 5-6 years with interferon), accelerated phase (median duration 3-9 months; median survival 8-18 months), and blast crisis (median survival 3-6 months) (Enright and McGlave 2000). Most patients however present in the chronic phase, characterized by splenomegaly and leukocytosis with generally few symptoms.

Imatinib revolutionized the treatment of Ph+ CML and changed the natural history of the disease, especially for patients diagnosed and treated in chronic phase (CP). Imatinib binds to the inactive conformation of BCR-ABL tyrosine kinase suppressing the Ph+ clone in CML (Giles et al 2005). For the past decade imatinib has been the standard of care for patients with Ph+ CML.

The initial efficacy and safety of imatinib in de novo Ph+ CML-CP was demonstrated in the IRIS study (International Randomized Interferon versus STI571) a phase III randomized study comparing imatinib to the combination of interferon and Ara-C (IFN + Ara-C), the former standard of care. After a median follow-up of 19 months, imatinib was shown to be superior to IFN+Ara-C based on the primary endpoint of progression-free survival. At 18 months the disease had not progressed in 92.1% of the patients in the imatinib group and 73.5% of patients in the combination therapy group (P < 0.001) (O'Brien et al 2003).

IRIS was also the first large study to evaluate BCR-ABL transcript levels in the blood as a possible surrogate endpoint for Ph+ CML-CP. Real-time quantitative reverse transcriptase polymerase chain reaction (RQ-PCR) of BCR-ABL was used as an exploratory endpoint and was measured in a subset of evaluable patients (n=240) who had achieved Complete Cytogenetic Response (CCyR) with 400 mg QD imatinib. MMR (Major Molecular Response) was defined in the study as ≥ 3 log reduction in BCR-ABL transcripts compared to the standardized baseline, while CMR (Complete Molecular Response) was defined as ≥ 4 log reduction in BCR-ABL transcripts. With standard dose imatinib (400 mg QD), the MMR and CMR rates were estimated to be 39% and less than 10% respectively at 12 months (data on file). With continued doses of imatinib 400 mg/day, the rate of MMR at 24 months was 54% in patients who obtained a CCyR at 12 months.

For patients who did achieve a CCyR and MMR at 12 months following imatinib therapy, the probability of remaining progression-free was 100 percent at 24 months, compared with 95% for patients who achieved a CCyR without a MMR (P < 0.001) (Hughes et al 2003)

The 8 year follow up data from the IRIS study has demonstrated that responses to imatinib have been durable and treatment has been well-tolerated with a predictable and manageable safety profile. In the IRIS study the estimated overall survival (OS) rate for patients randomized to imatinib was 85% at 8 years, and rates of relapse and progression were low, with an estimated event-free survival (EFS) rate of 81% and 92% freedom from progression to accelerated phase/blast crisis (AP/BC). Despite these results, approximately 20-30% of patients fail imatinib (either due to intolerance or resistance). IRIS also demonstrated that progression to AP or BC was highest within the first 3 years of starting imatinib therapy and that for these patients overall survival was significantly reduced (at 7 years 43% vs. 86%). Furthermore, patients with high Sokal risk were also shown to have lower response rates with imatinib therapy with complete cytogenetic response rates of 69%, 82% and 89% in high, intermediate and low risk patients respectively (Druker 2006).

Results from the TOPS study, a phase III, randomized trial comparing starting doses of imatinib 400 mg/day to imatinib 800 mg/day were published and demonstrated that there was no statistically significant difference in rates of MMR and CCyR between either study dosage (Cortes et al 2010). The two year update for TOPS presented at the American Society of Hematology meeting demonstrated that initial therapy with 800 mg/day imatinib did not lead to improved rates of CCyR, MMR, event free survival, progression free survival, or overall survival at 24 months compared to 400 mg /day (Baccarani et al 2009).

1.3 Introduction to investigational treatment(s) and other study treatment(s)

1.3.1 Overview of imatinib

Imatinib (Glivec®/Gleevec®, imatinib mesylate) is registered in many countries for both hematologic and solid tumor indications for greater than 10 years. For solid tumors, imatinib is indicated for the treatment of patients with KIT (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST), for the adjuvant treatment of adult patients following resection of Kit (CD117)-positive GIST and dermatofibrosarcoma protuberans (DFSP).

Imatinib received worldwide approval for the treatment of adult patients with KIT (CD117)-positive unresectable and/or metastatic GIST and dramatically changed the prognosis for such patients by prolonging the OS and the PFS and increasing the 5-year survival rate (Blanke et al 2008). Imatinib at doses ranging from 400 mg/day to 800 mg/day is used worldwide for the treatment of patients with unresectable and/or metastatic KIT-positive GIST. Imatinib of 800 mg/day significantly improves PFS in patients with advanced GIST harboring KIT exon 9 mutations compared to 400 mg/day.

Imatinib is also approved for adjuvant treatment of adult patients following resection of GIST based on RFS data from the ACOSOGZ9001 study and PFS and OS data from the

SSGXVIII/AIO study. Imatinib has an established safety profile and is well tolerated by the majority of patients with GIST.

Imatinib was originally approved by the FDA in May 2001 and by the European Commission (EC) in November 2001 for the treatment of adult patients with Philadelphia chromosome (BCR-ABL) positive CML in chronic phase after failure of interferon-alpha therapy, or in AP or BC. Following the initial approval, the FDA and EC in December 2002 approved imatinib for patients with newly diagnosed Philadelphia chromosome (BCR-ABL) positive (Ph+) CML including pediatric patients, for whom bone marrow transplantation is not considered first line therapy.

The approved recommended dosage of imatinib is 400 mg/day for adult patients in chronic phase and 600 mg/day for adult patients in AP or BC. In the IRIS study, patients were allowed to escalate from 400 mg to 600 mg and subsequently to 800 mg in the absence of dose limiting toxicities. The safety of 800 mg was comparable to 400 mg (chronic phase Ph+ CML) and 600 mg (advanced CML), although a somewhat increased frequency of GI hemorrhages, transaminases or total bilirubin increase, hematologic toxicities (mainly anemia and thrombocytopenia), and upper respiratory tract infections and conjunctivitis were noted.

1.3.1.1 Non-clinical experience - Not applicable

1.3.1.2 Clinical experience

1.3.1.2.1 Human safety and tolerability data

The majority of adverse events (AEs) in patients with GIST treated with imatinib were of mild to moderate grade. The most frequently reported drug-related AEs 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 local or general fluid retention AEs, including pleural effusion, ascites, pulmonary edema and rapid weight gain with or without superficial edema, have been observed. 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.

Imatinib was well tolerated in chronic phase CML patients. The majority of imatinib-treated patients experience adverse events at some point in time, but most were of mild to moderate grade, and in clinical trials drug discontinuations for drug-related adverse events was observed in 2.4% of newly diagnosed patients. The most frequent drug related adverse events were mild nausea, vomiting, diarrhea, myalgia, muscle cramps and rash, which were easily manageable. Superficial edemas were common in all studies and were described primarily as periorbital or lower limb edema. However these edematous events were rarely severe and can be managed with diuretics, other supportive measures, or in some patients by reducing the dose of imatinib. For further details please refer to the latest approved imatinib national/regional product label (e.g. in the EU Summary of Product Characteristics).

1.3.1.3 Clinical pharmacokinetics and pharmacodynamics

The pharmacokinetics (PK) of imatinib has been fully evaluated in studies in healthy subjects and patients with CML, GIST and other malignancies. In adults, imatinib is well absorbed after oral administration with Cmax achieved within 2-4 hours post-dose. Mean absolute bioavailability for the capsules was 98% (Peng et al 2004) when given with a high fat meal. In comparison to fasting conditions, the rate of imatinib absorption was minimally reduced (11% decrease in Cmax and prolongation of Tmax by 1.5 h and a small reduction in area under curve (AUC) (7.4%). From a PK perspective, imatinib may therefore be given with or without food (Reckmann et al 2001). The film-coated tablet is bioequivalent with the hard-gelatin capsules (Nikolova et al 2004). The increase in AUC was linear and dose proportional in the dose range 25-1000 mg after oral administration. There was no change in kinetics on repeated dosing, and accumulation was low (about 1.5-3 fold increase in both AUC (0-24h) and Cmax, between Day 1 and at steady state) when dosed once daily (Peng et al 2004). The elimination half-lives (T1/2) of imatinib and its major active metabolite, the N-desmethyl derivative, are approximately 18 and 40 hours, respectively. At clinically relevant concentrations of imatinib, binding to plasma proteins in in vitro experiments is approximately 95%, mostly to albumin and α1-acid glycoprotein

CYP3A4 is the major human isozyme catalyzing the biotransformation of imatinib. Thus, drugs such as ketoconazole that inhibit CYP3A4 activity could increase imatinib exposure (Dutreix et al 2004) and drugs that induce CYP3A4 (e.g. rifampicin, dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital or hypericum perforatum, also known as St. John's Wort) may reduce imatinib exposure (Bolton et al 2004). A single dose of ketoconazole increased mean Cmax and AUC of imatinib by 26% and 40%, respectively, confirming that imatinib is a CYP3A4 substrate. In two published studies, concomitant administration of imatinib and a product containing St. John's Wort led to a 30-32% reduction in the AUC of imatinib (Frye et al 2004). Further, co-administration with rifampicin, an inducer of CYP3A4, reduced plasma imatinib AUC by approximately 70%.

Imatinib is a competitive inhibitor of CYP3A4/5, CYP2D6, and CYP2C9, with Ki values indicating that inhibition of CYP3A4/5- or CYP2D6-dependent metabolism of co-administered drugs is possible. Two clinical Drug-drug interaction studies were conducted. Imatinib increased the Cmax and AUC of simvastatin by 2- and 3.5- fold in HV, respectively, indicating inhibition of CYP3A4 by imatinib. Glivec at 400 mg twice daily had a weak inhibitory effect on CYP2D6-mediated metoprolol metabolism, with metoprolol Cmax and AUC being increased by approximately 23%.

2 Rationale

2.1 Study rationale and purpose

The purpose of this study is to better characterize the long-term safety of imatinib to patients who are on imatinib treatment in a Novartis-sponsored, Global Drug Development & Global Medical Affairs (GDD&GMA) study, CCI
and are benefiting from the treatment as judged by the investigator. CCI

CCI All objectives of the parent study must have been reached, and the parent study must be in the process of being completed and reported.

Patients will continue to receive imatinib until one of the following occurs: the patient is no longer benefiting from the treatment, unacceptable toxicity develops, consent is withdrawn, there is non-compliance with the protocol, the investigator feels it is no longer in the patient's best interest to continue therapy, or the patient's death.

2.2 Rationale for the study design

This is a multi-center, open label, phase IV study to better characterize the long-term safety of imatinib in patients being treated in a current Novartis-sponsored, GDD&GMA study and who are benefiting from treatment with imatinib.

The study will not include a screening phase as patients will transfer directly from parent studies and will commence treatment with imatinib as soon as they are consented and meet the inclusion criteria of the roll-over protocol.

2.3 Rationale for dose and regimen selection

Imatinib will be provided as 100mg and 400mg tablets. The starting dose of imatinib should be the same dose which was given in the parent imatinib study. After the starting dose, the dose of imatinib is based on the investigator's judgment.

2.4 Rationale for choice of combination drugs

Not applicable

2.5 Rationale for choice of comparators drugs

Not applicable

2.6 Risks and benefits

Glivec/Gleevec is a marketed drug since 2001.

Imatinib is registered in many countries for both hematologic and solid tumor indications. A number of trials such as CSTI5710106, CSTI5710110, CSTI5710109, CSTI5710102, CSTI571A2108, CSTI571ADE10, CSTI571AAU02, CSTI571ADE04, CSTI571AJP0, CSTI571AUS01, CSTI571AFR09, CSTI571AIT04, CSTI571AJP01, CSTI571AUS01, CSTI571AFR09, CSTI571I2301, CSTI571B2225, and CSTI571B2222 have demonstrated the clinical benefit of Glivec/Gleevec in a variety of disorders. It is currently indicated for the treatment of patients with Philadelphia chromosome positive (Ph+) chronic myeloid leukemia (CML) in chronic phase (CP), CP after failure of interferon-α (IFN), accelerated phase (AP) and blast crisis (BC). It is also approved for patients with relapsed or refractory Ph+ acute lymphoblastic leukemia (ALL), hypereosinophilic syndrome (HES) / chronic eosinophilic leukemia (CEL), myelodysplastic/myeloproliferative diseases (MDS/MPD), and aggressive systemic mastocytosis (ASM). For solid tumors, imatinib is indicated for the treatment of patients with KIT (CD117)-positive unresectable and/or metastatic malignant gastrointestinal

stromal tumors (GIST), for the adjuvant treatment of adult patients following resection of KIT (CD117)-positive GIST and for dermatofibrosarcoma protuberans (DFSP).

Please refer to the latest approved imatinib national/regional product label for known anticipated risks and safety concerns of the study drug; special precautions and monitoring; concomitant medications and drug interactions; drug administration schedule; overdose; pregnancy, lactation and effects on fertility; and duration of therapy. The patients to be enrolled will be patients currently experiencing clinical benefit as attested by investigators to better characterize the long-term safety of the compound. These patients will get the opportunity to continue to derive medical benefit from the treatment with imatinib by participating in this study.

The risk to patients in this trial may be minimized by compliance with the eligibility criteria and study procedures, regular clinical monitoring and proactive dose modification and toxicity management.

In case patients do not tolerate the dosing schedule, dose adjustments are permitted in order to keep the patient on study drug. Dosing should always be adjusted/discontinued if the physician determines it is in the best interest of the patient.

Patients will continue to be treated in the roll-over protocol until they are no longer benefiting from the imatinib, develop unacceptable toxicities, withdraw consent, are non-compliant to the protocol, the investigator feels it is no longer in the patient's best interest to continue therapy, pregnancy occurs or the patient dies, whichever comes first. CCI [redacted] in accordance with the regulations of each respective country.

No further enrollment is expected on this study.

It is understood that doses and schedule of imatinib treatment will be different for each patient (depending on the parent study).

There may be risks with imatinib which could be serious. Refer to the latest approved imatinib national/regional product label.

3 Objectives and endpoints

Objectives and related endpoints are described in Table 3-1 below.

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		Refer to Section 10.4
To evaluate long term safety data (SAEs and AEs)	Frequency and severity of AEs /SAEs	
Key secondary		Refer to Section 10.5.1
To evaluate clinical benefit as assessed by the investigator	Proportion of patients with clinical benefit as assessed by the investigator at scheduled visits.	

4 Study design

4.1 Description of study design

This is a multi-center, open label, phase IV study to better characterize the long-term safety of imatinib in patients being treated in current Novartis-sponsored, Oncology OGD&GMA studies and who are benefiting from treatment with imatinib.

There will be no screening period for this study. At the enrollment visit the patient will be consented to the study and eligible patients will start their treatment with imatinib. At this time, a 6 month supply of imatinib will be dispensed to the patient/or as per local practice.

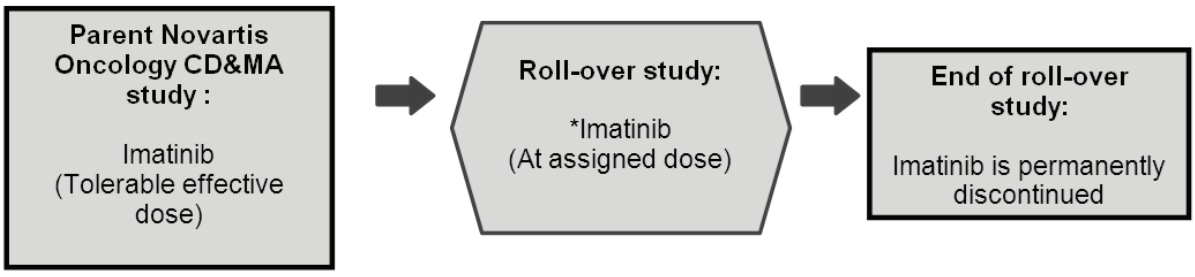
Patients will continue to be treated until they are no longer benefiting from imatinib treatment, develop unacceptable toxicities, withdraw consent, are non-compliant to the protocol, the investigator feels it is no longer in the patient's best interest to continue imatinib therapy, if the patient dies, CCI It is recommended that patients return to the study center on a quarterly basis (12wks+/- 1wk), however, the method of evaluation, whether on-site or remote is at the discretion of the investigator. Adverse event information will be collected at the quarterly visit, and in addition, the investigator is required to confirm that the patient continues to have clinical benefit and may continue receiving study treatment.

Patients must return to the study center on a 6 month basis (24 weeks +/- 1 week) for resupply of study medication at which time limited drug dispensing information will be collected. The patient may return to the clinic at any given time as per standard of care, however only quarterly visits will be recorded. All adverse events and serious adverse events will be collected throughout the study.

A patient will reach the end of study when imatinib treatment is permanently discontinued and the end of treatment visit has been performed.

CCI in accordance with the regulations of the respective country.

Figure 4-1 Study Design



*Note: The starting imatinib dose will be the same as in the parent study.

4.2 Timing of interim analyses and design adaptations

Not applicable.

4.3 Definition of end of study

End of study is defined as the date when all patients have completed their last assessment per protocol thirty days after end of treatment visit. The last assessment for each patient is the follow–up assessment that occurs 30 days after the patient's last dose of study treatment. Patients may continue on study treatment as long as they have clinical benefit. Patients may voluntarily withdraw from the study or be dropped from it at the discretion of the investigator at any time. Please refer to Section 7.1.5.1 "Criteria for Premature patient withdrawal."

4.4 Early study termination

The study can be terminated at any time for any reason by Novartis.

Reasons for early termination include (but not limited):

- Unexpected, significant, or unacceptable safety risk to patients enrolled in the study
- Discontinuation of study drug development

Should this be necessary, the patient should be seen as soon as possible and the same assessments should be performed as described in Section 7 for a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's health interests. The investigator will be responsible for informing IRBs and/or IECs of the early termination of the trial.

CCI [redacted]

5 Population

5.1 Patient population

The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered treatment in the study.

5.2 Inclusion criteria

Patients eligible for inclusion in this study have to meet **all** of the following criteria:

1. Patient is currently enrolled in a Novartis-sponsored, Global Drug Development & Global Medical Affairs study receiving imatinib and has fulfilled all their requirements in the parent study.
2. Patient is currently benefiting from the treatment with imatinib, as determined by the investigator.
3. Patient has demonstrated compliance, as assessed by the investigator, with the parent study protocol requirements.
4. Willingness and ability to comply with scheduled visits, treatment plans and any other study procedures.
5. Written informed consent obtained prior to enrolling in roll-over study.

6. If consent cannot be expressed in writing, it must be formally documented and witnessed, ideally via an independent trusted witness.

5.3 Exclusion criteria

Patients eligible for this study must not meet **any** of the following criteria:

1. Patient has been permanently discontinued from imatinib treatment in the parent study due to unacceptable toxicity, non-compliance to study procedures, withdrawal of consent or any other reason.
2. Patient has participated in a Novartis sponsored combination trial where imatinib was dispensed in combination with another study medication and patient is still receiving combination therapy.
3. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hcG laboratory test.
4. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they are using highly effective methods of contraception during the study and for 30 days after the final dose of imatinib.

Highly effective contraception is defined as either:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or total hysterectomy, bilateral tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
- Male sterilization (at least 6 months prior to enrolling). For female patients on the study the vasectomized male partner should be the sole partner for that patient.
- Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (i.e. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy, or bilateral tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

If a study patient becomes pregnant or suspects they are pregnant during the study or within 30 days of the final dose of imatinib, the Investigator/Study Doctor needs to be informed immediately and ongoing study treatment with imatinib has to be stopped immediately.

6 Treatment

6.1 Study treatment

Terms related to study treatment are defined below:

- Study treatment and investigational treatment refer to imatinib.

6.1.1 Dosing regimen

Table 6-1 Dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
Imatinib/STI571	Tablet for oral use	100-800 mg/day	Daily (28 day cycles)

Imatinib will be provided as 100 mg and 400 mg tablets. The investigational treatment is to be stored in a secure locked area while under the responsibility of the investigator. Receipt and dispensing of investigational treatment must be recorded by an authorized person at the investigator's site.

The starting dose of imatinib should be the same as the dose that was given in the parent imatinib study. After this, the dose of imatinib is based on the investigator's judgment.

Imatinib at doses of 400 mg/day to 600 mg/day should be administered orally, once daily with a meal and a large glass (8 oz/200 mL) of water. In patients with significant GI intolerance the daily dose may be taken with meals in divided doses. In patients receiving 800 mg/day, imatinib 400 mg should be taken twice daily with food.

In the event that the film-coated tablets cannot be swallowed, the tablets may be crushed and can be mixed with food or suspended with water or apple juice. The required number of tablets should be placed in the appropriate volume of beverage (approximately 50 mL for a 100mg tablet and 200 mL for a 400 mg tablet) and stirred with a spoon. The suspension should be administered immediately after complete disintegration of the tablet(s). If the crushed tablet(s) is mixed with food, then administration to the patient should be completed rapidly to assure the maximum potency of the formulation.

CCI [redacted] As per Novartis procedures, investigational treatment will only be shipped directly to the investigational sites.

6.1.2 Guidelines for continuation of treatment

The starting dose of imatinib should be the same as the dose that was given in the parent imatinib study. Following the starting dose patients may receive between 100mg to 800mg imatinib per day, based on the investigator's judgment of what dose is in the patient's best interest.

Treatment duration

Patients will continue to be treated until one of the following criteria is met:

- Patients are no longer benefiting from imatinib treatment
- Patients develop unacceptable toxicities
- Patients withdraw consent, are non-compliant with the protocol
- The investigator feels it is no longer in the patient's best interest to continue imatinib therapy or the patient dies.
-
- CCI [redacted] or there are new therapies for the indication

The visit schedule should be on a quarterly basis (12wks+/- 1wk), however, this left to the investigator discretion whether it should be on site or by remote call based on their evaluation. The adverse event information will be collected. At every quarterly visit, the investigator is required to confirm that the patient continues to have clinical benefit and may continue receiving study treatment. A patient will reach the end of the roll-over study when imatinib treatment is permanently discontinued.

6.2 Dose escalation guidelines

Not applicable

6.2.1 Starting dose rationale

The starting dose of imatinib should be the same as the last dose that was given in the parent imatinib study. After this, the dose of imatinib is based on the investigator's judgment.

6.2.2 Dose modifications

Please refer to the SmPC or PI for Glivec/Gleevec for further details.

6.2.3 Dose adjustment for hepatotoxicity and non-hematologic adverse reactions

If elevations in bilirubin >3 x institutional upper limit of normal (IULN) or in liver transaminases >5 x IULN occur, imatinib should be withheld until bilirubin levels have returned to a <1.5 x IULN and transaminase levels to <2.5 x IULN. In adults, treatment with imatinib may then be continued at a reduced daily dose (i.e., 400 mg to 300 mg, 600 mg to 400 mg or 800 mg to 600 mg). In children, daily doses can be reduced under the same circumstances from 340 mg/m2/day to 260 mg/m2/day or from 260 mg/m2/day to 200 mg/m2/day, respectively. If a severe non-hematologic adverse reaction develops (such as severe hepatotoxicity or severe fluid retention), Imatinib should be withheld until the event has resolved. Thereafter, treatment can be resumed as appropriate depending on the initial severity of the event.

6.2.4 Dose adjustment for hematologic adverse reactions

Dose reduction or treatment interruptions for severe neutropenia and thrombocytopenia are recommended as indicated in Table 6-2.

Table 6-2 Dose adjustments for neutropenia and thrombocytopenia

1) ASM associated with eosinophilia (starting dose 100 mg)	2) ANC < 1.0 x10^9/L and/or platelets <50 x10^9/L	1. Stop imatinib until ANC ≥ 1.5 x10^9/L and platelets ≥75 x10^9/L 2. Resume treatment with imatinib at previous dose (i.e. dose before severe adverse reaction)
3) Patients with Hyper-eosinophilic syndrome (HES) and/or Chronic eosinophilic leukemia (CEL) who have FIP1L1-PDGFRα fusion kinase (starting dose 100 mg)	4) ANC < 1.0 x10^9/L and/or platelets <50 x10^9/L	1. Stop imatinib until ANC ≥ 1.5 x 10^9/L and platelets ≥75 x10^9/L 2. Resume treatment with imatinib at previous dose (i.e. dose before severe adverse reaction)
5) Chronic Phase CML (starting dose 400 mg) 6) MDS/MPD, ASM and HES/CEL (starting dose 400 mg) 7) GIST (starting dose either 400 mg or 600 mg)	8) ANC < 1.0 x10^9/L and/or platelets <50 x10^9/L	1. Stop imatinib until ANC ≥ 1.5 x10^9/L and platelets ≥75 x10^9/L 2. Resume treatment with imatinib at original starting dose of 400 mg or 600 mg 3. If recurrence of ANC <1.0 x10^9/L and/or platelets <50 x10^9/L, repeat step 1 and resume imatinib at a reduced dose (300 mg if starting dose was 400 mg, 400 mg if starting dose was 600 mg)
9) Ph+ CML: Accelerated Phase and Blast Crisis (starting dose 600 mg) 10) Ph+ ALL (starting dose 600 mg)	11) ANC < 0.5 x10^9/L and/or platelets <10 x10^9/L	1. Check if cytopenia is related to leukemia (marrow aspirate or biopsy) 2. If cytopenia is unrelated to leukemia, reduce dose to 400 mg. 3. If cytopenia persists 2 weeks, reduce further to 300 mg 4. If cytopenia persists 4 weeks and is still unrelated to leukemia, stop imatinib until ANC ≥1 x10^9/L and platelets ≥20 x10^9/L and then resume treatment at 300 mg
12) DFSP (starting dose 800 mg)	13) ANC < 1.0 x10^9/L and/or platelets <50 x10^9/L	1. Stop imatinib until ANC ≥ 1.5 x10^9/L and platelets ≥75 x10^9/L 2. Resume treatment with imatinib at 600 mg 3. In the event of recurrence of ANC <1.0 x10^9/L and/or platelets <50 x10^9/L, repeat step 1 and resume imatinib at a reduced dose of 400 mg.
14) Pediatric newly diagnosed chronic phase CML (starting dose 340 mg/ m^2)	15) ANC < 1.0 x10^9/L and/or platelets <50 x10^9/L	1. Stop imatinib until ANC ≥ 1.5 x10^9/L and platelets ≥75 x10^9/L 2. Resume treatment with imatinib at previous dose (i.e. dose before severe adverse reaction) 3. In the event of recurrence of ANC <1.0 x10^9/L and/or platelets <50 x10^9/L, repeat step 1 and resume imatinib at a reduced dose of 260 mg/m^2.

16) Pediatric patients with chronic phase CML recurring after transplant or resistant to Interferon (starting dose 260 mg/m^2)	17) ANC < 1.0 x10^9/L and/or platelets <50 x10^9/L	1. Stop imatinib until ANC ≥ 1.5 x10^9/L and platelets ≥75 x10^9/L 2. Resume treatment with imatinib at previous dose (i.e. dose before severe adverse reaction) 3. In the event of recurrence of ANC <1.0 x10^9/L and/or platelets <50 x10^9/L, repeat step 1 and resume imatinib at a reduced dose of 200 mg/m^2.
ANC = absolute neutrophil count		

6.2.5 Hepatitis B reactivation

Hepatitis B virus testing should be performed during the study as indicated in Section 7.1 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.

6.2.6 Follow up on potential drug-induced liver injury (DILI) cases

Patients with transaminase increase combined with TBIL increase may be indicative of potential DILI, and should be considered as clinically important events.

The threshold for potential DILI may depend on the patient's baseline AST/ALT and TBIL value; patients meeting any of the following criteria will require further follow-up as outlined below:

- For patients with normal ALT and AST and TBIL value at baseline: AST or ALT > 3.0 x ULN combined with TBIL > 2.0 x ULN
- For patients with elevated AST or ALT or TBIL value at baseline: [AST or ALT > 2 x baseline AND > 3.0 x ULN] OR [AST or ALT > 8.0 x ULN], combined with [TBIL > 2 x baseline AND > 2.0 x ULN]

Medical review needs to ensure that liver test elevations are not caused by cholestasis, defined as ALP elevation > 2.0 x ULN with R value < 2 in patients without bone metastasis, or elevation of ALP liver fraction in patients with bone metastasis.

Note: (The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic (R ≤ 2), hepatocellular (R ≥ 5), or mixed (R >2 and < 5) liver injury).

In the absence of cholestasis, these patients should be immediately discontinued from study drug treatment, and repeat LFT testing as soon as possible, preferably within 48 hours from the awareness of the abnormal results. The evaluation should include laboratory tests, detailed history, physical assessment and the possibility of liver metastasis or new liver lesions, obstructions/compressions, etc.

1. Laboratory tests should include ALT, AST, albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time (PT)/INR and alkaline phosphatase.

2. A detailed history, including relevant information, such as review of ethanol, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.
3. Further testing for acute hepatitis A, B, C or E infection and liver imaging (e.g. biliary tract) may be warranted.
4. Obtain PK sample, as close as possible to last dose of study drug, if PK analysis is performed in the study.
5. Additional testing for other hepatotropic viral infection (CMV, EBV or HSV), autoimmune hepatitis or liver biopsy may be considered as clinically indicated or after consultation with specialist/hepatologist.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified should be considered as "medically significant", thus, met the definition of SAE (Section 8.2.1) and reported as SAE using the term "potential drug-induced liver injury". All events should be followed up with the outcome clearly documented.

6.3 Concomitant medications

6.3.1 Prohibited concomitant therapy

In general, concomitant medications/therapies deemed necessary for the supportive care of the patient is permitted.

Because of the inherent risk of either reduced activity or enhanced toxicity of the concomitant medication and/or imatinib, drugs known to interact with the same CYP450 isoenzymes (CYP3A4/5,CYP2D6 and CYP2C9) as imatinib should be used with caution (refer to Appendix1 in Section 14.1). Patients using concomitant medications known to be metabolized by these cytochrome p450 enzymes will not be excluded from the study. However, the patients must be carefully monitored for potentiation of toxicity due to individual concomitant medication.

Since warfarin is metabolized through the CYP450 system, therapeutic anticoagulation with warfarin (e.g. Coumadin® or Coumadine®) is discouraged on this protocol.

For further details refer to the latest approved imatinib national/regional product label

6.3.2 Use of bisphosphonates (or other concomitant agents)

Not applicable

6.4 Patient Numbering, treatment assignment or randomization

6.4.1 Patient Numbering

Each patient is identified in the study by a Patient Number (Patient No.), that is assigned when the patient is first enrolled in the roll-over study and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Patient No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential Patient Number suffixed to it, so that each patient is numbered uniquely across the entire database.

Upon signing the informed consent form, the patient is assigned to the next sequential Patient No. available to the investigator through the EDC system. Additionally, an eCRF will be completed that identifies the patient by gender and date of birth and previous study, site/center and Patient Number as well as relevant medical history.

6.4.2 Treatment assignment or randomization

All consented patients who meet all the inclusion criteria and none of the exclusion criteria are eligible to receive imatinib.

6.4.3 Treatment blinding

Not applicable

6.5 Study drug preparation and dispensation

The investigator or responsible site personnel must instruct the patient or caregiver to take the study drugs as per protocol. Study drug(s) will be dispensed to the patient by authorized site personnel only. All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record CRF.

Table 6-3 Preparation and dispensing

Study treatments	Dispensing	Preparation
Imatinib	Film coated Tablets (100mg and 400mg) including instructions for administration will be dispensed by study personnel on an outpatient basis. Patients will be provided with a 6 month supply of study treatment for self-administration at home until at least their next scheduled study visit.	Not applicable

6.5.1 Study treatment packaging and labeling

CCI [redacted] packed and labeled under the responsibility of Novartis, Drug supply management. Study treatment labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the drug but no information about the patient.

If imatinib is sourced and labeled in-country, the locally-approved form and packaging of imatinib will be used.

Table 6-4 Packaging and labeling

Study treatments	Packaging	Labeling (and dosing frequency)
Imatinib	Tablets in bottles*	Imatinib

* For centrally supplied medication. If imatinib is sourced and labeled in-country/locally, the locally-approved form, packaging and labeling of imatinib will be used.

6.5.2 Drug supply and storage

Study treatments must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated

site personnel have access. Upon receipt, the imatinib should be stored according to the instructions specified on the drug labels and in latest approved imatinib national/regional product label.

Table 6-5 Supply and storage of study treatments

Study treatments	Supply	Storage
Imatinib	Centrally Or locally supplied by Novartis	Refer to study treatment label or local product information

6.5.3 Study drug compliance and accountability

6.5.3.1 Study drug compliance

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver will be captured in the Drug Accountability Form. This information must be captured in the source document at each patient visit.

6.5.3.2 Study drug accountability

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

At study close-out, and, as appropriate during the course of the study, the investigator will return all used and unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.5.3.3 Handling of other study treatment

Not applicable

6.5.4 Disposal and destruction

The drug supply can only be destroyed once the study drug accountability check has been performed by the monitor. The study drug supply can be destroyed at the local Novartis facility, by Drug Supply group or by a third party, as appropriate.

7 Visit schedule and assessments

7.1 Study flow and visit schedule

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.

The table indicates which assessments produce data to be entered into the database (D) or remain in source documents only (S) ("Category" column).

Hepatitis B testing will be performed once and only once, at the next possible visit.

Table 7-1 Visit evaluation schedule

	Category	Protocol Reference Section	Enrollment	Quarterly (12 weeks +/- 1 week) visits during treatment phase	End of study treatment (EoT)	Safety Follow-up/End of study
Visit Number			**1**	**Visit 2,3,4 etc.**	**777**	778
Informed consent	D	7.1.2.	x			
Patients' previous study, site and patient number	D	7.1.2.3.	x			
Patients' gender and date of birth	D	7.1.2.3.	x			
Relevant medical history/current medical conditions	D	7.1.2.3.	x			
Inclusion/exclusion criteria	D	5.2 / 5.3.	x			
imatinib dosing	D	6.1.	x	x		
Pregnancy testing	D, S	7.1.4.	x	Monthly (at home) →		x
Hepatitis screen	D	7.2.2.1.		to be performed once and only once, at the next possible visit		
Confirmation of Clinical Benefit from Study Treatment	D	7.2.1.	x	x		
Adverse events and serious adverse events	D	8.1 / 8.2.	← Continuous →			x
End of study treatment	D	7.1.5.			x	
Study Evaluation Completion	D	7.1.5.				x

7.1.1 Molecular pre-screening

Not applicable.

7.1.2 Screening

At the enrollment visit the patient will need to complete a written informed consent. There will be no screening period for this study. Once consented, patients will be evaluated for eligibility via the inclusion and exclusion criteria.

7.1.2.1 Eligibility screening

Not applicable

7.1.2.2 Information to be collected on screening failures

Not Applicable

7.1.2.3 Patient demographics and other baseline characteristics

For patients that are eligible to participate in this roll-over study, the patients' gender, date of birth, previous study, site/center and Patient Number as well as relevant medical history will be collected.

7.1.3 Treatment period

The starting dose of imatinib should be the same as the dose that was given in the parent imatinib study. It is recommended that patients return to the study center on a quarterly basis (12wks+/-1wk), however the method of evaluation, whether on-site or remote is at the discretion of the investigator. The adverse event information will be collected. At every quarterly visit, the investigator is required to confirm that the patient continues to have clinical benefit and may continue receiving study treatment. At this time the dose of imatinib is based on the investigator's judgment.

A 6 month supply of imatinib will be dispensed to the patient/or as per local practice. Patients must return to the study center every 6 months (24 weeks +/- 1 week) for resupply of study medication at which time limited drug dispensing information will be collected.

7.1.4 Pregnancy and assessment of fertility

Since highly effective contraception is required during the study, female patients of child bearing potential are required to test negative for a pregnancy (either with serum testing if routinely/locally available or urine pregnancy test) before enrolling into the study.

Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they are using highly effective methods of contraception during the study and for 30 days after the final dose of imatinib.

Highly effective contraception is defined as either:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or total hysterectomy, bilateral tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
- Male sterilization (at least 6 months prior to enrolling). For female patients on the study the vasectomized male partner should be the sole partner for that patient.
- Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.

If patient has tested negative at the end of study on the parent study, no pregnancy testing is required if enrollment into this study is carried out on the same day or within few days (maximum 5 days) from each other.

Female patients of child bearing potential are required to perform monthly home urine pregnancy tests and complete a simple diary with the dates and the outcome of the home urinary test while on study treatment and during safety follow-up (30 days after the final dose of study medication).

A pregnancy test (either with serum testing if routinely/locally available or urine pregnancy test) on female patients of child bearing potential is required at the final study visit.

Any positive results will be recorded in the database and followed up as per Section 8.4.

7.1.5 Discontinuation of study treatment

Patients will continue to be treated until one of the following criteria is met:

- Patients are no longer benefiting from imatinib treatment,
- Patients develop unacceptable toxicities,
- Patients withdraw consent,
- Patients are non-compliant to the protocol,
- The investigator feels it is no longer in the patient's best interest to continue imatinib therapy or the patient dies,
- CCI [redacted] in accordance with the regulations of each respective country

At the time the patients discontinues study treatment, a visit should be scheduled as soon as possible, at which time the assessments listed for the End of Treatment (EOT) visit will be performed. End of Treatment information will be completed in the eCRF giving the date and reason for stopping the study treatment (see Section 7.1.5.1). e.g. physician decision, disease progression, cause of death, lost to follow up, withdrawal of consent, etc.

At a minimum, all patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for a safety evaluation during the 30 days following the

last dose of study treatment. The completion of the Study Evaluation Completion eCRF page will be required any time a patient discontinues from the study and must be completed 30 days after the end of treatment.

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

If a study withdrawal occurs, or if the patient fails to return for visits, the investigator must determine the primary reason for a patient's withdrawal from the study and record this information on the appropriate eCRF page.

A patient will reach the end of study when imatinib treatment is permanently discontinued and there will be **no** further follow-up study visits.

7.1.5.1 Criteria for premature patient withdrawal

Patients may voluntarily withdraw from the study or be dropped from it at the discretion of the investigator at any time.

Patients may be withdrawn from the study if any of the following occur:

1. Death.
2. Lost to follow-up.
3. Staying in the study would be harmful
4. Adverse event
5. Disease progression
6. Patient/guardian decision.
7. Physician decision.
8. Patient is non-compliant to protocol requirements.
9. Protocol deviation.
10. Patient becomes pregnant.
11. Study terminated by sponsor.

7.1.5.2 Replacement policy

Not applicable.

7.1.6 Withdrawal of consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a patient:

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the patient's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits by site team will not be collected in the CRF.

Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the patients study withdrawal should be made as detailed in the assessment table.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of patient's samples until their time of withdrawal) according to the applicable law.

7.1.7 Follow up for safety evaluations

All patients must be followed up for safety evaluations for 30 days after the last dose of study treatment. At the end of this period, the investigator should contact the patient to inquire about any adverse events or serious adverse events observed during this period. This could be done via a phone contact. Following this there are **no** further follow-up study visits

Patients lost to follow up should be recorded as such on the appropriate eCRF. 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.

Data collected should be added to the Adverse Events eCRF.

7.1.8 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw consent, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be considered lost to follow-up until due diligence has been completed. Patients lost to follow up should be recorded as such on the appropriate Disposition CRF.

7.2 Assessment types

7.2.1 Efficacy assessments

It is recommended that patients return to the study center on a quarterly basis (12wks+/- 1wk), however the method of evaluation, whether on-site or remote is at the discretion of the investigator. At every visit, the investigator is required to confirm that the patient continues to have clinical benefit and may continue receiving study treatment. It is the physician's discretion as to whether the follow up would be remote or on-site. In case of remote follow up, the enrolling physician may consult with the physician on the phone or follow up with a local physician who might physically evaluate the patient and then communicate their assessment to the enrolling physician. The site PI may order labs as needed. The protocol, however, does not

mandate any of these approaches as long as the enrolling physician provides the information requested on the CRF.

7.2.2 Safety and tolerability assessments

Safety will be monitored by collecting of the adverse events at every visit. For details on AE collection and reporting, refer to Section 8.

7.2.2.1 Hepatitis B testing

Patients will be tested once for the following hepatitis B serologic markers: hepatitis B surface antigen (HBs Ag) and antibodies to hepatitis B core antigen (HBc Ab / anti HBc).

Patients currently on imatinib should have testing performed at the next possible visit in order to identify chronic carriers.

7.2.3 Pharmacokinetics

Not applicable.

7.2.3.1 Analytical method

Not applicable.

7.2.3.2 Additional biomarker assessments

Not applicable.

7.2.4 Resource utilization

Not applicable

7.2.5 Patient reported outcomes

Not applicable

8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained.

Abnormal laboratory values or test results occurring after informed consent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

Any ongoing adverse events from the parent study will be captured as medical history in the roll-over database. Any AE that begins (or worsens) after signing of the informed consent for the roll-over and during the 30-day (or 28-day) safety follow up period defined in the parent protocol should be reported in both clinical databases.

Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

Adverse events will be assessed according to the current version of Common Terminology Criteria for Adverse Events (CTCAE).

If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, will be used. CTCAE Grade 5 (death) will not be used in this study; rather, information about deaths will be collected through the EOT eCRF page.

The occurrence of adverse events should be sought by non-directive questioning of the patient during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during the screening process 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 duration (start and end dates)
3. Its relationship to the study treatment (reasonable possibility that AE is related: No, Yes)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1.

If the event worsens the event should be reported a second time in the CRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the CRF noting the start date when the event improved from having been Grade 3 or Grade 4.

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event CRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST criteria for solid tumors or as per Cheson's guidelines for hematological malignancies), should not be reported as a serious adverse event.

Adverse events separate from the progression of malignancy (example, deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

Laboratory abnormalities that constitute an adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities that do not meet the definition of an adverse event should not be reported as adverse events. A Grade 3 or 4 events (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

8.1.3 Adverse events of special interest

Adverse events of special interest (AESI) are defined as events (serious or non-serious) which are ones of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them.

Adverse events of special interest are defined on the basis of an ongoing review of the safety data. AESIs are discussed in detail in the latest approved imatinib national/regional product label (e.g. in the EU Summary of Product Characteristics).

8.2 Serious adverse events

8.2.1 Definitionss

Serious adverse event (SAE) is defined as one of the following:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- 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

- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Note that hospitalizations for the following reasons should not be reported as serious adverse events:
  - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - 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
  - Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event

8.2.2 Reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until at least 30 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAE that begins or worsens after signing of the informed consent for the roll-over and during the 30-day (or 28-day) safety follow up period defined in the parent protocol should be reported as an adverse event in both clinical databases; however, only one SAE report will be sent to Novartis.

- Any SAE that begins or worsens during the 30-day (or 28-day) safety follow-up period specified in the parent study should have an SAE report submitted to Novartis with the parent protocol study number.
- Any SAE that begins or worsens after the 30-day (or 28-day) safety follow-up period specified in the parent study should have an SAE report submitted to Novartis with the roll-over protocol study number.

Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes 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.

It is important to use the right SAE form with the correct protocol number for these two scenarios, to avoid confusion in SAE processing. For a patient already on the roll-over protocol but follow up information is reported for the previous SAEs in the parent protocol, it must be clearly labeled that this is for the parent protocol number.

Any SAEs experienced after the 30 day safety evaluation follow-up period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report

Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the SAE submission process and requirements for signatures are to be found in the investigator folder provided to each site.

Follow-up information is submitted in the same way as the original SAE 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 and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the latest approved imatinib national/regional product label or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Chief Medical Office and Patient Safety (CMO&PS) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification, to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions 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.

8.3 Emergency un-blinding of treatment assignment

Not applicable. This is an open-label study.

8.4 Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment 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 oncology Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

8.5 Warnings and precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the latest approved imatinib national/regional product label (e.g. in the EU Summary of Product Characteristics). Additional imatinib safety information will be communicated in the national/regional product label (e.g. in the EU Summary of Product Characteristics) as safety reference This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

8.6 Data Monitoring Committee

Not applicable.

8.7 Steering Committee

Not applicable.

9 Data collection and management

9.1 Data confidentiality

Information about study patients will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed patient authorization informing the subject of the following:

- What protected health information (PHI) will be collected from patients in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research patient to revoke their authorization for use of their PHI.

In the event that a patient revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect follow-up safety information (e.g. has the patient experienced any new or worsened AEs) at the end of their scheduled study period.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

9.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, Novartis personnel (or designated CRO) will review the protocol and eCRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment 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 recorded on eCRFs must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent form (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 eCRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan.

9.3 Data collection

For studies using Electronic Data Capture (EDC), the designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and, allow modification or verification of the entered data by the investigator staff.

The Principal Investigator is responsible for assuring that the data entered into eCRFs is complete, accurate, and that entry and updates are performed in a timely manner.

9.4 Database management and quality control

For studies using eCRFs, Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

At the conclusion of the study, the occurrence of any protocol violations will be determined. After these actions have been completed and the data has been verified to be complete and accurate, the database will be declared locked and made available for data analysis. Authorization is required prior to making any database changes to locked data, by joint written agreement between the Global Head of Biostatistics and Data Management and the Global Head of Clinical Development.

For EDC studies, after database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

10 Statistical methods and data analysis

10.1 Analysis sets

The following analysis sets will be used for statistical analysis and data reporting.

10.1.1 Full Analysis Set

Not applicable.

10.1.2 Safety Set

The Safety Set includes all patients who received at least one dose of study medication after enrolling into the roll-over protocol.

10.1.3 Dose-determining analysis set

Not applicable.

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data characteristics will be summarized descriptively for the Safety Set.

10.3 Treatments (study treatment, compliance)

Dose administration data will be summarized using the Safety Set.

10.4 Primary objective

The primary objective is to evaluate long term safety as assessed by the occurrence of AEs/SAEs.

10.4.1 Variable

See Section 10.5.3.

10.4.2 Statistical hypothesis, model, and method of analysis

No hypothesis will be tested.

10.4.3 Handling of missing values/censoring/discontinuations

Not applicable.

10.4.4 Supportive analyses

No supportive analysis will be performed.

10.5 Secondary objectives

10.5.1 Key secondary objective(s)

Not applicable.

10.5.2 Other secondary efficacy objectives

The secondary objective of the study was to evaluate clinical benefit as assessed by the investigator. Proportion of patients with clinical benefit as assessed by the investigator will be summarized at scheduled visits

10.5.3 Safety objectives

The assessment of safety will be based mainly on the frequency of AEs and SAEs.

10.5.3.1 Analysis set and grouping for the analyses

The overall observation period will be divided into two mutually exclusive segments:

1. on-treatment period: from day of first dose of study medication to 30 days after last dose of study medication
2. post-treatment period: starting at day 30+1 after last dose of study medication.

10.5.3.2 Adverse events (AEs)

Summary tables of adverse events (AEs) have to include only AEs that started or worsened during the on-treatment period, the **treatment-emergent** AEs. However, all safety data (including those from the post-treatment periods) will be listed and those collected during the post treatment period are to be flagged.

The incidence of treatment emergent adverse events (new or worsening from baseline) will be summarized by system organ class and/or preferred term, severity (based on CTCAE grades), type of adverse event, relation to study treatment.

Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by type of adverse event.

10.5.3.3 Other safety data

Not applicable.

10.5.3.4 Tolerability

Not applicable.

10.6 Interim analysis

Not applicable.

10.7 Sample size calculation

Not applicable.

10.8 Power for analysis of key secondary variables

Not applicable.

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

This clinical study was designed, shall be implemented and reported in accordance with 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.

11.2 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. 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.

11.3 Informed consent procedures

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

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. The date when a patient's Informed Consent was actually obtained will be captured in their CRFs.

Novartis will provide to investigators, in a separate document, a proposed informed consent form (ICF) that is considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Any changes to this ICF 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.

11.3.1 Additional consent form

Not applicable.

11.4 Discontinuation of the study

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

11.5 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

11.6 Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements

for the protection of confidentiality of patients. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patients' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and patient files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study case report form (CRF) is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRFs and all other required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. Any change or correction to a paper CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For electronic CRFs an audit trail will be maintained by the system. The investigator should retain records of the changes and corrections to paper CRFs.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

11.7 Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

11.8 Audits and inspections

Source data/documents must be available to inspections by Novartis or designee or Health Authorities.

11.9 Financial disclosures

Financial disclosures should be provided by study personnel who are directly involved in the treatment or evaluation of patients at the site, prior to study start.

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 study 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.

12.1 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 at the study site should be informed according to local regulations (e.g. UK requires the notification of urgent safety measures within 3 days) but not later than 10 working days.

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14 Appendices

14.1 Guidance on concomitant medications with CYP3A4/5 and CYP2D6 interaction

Imatinib is a moderate inhibitor of CYP3A4 and CYP2D6 and weak inhibitor of CYP2C9 potentially increasing the concentrations of drugs eliminated by these enzymes. Caution should be exercised when co-administering imatinib with substrates of these enzymes.

As the information listed below may not be all inclusive, a list of CYP3A4 inhibitors and inducers may be found at http//medicine.iupui.edu/flockhart.

14.2 List of CYP3A4 inhibitors and inducers

Category	Drug Names
Strong inhibitors[a] of CYP3A	boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, eltegravir/ritonavir, grapefruit juice[1], idelalisib, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, LCL161, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, sequinavir/ritonavir, telaprevir, telithromycin, voriconazole, indinavir/ritonavir, tipranoavir/ritonavir, troleandomycin,
Moderate inhibitors[b] of CYP3A	amprenavir, aprepitant, atazanavir, atazanavir/ritonavir,, casopitant, cimetidine, ciprofloxacin, crizotinib, cyclosporin, duranavir, darunavir/ritonavir, diltiazem, dronedarone, erythromycin, faldaprevilr, fluconazole, fosamprenavir, grapefruit juice, imatinib, lomitapide, netupitant,nilotinib, schisandra sphenanthera, tofisopam, verapamil, Faldaprevir, Cyclosporine, Isavuconazole, Ferulaasafetida resin
Strong inducers[c] of CYP3A	avasimibe, carbamazepine, enzalutamide, mitotane,phenytoin, rifampin, St. John's wort[3], rifabutin, phenobarbital, fosphenytoin*, primidone *, Dexamethasone, Mitotane, Enzalutamide
Moderate inducers[d] of CYP3A	bosentan, efavirenz, etravirine, genistein[3], lersivirine, lopinavir, modafinil, nafcillin, ritonavir, semagacestat[4], talviraline[4], thioridazine, tipranavir, ,felbamate *, topiramate * (>200 mg/day), oxcarbazepin *, eslicarbazepin *, rufinamide *, modafenil
The list of CYP inhibitors and inducers was compiled from the FDA's "Guidance for Industry, Drug Interaction Studies;" from the Indiana University School of Medicine's "Clinically Relevant" Table and from the University of Washington's Drug Interaction Database. Note that this may not an exhaustive list. Please refer to footnotes.	
1. Effect seems to be due to CYP2C19 inhibition by ethinyl estradiol. 2. Fluconazole is a dual CYP3A4 and CYP2C9 inhibitor. Fluconazole is a strong CYP2C9 inhibitor based on the AUC ratio of omeprazole, which is also metabolized by CYP3A; fluconazole is a moderate CYP3A inhibitor. In case of indications for fluconazole doses of greater than 200 mg daily, contact the medical monitor to discuss administration of the study medication. 3. Herbal product. 4. Drugs not available in the US Market.	

Category	Drug Names
[a] A strong inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by equal or more than 5-fold. [b] A moderate inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 5-fold but equal to or more than 2-fold [c] A strong inducer for a specific CYP is defined as an inducer that decreases the AUC of a sensitive substrate for that CYP by equal or more than 80%. [d] A moderate inducer for a specific CYP is defined as an inducer that decreases the AUC of a substrate for that CYP by 50-80%.	
* These drugs are Enzyme Inducing Anti-Epileptic drugs (EIAED).This database of CYP inhibitors and inducers was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table; from the University of Washington's Drug Interaction Database based on in vitro studies; from the FDA's "Guidance for Industry, Drug Interaction Studies"; from the Indiana University School of Medicine's "Clinically Relevant" Table; and from Pursche et al (2008) found at http//medicine.iupui.edu/clinpharm/ddis/main-table	

14.3 List of medications that are sensitive CYP3A4 and CYP2C9 substrates with a narrow therapeutic index (TI)

Sensitive CYP3A4 substrates with narrow TI	**Sensitive CYP2C9 substrates with narrow TI**
Alfentanil	Warfarin
Cyclosporine	Phenytoin
Diergotamine, ergotamine	Torsemide
Fentanyl	
Pimozide	
Quinidine	
Sirolimus	
Tacrolimus	
Note: the following medications are not available in US: Astemizole, Cisapride, Terfenadine	